CAPSUGEL

Symposia series

Biopharmaceutics drug classification and international drug regulation

Seminars and Open Forums

Tokyo, Japan • July 15, 1997

Geneva, Switzerland • May 14, 1996

Princeton, NJ USA • May 17, 1995

Including
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Introduction

During our visit to Japan in November 1994 we discussed the theoretical principles of the Biopharmaceutics Drug Classification (BCS). We both came to the conclusion that creating the opportunity to discuss publicly with the scientific community through open discussion and presentation can significantly impact the future applications of the BCS. A significant step in the process towards international harmonization. Creating a platform for the exchange of scientic ideas is an established Capsugel commitment. Building upon worldwide interest, Capsugel was pleased to organize this series of symposia for the pharmaceutical scientific community.

Product quality and performance is an important concern of regulatory authorities because over the lifetime of a product there are often many changes in formulation, equipment, manufacturing process or site of manufacture. Furthermore, after patent expiration there may be multiple manufacturers of a given product which are approved for marketing on the basis of *in vitro* dissolution or bioequivalence tests without further demonstration of safety and efficiency. The BCS has been developed — with the support of the FDA — to facilitate rational and scientifically sound regulations in the assessment of product quality and performance. Until the issuance of SUPAC-IR, which includes an early form of the BCS, the regulatory approach was based on the concept of *in vivo* bioequivalence based on C-max and AUC rather than the mechanistic approach.

Our effort in creating these open forums was very well received. Comments from the participants and speakers have been very supportive and these scientific discussions outside of the regulatory arena raised many questions about the limitations and possible applications of the BCS. The classification system focuses mainly on bioequivalence, but can we integrate the first-pass hepatic metabolism in the BCS? What can be the agreed surrogates for human permeability? What about the hydrodynamics in the *in vitro* dissolution system? Can we develop the BCS so that in future it provides specific guidance on how to predict the bioavailability? Can we use the BCS to predict food-induced changes? It is significant that during this series of seminars the BCS served as a basis to focus the attention of the scientific community on these key issues.

Our ultimate goal in organizing and publishing these symposia was to provide timely industry output at the evolutionary stage of the FDA proposal. The lectures given in the three regions are combined into the proceedings. Your feedback will tell us if we achieved our objectives.

We are looking forward to hearing from you.

Gordon L. Amidon, Ph.D.
Professor of Pharmacy,
The University of Michigan (U.S.A.)

Roland Daumesnil
Director Global Business Development-
Pharmaceutical, Capsugel

Tokyo

Tokyo

Japan

July 15, 1997

Tokyo, Japan, July 15 1997

Opening Remarks

The title of this symposium is Biopharmaceutics Drug Classification and International Drug Regulation: seminar and open forum.

The theme is the development of oral drug formulations, especially from the regulatory perspective. To be more specific, it will deal with the evaluation and prediction of absorption, as well as with the associated drug development regulations and the challenges and issues involved, particularly from the perspective of the FDA. The symposium will especially focus on the basics: the theories and the mechanical perspectives.

The same symposium on the same theme has already taken place in two other parts of the world, the USA and Europe. In 1995, a symposium was held in Princeton and last year there was another in Switzerland, where Professor Newton of London University took the chair. Today's meeting completes the series by being held in Japan, the third major geographical zone relevant to the worldwide pharmaceutical industry. Till now, each zone has had its own regulations and guidelines but this is changing, and today offers you access to the latest information on the regulations.

Our programme includes speakers from abroad, as well as five Japanese contributors. Each of the speakers will first make their presentation, and this will then be followed by a panel discussion.

The panel discussion will start with short presentations by our distinguished Japanese contributors, who represent industry and academia, and then it will be opened up to general discussion on the international drug regulations and the classification of drugs.

We do have a simultaneous interpretation service today, although since all the international conferences which take place in Japan are held in English, you perhaps do not need one. However, since we will be dealing with regulations, it will be important to retain details in one's head, and this is why we decided to supply the service.

The first speaker is the co-chairman, Professor Gordon L. Amidon from the University of Michigan, who of course needs no introduction. He is an authority both on gastrointestinal (GI) absorption and on the *in vivo/in vitro* correlation. The title of his talk is the Rationale for a Biopharmaceutical Drug Classification System, which covers the whole area of today's symposium topics.

I would like to give the floor to Professor Amidon.

Professor Mitsuru Hashida, Chairman

Rationale of a Biopharmaceutics Classification System (BCS) for New Drug Regulation

Update July 1997

Professor Gordon L. AMIDON, Ph.D.

Rationale and Implementation of a Biopharmaceutics Classification System (BCS) for New Drug Regulation

Professor Gordon L. Amidon, Ph.D.
Charles R. Walgreen, Jr. Prof. of Pharmacy

The University of Michigan
College of Pharmacy
Ann Arbor, MI 48109-1065

Professor Gordon L. Amidon: Thank you Professor Hashida and I want to thank you personally for your effort in assisting in arranging this workshop and discussion. I also want to thank Dr. Lesko for his willingness to participate.

The workshop in the form sponsored by Capsugel was initiated at my request in the interest of having a scientific development-type of audience to listen, critique and provide input into what I think of as new biopharmaceutic and bioequivalent standards for drug development and drug regulation.

I believe that we are entering a new era in oral drug delivery sytems in drug delivery systems generally, of course, but particularly in oral drug delivery systems, where optimisation of oral delivery is going to be an increasingly important development effort. But optimisation is very difficult with current regulatory guidelines because of the complexity of associating the bioavailability and the clinical efficacy claims.

So, in order to improve drug delivery and drug regulation, we need scientifically-based, mechanistically-based, regulatory standards. But our current standard in the United States is just empirical, based on bioequivalent plasma levels.

The discussion and work with the FDA that I have been doing over the past six or seven years first began through a one-year sabbatical that I spent at the FDA, which led on to establishing a strong collaboration with Dr. Lesko and other scientists at the FDA, to develop new regulatory standards for bioequivalence. The situation now is that we are working on an FDA guidance on classifying drugs and we will present to you today its current status. We hope that you will comment on this approach to regulating drugs because I think it is essential and critical to have a good scientific basis for drug regulatory standards.

I myself am not a development scientist. I am an academic and so I do not have a full appreciation of many issues involved in the development, scale-up and clinical testing of oral drug delivery systems. So I welcome your comments and input because we want the regulatory standards to be mechanistically-based and useful in improving the quality and performance of drug products.

My original title was: *Rationale for a Biopharmaceutic Drug Classification System*, which I have now changed to: *Rationale and Implementation of a Biopharmaceutics Classification System (BCS) for New Drug Regulation*.

The two slight modifications in this title are important. The first is intended to show that it is a biopharmaceutic classification system we are talking about: there is no drug. The reason being that we want to regulate drug products, not just a drug but drug products. We are a drug product based-industry. The second modification is intended to show that our focus is on new drug development: how to facilitate and accelerate the Phase I, II, III or IV development of good formulations for human pharmaceuticals.

Properties of "Good" Drug	
- Efficacy	- Safety
- Half-life	- *Bioavailability*

Table 1: Nestor, J.J., in "Peptide-Based Drug Design", 1995.

Bioavailability is increasingly recognised as important today. It always has been important, but we now recognise it as important, and so this presentation will focus on bioavailability and bioequivalence.

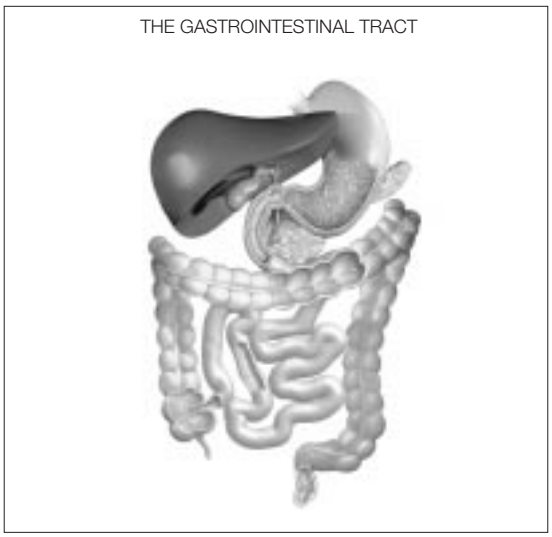

Figure 1.

For oral delivery, we need to consider the motility or transit, the luminal contents, and the presence or absence of food in the gastrointestinal tract. The intestinal tissue, the epithelial cell, is highly differentiated along the GI tract. This all makes predicting oral drug absorption a very complicated processs to do accurately.

We take oral absorption to be the transport across the intestinal membrane into the intestinal tissue. From there, substances move through the portal liver system and on into the systemic circulation. It is very important to distinguish between absorption and systemic availability since, to predict systemic availability, we need to estimate first-pass metabolism in the liver.

I will be focusing on absorption and the bioequivalence regulations, and the mechanistic approach to predicting absorption that then can be used for setting bioequivalence standards. First, absorption.

In the course of our daily fluid intake and output, a large volume — 1 litre per day — is intake volume,

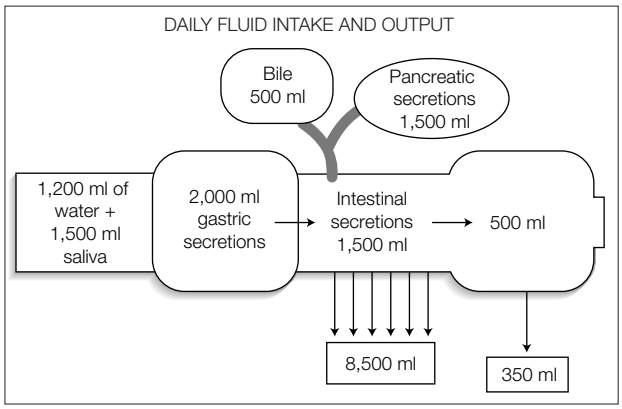

Figure 2.

but around eight litres are added to that from secretions (*Figure 2*). Of the nine litres, 8.5 litres are reabsorbed, and 500 mls arrive in the colon where 350 mls are absorbed. So of, say, about 10 litres, only 0.1 litre in volume is excreted per day. The GI tract is a very efficient organ.

Figure 3 emphasises the systemic availability of an oral dosage form in terms of the properties that we need to regulate in order to ensure quality: dosage form, drug release and drug absorption. We will understand absorption to be the step from the intestine into the portal system or into the intestinal tissue: systemic availability is shown to the right of the figure.

The mechanistic approach requires starting with the first principles, which would be mass transport and describing the rate of mass transport across the intestinal surface (see *Figure 4*).

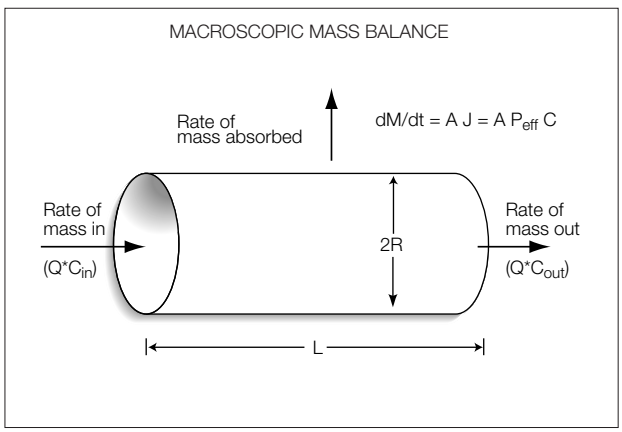

Figure 4.

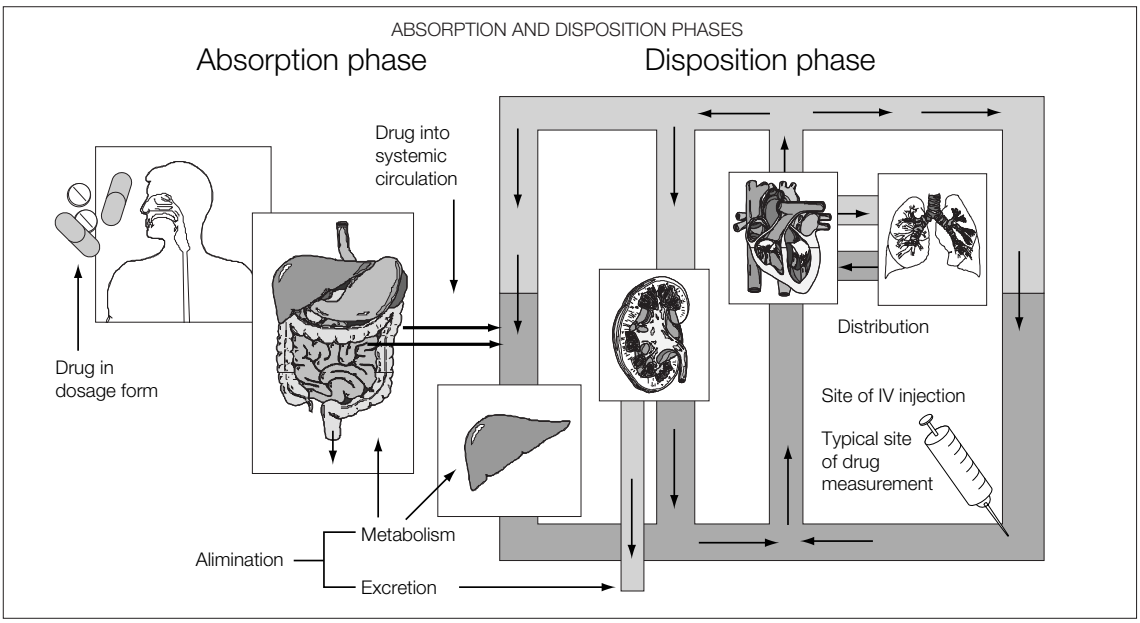

Figure 3.

Fick's first law applied to a membrane
$J_{wall} = P_{wall} \cdot C_{wall}$

Table 2.

Rate and extent of absorption	
Rate:	$dM / dt = \iint_A P_w C_w dA$
Extent:	$M(t) = \int_t \iint_A P_w C_w dA dt$

Table 3.

The starting point must be diffusion or convective diffusion and that would be a Fick's first law applied to a membrane. This law says that the mass per unit area per unit time — the drug absorption rate per unit area — is permeability times concentration (P x C) under sink conditions. So *Table 2* essentially shows fixed first law applied to a membrane where we assume that there are sink conditions on the plasma side at some point.

This is a common assumption, but the difficulty is that the concentration and permeability are position- and time-dependent, particularly the concentration, of course. The result is that we have the drug dissolving and then distributing along the gastrointestinal tract in a complex manner.

However, we can formally say that the absorption rate, the dM/dt (or the mass absorbed per unit time), is equal to this permeability times concentration (P x C) at the intestinal membrane or intestinal wall, just integrated over the surface area of the intestine. So, at any time we can add up the drug absorbed across the surface and that is the mass per unit time which is being absorbed. From this, we can formally say that predicting drug absorption, or the mass absorbed per unit time simply requires that we determine P x C product. Once we can determine those in some way, we can predict M (t). This, however, is complicated.

Mass absorbed is permeability times concentration integrated over the area and then the time, but this is complicated to do theoretically. Nevertheless, two very important conclusions can be drawn from this relationship.

The first is that the intestinal membrane permeability, P, is a very important determinant, maybe the most important determinant, and the mass absor-

Total mass of drug absorbed

$$M(t) = \int_0^t \iint_A P_w C_w \, dA dt$$

Table 4.

bed is a function of time. So one parameter controlling drug absorption is permeability and the other parameter is concentration.

While this is time-dependent, there is a case where it is a little bit simpler, and that is when the drug is insoluble. If the drug is insoluble, then the concentration is replaced by solubility.

That leads to the two principal factors controlling drug absorption — permeability and solubility — that will become the basis for the classification system, because they are the two fundamental parameters controlling the drug absorption rate and extent.

So, while this workshop will present further discussions on this approach, I want you to appreciate that it is a very fundamental mechanistic approach based on regulating drug absorption rather than simply measuring plasma levels with C-Max and AUC. This is a very important philosophical difference in how we are viewing bioavailability and bioequivalence.

However, this is all very complicated, so what to do now? The approach that I took is that we can measure permeabilities. We measured the first permeability of a drug, alphamethyldopa, in humans more than 15 years ago. More recently, using newer methodology, we have developed an extensive database as part of the collaboration between the University of Uppsala and the FDA.

First, let me describe the method for measuring permeability in humans. This is based on a multilumen tube which was developed at the University of Uppsala (see *Figure 5*). It has two ports for balloons, you inflate the balloons and isolate 10 centimetres of jejunum. The fluid flows in the central port and then flows upstream and downstream similarly to when under segmental contraction in the fed state.

We expose 10 centimetres of intestine to drug and then we collect the perfusate through one of the collection tubes and analyse it for drug absorption. In addition there are motility probes and aspiration ports for two of these tubes, and also a stomach tube to remove fluid accumulated due to gastric secretions.

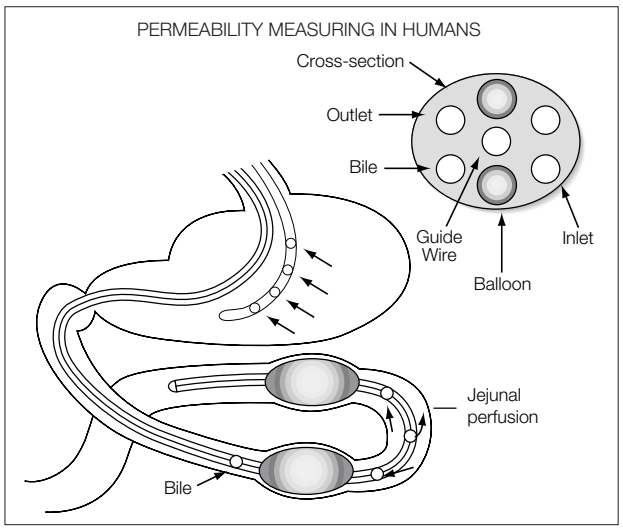

Figure 5.

This study can be done in one day. It takes about an hour to place a tube and then maybe another hour to prepare the subject and about two hours to carry out the study. So a permeability in humans can be determined in four to six hours.

Figure 6 shows the database of human permeabilities which has been developed under the collaboration between the University of Uppsala and the University of Michigan. So far, the highest permeability measured is for glucose, which is around 10 x 10^{-4} centimetres per second. The lowest permeability measured to date is for enalaprilat.

Enalaprilat is the active di-acid ACE inhibitor that is available for IV administration. The oral dosage

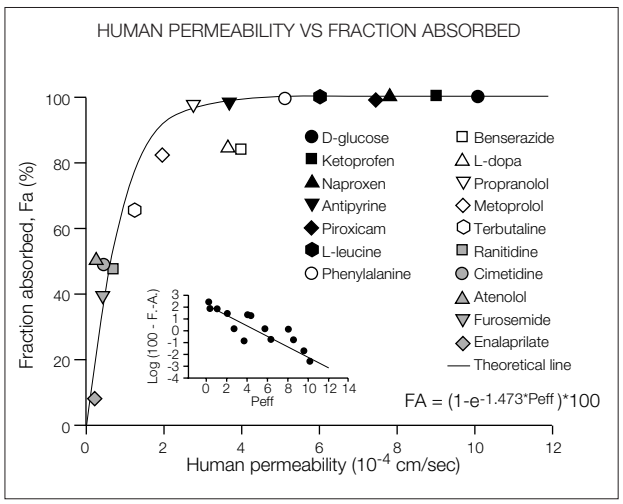

Figure 6.

form is enalapril, a pro drug, which has a higher permeability. We have recently measured enalapril permeability in humans and it is around 2; it is a high-permeability drug absorbed by the peptide carrier.

Another drug of interest, I think, is metoprolol. Metoprolol is a drug that is about 95 per cent absorbed and its permeability is around 1 to 1.5. So in determining permeability — high permeability, low permeability — metoprolol is a drug that would appear to be on the boundary. However, we know that metoprolol is available in oral controlled-release dosage forms, so where there is absorption from the colon we would probably define metoprolol as being a high-permeability drug.

Terbutaline, frusemide and atenolol are low-permeability drugs. A low-permeability drug is one that is less than 100 per cent absorbed. In, for example, the case of atenolol, it is not metabolised; 95 per cent of atenolol IV is excreted unchanged in the urine. The oral dose is 45 per cent excreted in the urine and 45 per cent bioavailable. So atenolol is very definitely a polar permeability-limited drug. The absorption processs controlling absorption for atenolol is typically permeability, not formulation.

So the classification system on permeability will be a means of dividing drugs into high and low permeability.

Permeability depends on position, time and concentration, and so there is no single permeability for a drug. There is, though, a permeability under defined conditions, and we have developed a reference permeability around this concept.

Table 5 shows a typical perfusing solution. We use a low drug concentration, isotonic solutions, average jejunal Ph, and then we simultaneously perfuse four markers plus the test drug. This standardised approach represents the reference conditions under which we are determining a permeability and hence becomes a reference permeability for drug classification and drug regulation. We have set a reference standard based on these perfusing conditions.

Standard perfusing conditions	
- Low concentration	
- Zero water flux	
- pH = 6.5	
Isotonic:	Glucose (10 mM), Phosphate Buffer, KCl, NaCl, Mannitol
Markers:	PEG 4000 (Non absorbable marker, cold) Phenylalanine (High P, nutrient) Propranolol (High P, passive) PEG 400 (Low P, passive)

Table 5.

The permeability in vivo, however, would generally be different because of the differing luminal environment and the differing positions in the gastrointestinal tract.

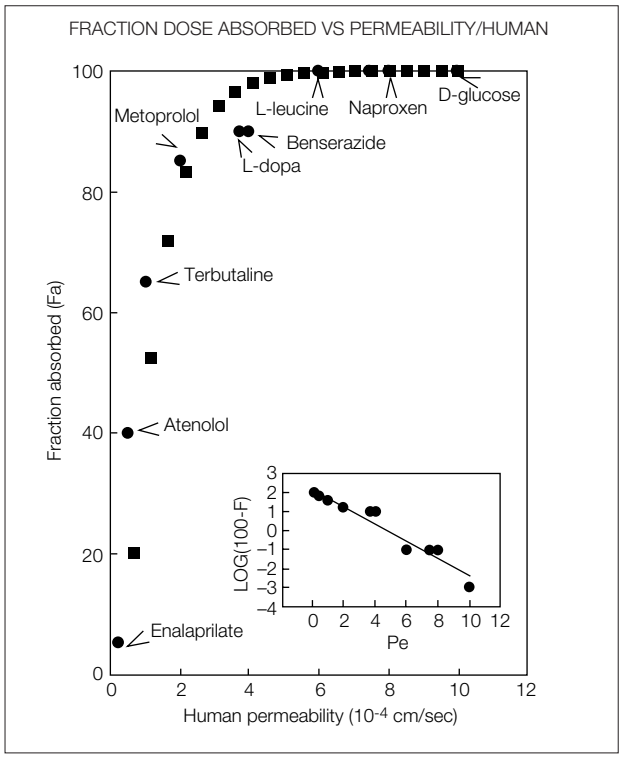

Figure 7.

We now move on to *Figure 7*, which represents a set of reference standards between human permeabilities measured under standard conditions, and the fraction absorbed. Note, it is the fraction absorbed — this is not systemic availability, but fraction absorbed. The estimation of fraction absorbed can be complicated for some drugs but for the drugs listed we are quite confident of the determined fraction absorbed, typically based on mass balance and radio label studies. Here, metoprolol will be a key drug, in that the border between high and low permeability will be in this region.

One of our proposals is to define high-permeability drugs as drugs where the fraction absorbed in

humans is 90 per cent. That would be a permeability of about 1 to 2 x 10^{-4} centimetres per second, or 0.7 centimetres per hour, which can be estimated to be an absorption half-time of about one hour.

High permeability drugs
F = 90% in humans P_{eff} = 2 x 10^{-4} cm/sec = 0.72 cm/hr (Absorption half-time - 1 hr)

Table 6.

The specific limits for high and low permeability are still being evaluated, because to determine the limits one needs a good database and statistical analysis and we are, through FDA-sponsored research, establishing that database and limits at the present time. But I think we will take approximately 90 per cent or higher to be well-absorbed high permeability: F should be greater than or equal to 90 per cent (F = 90 per cent), and a permeability of 1 to 2 x 10^{-4} cm/sec.

Low solubility drugs
$J^{max} = P_{eff}\ C_s$

Table 7.

The previous correlation that I showed on permeability and fraction absorbed was for drugs that are soluble, drugs that are in solution. That graph is more complicated when you have low solubility, and dissolution considerations. We need to add-in solubility and dissolution rate because the permeability for low-solubility drugs — the maximum absorption rate per unit area — is permeability (P), times solubility.

So now we need to consider solubility in the gastrointestinal tract. The theoretical model or analysis for low-solubility drugs would be to model the dissolution of particles, then the absorption (see *Figure 8*).

For dissolution we use the model with the boundary layer equal to the particle radius. *Figure 9* shows the small-particle boundary layer approximation which has been used since the 1960s, when it was originally developed and applied to pharmaceutical systems by my major professor, Professor W.I. Hiquchi, whom I am sure you know very well.

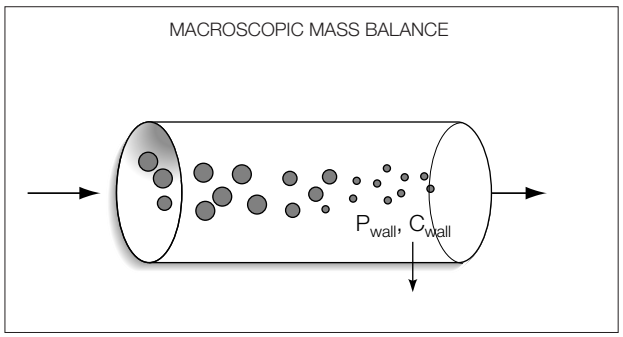

Figure 8.

It is the small-particle limit operative under conditions where particles are less than perhaps 30 microns, which would be the situation for most water-insoluble drugs, though not all. Otherwise you need a different constant boundary layer analysis.

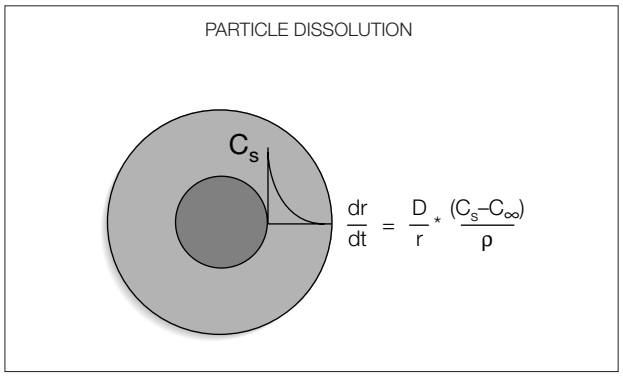

Figure 9.

For evaluation of the impact of solubility and dissolution we need to add in the particle dissolution and the drug absorption from solution. The particle dissolution figure is from the previous *Figure 9*. Then we have the drug absorption, now with the co-efficient being the absorption number; the drug dissolution with the dissolution number, and the dose number, which is essentially a surface area term.

Dimensionless mass balance on a tube	
Mass balance on particle	$\frac{dr^*}{dz^*} = -\frac{Dn}{3}\frac{(1 - C^*)}{r^*}$
Mass balance on solution	$\frac{dC^*}{dz^*} = Do \cdot Dn \cdot r^*(1-C^*)-2An \cdot C^*$

Table 8.

Table 9 gives the definitions of the co-efficients from the model shown in *Table 8*. Dose number is a mass or dose divided by reference volume, divided by solubility. The dissolution number is the residence time divided by the dissolution time. And the absorption number — the residence time divided by the absorption time. This model, then, accounts for the finite transit time in the gastrointestinal tract, and the permeability and dissolution parameters are important relative to transit.

Co-efficient definitions

Do = Dose Number = $\frac{M_0/V_0}{C_S}$

Dn = Dissolution Number =

$$\frac{DC_S}{\frac{4\pi r_0^2}{\frac{4}{3}\pi r_0^3 \rho}} \cdot t_{res} = t_{res} \cdot 3DC_S/\rho r_0^2 = t_{res}/t_{Diss}$$

An = Absorption Number = $\frac{P_{eff}}{R} \cdot t_{res} = t_{abs}^{-1} \cdot t_{res}$

Table 9.

So for a low-solubility drug with high membrane permeability, we would have a high absorption number like 10 (see *Figure 10*). Glucose or piroxicam or perhaps naproxen would have an absorption number of 10. They are characterised by very high permeability, with a very short absorptive time relative to transit time.

So now let's turn to the dissolution number and dose number with two classic pharmaceutical examples, digoxin and griseofulvin. Digoxin and griseofulvin have the same solubility, about 20 micrograms per ml. But, — as can be seen in *Table 10* — the dose is 1,000-fold different, so that the volume required to dissolve the dose is 20 mls for digoxin but 33 litres for griseofulvin. Thirty-three litres is a huge volume, of course, so griseofulvin becomes a solubility-limited drug while digoxin is dissolution-limited.

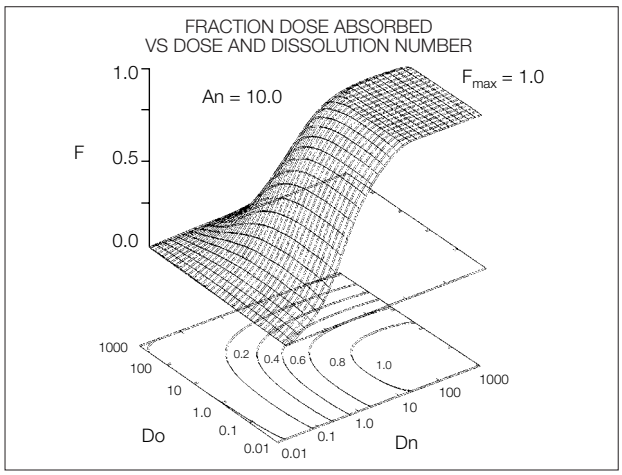

Figure 10.

The dose number is the dose divided by the volume, divided by the solubility; the volume we take as 250 mls. In the United States, when we do bioequivalent studies based on 250 mls, we use a glass of water, and in the United States a glass of water is eight ounces. I have noticed in Japan that it is

Calculated parameters for representative drugs

Drug	Dose (mg)	C_S^{min} (mg/ml)[a]	V_{Sol} (ml)[b]	Do[c]	Dn[d] (est. intrinsic)
Piroxicam	20	0.007	2,857	11.4	0.15
Glyburide	10	0.0034	2907	11.6	0.074
Cimetidine	800	6.000	133	0.53	129
Chlorthiazide	500	0.786	636	2.54	17.0
Digoxin	0.5	0.024	20.8	0.08	0.52
Griseofulvin	500	0.015	33,333	133	0.32
Carbamazepine	200	0.260	769	3.08	5.61

a: Minimum physiologic solubilities were determined in the physiological pH range (1-8) and temperature.
b: Volume of solvent required to completelty dissolve the dose at minimum physiologic solubility.
c: Do = Dose/V_O/C_S^{min}, initial gastric volume, V_O = 250 ml.
d: Assumptions: r_O = 25 µm, D = 5 x 10^{-6} cm^2/sec, ρ =1.2 gm/cm^3, < t_{res} > = 180

Table 10.

maybe four or six ounces, so maybe there is a harmonisation issue here. But in the United States it is 240 mls, so we say 250. Consequently, griseofulvin requires 133 glasses of water to dissolve.

Turning back now to *Table 9*. Digoxin has a low dose number and, by micronising or solubilising, we can increase the dissolution rate to get good absorption profiles, so by improving the delivery we can get good absorption. However, griseofulvin has a high dose number, so it is very much more difficult to improve the bioavailability for griseofulvin. These examples illustrate the importance of solubility and dose in determining the factors limiting oral absorption.

I have been talking about solubility and the question, of course, is solubility in what? In the gastrointestinal tract it is complex. So I want to show some of our work on micelle and emulsion systems to present some insight into that process (*Figure 11*).

We studied a variety of surfactants — sodium lauryl sulphate (SLS), dodecyltrimethylammonium bromide (DTAB) and tween 20 (TW 20) ñ and we referenced some work on bile salts by Dan Cromalin at his laboratory in Utrecht and studied an emulsion with tween 20. I want to show some selected results and our conclusions from the study.

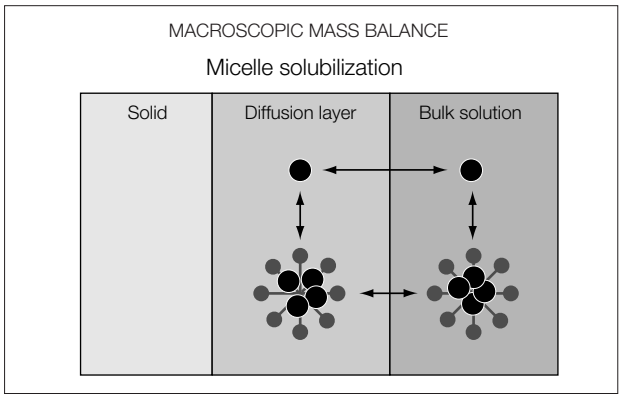

Figure 11.

The reason for studying micelles and surfactants is their potential use as *in vitro* dissolution media, not perhaps for quality control, but for bioequivalence reasons. If you want to ensure that a drug product dissolution profile after a change is the same as in vivo, we should reflect the *in vivo* process in our dissolution media. Surfactants are one approach.

Surfactant facilitated dissolution	
• SLS	• Bile Salts
• DTAB	• TW 20 emulsion
• TW 20	

Table 11.

I would like to show a few key pieces of data on griseofulvin. *Figure 12* represents the solubility enhancement, with the enhancement for sodium lauryl sulphate being up to 150 times. The other surfactants are significantly less, including the sodium cholate.

Solubilisation was 150-fold, but the dissolution or flux enhancement was only about 40-fold (see *Figure 13*). The solubilisation, increases 150-fold but the dissolution rate only 40-fold. The reason for that is that the micelle diffusion coefficient is significantly lower.

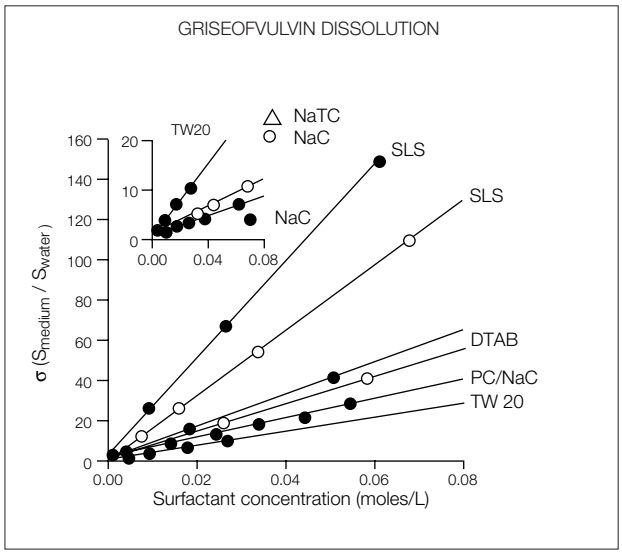

Figure 12.

The effective diffusion coefficient decreases as you increase the surfactant concentration. This is analagous to mass public transport in the sense that you can drive to work in a car or take a bus, but the bus goes much slower although it has a much higher capacity. Total mass transport is therefore increased, but not as much as if the bus could go as fast as a car. Overall, the bus makes total mass transport higher, but it is slower and as you fill up the bus, everything moves at the speed of the bus.

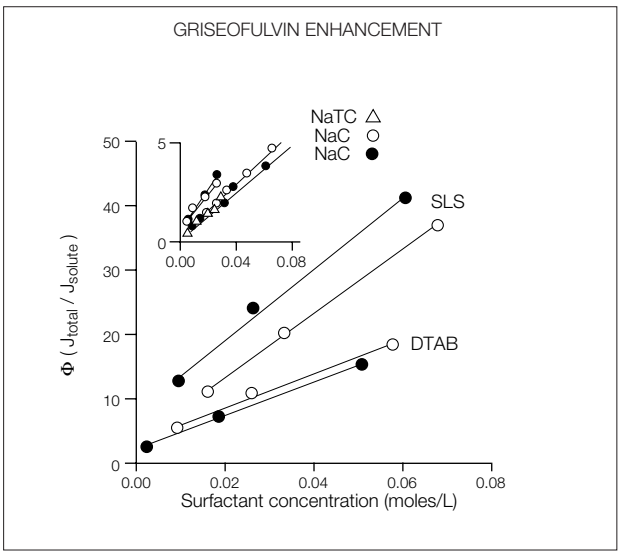

Figure 13.

The conclusions from many studies with a variety of surfactants are on *Table 12*. Enhancement is proportional to solubilisation. So I would put a very strong emphasis on solubilisation because the factor important *in vivo* is solubilisation. However, enhancement is reduced four-fold by diffusivity of the micelle, being slower. And pharmaceutical surfactants are as good as bile salts plus lecithin for *in vitro* dissolution.

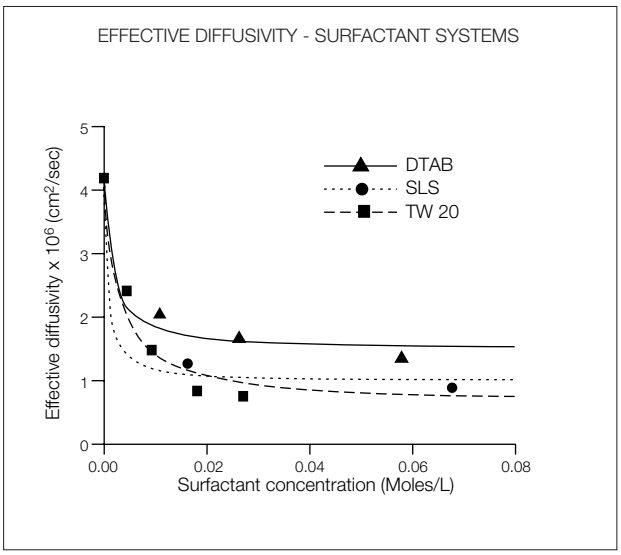

Figure 14.

Now for *in vivo* and perhaps in vitro we should consider some monoglycerides and fatty acids. So *in vivo* or in *in vitro* dissolution media reflective of the *in vivo* state are worth discussing, and I think Professor Dressman will address some of those issues in her presentation.

Surfactant dissolution
- Enhancement proportional to solubilization
- Enhancement reduced – 4 fold by diffusivity
- Pharmaceutical surfactants as good as bile salts + Lecithin for *in vitro* dissolution

Table 12.

So, the bottom line is that surfactant dissolution and solubilisation is important, and pharmaceutical solvents or pharmaceutical surfactants are excellent solubilisers. However, dissolution in micelles is only one part; the other is emulsions.

The drug can also dissolve in the emulsion particle and if the drug is a car and the micelle is a bus, then I guess this is a train. It is very much larger, similar in size to the boundary layer associated with a dissolving micron-sized particle.

The transport analogy becomes more complicated with diffusion in the particle, and interface transport resistance becomes potentially important.

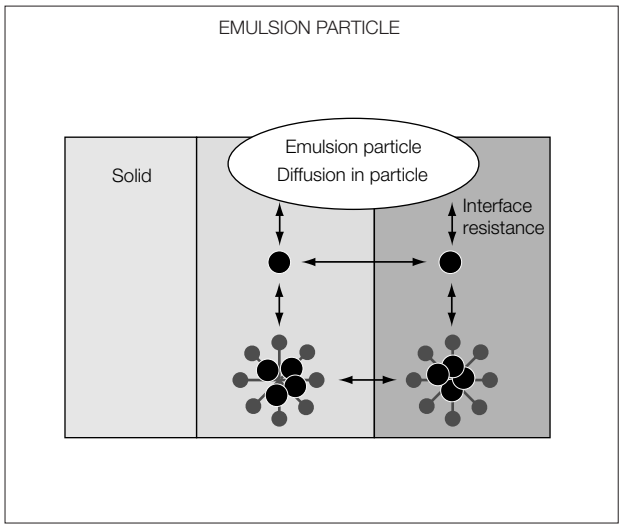

Figure 15.

The following two figures give two results from studies on emulsions. *Figure 16* shows the flux or dissolution rate increase. The dissolution rate is only increased about 10 times, so the conclusion from this dissolution study is that the emulsion particle does not greatly influence the rate of dissolution.

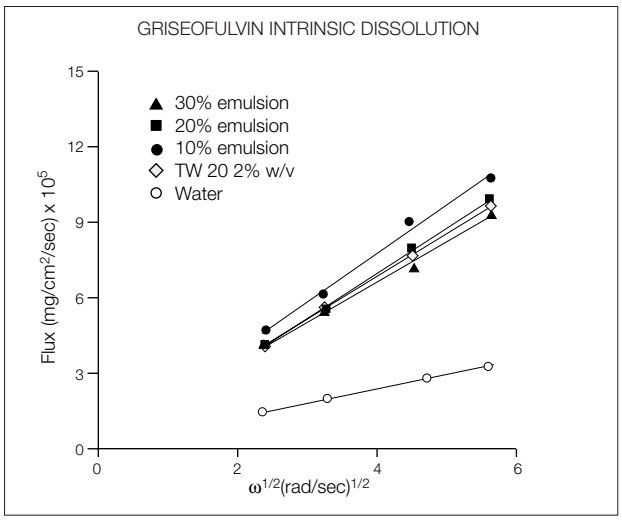

Figure 16.

Following over time, the emulsion is slow. In fact, just the surfactant solution alone is faster, because it is smaller. The emulsion particles diffuse so slowly that they can only contribute to a dissolution rate to a very small extent.

However, eventually the emulsion will continue while the surfactant plateaus, making emulsions important for total solubilisation because of the lipid solubility. But they do not have a big impact on rate, only on the extent. In additional studies, we have been able to show that it is the micelle phase in the emulsion which is principally responsible for the rate enhancement, not the emulsion particles.

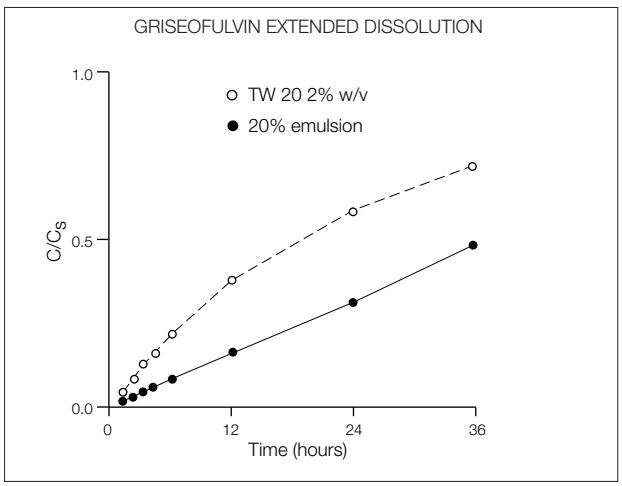

Figure 17.

Emulsion dissolution
- Small effect on rate
- Significant effect on extent

Table 13.

So the conclusion from studying emulsions is that they have a small effect on rate but a significant effect on extent. Consequently, for evaluating dissolution rate-limited drugs, I believe that surfactant solutions are completely adequate for characterising the *in vivo* dissolution rate.

Now some comments on *in vitro* dissolution. To ensure bioavailability and bioequivalence, the *in-vitro* dissolution media should approximate to *in vivo* solubilisation. The micelle solubilisation is most important for rate enhancement, high dose or dose number, and for extent determined by lipid-phase solubility. This lipid-phase solubility may be one of the factors — perhaps the direct factor — responsible for the food effect on many drugs and dosage forms. The food effect is complex but this is one factor.

In vitro dissolution media
- Should approximative *in vivo* solubilization
- Micellar solubilization is most important for rate enhancement
- High dose (number) extent determined by lipid phase solubility
- Food effect

Table 14.

Turning now to the regulatory side. You are familiar with the US definition of bioavailability and bioequivalence, so I will just remind you that in the official government definition that is published in the Code of Federal Registers, bioavailability means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the *site of drug action*.

I emphasise the phrase ‘site of drug action’ because our usual surrogate for that today is plasma level; we measure plasma levels. However, ‘site’ is not a good term because it should be ‘sites’. But then that makes things awfully complicated, so again it is not a helpful definition.

Bioequivalent
CFR 21.310.1 (Definitions)
Bioavailability means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the *site of drug action*.

Table 15.

Let’s try to come at this from a different direction. Of course our goal is to ensure efficacy. And if we change our focus to the phrase ‘is absorbed’ and we regulate the absorption, then we have a much more powerful approach to determining *in vitro* standards and establishing *in vitro/in vivo* correlations.

So this is the key term — the ‘is absorbed’. If we can ensure that the absorption is equivalent, then we have ensured bioequivalence. The usual standard is that the 90 per cent confidence interval on the test product must lie between -20 and + 25 for the reference. This applies both to C-Max and also to AUC, so it is a fairly simple, straightforward empirical test to determine when two products are bioequivalent. But it’s not mechanistic, it’s empirical.

The mechanistic approach would say that if we want to regulate the rate and mass absorbed, we need to regulate permeability times concentration (P x C). If we can ensure this similarity we have ensured bioequivalence.

So the equation (*Table 4*) implies the following. If two drug products containing the same drug have the same permeability/concentration/time profile at the intestinal wall, they will have the same rate and extent of drug absorption. This means that if we can ensure that the permeability times concentration (P x C) is the same, the two products will be bioequivalent.

So permeability is one factor, concentration or solubility is the second.

The current basis for classification takes solubility to be the lowest solubility in the physiological pH range. It’s a very conservative standard, probably too conservative, but we need data to determine the solubility standard we should set. The reference permeability is the human jejunal permeability of pH 6.5 at a low-dose range.

Table 16 shows the key *in vitro/in vivo* correlation expectations for immediate-release products based on biopharmaceutic class. We classify high and low

In vivo-in vitro (IVIV) correlation expectations for immediate release products based on biopharmaceutics class

Class	Solubility	Permeability	IVIV correlation expectation
I	High	High	IVIV correlation if dissolution rate is slower that gastric empying rate, otherwise limited or no correlation
II	Low	High	IVIV correlation expected if *in vitro* dissolution rate is similar to *in vivo* dissolution rate, unless dose is very high (see discussion)
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIV correlation with dissolution rate
IV	Low	Low	Limited or ni IVIV correlation expected

Table 16.

based on the standard set stated; for example, high solubility, high permeability.

An *in vitro/in vivo* correlation can be expected if the dissolution rate is slower than gastric emptying, otherwise there is limited or no correlation. For example, for a high-permeability drug that dissolves rapidly in the stomach, the absorption rate is determined by the gastric-emptying rate, not the dissolution rate. There is no correlation, there is no scientific basis for expecting an *in vitro* dissolution rate/*in vivo* absorption rate correlation.

On the other hand, for the low-solubility, high-permeability lipophilic drugs that commonly come through from drug discovery nowadays, we expect an *in vitro*/in vivo correlation if the *in vitro* dissolution rate is similar to the *in vivo* dissolution rate. Here, *in vitro* dissolution/*in vivo* dissolution is very important.

So if we have a media and dissolution methodology reflecting the *in vivo* dissolution process, we should expect and require an *in vitro/in vivo* correlation, unless the dose is very large — I mentioned solubility-limited drugs like griseofulvin.

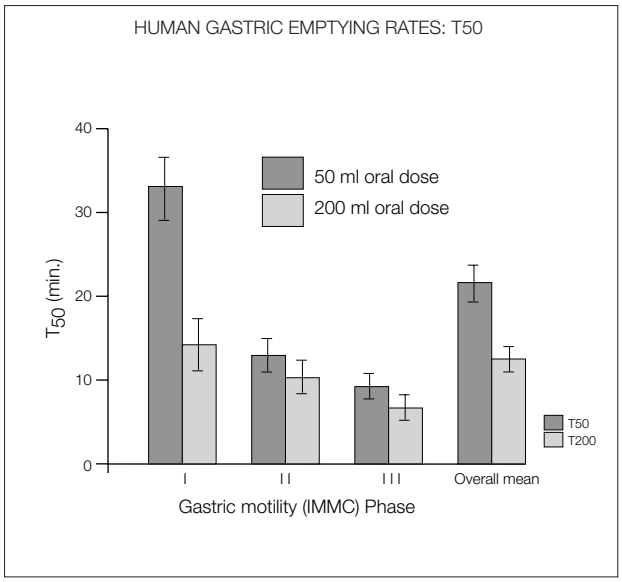

Figure 18.

This particular table within the classification allows us to set out *in vitro/in vivo* correlation standards for immediate-release products and this will be one of the principal uses of the classification system.

Returning to the topic of gastric emptying which I mentioned earlier. Some 10 years ago, we intubated subjects and measured the gastric-emptying rate by perfusing a drug into the stomach and into the duodenum, and I will show a summary of our results of human gastric-emptying.

These are the human gastric-emptying rates at T50, timed for 50 per cent emptying. The rate of gastric emptying is a function of gastric motility (*Figure 18*).

The overall average for 200-ml oral doses is about 12 minutes, the average for 50 mls is about 20 minutes. So there is a volume dependence on the gastric-emptying rate. The gastric-emptying rate varies with the contractile phase — quiescence is longer and active is much shorter — but takes 10 to 20 minutes on average, depending on volume.

Remember how I pointed out earlier that the US glass of water was 250 mls and it appears to me that the Japanese glass of water is maybe less? Volume is important for gastric-emptying rate, and so my comment was serious. Volume influences gastric-emptying rate, therefore that will influence the rate of absorption for high-solubility, high-permeability drugs that rapidly dissolve.

So, to summarise. I think permeability-limited drugs would probably have a limited *in vitro/in vivo* correlation. For rapidly dissolving drugs, you would expect no correlation. For dissolution-limited drugs an IVIVC should be possible, but media and methods need to be developed. Then for very high-dose, solubility-limited drugs there may be limited correlation for very high dose drugs between dissolution rate and absorption rate.

One final point would be that the solubility I mentioned was the the lowest solubility in the physiological pH range. I have suggested that we consider a solubility classification that is more reflective of the *in vivo* situation.

Under this, high solubility would mean a drug that dissolves in a 250-ml glass of water, over pH 1 to 8, and a low-solubility drug would be one that requires more than 250 mls for all pH, but an intermediate would be a drug which dissolves in this range in 250 mls. This means that the drug is soluble in the stomach or intestine.

This approach would allow for drugs like carboxylic acids, that dissolve rapidly upon entering the duodenum, to be classified as high-solubility, rapidly dissolving drugs. However, this requires considerable further discussion and evaluation of data to determine how to set the solubility standards.

So I would conclude this part of the seminar with the comments that I think the classification system is a very important new approach to viewing and developing drug regulatory standards, because it is based on mechanistic understanding of processes controlling *in vivo* availability. On that basis we can simplify regulatory standards, and simplify the drug development processes — Dr. Lesko will indicate how this classification system may be used at the investigational new drug (IND) stage, or the Phase I stage of drug development.

I think that even further in the future the system will allow for the development of better-optimised oral delivery systems, because we have more rational and sensible *in vitro* standards and *in vitro*/in vivo correlations.

Thank you very much.

Professor Mitsuru Hashida: Thank you very much for your very interesting and comprehensive talk on drug absorption. Your introduction was very useful in guiding us on how to discuss the study of absorption in quantitative terms, and also in laying the general fundamentals for that kind of discussion.

I would like to invite questions or comments from the floor.

Question: You said that permeability is dependent on time, is a function of time. From your experience, what is the level of the time-dependence of permeability? If it is very much time-dependent, will we perhaps have to consider a time-dependent element when conducting a bioequivalence test? What do you think?

Professor Amidon: Permeability is time-dependent. But for most drugs — those with passive absorption — I think the time-dependence is not too strong. For carrier-mediated drugs it can be more complicated.

Virtually all of our drugs were passive, for a number of reasons. Where permeability is very time-dependent, I think it is much more complicated, so it needs to be considered very carefully.

The classification system, and permeability and solubility, will not simplify every drug.

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The Biopharmaceutics Classification System: a Policy-Implementation Approach

Update July 1997

Dr. Lawrence J. LESKO, Ph.D.

The Biopharmaceutics Classification System: a policy-implementation approach Update July 1997

Dr. Lawrence J. Lesko, Ph.D.

Director
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Professor Hashida: Our second presentation is by Dr. Larry Lesko of the US Food and Drug Administration (FDA), whose subject is the Biopharmaceutics Classification System: A Policy-Implementation Approach.

Dr. Lesko is Director of the Office of Clinical Pharmacology and Biopharmaceutics, which is part of the FDA's Center for Drug Evaluation and Research. His office is responsible for evaluating and reviewing investigational new drugs (INDs) and new drug applications (NDAs), as well as information related to biopharmaceutics, pharmacokinetics and pharmacodynamics, and these activities mean therefore that it also has special expertise in evaluating Phase I and II data.

This is the standpoint from which Dr. Lesko will be telling us about the FDA's attitudes, and especially the recent picture regarding guidances. Dr. Lesko, please.

Dr. Larry Lesko: I want to begin by sharing with you some of the perspectives of the Food and Drug Administration as they pertain to the biopharmaceutics classification system (BCS). The FDA takes the view that public meetings and scientific exchanges, such as the one here today, are extremely important in developing scientific standards or regulations that have an impact or influence, not only in the United States but also world wide. I think it is important, particularly in this area of the classification of drugs, that we hear about global perspectives on science and explore how standards might best be implemented in regulatory decision-making.

So I am delighted to be here and I am looking forward to the remaining speakers and the remarks they have to make, as well as to the comments of the panel and also, of course, to the questions and dialogue which will come from you, the audience.

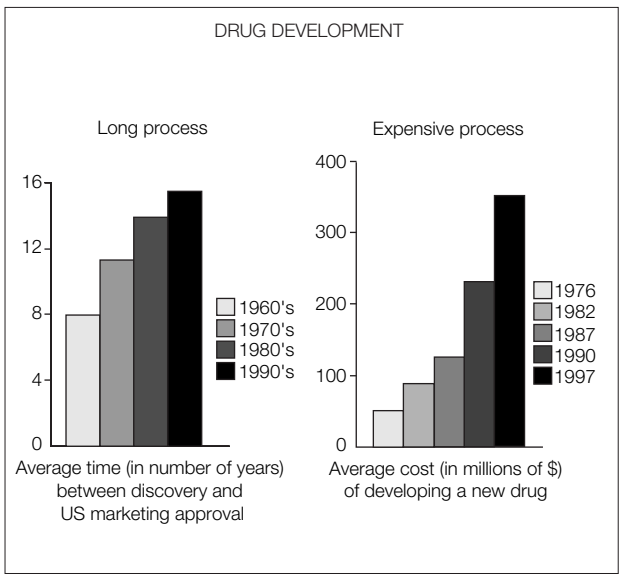

Figure 1.

I would like to start by setting out the framework of the problem. The problem that the agency is trying to deal with is that drug development has become a long and expensive process. I think the

pharmaceutical industry is to be complimented for the high quality and performance of dosage forms that they produce. But now, for a new chemical entity (NCE), the process has become excessively long; the current development time-frame for a new molecular entity is some 15 or 16 years. It is also a costly process, with the average cost for developing a new chemical entity beginning to approach $350 million.

Over the last three years in the United States, we have had a reform initiative called 'Reinventing Government'. The purpose of this initiative, which originated with President Bill Clinton, was for government agencies to look at their regulations to determine if they are still in line with the technology in their particular field, whether they are overly burdensome and (in the case of the FDA) whether some changes could be made in regulations to streamline drug development without sacrificing the high quality and performance of products in the market place.

So this is the challenge we have had at the FDA over the last couple of years, to look at where regulations are unnecessarily burdensome and to try to find ways of streamlining drug development.

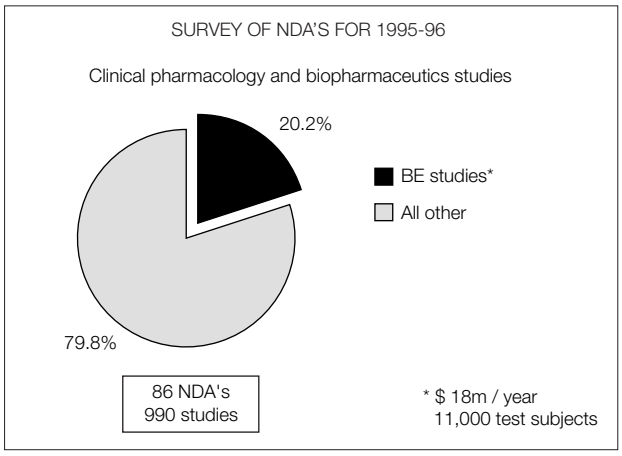

Figure 2.

Illustrative of the problem of the cost of drug development is the area of bioequivalence studies. Over the years, bioequivalence testing has emerged and evolved as a gold standard for comparing the relative performance of two drug products.

Recently, we conducted a survey of new drug applications for the period 1995-1996. What we were interested in was the type of clinical pharmacology and biopharmaceutic studies they contained. These would be studies that companies would typically conduct in the Phase I and Phase II periods of drug development, and that in turn we would review in our office.

In that year we had 86 new drug applications and almost 1,000 Phase I and Phase II studies. Approximately 20 per cent overall, or nearly 200 studies, were bioequivalence studies. The rest were pharmacokinetic and pharmacodynamic studies of different sorts, with various objectives. What we were particularly interested in, though, were those bioequivalence studies, because they represented a fairly high cost in drug development of the order of $18 million a year, as well as involving a significant human resource and, we estimate, approximately 11,000 test subjects.

Furthermore, we went to the reviewers and asked them what percent of these studies they actually reviewed, and which percent was pivotal to their regulatory decision-making. We were concerned at discovering that a number of these studies were not being reviewed and were considered redundant or unnecessary for the purposes of reaching regulatory decisions. So we found that there was some potential for savings and reducing regulatory burden, particularly in the area of bioequivalence studies, by applying the biopharmaceutic classification system.

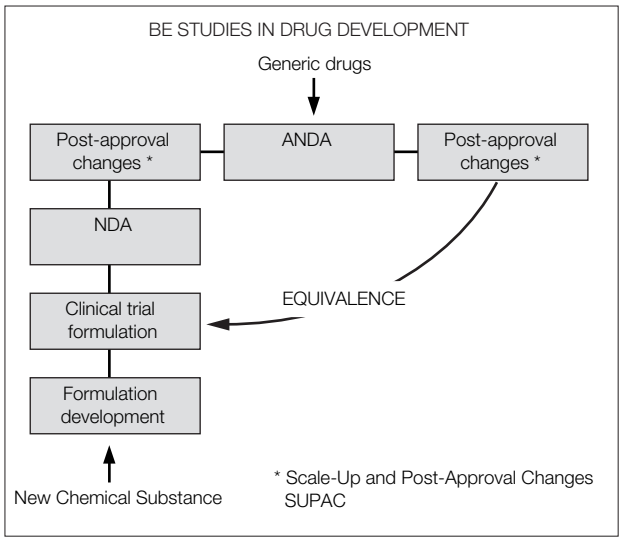

Figure 3.

Now when we think about where these studies are actually conducted within the drug development process, we can start at the bottom right-hand column of *Figure 3* with a new chemical substance.

The studies from that survey were really conducted within the framework of this part of the process, beginning with the development and optimization of formulations for a new chemical entity, going into the clinical trial formulation, which is the anchor formulation for the demonstration of efficacy, and finally leading up to the approval of the NDA. So those 200 bioequivalence studies represented the studies conducted within this time-frame of drug development.

Now what the survey did not consider is the fact that many other bioequivalence studies are conducted during the life cycle of that new chemical substance. For example, prior to patent expiration, an innovator company may make changes in its formulation or its site of manufacture, perhaps in its equipment, and these changes in the past have generally led to a bioequivalence study to document the continued equivalence.

Once the patent expires on that new chemical substance, the product is open to multi-source competition and we review the biopharmaceutics of ANDAs (abbreviated new drug applications) primarily on bioequivalence studies. So generic drugs are also approved on the basis of bioequivalence studies, and we are increasingly conducting more of them.

Finally, there is the post-approval period for generic drugs, when manufacturers make changes similar to those made by the innovator company. In the past, these have also required bioequivalence studies.

The purpose of all of these studies is to continue to link all of the formulations in terms of their equivalence to the pivotal formulation which was originally used in the clinical trial. In this way, by demonstrating equivalence for the entire life cycle of the chemical substance we can ensure that the products in the market place, both innovator and generic, are effective.

So, as you can see, the opportunity for reducing the regulatory burden by reducing bioequivalence testing is substantial, and the agency has taken some first steps towards this by dealing with testing in the post-approval period. In November of 1995 the agency issued a guidance for immediate-release (IR) products which we call SUPAC-IR (Scale-Up and Post-Approval Changes), which defines either the dissolution or bioequivalence requirements for changes. This guidance utilizes the biopharmaceutical classification system to make that decision.

Regulatory challenge
How to assure product “sameness“ following manufacturing changes over the lifetime of the innovator product, and following patent expiration, over the lifetime of multi-source generic products?

Table 1.

So as we approach the regulatory implementation of the science, which is what my talk is dealing with, our challenge is to ensure product sameness or equivalence or interchangeability following changes over the lifetime of the innovator product and, after patent expiration, over the lifetime of multi-source generic products. It is a considerable challenge and in this context the BCS has become,

Regulations and bioequivalence
A drug shall be considered to be bioequivalent to a reference drug if…
…the rate and extent of absorption of the drug do not show a significant difference in the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single for multiple doses.
Food, Drug and Cosmetic Act Section 505(j)(7) - Bioequivalence

Table 2.

I think, extremely valuable.

There have been previous regulatory definitions of bioequivalence. One example relevant to pharmaceuticals comes from Section 505 (j) (7) of the US Food, Drug and Cosmetic Act. It says that a drug is considered bioequivalent when we have similarity in the rate and extent of absorption between a test and reference product. And here, along with Professor Amidon, I believe that the key phrase is: ‘the rate and extent of absorption.

What we actually want to regulate is the equivalence of rate and extent of absorption and I think approaching this from the standpoint of permeability times concentration (P x C), as Professor Amidon described, is entirely logical and consistent with the regulatory requirements for demonstrating bioequivalence.

Demonstration of equivalence
- *in vivo* bioequivalence PK studies
- *in vivo* bioequivalence PD studies
- Comparative clinical trials
- Animal studies
→ *in vitro* dissolution
21 CFR 320.33 - Waivers possible

Table 3.

Now, the definition under the Food, Drug and Cosmetic Act was originally made in 1977 — and regulations are subject to interpretation. So we have been living with that definition of bioequivalence for over 20 years and over time we have interpreted the regulation in different ways. This has given us the flexibility to accept one or more different types of studies in the demonstration of equivalence.

Perhaps the one most people are familiar with is the *in vivo* bioequivalence pharmacokinetic (PK) study. It is the most common, and the most reliable, and we see it in almost all of the cases in the last 10 or 15 years. More recently, we have begun to use pharmacodynamic (PD) studies to demonstrate bioequivalence for those products that do not have measurable systemic absorption, such as topical ointments containing corticosteroids, or metered-dose inhalers.

We also have an option of accepting comparative clinical trials. However, they are not only expensive, they are also insufficiently sensitive and discriminatory when it comes to assessing differences between products. Then there are animal studies, which I would say are rarely, if ever, used in bioequivalence testing these days and, finally, we come to in vitro dissolution testing which we have begun to focus on most recently, as part of our consideration of the BCS.

So the rest of my remarks will concentrate on dissolution testing as it is being dealt with in the implementation of policy for bioequivalence testing.

It is very important to realise that under the Code of Federal Regulations 21 (21 CFR), 320.33, the agency has the discretion to waive bioequivalence testing, and that waivers of bioequivalence can be applied in situations where equivalence between two products is obvious. One example might be an intravenous injection, another might be the oral administration of two solutions.

Waivers of *in vivo* BE
Solution dosage forms
- Same concentration of active ingredient
- Excipients do not affect absorption of active
21 CFR 320.22 - Section 3(i),(ii)

Table 4.

This concept of waivers is important, at least for highly-soluble, highly-permeable drugs, because we think of dissolution occurring so quickly with these products that, functionally speaking, we are comparing two solutions for the purpose of bioequivalence. It is for this class of drugs that we have recommended in the SUPAC guidelines waiving bioequivalence and utilising dissolution testing, to simplify changes that might occur post-approval.

So, in short — and as laid down in 21 CFR, 320.22, Section 3 (i), (ii) waivers of bioequivalence are applied to solution dosage forms when specific conditions are met: they must have the same concentration of active ingredient and the excipients must not affect the absorption of the active ingredient.

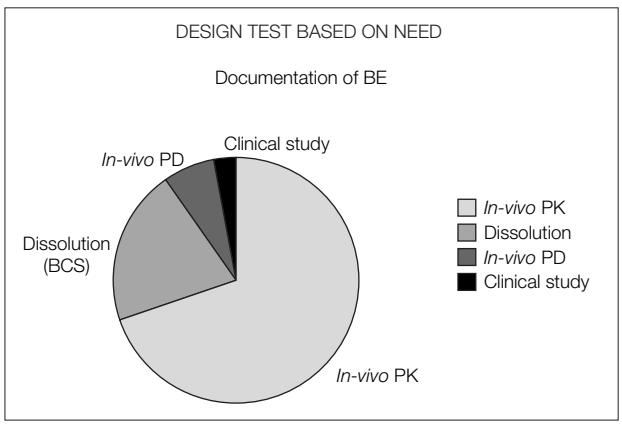

Figure 4.

It has been interesting how dissolution has emerged as a viable alternative for bioequivalence testing. Through the years since 1962, there have been very few instances where bioequivalence has been accepted on dissolution alone. Instead, bioequivalence based on pharmacokinetic measurements has become the routine. I think that is changing now, in the light of the science that has emerged from the biopharmaceutic classification system.

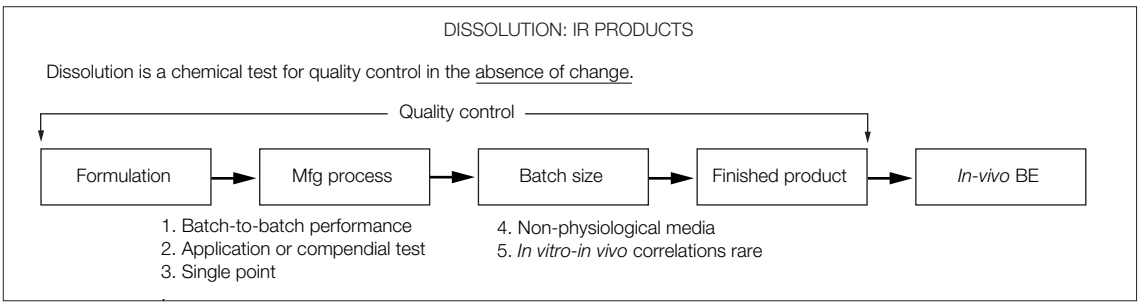

Figure 5.

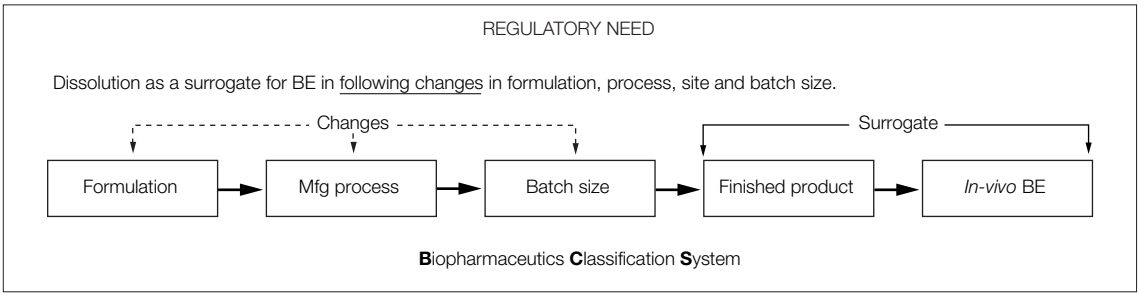

Figure 6.

In all of that time, dissolution has been viewed primarily as a chemical test for product quality, rather than as a surrogate for bioequivalence. Dissolution has served us well when we want to assess the performance of the manufacturing process in the absence of change, and we frequently see it being used to assess batch-to-batch performance.

We also see it in the form of an application for a pharmacopoeial or compendial test, where often the specification for dissolution is a single point such as 85 per cent in 60 minutes, the media used are frequently not physiological, and for immediate-release products we do not see many opportunities for *in vitro/in vivo* correlations.

So it is for these reasons, then, that when changes were made in the manufacturing process, especially in the post-approval period, dissolution was viewed as a rather weak measure of bioequivalence. Instead, for many years, bioequivalence testing in humans was the standard for post-approval change.

More recently, however, we have come to appreciate the value of the mechanistic approach to drug absorption and dissolution and, in the context of BCS, we now view dissolution somewhat differently. In the face of changes that might affect formulation, process or batch size, we regard dissolution — when approached from a biopharmaceutics classification standpoint — as a more valid surrogate for *in vivo* bioequivalence testing. It is viewed as being more reliable and more predictive of bioequivalence than the previous dissolution-test systems that were used for quality control, and it is this confidence that is leading us to utilize the BCS, not only in the SUPAC guidance that we have already released but also in related types of guidance that we expect to issue in the near future.

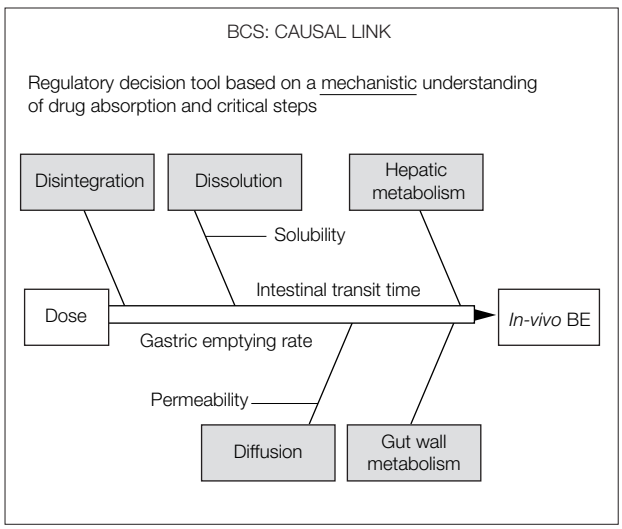

Figure 7.

The appeal of the dissolution system to reviewers in the agency is that it helps them to understand the dose-effect relationship, or the dose-response relationship, where response in this case is bioequivalence. What *Figure 7* illustrates is the key mechanistic steps in the dose-bioequivalence relationship, starting off with the disintegration of a solid oral dosage form and the dissolution of that dosage form — the two critical steps related to the dosage form or delivery.

Furthermore, we have a diffusion step, which we think of as a property of the drug substance, and we also have the hepatic metabolism and gut-wall metabolism steps indicative of the pharmacokinetic characteristics of the drug substance. Overlaid on these critical steps are the physiological parameters of the gut that can influence the dose-response relationship; namely, gastric emptying and intestinal transit.

When we consider these steps in terms of rate-limiting drug absorption, we come back to measures of solubility and permeability, the two biopharmaceutical properties that reflect in turn the rate-limiting steps of dissolution and diffusion for the respective drug classes. So, mechanistically, this becomes an appealing classification system for understanding and setting dissolution standards.

Two examples illustrate this conceptually and the first example (*Figure 8*) is the easier one to follow. I have selected for purposes of illustration a drug that has high solubility and high permeability.

With respect to dissolution, a drug with high solubility might have the dissolution profile shown in *Figure 8*, where the percent remaining to dissolve gets shorter and shorter and smaller and smaller very quickly. This represents the permeability or diffusion of that drug substance, and with a highly permeable drug it is likely that absorption is going to be complete and the C-Max for that product observed within 30 minutes of dose administration.

The dotted line on *Figure 8* indicates the half-time for gastric emptying, 15 to 20 minutes, which corresponds to data Professor Gordon Amidon also showed on a figure near the end of his presentation. So when one thinks about the solubility and dissolution proceeding on a rate that looks like this, and

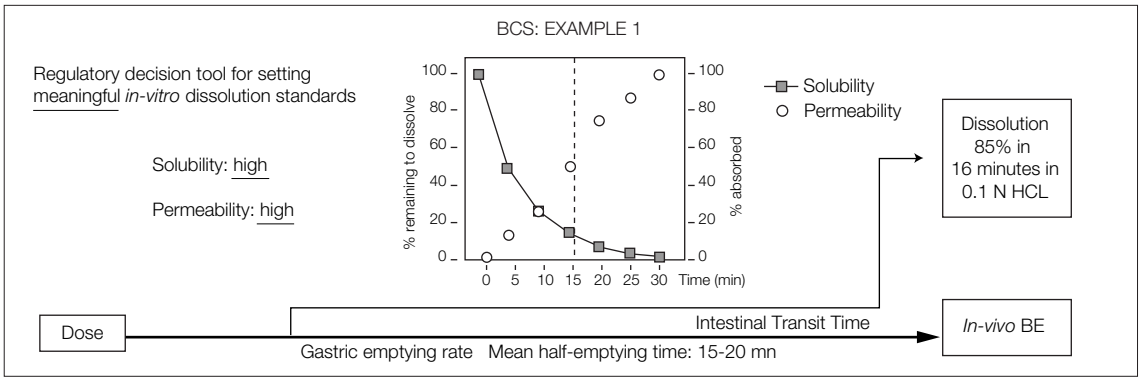

Figure 8.

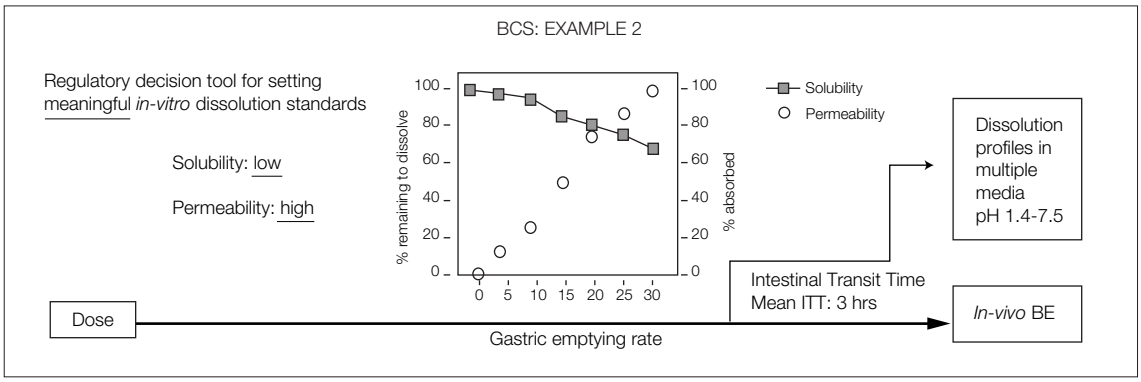

Figure 9.

Role of BCS				
	Class I HS/HP	Class II LS/HP	Class III HS/LP	Class IV LS/LP
Absorption rate Control	Gastric emptying	Dissolution	Permeability	Case by case
Potential for IVIVC	Low	High	Low	Case by case
Dissolution media	0.1 N HCl	pH 3.5-6.8 buffers	Compendial or application	Case by case
Dissolution standard	Single point	Multiple profiles	Single profile	Case by case

Table 5.

permeability profiles that look like this, it is not difficult to consider a dissolution specification of 85 per cent in 15 minutes in gastric acid, or 10^{8} Cl.

In this example, one would imagine that neither dissolution nor permeability are rate-limiting with respect to drug absorption; rather, with rapid dissolution, gastric emptying very often becomes the rate-limiting step.

The second example is more interesting. It is what we would call a Class II situation, where the solubility of the drug is now low rather than high, but permeability remains high. If we consider gastric residence: the amount of drug that might dissolve might be following the type of profile shown in *Figure 9*, whereas the permeability and diffusion might still be rapid, as also indicated on the figure.

However, because it is likely that the rate of dissolution for this product is going to be slower than the rate of gastric emptying, it requires a more stringent dissolution test to mimic *in vivo* dissolution. For this type of drug, we have recommended multiple profiles in multiple media over a pH range of 1.4 to 7.5.

This more stringent dissolution specification allows for the risk of bio-inequivalence based on a dissolution standard and also takes into account the transit time and site-specific absorption found in this type of drug with low solubility.

The role of the biopharmaceutical classification system in the regulatory world is comprehensive. *Table 5* indicates the four BCS classes that have been defined on the basis of solubility and permeability, and the major parameters of interpretation relative to each. Agency reviewers looking at INDs and NDAs can now refer to the BCS the better to understand what questions they need to ask and the appropriateness of standards being proposed by the pharmaceutical sponsor.

For example, the BCS defines the likely absorption rate-controlling step, whether it be gastric emptying, dissolution or permeability. It defines the potential for an *in vitro/in vivo* correlation (IVIVC), whether it is low, high — or unpredictable, as it is in Class IV.

It also defines the dissolution media which are physiologically meaningful; from gastric acid, to a range of buffers reflective of small intestinal pH, to the compendial or pharmacopoeial or application standard. And finally, in terms of the dissolution standard, specifications range from a single point, to a single profile, to multiple profiles, depending on the need dictated by the solubility and permeability of the drug substance.

So this gets us to one of the principles of the regulatory view of biopharmaceutical classification. Rather than needing, as sponsors, to conduct *in vivo* PK studies for all of the post-approval changes, we find that the BCS (as laid down in SUPAC) now gives us the opportunity to utilize dissolution in some of these cases. It gives us, in a sense, tools to apply to the need. When the need is high, we would use a PK study, when dissolution can do the job, then we utilize dissolution. The BCS has given us the opportunity for selective application of *in vivo* measures or in vitro measures that we can use with confidence.

Now, whenever we think about a policy-implementation approach in the FDA, we have to be very cautious about moving the science — and the

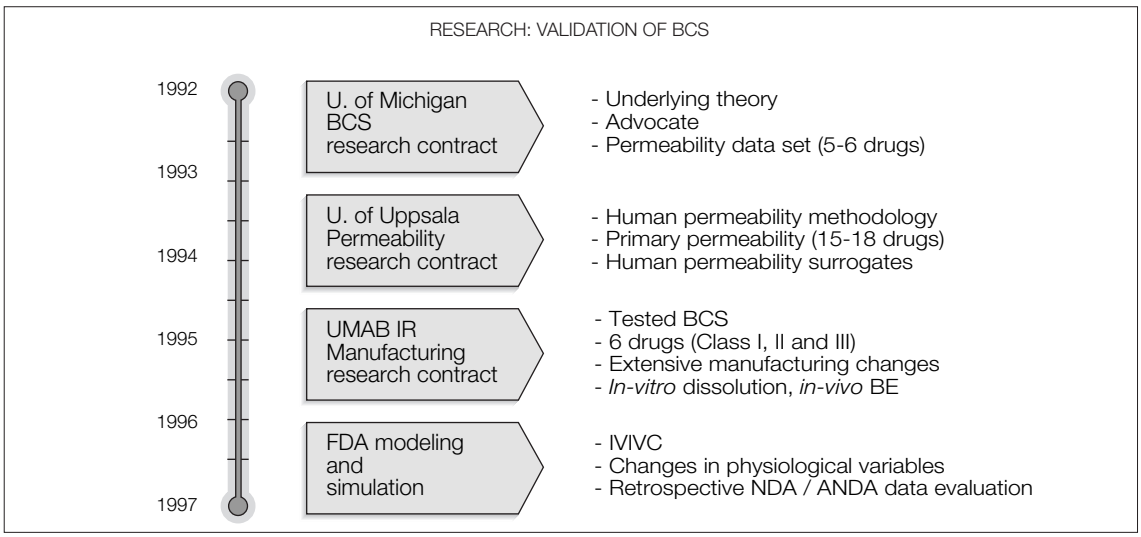

Figure 10.

theory and hypothesis that Professor Amidon described — to regulatory decision-making, because these decisions impact products in the market place, and the primary role of the FDA is to protect the public health. So we generally proceed very cautiously in policy implementation.

With respect to the BCS, the time-line in *Figure 10* reflects the cautiousness that we have had in developing regulatory applications of a science. It shows over the last five years the major steps that have allowed the implementation of the BCS and regulatory decision-making, beginning with the contract with Professor Amidon at the University of Michigan in the US.

He is responsible for much of the underlying theory that we are talking about. He has been an advocate of the BCS system from a scientific perspective, and conducted permeability studies on a number of drugs that represent part of our database.

In 1993 we began work with Professor Hans Lennernäs at the University of Uppsala in Sweden, and his primary goal was to develop a database on human permeability. To date, he has looked at about 15 to 18 drugs. Most recently, his work at Uppsala has been based on looking at alternatives to predicting human permeability, such as Caco-2 cells and rat jejunal preparations that in the future could be used to characterise a drug in terms of biopharmaceutical classification.

Finally, a critical step in the validation of the BCS was a contract that we had with the University of Maryland in the US where we tested the hypothesis of the BCS with six drugs representing the three main classes of the system. What we did in this research was identify critical variables in the manufacturing process, look at *in vitro* dissolution under a wide variety of conditions, and then conduct *in vivo* bioequivalence studies.

Before moving on to discuss some of that data, let me mention that, even today, within the Office of Clinical Pharmacology and Biopharmaceutics we are conducting a series of modelling and simulation experiments to look at the potential impact of changes and physiological variables, such as gastric emptying, on the validity of the BCS.

We are also conducting a retrospective review of our new drug application (NDA) and abbreviated new drug application (ANDA) database to see if we can find evidence of failure of this classification system to predict bioequivalence. We are very interested in 'false-positives'as we would call them — instances where the classification system predicts bioequivalence, but in practice we see bio-inequivalence. And I am happy to say that, looking at that database, we have no evidence to this date showing that the classification system has misled us.

Much of the work we did at the University of Maryland as part of the validation of BCS has now been accepted for publication, and some of these articles have appeared in recent issues of Pharmaceutical Technology. I want to show you two examples which come from the Class I or high-solubility, high-permeability class and I have selected two drugs that we studied in detail. The first example, propranolol, if you recall from Professor Amidon's figure, had a permeability in the order of 4×10^{-6} centimetres per second; in other words, a highly permeable drug and one with very good solubility.

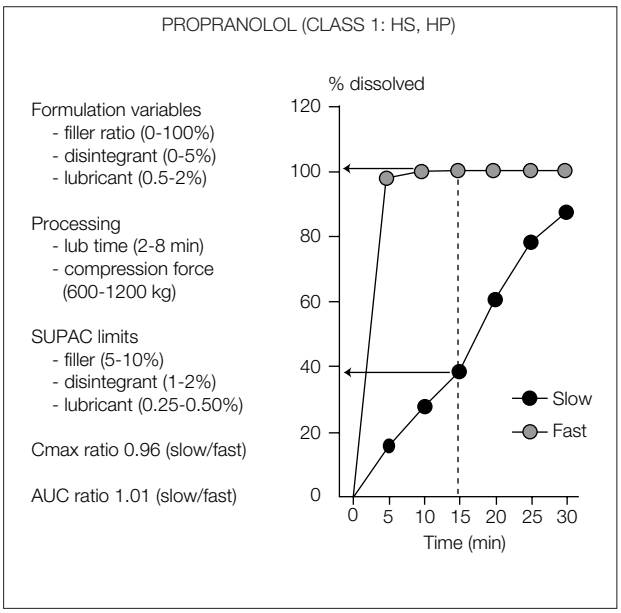

Figure 11.

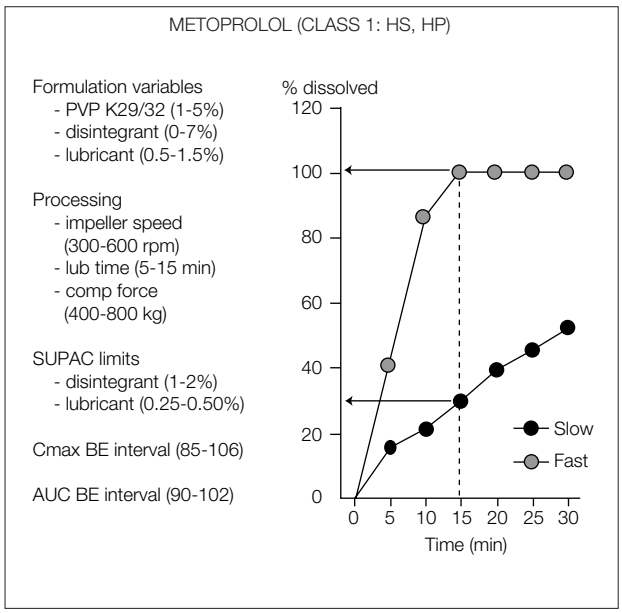

Figure 12.

In the research to validate the BCS we identified critical manufacturing variables and then prepared many different formulations utilising ranges of these various parameters. We defined certain limits, which eventually made their way into our SUPAC guidance, as a way of validating that guidance, and then we conducted a general four-way crossover bioequivalence study.

In the four-way study we included a reference product — the example here is Inderal, the market leader for propranolol — and then included in the study three formulations that had slow, medium and fast dissolution characteristics, as prepared by modifying these manufacturing variables.

In this graph (*Figure 12*), what I have shown are the dissolution profiles of only the slow and the fast formulations that we prepared, and what I want to point out is that the fast formulation was virtually completely dissolved in five minutes while, in the other boundary condition, at 15 minutes it was only 40 per cent dissolved. When we compared these two products in the bioequivalence study, the C-Max ratio was well within the criteria of 80 to 125 that we consider bioequivalence. Also, the extent of absorption as measured by the AUC was virtually superimposable and bioequivalent.

So, as you can see, the bioequivalence was easily demonstrated with these products, even though the dissolution at 15 minutes did not meet the 85 per cent mark that we had set as a standard for this classification system.

As we gather more data of this type, one could imagine relaxing that specification to perhaps 85 per cent in 30 minutes for something that is less conservative than we currently use in our guidances.

Metoprolol is interesting because this is the boundary drug that Professor Amidon mentioned, and in this case we did the same thing, modifying formulation variables and then again comparing the slow and the fast formulation in a bioequivalence study. While the range was a little bit wider in terms of confidence intervals, it very easily met those intervals and was deemed bioequivalent. So again this type of data gave us much confidence that, for this class of drugs, 85 per cent in 15 minutes was a very reasonable standard for predicting *in vivo* bioequivalence.

I mentioned the SUPAC guidance which was the first application of the BCS, and I will just show one or two figures (*Figure 13 and 14*) on this to illustrate how the science of the BCS was moved into policy-making. With the SUPAC for immediate-release products, we defined magnitudes of change (see *Figure 14*). They ranged from 1, which was a minor change, not likely to have an impact on *in vivo* bioequivalence; 2, which was a level of change that possibly could impact *in vivo* bioequivalence; and 3, which is not shown on the figure, a level of change that most likely impacts bioequivalence.

Under the column heading of Classification (*Figure 13*), what does the change apply to? Changes

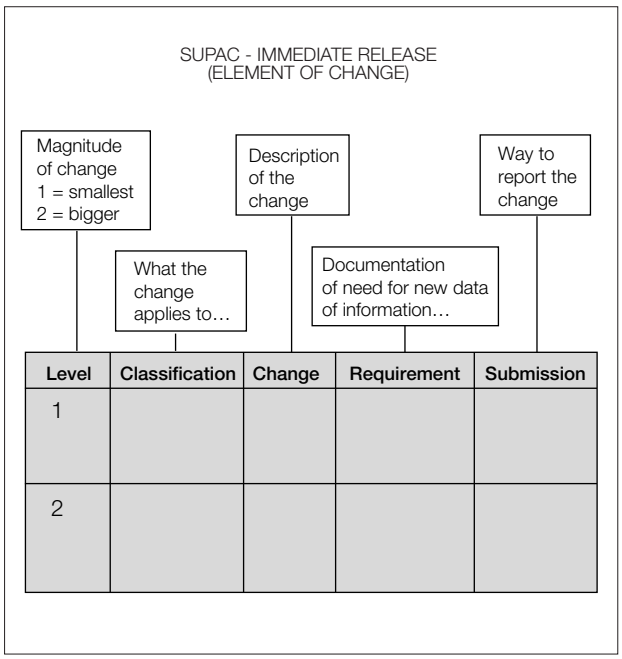

Figure 13.

can apply to formulation, the manufacturing process, manufacturing equipment, batch size and site of manufacture. The description of change (see *Figure 13* for column headed Change) refers to the magnitude of change, either a percentage change or a batch-size change.

Most importantly, we defined the documentation for information related to demonstration of equivalence and under the column headed Requirements (see *Table 6*) we have dissolution requirements or bioequivalence requirements defined on the basis of the classification system.

Figure 13 showed the general approach to SUPAC and regulatory decision-making with the BCS, *Table 6* illustrates the principles of that guidance. I won't go through it all, but again here are the levels of change: 1, 2 and 3, from minor to major, along with the areas for possible change and then whether we need dissolution or bioequivalence.

As you can see from *Table 6*, in the beginning with a level 2 change, the need for dissolution — either a single point, a single profile, or multiple profiles — or for bioequivalence studies depends upon what class of drug we are talking about.

We did introduce a third variable into this guidance, unrelated to the biopharmaceutics, and that was the therapeutic index. So you will see that in some areas, full study is required. Generally, full study refers to those drugs which have a narrow therapeutic index; we felt that this was necessary for an added measure of safety.

This is where the impact of SUPAC has, I think, been significant. There are only two instances where a full study is really going to be routinely required, whereas in the past, the bioequivalence study may well have been required in all these other areas where we now utilize dissolution.

SUPAR-IR Guidelines (1995) - Regulatory decision making

Level of change	1	1	2	2	3	3
	Dissolution	BE	Dissolution	BE	Dissolution	BE
Components and composition	Compendia	None	Biopharmaceutics class dependent	Biopharmaceutics class dependent class II and III only	Biopharmaceutics class dependent	Full study
Site	Compendia	None	Biopharmaceutics class dependent	None		
Scale-up	Compendia	None	Biopharmaceutics class dependent	None		
Manufacturing equipment	Compendia	None	Biopharmaceutics class dependent	None		
Manufacturing process	Compendia	None	Biopharmaceutics class dependent	Full study		

Table 6.

Excipients
Perturb expected dissolution *in vivo*
Physical or chemical interactions (binding)
Physiological effets - gut motility - intestinal wall permeability - luminal or hepatic metabolism
Perspective - exception, not the rule - few known excipient effects - screen *in vitro* - effects diluted *in vivo*

Table 7.

One of the questions that has frequently come up in different public meetings on the biopharm classification system is the role of excipients. The concern here is that if two products meet an in vitro dissolution standard of, for example, 85 per cent in 15 minutes, it is possible that *in vivo* those products would be inequivalent because of some activity of the excipients. That activity may stem from some physical or chemical interactions or perhaps some physiological effects on motility, permeability and metabolism.

In general, though, as we looked at this issue — and it is not completely resolved, we need to think about it some more — we have concluded that at this point in time, excipient effects would be an exception to the classification, an exception to the science and not the rule. We thoroughly searched the literature and our own application file for excipient effects on any of these parameters and we came up with very few. In some cases we found excipients like oleic acid that may have an effect on permeability that would be unpredictable from the in vitro classification but by and large there are very few. Furthermore, we see in the future the possibility of screening for these effects in vitro if there is any suspicion that they may adversely affect our expected performance in vivo.

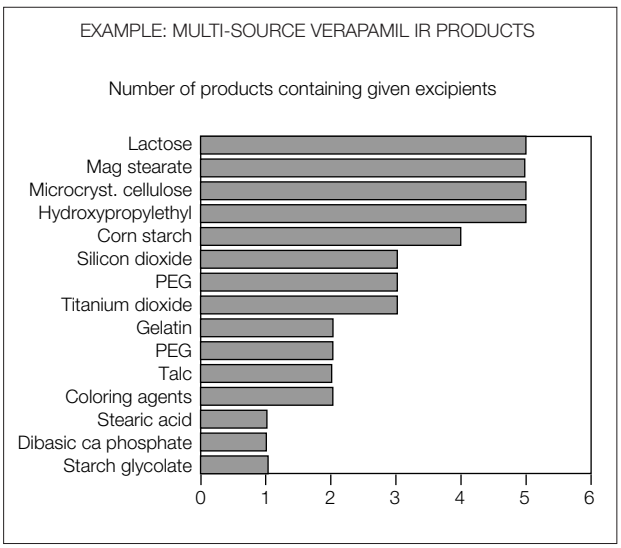

Figure 14.

To give you an idea of this, I have a figure on verapamil (see *Figure 14*). We have approved five multi-source generic products for verapamil and I have illustrated the cross-section of excipients that appear in these formulations.

Looking at the number of product formulations shown on the figure, we can see that the lactose, magnesium stearate, and so on, are contained in all five formulations. Other excipients of different molecular weights — PEG, for example — and other types of excipients are contained to a more or less degree in the remaining formulations. The point of this is that the excipients used in immediate-release products are by and large very well-understood, very well-characterised additions and they carry with them no adverse effects that we know of on the permeability or *in vivo* absorption of drugs.

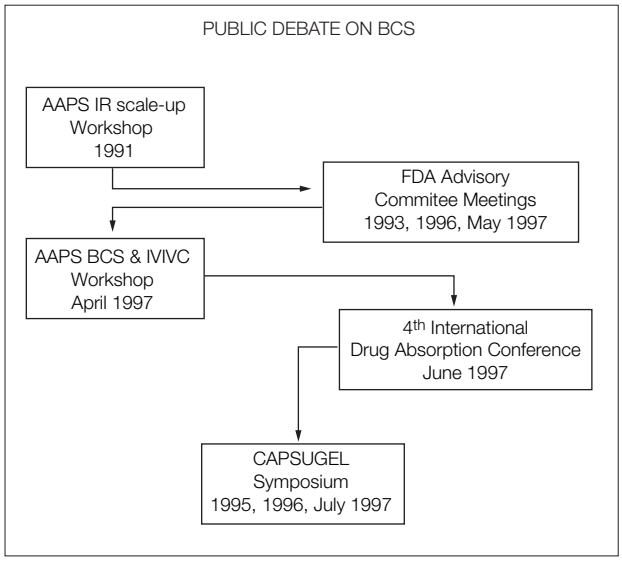

Figure 15.

When we talk about policy implementation, it is a normal part of the process (one that is now actually defined in our Good Guidance Practice regulations), to have extensive public debate on the BCS. I think this hypothesis classification of drugs has evolved very nicely from a regulatory perspective, beginning in 1991.

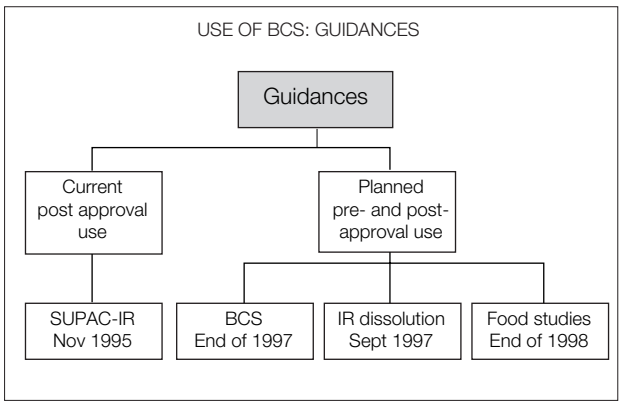

Figure 16.

We have had several advisory committee meetings on the topic at the FDA and this year we have had a series of very important workshops with the American Association of Pharmaceutical Scientists (AAPS) in Washington, and with the International Drug Absorption Conference in Edinburgh — and, finally, with the Capsugel Symposium here — to add to the others that we have talked about before. I mention this because we have had a fair amount of input, critique and helpful advice on the classification system and one of the objectives of our meeting today is to continue to get that critique and advice as this new science emerges in terms of the regulatory applications.

Now I would like to update you on where we stand with the use of the classification system in the guidance documents that we have either released or are working on.

The first guidance utilising the BCS to come out of the agency was our SUPAC-IR guidance, issued in November of 1995. It applies to post-approval changes. What we are planning in the near future is further application of the BCS in pre- and post-approval uses.

Use of BCS: drug development

- Discovery
  - primary screen for lead candidates
  - determine solubility and permeability
- Early clinical studies
  - phase I or phase II
  - validation *in vivo* BA
- Application
  - formulation development
  - changes in marketed formulation
  - waiver of *in vivo* BE

Table 8.

In September of this year we will release an IR dissolution guidance which will utilize the classification system in setting specifications for new drug substances. By the end of the year we will have a document on the BCS itself, which will go into the classification in more detail than in the current guidance and also include some additional applications, particularly in the pre-approval period.

Finally, our food studies working group within the FDA is looking at the potential applications of BCS in predicting food study effects in the area of bioequivalence.

In looking ahead to new drug development, keeping in mind that SUPAC only dealt with the post-approval period, we see the BCS being used in a number of ways. We would encourage firms to classify their drugs early in the drug development process and, indeed, many firms look at permeability and solubility as criteria for selection of the lead compounds. It is a way of anticipating bioavailability and formulation problems and explaining some of the variability later on in the bioequivalence testing itself.

We envision that the early clinical studies might be used to confirm the validity of the classification in terms of defining the extent of biovailability, or the bioequivalence of formulations that might be utilized as part of formulation development. We would hope that the BCS would be used to reduce the number of bioequivalence studies that are currently conducted in the formulation development area. At least, we want to send the message that the agency does not require these studies, but rather that links could be made between formulations on the basis of our biopharmaceutic classification system.

Further changes in marketed formulation will continue to be an application, and the final application is the waiver of *in vivo* bioequivalence in both the pre-approval and post-approval drug development period.

Because the title of my talk was policy implementation, I wanted to give you a sense of how to utilize science and move the science from data, theory and hypothesis to actual policies for the pharmaceutical industry.

Table 9 shows a paradigm that we utilize in the agency called Research to Policy to Review. It is based on the concept that good research and good science should be the underpinning and the foundation for regulatory policies. If we have good regulatory policies, we feel that this will facilitate drug

Paradigm: Research - Policy - Review

Collaborative research →	Regulatory policy →	Review management
FDA - Industry Acamedia Consortium	Coordinating Committees	Good Review Practice Manual
Research initiatives	Industry guidances	Reviewer policies
1. Product quality Biopharmaceutics Chemistry, Manufacturing 2. Safety and efficacy Clinical pharmacology Clinical trials	1. Biopharmaceutics 2. Chemistry, Manufacturing 3. Medical policy 4. Pharmacology and toxicology 5. Research 6. Clinical pharmacology	1. Biopharmaceutics 2. Chemistry, manufacturing 3. Clinical pharmacology 4. Clinical trials 5. Environmental assessments 6. Microbiology 7. Pharmacology and toxicology

Table 9.

development and allow high-quality reviews of product applications.

With regard to the 'Research'in the paradigm, there are two consortia that the agency is involved with — industry and academia — and we have research initiatives in two broad areas. The first we call 'product quality', which focuses on discipline in biopharmaceutics, chemistry and manufacturing, and there is another focusing on safety and efficacy. What we are talking about in this — meaning the biopharmaceutic classification system — is one of many initiatives in the area of product quality.

When we talk about 'Policy', policies in the agency are produced by co-ordinating committees that are discipline-specific. So we have, for example, a biopharmaceutics co-ordinating committee that is responsible for writing the guidance on the BCS. And then finally, once a guidance is released to the industry, we employ that guidance in our review through a Good Review Practice Manual; this is like a standard operating procedure (SOP) for reviewers. Lastly, the reviewer policies, again, are discipline-specific.

So if you think of the BCS in terms of a policy-implementation approach, it moves from research at Michigan and Uppsala, into a working group at the FDA to develop a guidance, finally it is released to the industry and then our reviewers utilize the guidance in conducting their reviews. I might add that more recently we have employed another step in the process and that is a training step, where we have extensive training for the industry and for our reviewers on the interpretation and application of that guidance.

Finally, I wanted to acknowledge many of the connections that were part of this classification system, and emphasise that it was indeed multi-factorial in the sense that we have the academic links with Michigan, Uppsala and the University of Maryland. We also had considerable help from the Swedish Medical Products Agency, led by Drs. Tomas Salmonsson and Siv Jonsson, who helped facilitate the research that underpinned the biopharmaceutic classification system and finally the leaders within the FDA who have been instrumental in getting the classification system implemented as policy: Drs. Roger Williams, Ajaz Hussain and Vinod Shah.

Finally, as Professor Amidon and Professor Hashida have mentioned, this is the third Capsugel symposium on the topic and I would like to thank Capsugel for creating this opportunity for scientific interchange on what I think is a very exciting innovation in pharmaceutical sciences. Thank you.

Acknowledgments

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    Dr. Siv Jonsson
  - Food and Drug Administration
    Dr. Roger Williams
    Dr. Ajaz Hussain
    Dr. Vinod Shah

Physiological Aspects of the Design of Dissolution Tests

Professor Jennifer B. DRESSMAN, Ph.D.

Physiological Aspects of the Design of Dissolution Tests

Professor Jennifer B. Dressman, Ph.D.

JW Gœthe University
Frankfurt, Germany

Professor Hashida: Our first speaker this afternoon is Professor Jennifer Dressman, who currently teaches at the Goethe University in Frankfurt. Originally from Australia, she studied for her Ph.D. with Dr. Takeru Higuchi at the University of Kansas. From there, she went to the University of Michigan before moving on to Goethe University. Her subject today is 'Physiological Aspects of *in vitro* Dissolution and *In vivo/in vitro* Correlations' — the topic on which she has focused her attention since her days at the University of Michigan.

Professor Jennifer Dressman: Before I begin, I would like to thank Capsugel for the kind invitation to speak at this Symposium, and especially Mr. Daumesnil and Mr. Oka for making the arrangements for my visit in Japan. In 1989 I had the great pleasure to spend six weeks at the National Institute for Hygienic Sciences here in Tokyo and it is wonderful to be back again.

Today I have been asked to speak about physiological aspects of the design of dissolution tests. First, I would like to put the dissolution of the drug from the dosage form in perspective with the other steps and limitations to oral drug delivery. Then, I will use the framework of the Biopharmaceutics Classification System to highlight the drugs for which one might expect a good correlation between the dissolution test results and the *in vivo* bioavailability characteristics. The important parameters in dissolution will be used to identify which elements of the gastrointestinal physiology can be crucial to the release of the drug from the dosage form. I will then show data for each of these physiological parameters and describe, with examples, how we can design physiologically meaningful dissolution tests to predict drug absorption and changes in drug absorption under different dosing conditions.

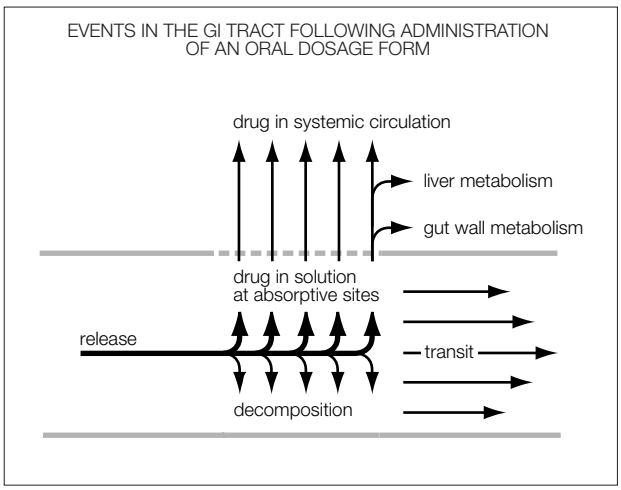

Figure 1.

Whether or not a drug will be completely absorbed after oral administration depends on the events depicted in *Figure 1*, their importance relative to another and the rate at which they occur. *Release* and *Absorption* must occur within the available *Transit Time*. Also to be considered are the *Stability* of the drug in the luminal fluids and the possibility of *First Pass Metabolism* in the gut wall and/or liver.

The Biopharmaceutics Drug Classification Scheme

Aim: to provide guidance as to when in vitro studies may be used in lieu of clinical studies to establish bioequivalence of two products

Class 1	Class 2	Class 3	Class 4
High Solubility	Low Solubility	High Solubility	Low Solubility
High Permeability	High Permeability	Low Permeability	Low Permeability

Table 1.

For immediate release dosage forms, the release rate relative to the transit rate and the permeability profile of the small intestine to the drug are crucial to both the rate and the extent of absorption.

The Biopharmaceutics Classification System, first proposed by Prof. Gordon Amidon, classes drugs into four categories, depending on their solubility and permeability characteristics. According to this scheme, Class I drugs are those with no intrinsic bioavailability problems. Provided they are well formulated, Class I drugs should be more than 90% absorbed. Class II drugs are those with solubilities too low to be consistent with complete absorption, even though they are highly membrane permeable. Class III is the mirror image of Class II. These drugs have good solubility but are unable to penetrate the gut wall quickly enough for absorption to be complete. Class IV compounds have neither sufficient solubility nor permeability for absorption to be complete. Note, though, that although they certainly do not possess optimal properties, some drugs in this category may still be absorbed well enough to permit oral administration.

Correlation of *in vivo* results with dissolution tests is likely to be best for Class II drugs, because in this case the solubility is the primary limiting aspect to absorption.

Identification of physical and physiological factors important to drug dissolution

parameter	physical factor	physiological factor
surface area	particle size	native surfactants
diffusion coefficient	molecular size	viscosity of the lumeral contents
boundary layer thickness		motility patterns flow rates
solubility	hydrophilicity crystal structure	pH, buffer capacity bile, food components
concentration of drugs in solution		permeability
volume of GI contents		secretions administered fluids

Table 2.

Which parameters affect the dissolution of a Class II drug?

Factors important to dissolution can be identified from the following modification of the Noyes-Whitney equation:

$$DR = \frac{dX}{} = \frac{A \bullet D}{} \bullet \left(C_S - \frac{Xd}{} \right)$$

The dissolution rate, DR, is a function of:

- A the surface area of the drug,
- D the diffusion coefficient of the drug,
- h the effective boundary layer thickness,
- Cs the saturation concentration of the drug under the local gastrointestinal conditions,
- V the volume of the fluid available to dissolve the drug,

  and
- Xd the amount of drug already dissolved.

As well as the physical features of the drug, many physiological parameters can also play a role in determining the dissolution rate. The physical parameters relevant to drug dissolution are tabulated in *Table 2*, along with their partner parameters in the Noyes-Whitney equation for drug dissolution.

The particle size of the drug will be an important physical determinant of the surface area available

for dissolution. Through wetting effects, the native surfactants in the gastrointestinal tract will also influence the effective surface area available.

The solubility of the drug is not only a function of its crystallinity and lipophilicity, but also depends on the medium into which it must dissolve. In the gastrointestinal tract, surfactants, pH, buffer capacity, and food components can all play a role in determining the local solubility of the drug.

The boundary layer thickness is dependent on the hydrodynamics, which we can interpret in terms of gastrointestinal physiology as the mixing patterns and flow rates in the gastrointestinal tract.

The volume into which the drug must be dissolved is a function of the volume of coadministered fluids, as well as secretions into the lumen from the paragastrointestinal organs. These secretions tend to occur at very different rates, depending on whether baseline conditions are in effect or secretion is occurring in response to a meal, with chronological and pathological changes, and with coadministration of certain types of drugs.

The concentration of drug already in solution, Xd/V, has an influence on the driving force for dissolution, which results from the difference between the solubility and the concentration in the solution. Highly permeable drugs will be quickly absorbed and therefore will stay at lower concentrations in solution, thus maintaining a maximal driving force for dissolution. Therefore, the permeability of the gut wall to the drug can also indirectly affect the dissolution rate of the drug.

Considering these parameters, we can summarize by saying that to simulate the GI environment accurately, we need to think about the *composition of the medium* and its volume, the *hydrodynamics* of the test system and the *duration* of the test.

First let's look at the composition of the medium, how that can affect the dissolution rate, and how this can be correlated with *in vivo* results.

The first aspect to consider is the pH in the stomach and small intestine. The profile in *Figure 2* shows typical pre- and postprandial pH values in a young, healthy individual. In the fasted state, the pH is usually low. When a meal is eaten, the components of the meal buffer the pH to a higher value, then, as gastric juice is secreted, the pH value returns to the baseline level, usually within two to three hours after the meal. Of course, for patients who have low gastric acid output, such as those receiving proton pump inhibitor therapy or who have developed achlorhydria with aging, the pH in the stomach can be considerably higher.

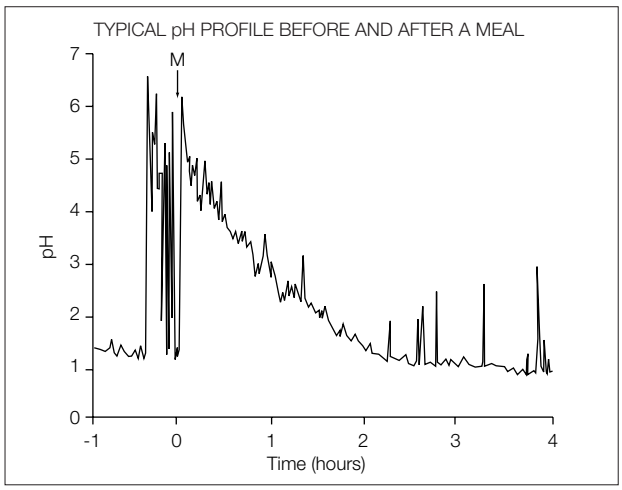

Figure 2. Typical pH profile in the stomach (Subject J.L.). Meal administration is indicated by the letter M.

Gastric acid arriving from the stomach is neutralized by the secretion of bicarbonate-containing juice from the pancreas. The increase in pH occurs mostly in the duodenum, with a further gradual increase along the jejunum and ileum. Since a greater output of gastric juice occurs in response to meals, and since this is not completely offset by the increase in output of bicarbonate from the pancreas, the pH in the duodenum tends to be about a pH unit lower in the fed than in the fasted state. In the

pH in the small intestine in healthy humans in the fasted and fed state

Site	Average pH, fasted state	Average pH, fed state
mid-distal	4.9	5.2
duodenum	6.1	5.4
	6.3	5.1
jejunum	4.4 - 6.5	5.2 - 6.0
	6.6	6.2
ileum	6.5	6.8 - 7.8
	6.8 - 8.0 (range)	6.8 - 8.0
	7.4	7.5

from Gray et al. (Pharmacopeial Forum 22; 1943-1945, 1996)

Table 3.

ileum, however, there is little difference between fed and fasted state pH values.

In terms of designing a dissolution test pH based on the physiology, it is more reasonable to use proximal values than distal values, because the drug must dissolve in the proximal part of the small intestine in order to allow adequate access to the absorption sites in the jejunum and ileum.

The bile salts are the natural surfactants in the gastrointestinal tract and can serve to wet and solubilize the drug. Therefore, their concentration can be very important to the dissolution of the drug. From the data in *Table 4*, we can see that bile salts are almost always present, even in the fasted state, although values vary widely on an individual basis. Also, it is worthwhile to remember that in the presence of lecithin the critical micelle concentration of the bile salts drops to less than 1 millimolar, which means that even in the fasted state micelles are usually present.

Fasting and fed state bile salt concentrations in the small intestine

	duodenum	upper jejunum	lower jejunum
	fasted state		
fasting	6.4 ± 1.3 4.3 ± 1.2	5	6
fed			
0-30 min	14.5 ± 9.4	16.2 ± 1.5	
30-60	5.2 ± 2.3	9.7 ± 1	
120-150		6.5 ± 0.9	

Table 4.

Bile output increases immediately upon ingestion of a meal, due to contraction of the gall bladder. With time, the bile is diluted by other secretions and the chyme, so concentrations decrease gradually back to the baseline level. Since bile salts are actively reabsorbed from the ileum, concentrations in the distal part of the small intestine are negligible. Therefore, solubilization and wetting effects are confined mostly to the duodenum and jejunum.

Table 5 and *Table 6* show the composition of media that are useful for investigating the dissolution properties of a Class II drug under conditions typical of the small intestine in the fasted and fed states.

FaSSIF medium simulating fasting state conditions in the small intestine

KH_2PO4		0.029 M
NaOH	qs	pH 6.8
NaTaurochocolate		5 mM
Lecithin		1.5 mM
KCl		0.22 M
distilled water	qs	1 L

pH = 6.8
osmolarity 280-310 mOsm
buffer capacity 10 ± 2 mEQ/L/pH

Table 5.

FASSIF, the fasted state medium, contains a phosphate buffer to achieve a pH of 6.8 and a buffer capacity of 10 milliequivalents per Liter per pH unit. Bile salt and lecithin levels in this medium are typical for the fasted state. The medium is adjusted to approximately isoosmolar with potassium chloride.

FESSIF, the fed state medium, contains an acetate buffer instead of a phosphate buffer, because in the fed state we need to use a pH of about 5 in order to adequately simulate the conditions in the upper small intestine. The buffer capacity of 75 milliequivalents per Liter per pH unit is considerably higher than in the fasted state medium, reflecting the contributions of food and secretions. Bile salt and lecithin levels in this medium are likewise higher than for the fasted state, at around 15 and 4 mM, respectively. The osmolarity is also somewhat higher, at approximately 500 milliosmolar.

FeSSIF medium simulating fed state conditions in the small intestine

Acetic acid		0.144 M
NaOH	qs	pH 5
NaTaurochocolate		15 mM
Lecithin		4 mM
KCl		0.19 M
distilled water	qs	1 L

pH = 5
osmolarity 485-535 mOsm
buffer capacity 75 ± 2 mEQ/L/pH

Table 6.

Next I'd like to show results for three case examples, two of which are poorly soluble and one of which is highly soluble, in these two media and to compare the results in the physiologically based media with dissolution under standard conditions and also with *in vivo* data.

The first example is danazol, a steroid used in the treatment of endometriosis. The compound is neutral, has an aqueous solubility of about 1 microgram per milliliter and is quite lipophilic, with a log partition coefficient of 4.53. From these physical properties, it is expected that danazol would fall into Class II.

Rotating disk experiments (*Figure 4*) indicate that the dissolution of pure danazol is highly influenced by bile salts, in this case Sodium Taurocholate. As the concentration is increased over the physiological range from 1-30 millimolar, we see a large increase in the dissolution rate of danazol.

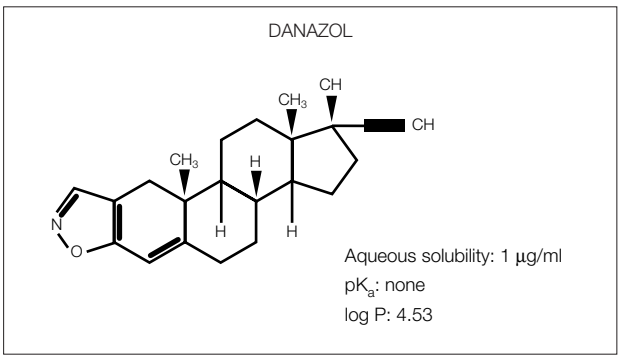

Figure 3.

In *Figure 5* we see the dissolution profiles of danazol from the commercial product, Danatrol®, in various media at 100 rpm. Dissolution in media containing no bile salts, e.g. SIF and water, is negligible. In the presence of bile components, the dissolution is detectable, although not complete. The dissolution of danazol in the fed state medium, FeSSIF, is faster than in the fasted state medium, FaSSIF.

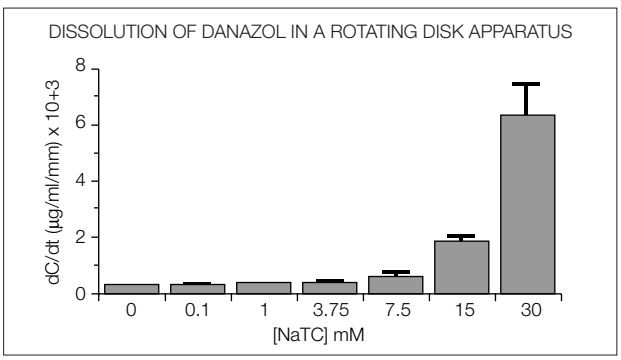

Figure 4.

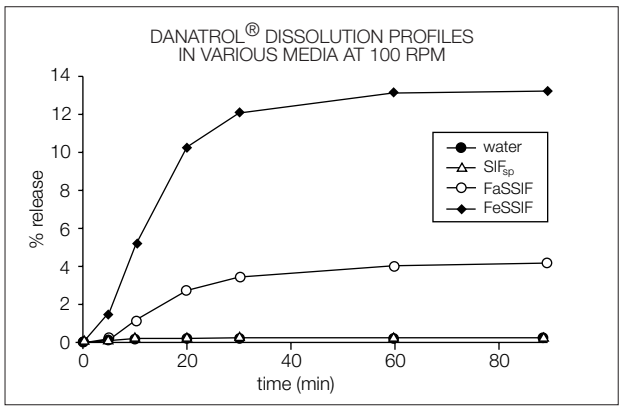

Figure 5.

From a comparison of FaSSIF and FeSSIF data, one would predict a threefold increase in the absorption of danazol from Danatrol tablets when administered with food.

Results of Charman et al. in healthy human volunteers, published in the Journal of Clinical Pharmacology in 1993 (*Figure 6*), are consistent with our predictions from the two physiologically-based media. When danazol was administered in the fed state, both the peak concentration and the area under the curve were about three times higher than when the drug was administered in the fasted state.

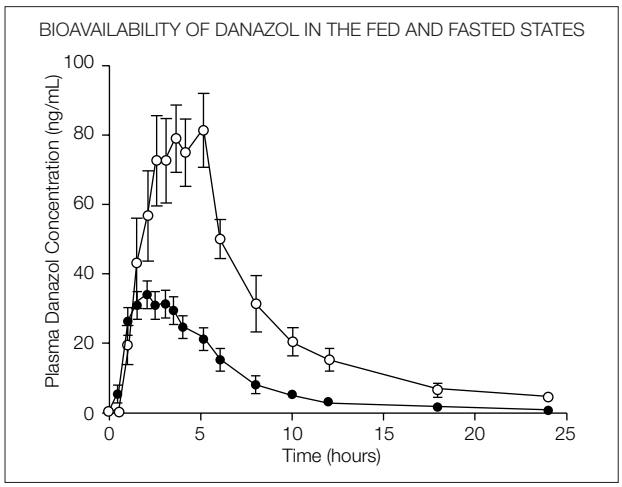

Figure 6.

The second case example is ketoconazole, which is a bit more complicated than danazol in that it is not only poorly soluble but also exhibits strongly pH dependent solubility. With basic pKas at 6.5 and 2.9, this compound's solubility increases dramatically under acid conditions. Therefore, we expect two effects. First, when gastric pH is elevated, for e.g. with H2 blockers, administration in the fasted state should result in poor absorption.

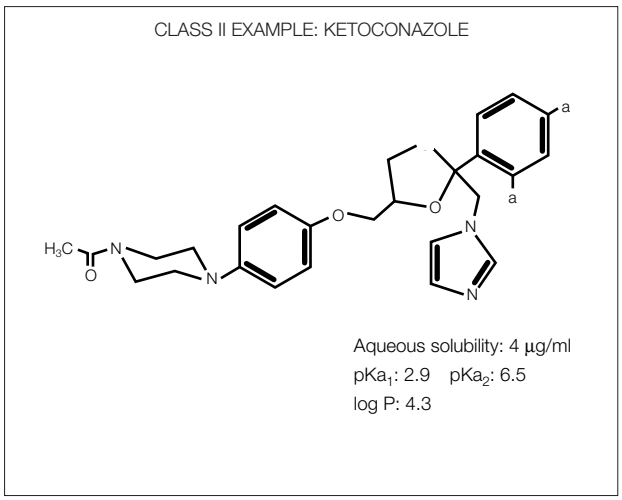

Figure 7.

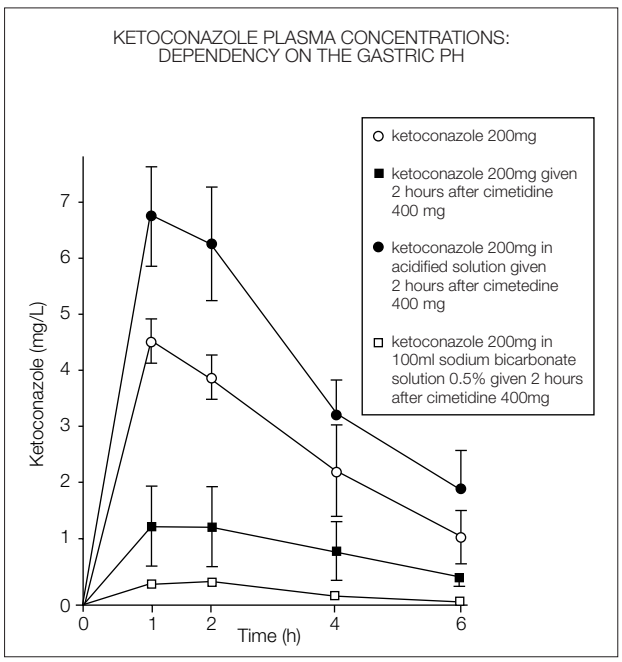

Figure 8. Ketoconazole plasma concentrations in healthy fasting volunteers.

This is indeed the case. In a study published by Lelawongs in 1977, ketoconazole was administered to healthy volunteers under four different dosing conditions: 1) in an acid solution, 2) alone, 3) two hours after administration of 400 mg cimetidine, and 4) with bicarbonate two hours after administration of 400 mg cimetidine. These data (*Figure 8*) clearly show that ketoconazole is far better absorbed when the stomach is acidic than under neutral gastric pH conditions.

The second effect that we expect for ketoconazole is, that because of micellar solubilization, we

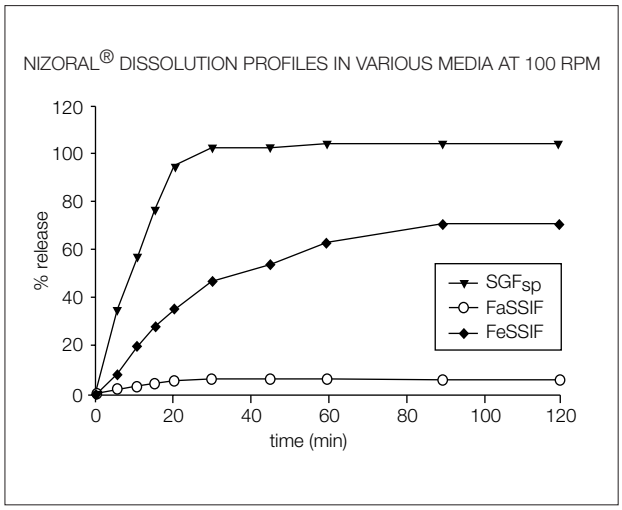

Figure 9.

expect that administration in the fed state will lead to improved absorption. In the absence of acid or bile salts, dissolution is negligible. Fed state vs. fasted state intestinal media indicate that dissolution would be better under fed state conditions, even though the pH value of FeSSIF is lower than that of FaSSIF (*Figure 9*).

Clinical results taken from the literature (*Figure 10*) indicate that at all but the highest doses, the AUC is higher when the drug is taken with food than when taken on an empty stomach. Thus, the clinical data are consistent with the results in the fasted and fed state media.

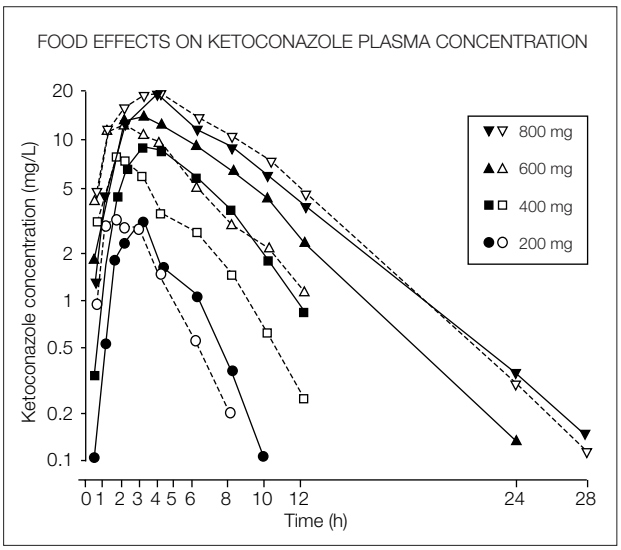

Figure 10. Effect of food on ketoconazole administration. Open symbols represent administration whil fasting, closed symbols represent administration with food.

Of course, there are many drugs on the market that are poorly soluble. A selection of these, along with their physicochemical characteristics and fraction absorbed values, are shown in *Table 7*. I chose this selection to highlight the fact that poorly soluble drugs can be found in a number of therapeutic classes. In fact, it seems that in the last decade or so, the percentage of drugs being developed that are poorly water-soluble has been increasing. For such compounds the composition of the medium is crucial to the ability to predict *in vivo* dissolution *in vitro*.

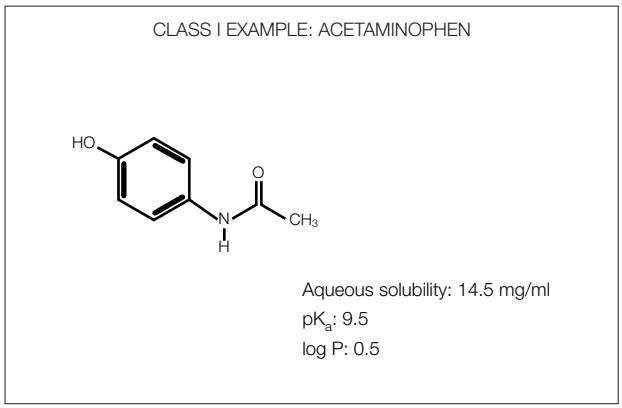

Figure 11.

Nevertheless, there are still many cases in which the drug is highly soluble. For these drugs, the composition of the dissolution medium may be relatively unimportant. Such a drug is paracetamol (acetaminophen), a Class I drug (*Figure 11*).

Some examples of low solubility drugs

Class	Example	So	pKa	LogPC	fa
diuretic	chlorothiazide	400 ug/mL	6.5	0.54	25-50%
	furosemide	29 µg/mL	3.9	est. 2.3	65
steroids	prednisolone	235 ug/mL	-	1.6	99%
	hydrocortisone	28ug/mL	-	1.6	> 80%
	betamethasone	6.7ug/mL	-	2.0	«good»
	danazol	1 ug/mL	-	4.5	NM
antiepileptic	phenytoin	14 ug/mL	8.3	2.5	90% (Na)
cardiac	digoxin	20 ug/mL	-	1.7	40-100%
	dipyridamole	6.7 ug/mL	6.4…*	est. 2.1	50
NSAIDs	mefenamic acid	0.5 ug/mL	4.2	5.3	NM
antifungal	griseofulvin	15 ug/mL	-	2.2	15-40
	ketoconazole	4.5 ug/mL	2.9, 6.4*	4.3	75% (?)
	itraconazole	< 1 ng/mL	3.4*	5.7	100
antidiabetic	glibenclamide	< 30 ng/mL	5.3	est. 4.8	«good»
vitamins	ß-carotene	< 1 ng/mL	-	est. 16	low

Table 7.

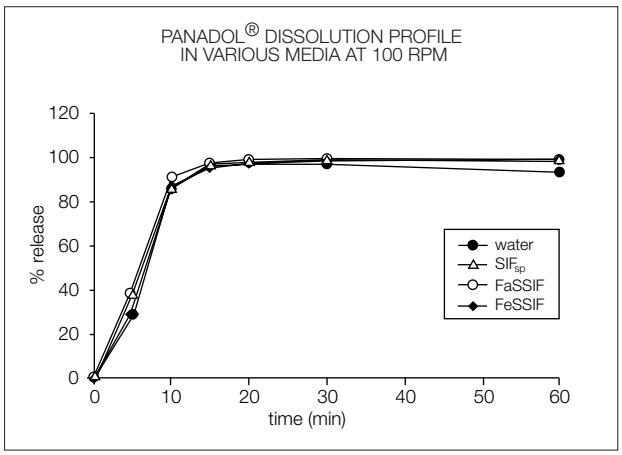

Figure 12.

As can be seen from this comparison of the dissolution behavior of Panadol® tablets in water (*Figure 12*), SIF, FaSSIF and FeSSIF, the take-home message is that the number one criterion for the dissolution medium is that it must be wet!

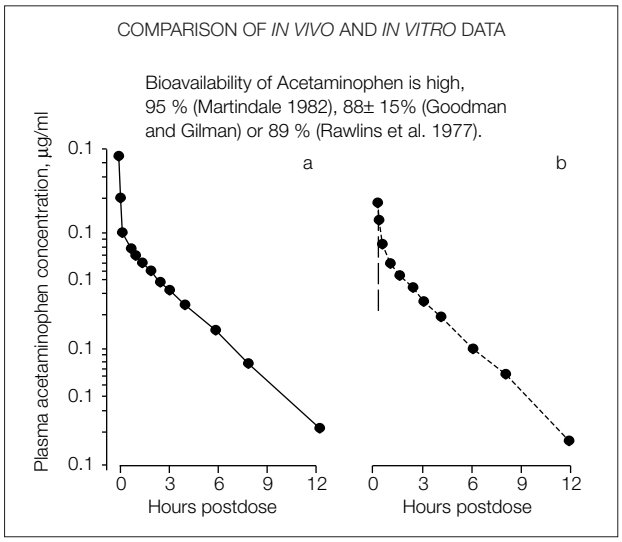

Figure 13. Plasma concentration-time profiles in the fasted state after intravenous (a), or oral (b) application of a 650mg dose of Acetaminophen.

And when we compare the serum profiles of paracetamol after intravenous and oral administration — (*Figure 13*) we see that indeed, there are no GI limitations to the oral absorption of paracetamol — the drug is almost 100% bioavailable.

In addition to the composition of the medium, the volume of the medium and the mixing patterns will also be important to the dissolution. *Figure 14* shows typical USP Type I apparatus, in which the volume of the medium is fixed, normally at 900 or 1000 milliliters, and the baskets are rotated during the test at a predetermined rate.

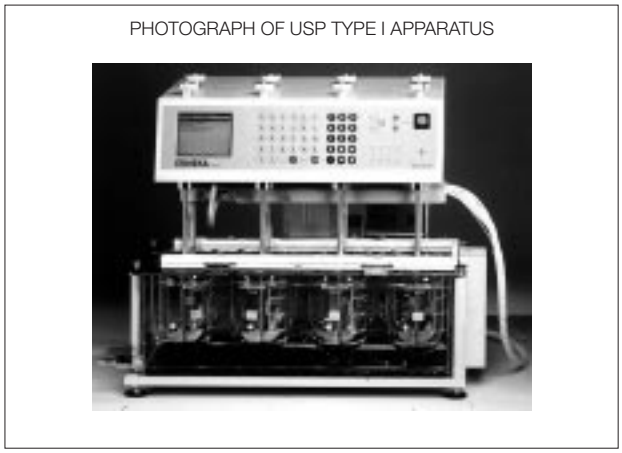

Figure 14.

The question is, are these volumes really representative of *in vivo* conditions? *Figure 15* summarizes volumes entering and leaving the intestine over a 24 hour period.

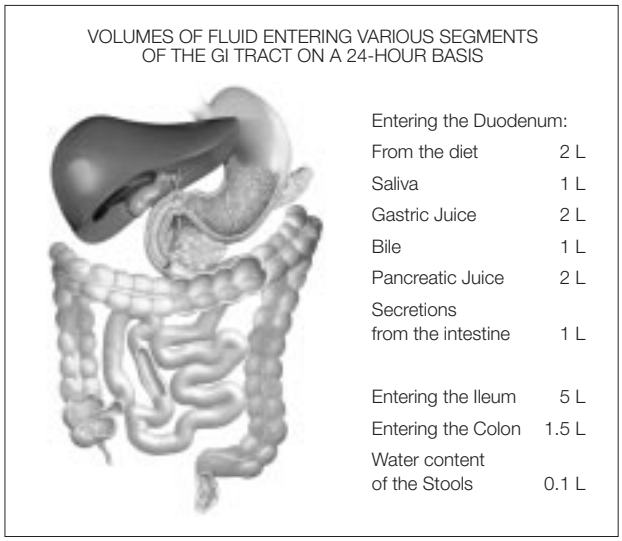

Figure 15.

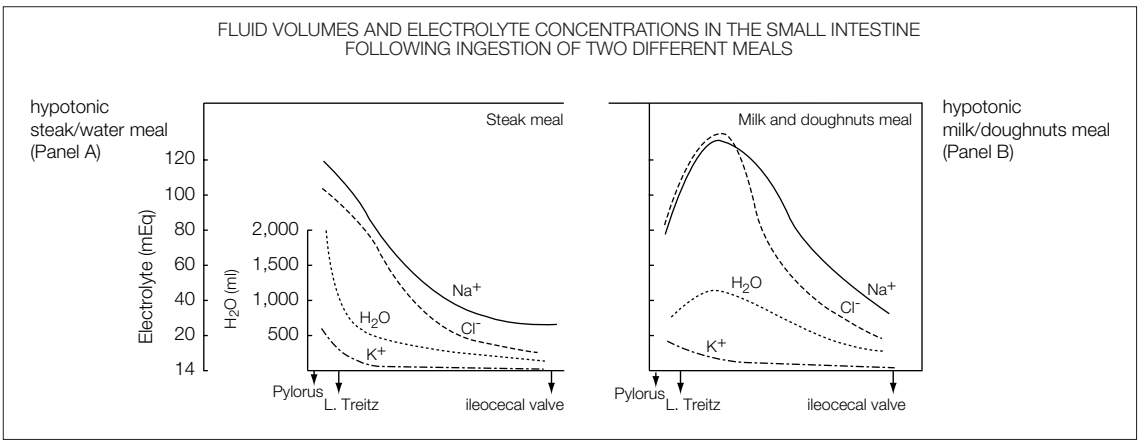

Figure 16.

But we'd also like to know what happens on a shorter term and more local basis. *Figure 16* shows fluid volumes as a function of location in the intestine after a steak and water meal, and after a milk and donuts meal. Two points are clear here: first of all, the osmolarity of the meal has a strong influence on the fluid volume in the intestine, and second, that fluid volumes tend to be higher proximally than distally. For both types of meal, though, fluid volumes in the upper small intestine are in the range 500 to 1,000 milliliters - not so very different from the volumes used in the standard dissolution testers.

In the case of the flow-through tester design, the flow rate, rather than the volume, is the key parameter to consider.

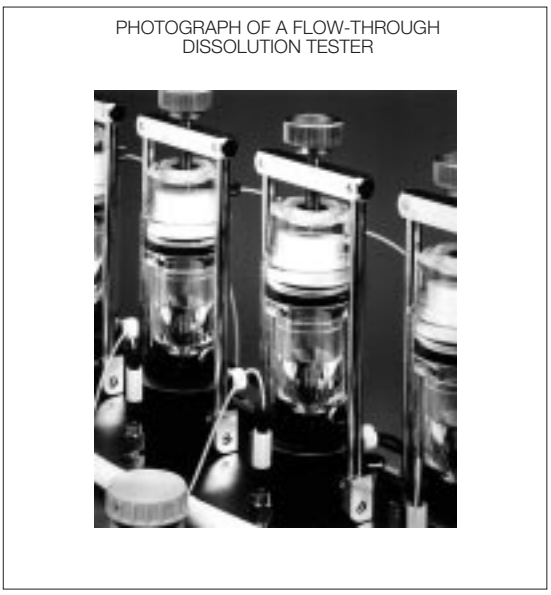

Figure 17.

The rate of emptying of a meal and associated secretions from the stomach is shown in *Figure 18*, taken from a study published by Malagelada in Gastroenterology in 1977. These results show that the flow rate out of the stomach peaks at about 8 milliliters per minute and has an average value of about 4 milliliters per minute.

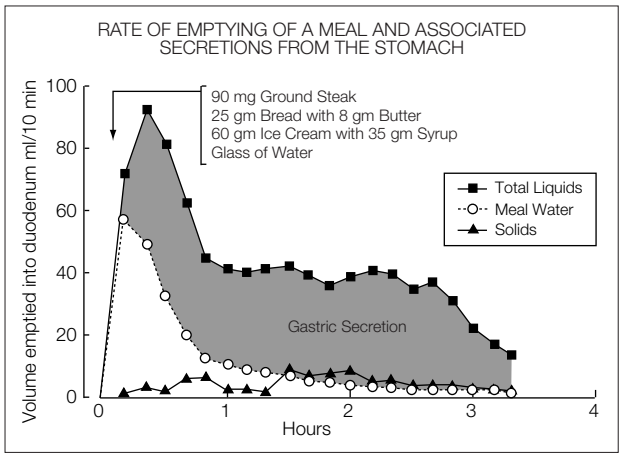

Figure 18. Average rate of emptying solids and liquids of a meal and the accompanying secretion.

Flow rates in the small intestine tend to be slower than those out of the stomach. The data in Table 8, taken from Kerlin's 1982 article in Gastroenterology, show that usual values in the fasted state are about 0.5 to 1 milliliter per minute, and that after a meal flow rates increase to about two to three milliliters per minute. Also, flow rates in general tend to be higher in the duodenum and jejunum than in the ileum.

Flow rates in the small intestine (ml/min.)				
Location	mean	Fasting Phase III	Phase I/II	Fed mean
jejunum	0.73	1.28	0.58	3.00
ileum	0.33	0.50	0.17	2.35
terminal ileum	0.43	0.65	0.33	2.09

Data from Kerlin et at., Gastroenterology 82: 701-706, 1982.

Table 8.

The standard flow rates of 8 or 16 milliliters per minute currently suggested by the USP are very high in comparison to these values. So although the flow through testers in principle can be used to simulate flow conditions in the intestine, we need to adjust the rates being used to make them more consistent with the physiology.

The third and final question is, how long does the drug have to be released from the dosage form and go into solution? The answer depends on the permeability profile of the intestine to the drug - for example, if the duodenum is the primary absorptive site, dissolution should occur in the stomach, whereas if the jejunum and ileum also exhibit good permeability to the drug, dissolution in the small intestine will suffice.

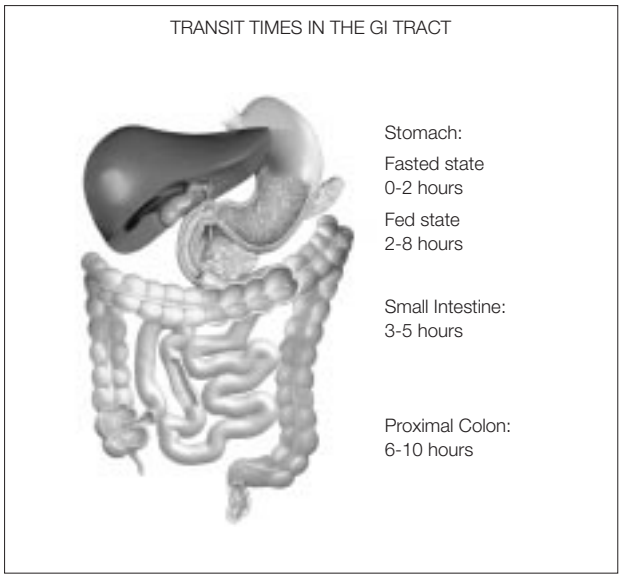

Figure 19.

The residence time in the stomach is variable and differs between the fasted and fed states. In the fasted state, the gastric residence time depends on when the dosage form is ingested compared to when the next strong contraction pattern, sometimes known as the «housekeeper wave», passes through. This can range from immediately to about two hours, which is the usual periodicity of the housekeeper wave cycle. In the fed state, the residence time depends on how big the meal is, since bigger meals take longer to empty, and on whether the dosage form disintegrates or not. Disintegrating dosage forms tend to empty with the meal, whereas non-disintegrating dosage forms may be held back until meal emptying is complete. This is especially likely to happen if the dosage form is bigger than 3-5 mm in diameter und does not disintegrate. So in the fed state, emptying may occur over a period as short as one or two hours, or as long as six to eight hours.

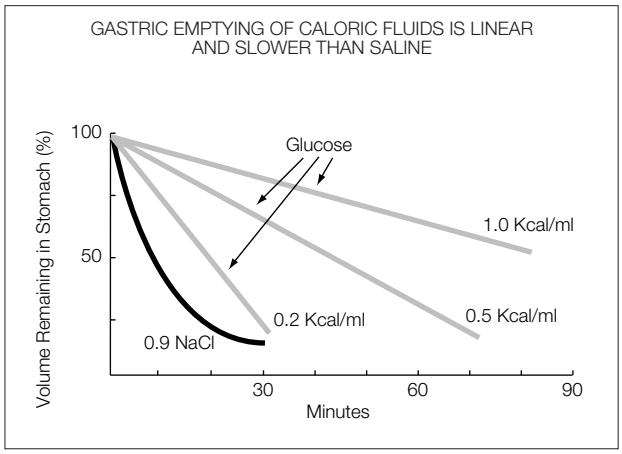

Figure 20.

When a non-nutrient fluid like saline is ingested, it empties in about a half-hour. In *Figure 20* we see an idealized first-order emptying pattern, but often there is a lag-time before emptying starts, and sometimes there is an uneven emptying pattern.

If a calorie-containing fluid is administered, emptying tends to be slower and more linear. The three upper curves demonstrate that the greater the calorie concentration of the fluid, the slower it will be emptied from the stomach.

Transit through the small intestine is much more consistent, with the journey usually taking three to five hours.

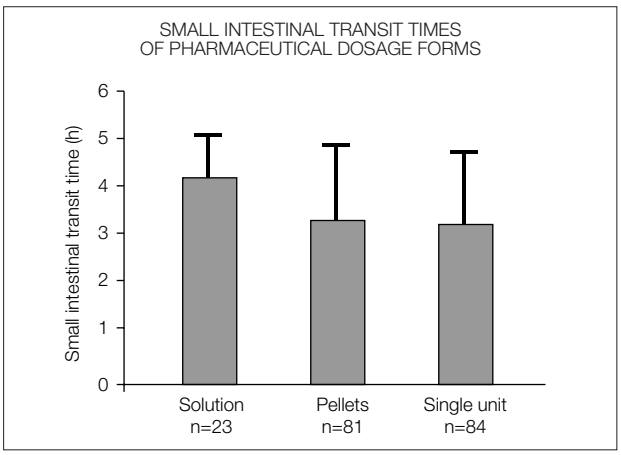

Figure 21.

Furthermore, the intestinal transit time tends to be fairly independent of the type of dosage form. *Figure 21*, taken from an article published by Bob Davis and colleagues from the University of Nottingham, shows that, irrespective of whether the drug is administered as a solution, a pellet or a tablet, the transit time through the small intestine is about three to five hours.

By considering both the transit time data and the permeability profile of the drug, one can estimate how long the dissolution test should last, and in which medium it should be run. For example, for a drug that is best absorbed in the duodenum and is given in an immediate release tablet in the fasted state, a dissolution test in simulated gastric conditions with a duration of 15 to 30 minutes would be a good, physiologically relevant design. This design is covered by Case A in the SUPAC Guidance published by the FDA in November, 1995. At the other end of the spectrum, if the drug is well absorbed throughout the jejunum and ileum, and is given with meals, testing in the fed state medium, FESSIF, with a test duration of two to three hours may be entirely reasonable in terms of the physiology. This design would be consistent with the Case C conditions mentioned in the Guidance, which allows the use of a suitable surfactant when its addition can be justified. Thus, the SUPAC Guidance already contains elements of a physiologically based dissolution test design.

In summary, since release, dissolution and absorption must all occur during the transit time from the mouth to the last good absorption site for the drug, it is necessary to first identify the permeability profile of the drug. Once this is done we have to think about using appropriate media to simulate the *in vivo* dissolution profile, and about using an appropriate volume, relevant hydrodynamic conditions and an appropriate test duration. Only then can the *in vitro* test accurately predict the *in vivo* performance of the dosage form.

Before I close, I would like to acknowledge the efforts of my colleague at the University of Athens, Prof. Christos Reppas, with whom I work closely, and those of my graduate students, Eric Galia and Dirk Hörter, who obtained many of the results I have shown today. I would also like to acknowledge the FDA for financial support of the danazol and acetaminophen studies, and Janssen Pharmaceuticals for their sponsorship of the ketoconazole studies. And last but not least, I would like to thank you for your attention.

Rationale Approach to Predict Human Drug Absorption from *in vitro* Study

Professor Shinji YAMASHITA, Ph.D.

Rationale Approach to Predict Human Drug Absorption from *in vitro* Study

Professor Shinji Yamashita, Ph.D.

Faculty of Pharmaceutical Sciences, Setsunan University
45-1, Nagaotoge-cho, Hirakata, Osaka 573-01, Japan

Professor Hashida: Now I would like to introduce our next speaker, Professor Shinji Yamashita from Setsunan University. He graduated from Kyoto University and also studied at Jyosai University. He is now an Associate Professor at Setsunan University, and in the course of this appointment he has been able to spend a period studying at Michigan University under Professor Amidon. Today he is going to talk about the Rational Approach to Predict Human Drug Absorption from *in vitro* Study.

Professor Yamashita, please.

Professor Shinji Yamashita: Thank you very much for your kind introduction. It is a great honour to have this opportunity to talk to you in the presence of Professor Amidon and Professor Hashida.

Today I would like to speak on the Rational Approach To Predict Human Drug Absorption from *in vitro* Study. As researchers with a particular interest in knowing about and being able to predict human drug absorption patterns, we are dependent on the *in vitro* study. I shall be talking about the use of Caco-2 monolayer cells within these studies, and discussing their advantages and limitations. I would also like to talk about my general experience of conducting the studies, and to show the results.

As you know, with regard to oral drug absorption, there are several parameters on the drug side, and others on the patient's side which have to be taken into account, including gastrointestinal (GI) tract conditions.

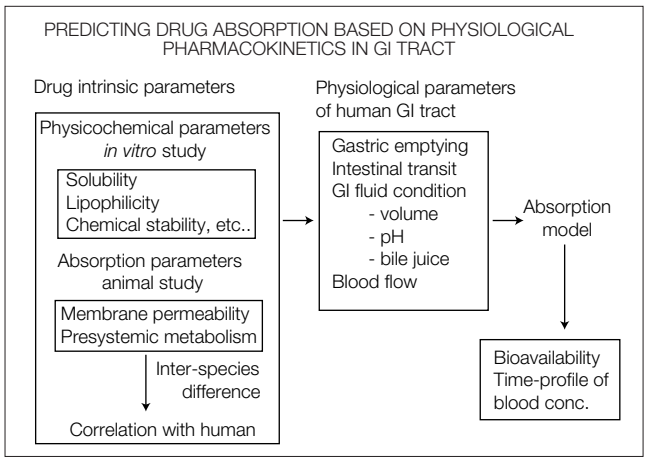

Figure 1.

The time course or absorption trend can be said to depend on GI conditions in the dog or other animals on which we carry out studies. Sometimes it is very difficult to apply the results of our animal studies to humans because of the many inter-species differences. And physiological parameters can vary greatly between individuals, sometimes even within one individual.

Given this, is it possible to produce a single methodology to cover this range of variability?

We collected a large amount of data through carrying out several *in vitro* studies and, based on these results and on the physiological pharmacokinetic models we set up, I think that we have come up with some models that we can use for prediction.

A critical question, especially when trying to predict the absorption rate is: how can these very important physiological parameters be picked up when we carry out *in vitro* studies? When we limited this to early-phase prediction, we found the most important thing is absorption fraction.

Absorption fraction has to be understood by looking at a number of parameters on the drug side rather than those on the patient's side (see *Figure 1*). This means looking at solubility, membrane permeability and pre-systemic metabolism, in order to come up with some kind of model that we can use to predict biovailability.

As both Professor Amidon and Professor Dressman have given presentations on the subject of solubility, I would like to talk about membrane permeability studies, in relation to pre-systemic metabolism. I would like to start by explaining the basis of the thinking that led up to my study, and then show how we can pick up these important parameters, and I would also like to bring in the question of correlation with humans.

First I would like to talk about permeability; that is, permeability to the intestinal membrane (see *Table 1*). As Professor Amidon stated earlier, it is possible to carry out an *in vivo* intubation study, but this is not appropriate as a screening study.

Caco-2 monolayer materials are used to calculate the permeation. This technique compares favourably with two very important test results (*Figures 2 and 3*). *Figure 5* illustrates the results of a perfusion study using rat small intestine which Professor Amidon carried out, and it shows a very good correlation with humans. Based on work carried out by Professor Artursson, concerns Caco-2 monolayer studies, and again, there is correlation with humans.

Estimation of drug permeability to intestinal membrane	
in vivo	intubation study human, dog
In situ	perfusion study rat, rabbit
in vitro	permeation study isolated intestine (rat, rabbit) culture cell system (Caco-2 monolayer artificial lipid membrane)

Table 1.

These results suggest that either approach will be very effective. However, they each have some problems. The basis of the in-situ perfusion study is disappearance in the intestine, but if there is any metabolism taking place in the GI tract then the results will become very ambiguous. Another problem concerns the Caco-2 monolayer because it will not be suitable for carrier-mediated drug evaluation; it may be better suited to passive diffusion.

In order to say that Caco-2 has value in studying absorption then we have to carry out studies like the one shown in *Figure 3*, where we isolated rat jejunum and colon by using a chamber system,we observed the lipophilic effects. Permeability is shown on the vertical axis and, as lipophilicity increases, permeability, too, becomes greater.

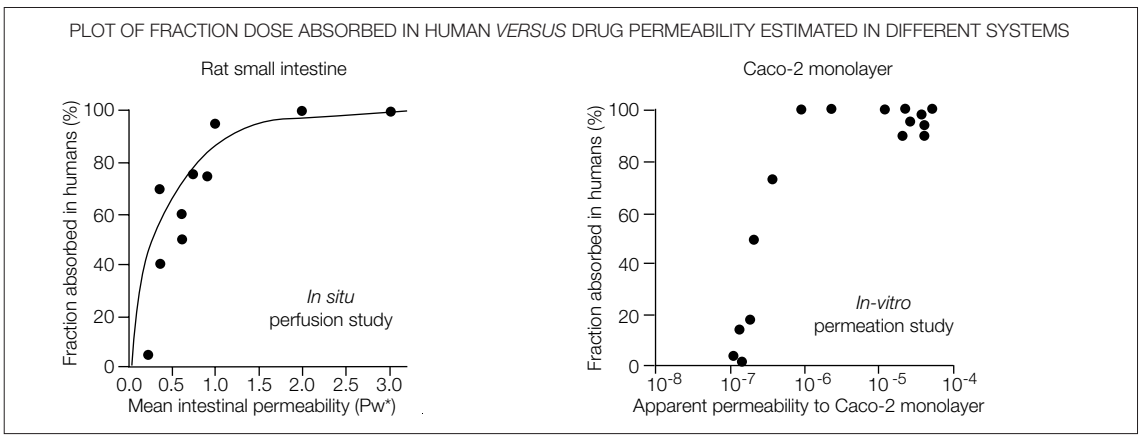

Figure 2. (Left) Amidon, G.L. et al., Pharm. Res. 5,651 (1988) - (Right) Arthursson, P., & Karisson, J., Biochem. Biophys. Res. Comm. 175, 880 (1991)

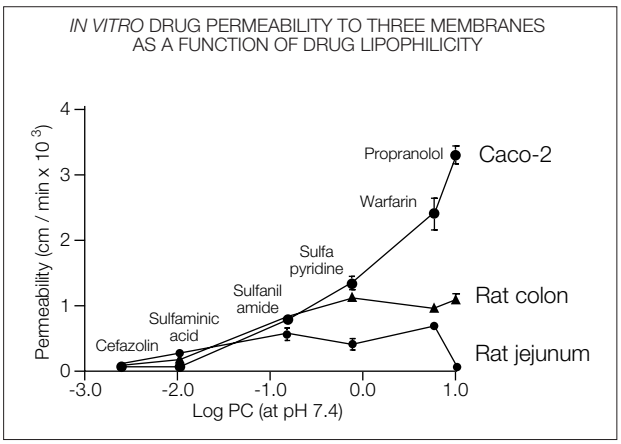

Figure 3.

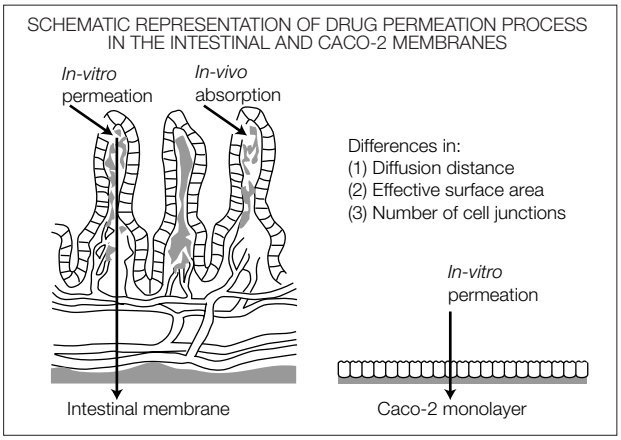

Figure 5.

However, *in vitro* study of rat jejunum does not show a very good correlation between lipophilicity and permeability, and here the Caco-2 results seem to be better. This is supported by the data from three sets of studies shown in *Figure 4*, showing the relationship between *in vivo* and *in vitro* drug permeability, where Caco-2 produces a very good correlation. There is less correlation in the other two studies, so one has to conclude that they are quite inappropriate for use in predicting what is happening in human beings.

Figure 5 illustrates the differences between *in vivo* absorption and *in vitro* permeation. With the *in vivo* absorption process, the drug passes through the epithelial layers following the rapid clearance into the blood stream. In the standard *in vitro* permeation environment, it goes through the diffusion phase in the lamina propria. The situation seems to be different where I believe that this particular *in vitro* diffusion is a limiting factor.

As *in vitro* permeation studies utilising the Caco-2 monolayer do not involve the diffusion phase found with lamina propria, the results seem to be closer to *in vivo* absorption. So even in *in vitro* permeation studies Caco-2 seems very useful.

Caco-2 has value with regard to passive diffusion-type drugs, as Artursson and others have confirmed. We compared four studies carried out at different laboratories (*Figure 6*). Absorption in humans is shown by a vertical axis and apparent permeability is shown on the horizontal axis. Similar trends are seen across all four studies, although the absolute number differs widely.

Therefore, in order to use Caco-2 as a worldwide validated system, we have to come up with some kind of formalised method. We need appropriate guidelines so that we can universally use Caco-2 methods in a more standardised manner.

Now I would like to turn to carrier-mediated drug transport and the effectiveness of Caco-2

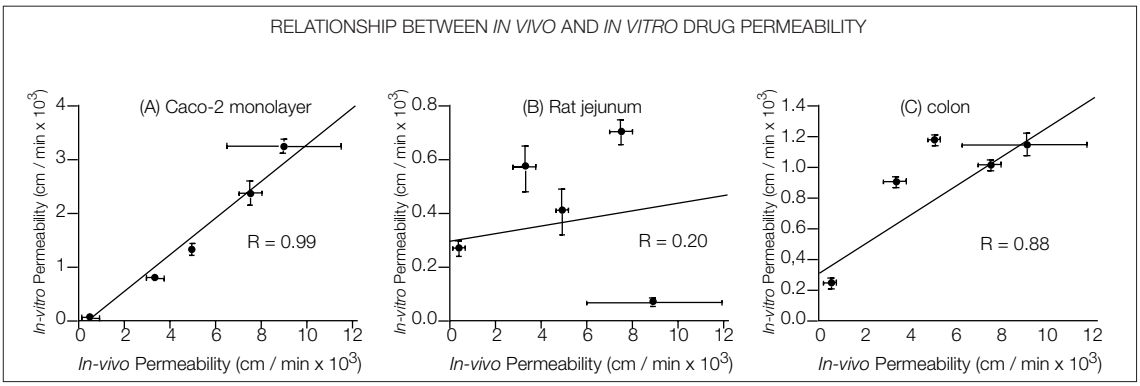

Figure 4: in vivo *drug permeability to rat jejunum was estimated by single-pass perfusion experiments.*

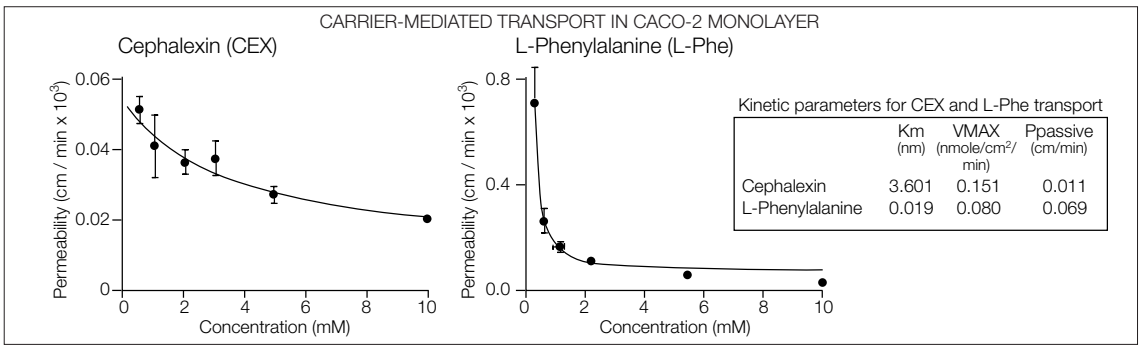

Figure 7: in vivo *drug permeability to rat jejunum was estimated by single-pass perfusion experiments.*

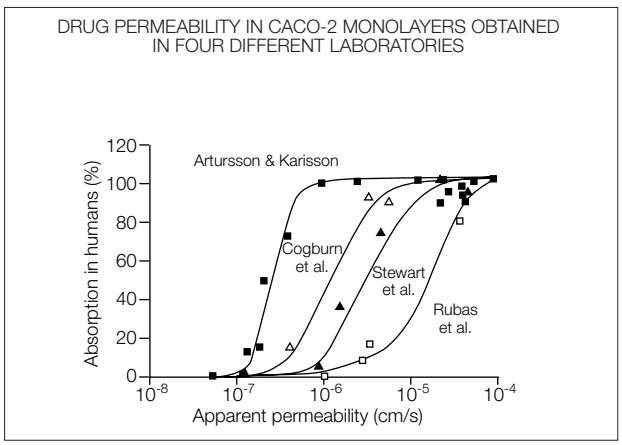

Figure 6.

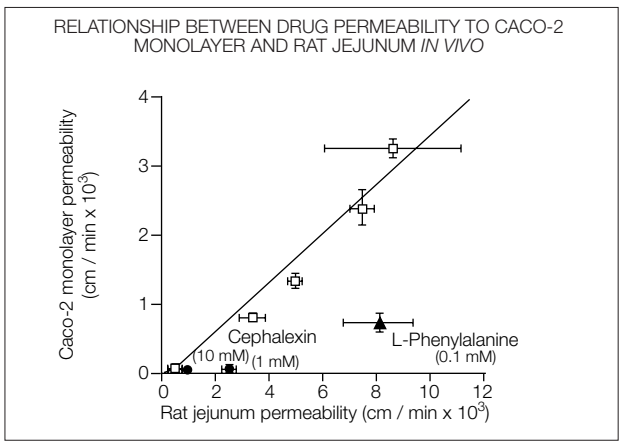

Figure 8.

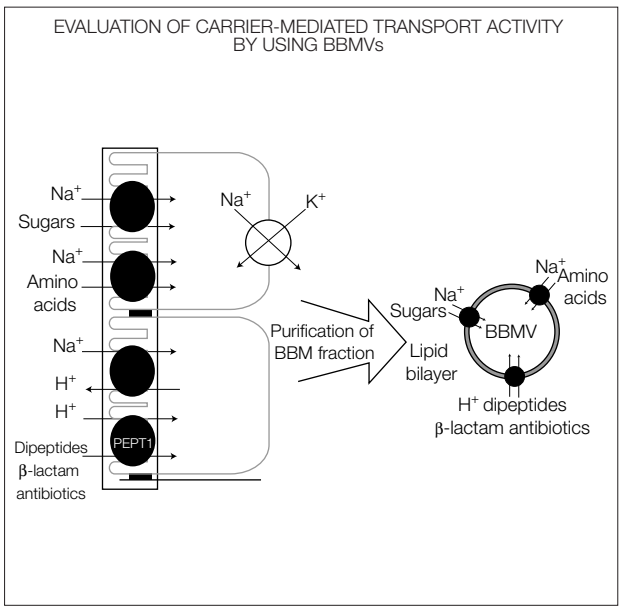

Figure 9.

monolayers in this area (*Figure 7*). It appears that Caco-2 monolayers can sometimes be quite effective even with the carrier-mediated transport-type drug, cephalexin.

It appears, then, that the carrier is working properly. But is there any difference from the passive diffusion-type of drug? *Figure 8* shows the correlation between rat jejunum permeability *in vivo* and Caco-2 monolayer permeability, where the permeation of cephalexin and an amino acid by Caco-2 seems to be very low. The results deviate quite markedly from the line so much so that if we use the line in order to predict cephalexin absorption, we run the risk of error. So although there is some carrier expression, it seems to be at a very low level.

In a separate study (*Figure 9*), we cultured Caco 2 monolayer cells to prepare brush border membrane vesicle (BBMV). We then observed the uptake of drugs by BBMV prepared from Caco-2 and rat. *Figure 10* shows the results of the res-

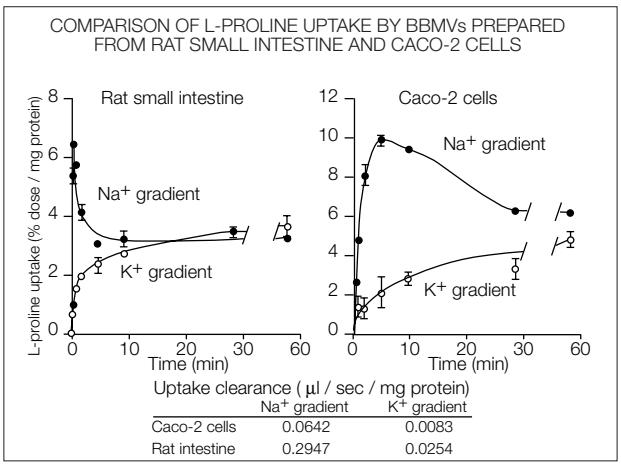

Figure 10.

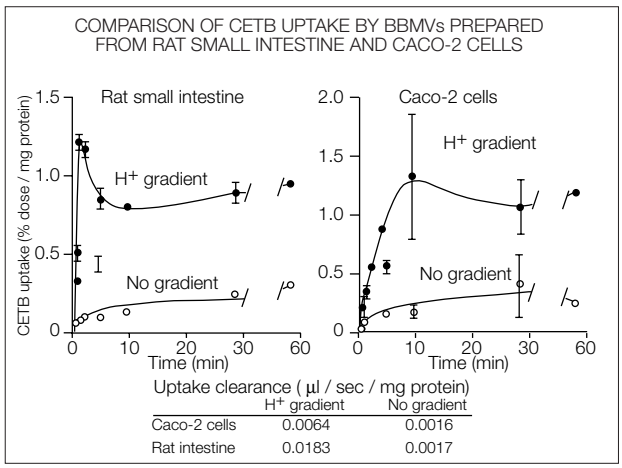

Figure 11.

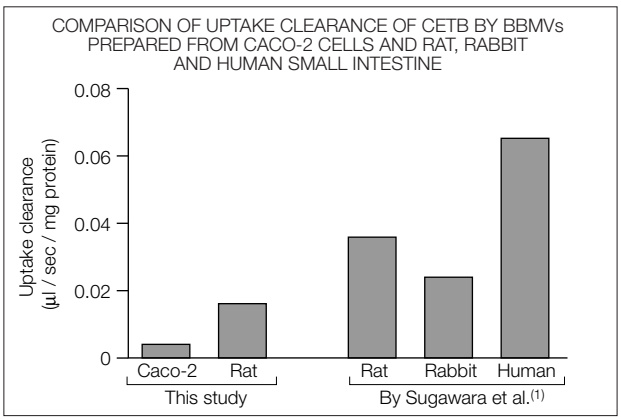

Figure 12: (1) Study by Sugawara et. al, J. Pharm. Pharmacol., 46, 680-684 (1994).

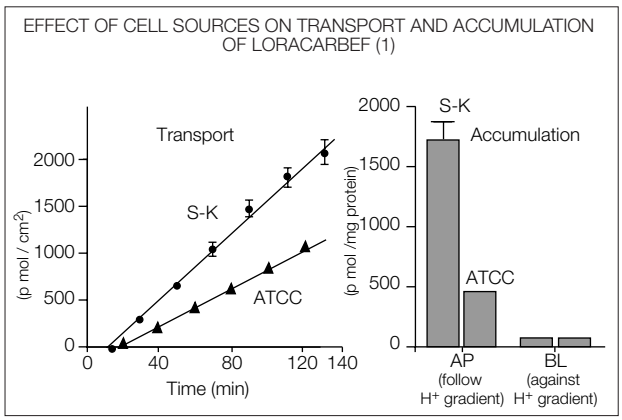

Figure 13: Ming Hu et al., J. Drug Targeting, 3, 291 (1995).

pective performance of rat small intestine and Caco-2 cells in the comparison of L-proline uptake by BBMVs. Certainly, some carriers are expressed. However, after we calculated clearance from these uptake measurements, carrier expression remained very low with the Caco-2 cells. Of course, it depends on how we prepare membrane vesicles, but even if we take that into consideration we still have to say it is very low.

Figure 11 shows ceftibuten uptake by peptide carrier, where an H^+ gradient dependency was observed in the rat small intestine studies. A similar trend can be seen with the Caco-2, but uptake takes place very slowly, reaching a level that is about one-third that of rat intestine. This result was compared with the research data from Hokaido University shown in *Figure 12* which indicates the uptake in humans, rabbits and rats. Caco-2 uptake comes out at one-third and one-quarter of the two sets of results with rats. It seems that expression of carriers in Caco-2 cells is also very low in comparison with that in humans.

Clearly, then, although Caco-2 cells do have some carrier transportation capabilities, this is at such a low level that if we want to use Caco-2 to make some kind of prediction then we have to find a way of inducing a higher level of activity, otherwise we will make errors.

Figure 13 shows a work aimed precisely at inducing higher activity, carried out by Dr. Ming Hu and colleagues at Washington University. The two different cell lines used were from the Sloane-Kettering (S-K) Research Institute and from another group called ATCC. They measured transport speed and accumulation and found that by controlling the culture conditions, it is possible to increase the transport rate, thus offering the prospect of being able to use Caco-2 with a higher transport rate.

Still to be resolved are the issues of just how high the transport rate should be, or what is the most appropriate level of expression. It is very difficult to adjust the expression level, as is evident from the slide. Changing the culture conditions slightly, greatly alters the carrier activity, so it is likely that control will be difficult to achieve. Of course, it is also very difficult to evaluate a range of drugs within a single study.

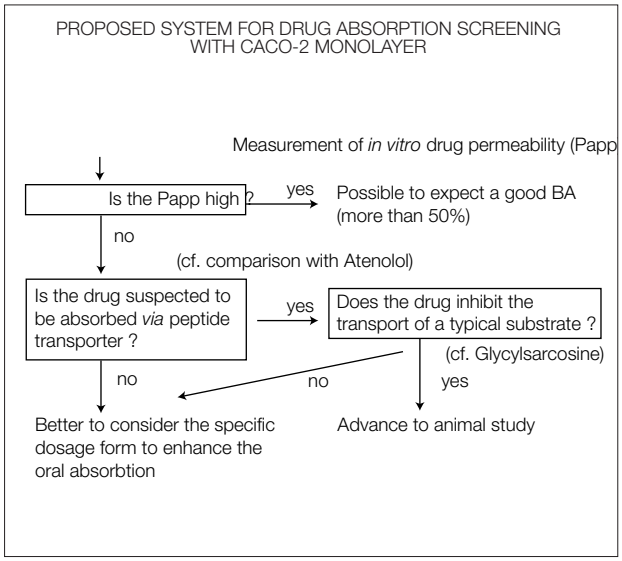

Figure 14.

Nevertheless, I would propose how we can use Caco-2 cells to measure permeability as part of early-phase absorption screening (*Figure 14*). Where a drug matches the standard of, say, atenolol, with its 50 per cent absorption, then good bioavailability (BA) can be expected. Anything slower than that means that a good BA is unlikely.

Where drug absorption is thought to be via peptide transport, then we can alter the drug dose and try again. But the concentration-dependent curve in such a case is not easy to draw up, so a typical transport substrate like glycylsarcosine can be used to enhance the possible response to this material.

No doubt somebody will say we can skip this process and move directly to the advanced animal study instead. But what the work is showing us so far is that since the inhibition effect can now be measured, it should be possible to calculate the absorption rate from it; in other words, the degree of inhibition will give us the absorption. This is simply a hypothesis, a necessary step towards being able to calculate or measure BA in two ways. However, if this can be established, then the use of Caco-2 monolayers will become more effective.

Let me change the subject a little, to move on to the topic of pre-systemic metabolism — metabolism at the GI tract — which has been much discussed recently. What are the features of this metabolism? One is the presence of hydrolyzing enzymes; esterase, protease or peptidase are some examples. Recently, it has been suggested that cytochrome P450 (CYP 3A4) need to be looked into. As well as this, intestinal microflora are also responsible for metabolism. Caco-2 may be effective to a certain degree in evaluating metabolism — we do not know, we will have to look into that.

Now I would like to turn to the metabolism of peptides and the membrane permeability of these drugs. *Figure 15* shows barriers for peptide drug, often thought of as a permeation and enzyme barrier. Within the enzyme barrier at the membrane site or the cytosolic site, locations where there is quite a lot of active metabolism of small peptides taking place, so absorption measurements have to take that into consideration.

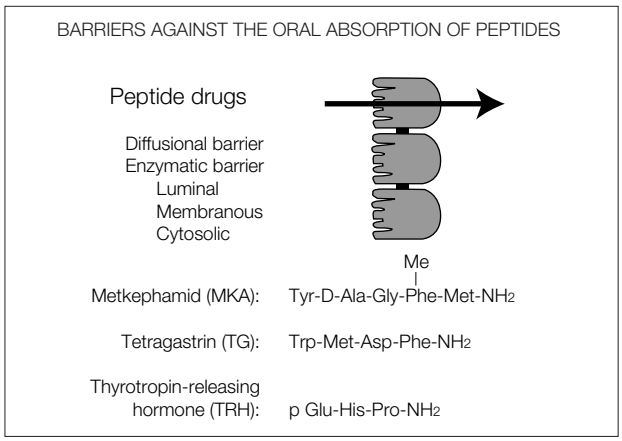

Figure 15.

I am now going to talk about the studies with metkephamid (MKA), tetragastrin (TG) and thyrotropin-releasing hormone (TRH).

So far, we have discussed how to establish ways of determining or identifying permeability, but now we need to bring in a new parameter, for degradation. We have been attempting to come up with something that can be expressed as clearance through trying to relate these two parameters.

These parameters are based on the peptide's AUC in the intestinal tract. If we can obtain these

data, then we will be able to calculate the value of the average clearance (*Figure 16*).

The vascular perfusion experiment in *Figure 17* will give us the total amount of drug eliminated as well as the membrane permeated amounts. To do this, we used MKA; the results presented represent our raw data.

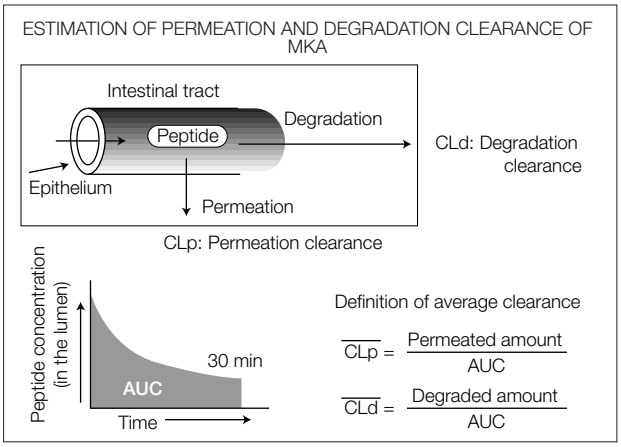

Figure 16.

Within 30 minutes, 80 per cent of MKA was eliminated from the GI tract. But in the blood vessels there was only about 1 per cent, so most was decomposed. We then calculated two clearance, degradation (CLd) and permeation (CLp), and found there was a difference of about 100 times between the two. If inhibitor is used, CLd declines and membrane permeability increases.

Keeping this relationship in mind, how can we evaluate the absorption? Professor Amidon talked about 3D and he introduced titred dimension of Absorption Number, Dissolution Number, and Dose Number. I think this set of results is similar to his. When permeation clearance (CLp) goes up, then absorption will come close to 100; however, if the degradation rate increases it drops, so it is like a 3D perspective.

But evaluation is difficult, so I will just run through the key parts. The equation in *Figure 18* assumes that all the drugs have been eliminated from the GI tract and everything is absorbed or metabolised. At that point we can see what the maximum level of absorption is. FD equals the extent of absorption — AUC multiplied by CLp. So if we obtain the ratio of both clearance, the CLd divided by CLp, CLp becomes larger, then it becomes one, and if degradation becomes larger then it becomes zero. So we can work absorption out from that equation.

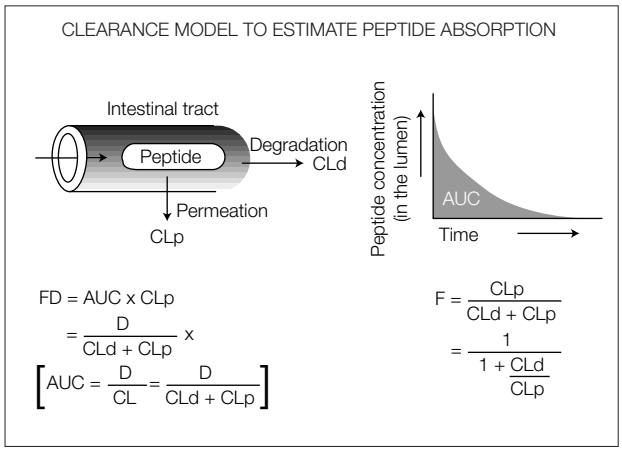

Figure 18.

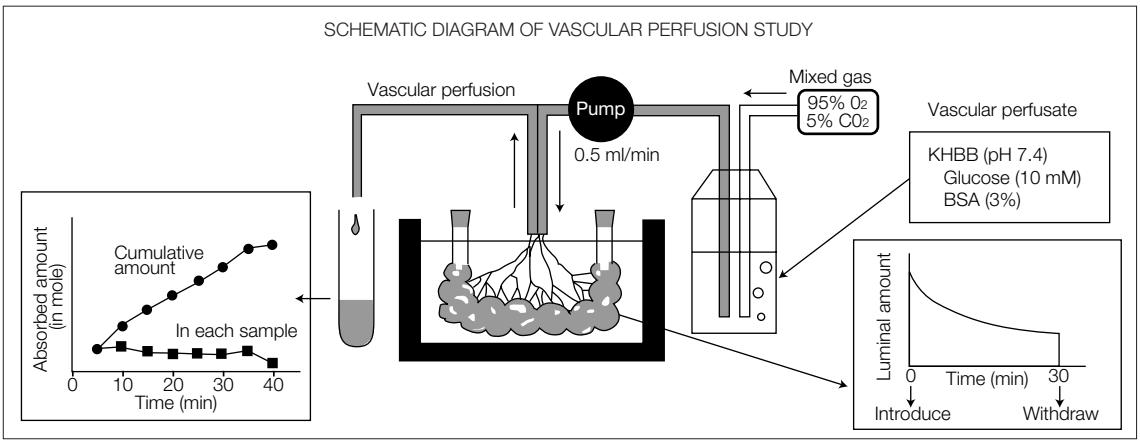

Figure 17.

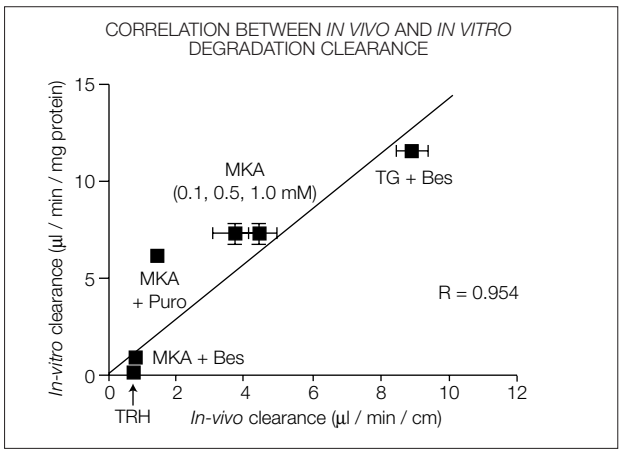

Figure 19.

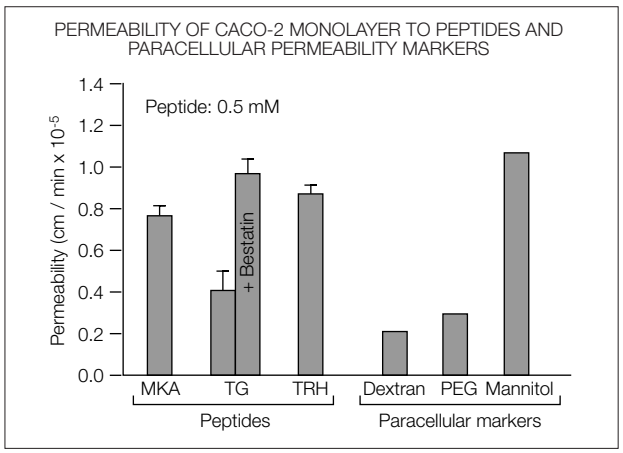

Figure 20.

So we end up with two clearance figures, obtained from separate *in vitro* studies, and we then see if we can evaluate the degradation clearance, or should I say, we look to see whether we can get a correlation. *Figure 19* shows *in vitro* degradation in rat homogenate, using MKA or TG and other drugs. The *in vivo* clearance, using vascular clearance at perfusion, gives a good correlation. So although this is a rough estimate using homogenate, we do see a certain degree of correlation as far as peptide drugs are concerned.

Next I will look at permeability using Caco-2 (*Figure 20*). Since there is a known correlation with humans and rats, we take measurements to establish the value we should use. All the results show low values, at the same level as mannitol, suggesting that permeability is probably low, too, so that is the value we use.

In *Figure 21* we return to the equation: F is determined from the relationship between the two clearances — rat homogenate degradation clearance and permeation clearance in Caco-2. This is absorption in rats, and so the question is whether we can predict rat absorption using this equation. Even this correlation between *in vivo* and *in vitro* will have a certain co-efficient which has to be taken into consideration: wherever there is a variation, the two lines do overlay. So even with a simple equation, absorption of rats can be evaluated from rat homogenate degradation and Caco-2 permeation.

However, where clearance is concerned (*Figure 22*), if we use human homogenate then we should be able to obtain a human? and so Caco-2's usefulness can be furthered by the use of this simple equation.

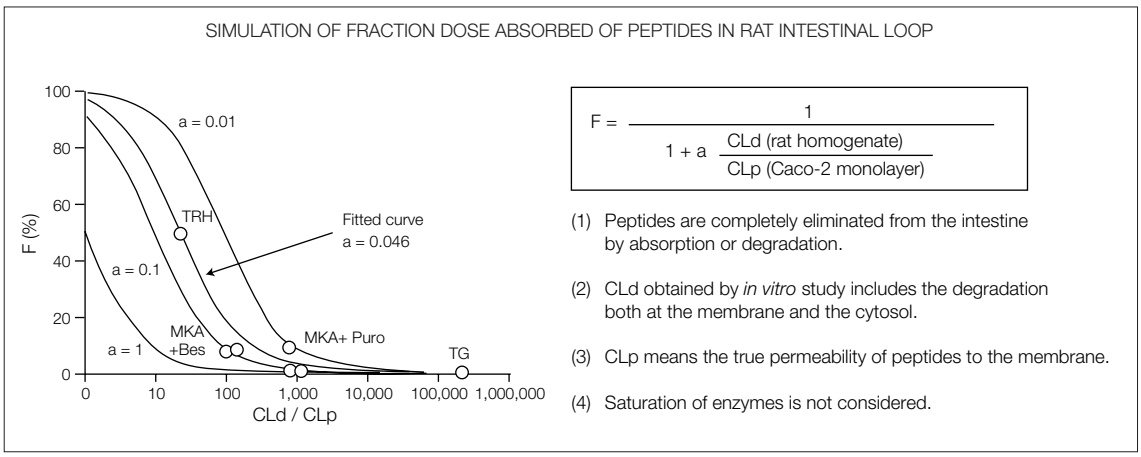

Figure 21.

Caco-2 might also prove useful in degradation studies, and we tested this hypothesis. We found that where there is a good correlation we can use Caco-2, but with Caco-2 some results are high and others are low, so there is no fixed correlation. We can only conclude that attempting to find peptide degradation using Caco-2 is an extremely unreliable method.

So while Caco-2 can be used for permeability, it would only be an approximation for degradation, although we can still work out absorption to a certain extent by using the degradation figure.

Testosterone 6ß-Hydroxylase and Cytochrome P450 contents for microsomal fractions prepared from Caco-2 cells bearing the CYP3A4-expression plasmid p220CMV3A4 and human lymphoblasts co-expressing CYP3A4 and OR (1)

Cell-source	Testosteron 6ß-Hydroxylase activity (pmol/mg min)	P450 content (pmol/mg)	Turnover number (per min)
Caco-2 untransfected	8	ND	NA
Caco-2 p220CMV3A4 -bulk	634	49	13
Caco-2 p220CMV3A4 -clone-4	983	45	22
Lymphoblast-CYP3A4 + reductase	2200	60	37

Table 2. (1) Cahries, L. et al., Pharm. Res., 13, 1635 (1996)

We recently saw a very impressive paper from the Gentex group at Washington University where the CYP3A4 gene is transfected to Caco-2. Usually, there is no expression, but this method promotes expression in the presence of cyclosporin and other given drugs (*Table 2*).

Of course, metabolism also can be evaluated with Caco-2. So in the future perhaps this method will become useful.

The question is, what level of expression is necessary and how should it be maintained? The methodology I have been describing is one approach. If we could establish a system for determining degradation clearance, from there we may find a new way of obtaining absorption using Caco-2.

Professor Hashida: Thank you, Dr. Yamashita. I would now like to invite questions on the subject — absorption in humans in general, and how animal experiments based on *in vitro* study can be correlated to human application. Dr. Sugiyama.

Question: Dr. Sugiyama, *of the University of Tokyo:* This is a conceptual question. When using Caco-2, I have found that in the case of carrier-mediated transport many transporters are down-regulated, so the prediction is not always reliable. You said that yourself, and I agree with you. So the question is, why do you use Caco-2?

I believe that it is effective in the early stages of the drug screening process. So, based on the assumption that good absorption is positive and poor absorption is negative, I think that a category of false-negative expression should be allowed. In other words, it is possible for absorption to be a false-negative, whereas cases that have been positively predicted must always be positive. I think this is the only way to use this methodology.

Over and above that, I agree with what you said. For example, if an additional assessment of inhibition could be made by using a microplate system to enable rapid assessment of a very simple oral dosage of glycoglycerine, then you could perhaps put a question mark against the negative results, for full-scale evaluation later.

I think that while your approach is sound, the false-negative should be allowable. I would like to know your views on this.

Professor Shinji Yamashita: I agree with you. To continue a development which turns out to be negative is wasteful, and we want to eliminate such waste. But what is the significance of the use of Caco-2, can it be only used for possible diffusion? If that is the case, I do not think we need to use Caco-2 for the profile. There are other factors which determine the molecule design and I think to a certain extent absorption can be predicted by using several other parameters. Once absorption is obtained, then Caco-2 is no longer necessary.

Although Caco-2 does express carrier, and peptidase and CYP3A4 are also expressed, it has to have additional merit, otherwise its future is not so bright. I am using Caco-2 right now, so I would like to see some potential in its use.

Professor Hashida: I am sure there is still a lot of potential discussion with regard to this point, which we can continue during the panel discussion. Thank you.

The Present Status of Formulation Design of Oral Dosage Forms in the Japanese Industry

Dr. Akira KUSAI, Ph.D.

The present status of formulation design of oral dosage forms in the Japanese industry

Dr. Akira Kusai, Ph.D.

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Professor Hashida: Now we have the last presentation for today. We have been talking about absorption and the current status of related regulatory perspectives. Dr. Lesko has taken us through the topic from the point of view of the regulatory considerations, and we have also had input from the academic side.

Our last speaker is from the Japanese industry, and he will be moving the subject on, to tell us what is currently happening in the Japanese industry.

Dr. Akira Kusai is from Sankyo and his subject is the Present Status of Formulation Design of Oral Dosage Forms in the Japanese Industry. He will be discussing the current status of drug development in the Japanese industry with reference to formulation design and development. Dr. Kusai, please.

Dr. Akira Kusai: Thank you very much for your kind introduction, and let me also thank you for inviting me to speak here. I would also like to thank Professor Amidon and Dr. Lesko.

As Professor Hashida has already indicated, I will be talking to you about the Japanese industry and the present situation regarding formulation design of oral drugs, or oral dosage forms. I should point out that you will be hearing the opinion of one person who is involved with drug development in a particular corporation, and so my presentation is likely to omit a number of issues, for which I apologise in advance.

I would, however, like to base my talk on the sorts of issues we face in the course of our everyday activities.

Our ultimate mission as research scientists in the pharmaceutical industry is to contribute to medical care through the development of effective, safe, reliable and useful pharmaceutical products. If we can also find ways of doing so quickly, while ensuring that the pharmaceutical development process goes through smoothly, we are more than happy.

Figure 1 is a busy slide. The left-hand column shows the various steps within the drug R&D process, while the right-hand column indicates our corresponding development activity at each step, and the contributions from the different departments which support the discovery process.

For both drug discovery and the related support activities, the emphasis in the initial stages is on the optimization of the compounds. The activity then

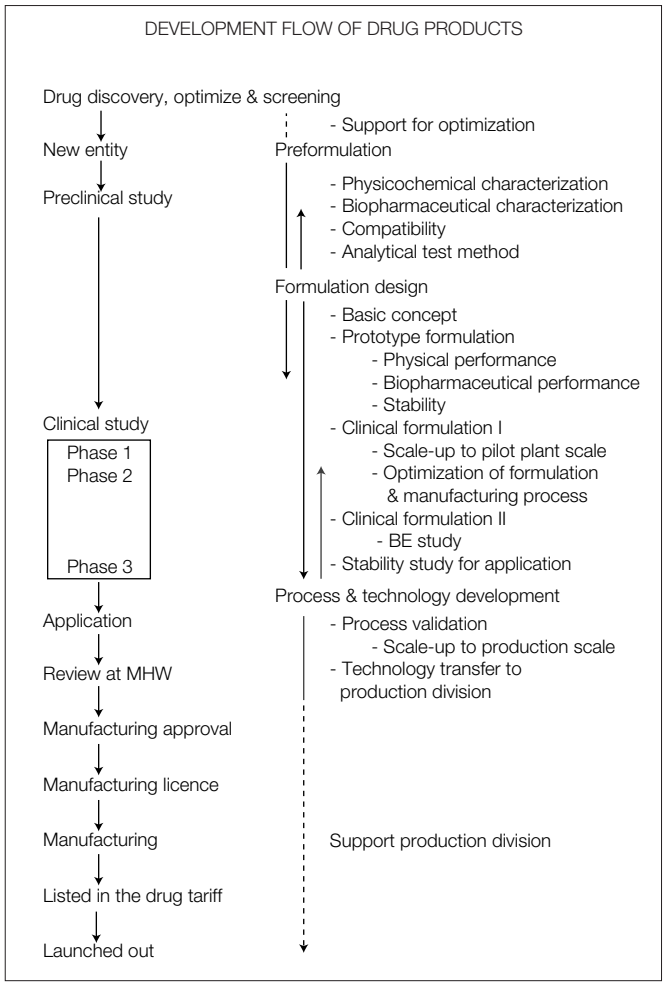


Figure 1.

shifts into preformulation and formulation design, and the process and technology development that will lead to product manufacture. Once the basic decision has been made to go ahead with a compound, these various development steps, which also play important roles in the course of the process, come into play.

So, as far as the biopharmaceutical classification study is concerned, we can define the basic study required either in terms of a research-oriented study or in terms of a product-oriented study (*Table 1*).

To turn now to the basic study. The type of information on dosage and administration forms which the international regulations require is new to us in Japan. The associated technology and methods of evaluation which we now need to develop are also new for us.

Basic study
- Study on mechanism of drug disposition *In vivo - in vitro* correlation Animal scale-up Unification of PK, PD & TK
- Development of new concepts of dosage form
- Development of new technology and new evaluation measures

Table 1.

A recent report on the subject of how we carry out formulation studies in Japan is highly illuminating in this regard. *The Research Report on Pharmaceutical Formulation: the environment today and future prospects* is based on a series of meetings between senior executives in six companies, and their counterparts in the engineering industry. From May to September 1996, they met regularly to examine drug development activities in the Japanese industry.

The meetings looked at efficiency and quality development, and the detailed back-up studies these require. But the report's findings suggest that these studies are carried out in a non-individualized way. All the companies take the same uniform approach, and mainly base their studies on *in vitro* and animal work (*Table 2*).

According to the report, we Japanese also take a rather conservative attitude towards introducing

Characteristics of our formulation design
Perform very efficiently & finely with limited amount of drug substance from preformulation to technology transfer.
Develop products of good appearance and high quality, but standardized character.
Mainly performed with *in vitro* & animal study. Rather conservative about a new concept: - Have not proposed, but accepted GLP, GMP, GCP - Left behind to originate a novel concept in dosage forms - Left behind to give shape to a novel concept - Have little atmosphere to accept a venture technology
Research Report on Pharmaceutical Formulation; Environment Today and Future Prospects (Yakuzaigaku, 57. 114-123, 1997)

Table 2.

new concepts to formulation design (Table 2). We did not initiate the global trends towards good laboratory practice (GLP), good manufacturing practice (GMP) and good clinical practice (GCP); we simply accepted them. Nor are we good at pioneering and developing novel concepts, an area where we trail behind others. We are pulled back by our traditional cultural outlook, which does not easily adjust to a technology venture climate.

Some of the possible reasons for this situation are outlined in *Table 3*. Not only does it take a long time to develop a product, but because it is to be used by patients, the final product form reflects more than just market-driven factors. It has to incorporate regulatory input from the Ministry of Health and Welfare, and also keep generally in line with what society will accept. Current social trends still make it harder to conduct human clinical studies in Japan than elsewhere, for example.

All the same, these days drug development activity is very busy, and many different manufacturers are coming up with new ideas and creative ways of thinking.

Possible reasons
1. Take long time to develop a product
2. Require idea plus market needs, MHW, social trends
3. Harder to conduct human clinical study
4. Very busy with developing nice looking products, improve the formu-lation & manufacturing process and manufacturing clinical samples
5. Tend to self-completion, not mutual utilization

Research Report on Pharmaceutical Formulation; Environment Today and Future Prospects (Yakuzaigaku, 57. 114-123, 1997)

Table 3.

I would now like to concentrate my presentation on oral dosage forms. The latest concept behind oral dosage forms is the idea of time-controlled products, rather than thinking about them as slow-release products *(Figure 2)*.

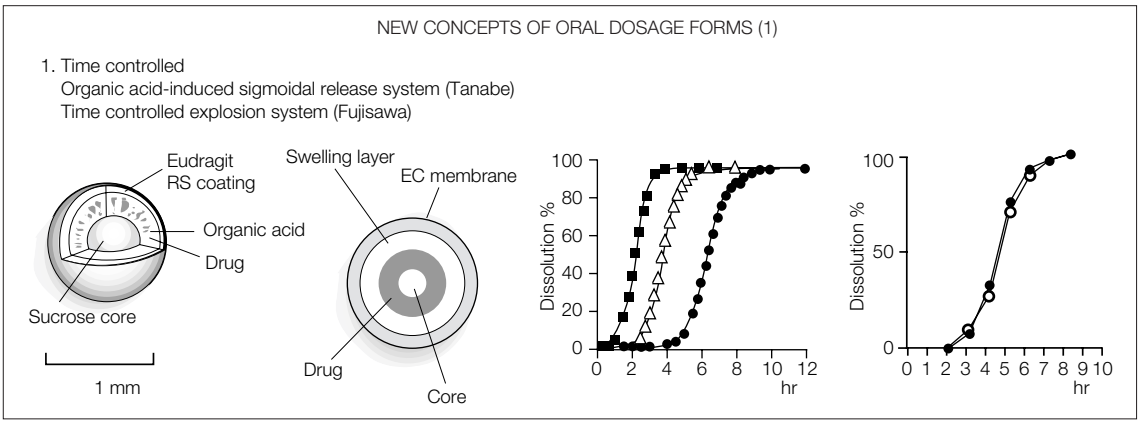


Figure 2.

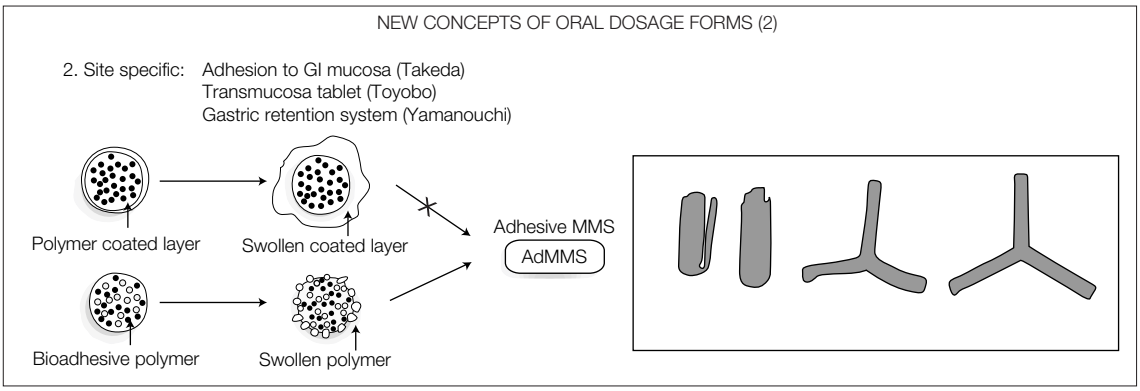


Figure 3.

Figure 2 shows two new systems. In the diagram in the left-hand column, the organic acid drug layer surrounding the core acts directly to dissolve the Eudragit slow-release coating. The second system, shown in the right-hand diagram, works on a different principle. Fluid enters via the outside membrane, and is drawn through a hygroscopic layer that swells increasingly with the entry of more fluid, eventually bursting through the membrane and releasing the active contents.

These are time-controlled oral dosage forms.

There are also site-specific oral dosage forms (*Figure 3)*, containing a gastrointestinal (GI) mucosa attachment or adhesive substance. Because these are made of polymer, they are not retained in the gastric lumen.

Figure 4 illustrates other new types of oral dosage forms. Although these are technically still slow-release products, drug is confined to specific zones within the capsule. Basically, these systems share the principle that fluid penetration over time continually exposes a new release layer, until only a ghost matrix is finally expelled.

Then there is a very ingenious and useful new idea, targeted on colon delivery (see diagram within *Figure 4*). A slow-release drug often has a gel layer surrounding a non-gel core, and because there is only limited fluid penetration before it reaches the colon — hence very little, if any, disintegration — we can describe it as a rapid gel form. A virtually intact gel form in the gastric tract is not only easier to release than were earlier slow-release types of drug, but the volume of gel layer is some eight times greater.

Now to consider the product-oriented study (*Table 4*). Here, the preformulation study and formulation design, as well as process and technology development, are all very important, but I would like to focus on the first two areas.

The product-oriented study
Preformulation study
Formulation design
Process & technology development
Scale-up
Process validation
Technology transfer to production division

Table 4.

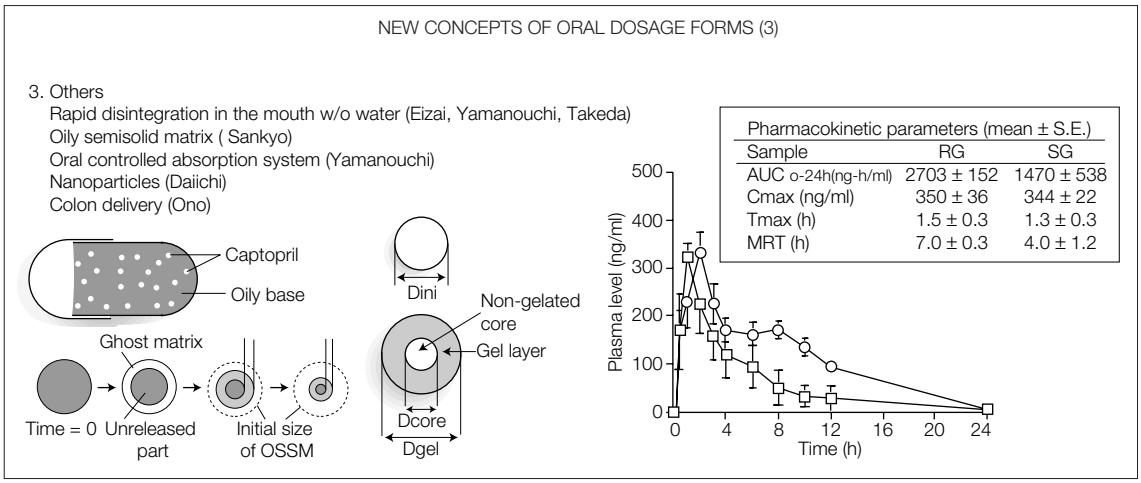


Figure 4.

In the preformulation study, as part of the selection of a new entity, characteristics such as solubility will be worked on and clarified, and useful information collected from such formulation data (*Table 5)*.

The preformulation study
Selection of new entity
Collection of useful information for formulation design

Table 5.

So exactly what information is required for formulation design (*Table 6)*?

Information required for formulation design
Dosage
- Dosage form, standard formulation, size, extent of impact of entity
Physicochemical characteristics
- Crystallinity & polymorphism, hygroscopicity, particle characterization,bulk density, compressibility, flow properties, impurities.
- Solution stability, solid state stability, pKa, melting point, partition cœfficient, solubility, pH profile, solubilization, dissolution, wettability, contact angle
- Analytical method
Biopharmaceutical characteristics
- Bioavailability, absorption site & mechanism, first pass effect
- Protein binding, distribution, metabolism, accumulation, urinary excretion, enterohepatic circulation
Safety
- MSDS (powder explosion), protection of research scientists.
Excipients
- functions & characteristics, compatibility, pharmacopeia, pharmacological active compound as additives, used as additives?
Manufacturing process
- Unit process: milling, mixing, granulation, drying, sizing, classification, tableting, capsule filling, coating

Table 6.

First of all, dosage. Obviously, the existing standard formulation will depend on the type of dosage form. Each company will take the existing standard into account when deciding on its own version's standard formulation.

Size is another factor. In the case of a round tablet with a diameter of nine millimetres and a number 1-sized capsule, with added excipient, 300 mg would be the maximum as total weight. If it goes above that then we need to have a multiple dosage, or it may be possible to consider granular or powder forms. The extent of impact of the entity should also be studied.

Professor Dressman talked about the physicochemical characteristics of formulation design, but there are further chemical aspects as well as dissolution-related factors, which I have classified on *Table 6*. In terms of biopharmaceutical characteristics, you will see that the list includes factors related to absorption and post-absorption. Safety is another issue, as are excipients, and comprehensive information on these areas must also be put together.

Capsules or tablets
- Compressibility
- Densification
- Size
- Cost
- Manufacturing speed
- Moisture
- Cross-linking during storage*

** Second dissolution test (with pepsin or pancreatin) Parmacopeial Forum 23 (2) 3844, Mar. Apr. (1997)*

Table 7.

I would like to mention a few manufacturing issues (*Table 7)* surrounding the choice of capsules or tablets. If compressibility is poor, then the product should be in capsule form. Densification is another factor we have to take into consideration, as well as size, cost and manufacturing speed.

Although there are some very good capsule-filling machines around, they are slower than tableting machines. As well as this, automated tableting systems can be run for 24 hours a day. So, for the present, the tableting machines available score over capsule-filling machines.

Another disadvantage is that capsules have a moisture content of between 15 and 16 per cent, equilibrium to 40 to 45 per cent humidity. If the new entity is sensitive to moisture, then we cannot run both on the same line. So I think that moisture is another very important factor we have to take into consideration.

Also, when capsule products are left in storage, then cross-linking may take place. FDA currently approved the second dissolution test for such cases, that is, the dissolution test with pepsin or pancreatin. As far as the stored products pass the test, this does not constitute any problem. We do not know when MHO may accept this idea.

Professor Hashida and colleagues are studying rational formulation for humans, and his research group carried out a survey of formulation scientists in 12 companies to discover which areas of formulation design pose the greatest difficulties for them (*Table 8*). According to the survey, most researchers place poor permeability and low bioavailability at the top, followed by poor chemical stability. Although high dosage is also perceived as very difficult, it appears at the bottom of the list.

The factors to be considered for formulation design (*Table 9)* include control of bioavailability, improved patient compliance, quality assurance and ease of production. I would like to restrict my talk to the control of bioavailability.

The control of bioavailability is related to the control of motility in the GI tract absorption site and the reaction site. If these sites are limited, then other ways are open to us, such as improving the residence property within the gastric environment. For stabilisation in the GI tract, for instance, a film coating will work effectively, and it will control and

Relative difficulty in formulation design

- Poor in permeability through GI membrane
- Low bioavaibility due to first pass effect
- Poor in chemical stability
- Low solubility
- Instability in GI tract
- High dosage

Based on questionnaire to formulation scientists of 12 pharmaceutical companies.

Table 8.

Factors to be considered for formulation design

Control of bioavaibility (GI targeting)
- Control of motility in GI tract
- Stabilization in GI tract
- Control and improvement of dissolution
- Enhancement of membrane permeability

Improve of compliance
- Gentle to the patients
- Easy to handle at dispensary

Quality assurance
- Qualitative & quantitative uniformity
- Stability
- Packaging materials

Productivity
- Manufacturing process & capacity
- Process variation
- Designed quality = product quality
- GMP

Table 9.

ORDER OF ABSORPTION / RATE-LIMITING STEP

Order of absorption	Rate limiting step
Capsule < suspension < solution	Disintegration, dissolution
Capsule < suspension = solution	Disintegration
Capsule = suspension < solution	Dissolution
Capsule = suspension = solution	—

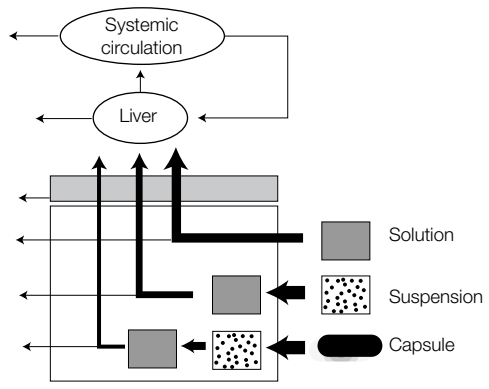


Figure 5.

improve dissolution. These may be very effective ways of solving such problems.

Moving on *(Figure 5)* to the evaluation of absorption. There are three different types of absorption process, related to capsule, suspension and solution forms. If we need to enhance absorption, we have to estimate these three different categories in terms of which is the rate-limiting factor based on the results of these three different dosage forms.

How to improve dissolution behaviour

Drug itself	Drug with excipients
Micronization	Ground mixture
Polymorphism	Solvent deposition
Salt formation	Solid dispersion
Hydrate, solvate	Ordered mixture
	Complexation
	Wetting agents
	Oily solution

Table 10.

How to improve dissolution behaviour with regard to the drug substance? As Professor Dressman stated *(Table 10)*, we have to increase the surface area. But micronisation is easier to talk about than to implement because we have to set a standard for how small the granules should be (*Table 10*). Polymorphism and salt formation may be other considerations in trying to increase dissolution, but if we are not careful enough then we can come up with a different compound. Other ways include adding excipients to the ground mixture, and so forth.

I would like to mention in particular solid dispersion in *Figure 6*, which is aimed at decreasing crystallinity. Solid dispersions are prepared by the melting method or the solvent method. With respect to the melting method, the high temperatures required may lead to unexpected degradation, while the solvent method requires to use solvents. But we are then left with the problem of the solvent recovery and the residual solvent in the products.

Nippon Shinyaku has brought out a new alternative approach, the twin screw extruder method, and is using it with niphedipine and HPMCP. It is a kind of melting method where pressure is applied instead. *Figure 6* shows dog experiment results which seem to indicate very good bioavailability.

All in all, although the twin extruder method appears very promising, however, our own experience with solid dispersion does tend to make the products larger size and there is also a need to take great care over storage conditions, especially moisture level.

Evaluation of absorption from dosage form

Animal model	Rabbit, beagles, pig, monkey Beagles: gastric pH, length of GI tract, GI motility, destructive force
Human	Dosage form for Phase I clinical study Possibility in screening of formulation Possibility to estimate absolute bioavailability

Table 11.

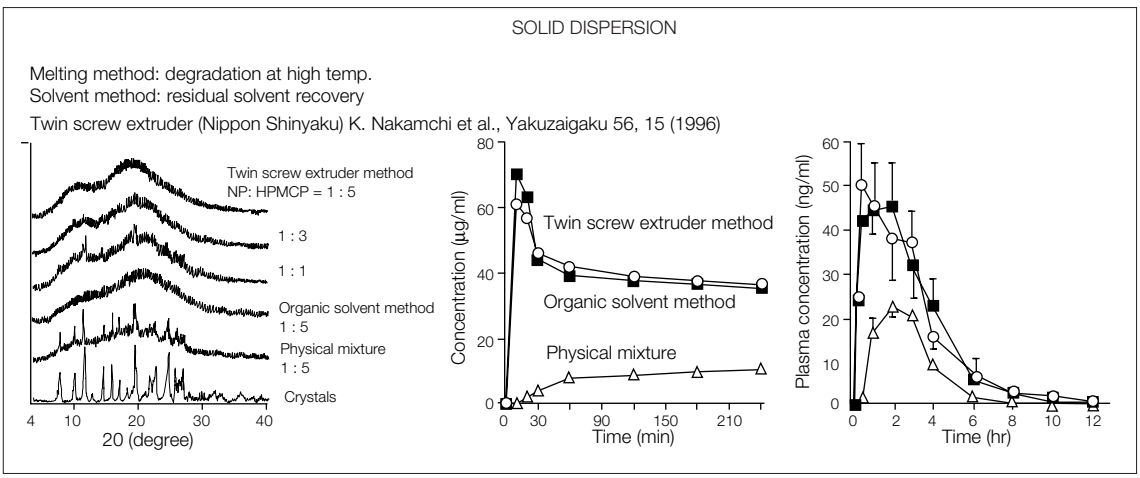


Figure 6.

Now *(Table 11)* to turn to the regulatory requirements regarding absorption from dosage form. We have heard several proposals on this in the presentations today, suggesting the kind of things we should be discussing in Japan, and encouraging the use of animal models.

With regard to the choice of test animals, they should be large enough to be able to take the dosage. Rabbits, beagles, pigs and monkeys are all being used, although beagles seem to be the easiest for us to handle.

Among the very important factors that we still have to fully discuss in Japan are gastric pH, the length of GI tract, GI motility and destructive (crushing) force. I will come back to destructive force later.

Which dosage form is used for Phase I clinical study is very important. But it is a topic which has aroused conflicting opinions in Japan. Some people say it should be very simple, just bulk filled capsule, while others say that it should be closer to the final form. There are many opinions about this.

Then there is the question of using humans in formulation testing, where some voices have expressed doubts over whether using humans for screening can be justified. Certainly, as Professor Amidon proposed this morning, it may be possible to set up alternative rational ways towards that goal, but there are places where people are using this as a screening method.

Although there have been signs recently of some changes taking place, the general idea which many people hold is that Phase I comes one step before Phase II; consequently, they do not consider Phase I as screening. In other words, the assumption is that dosage form used for Phase I should be close to the final formulation. Again, when we say that we use animal models for screening, some of our critics ask: are you developing a drug for animals?

The third point regarding the human dosage form in Phase I study is the possibility of estimating absolute bioavailability. This is not part of the requirements in Japan. However, if we want to develop our products in Europe and the United States, then we will have to submit data with regard to absolute availability.

Earlier, I referred to GI tract motility, and here I'd like to talk about the results of a study which we carried out, using a Teflon-matrix tablet (*Figure 7)*. The aim was to estimate GI tract motility by making relations to tableting pressure.

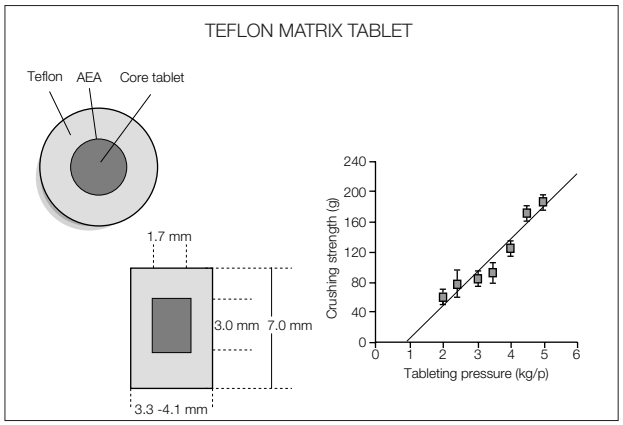


Figure 7.

To do this, we first coated the tablet with Teflon by compression, then we applied pressure to the outer layer and measured the crushing strength involved (the destructive force which I previously mentioned).

We then administered the tablets to beagles and humans, at a range of different crushing strengths. The results are given in *Figure 8*.

You can see the crushing strength is greater in beagles than in humans. The open circles present

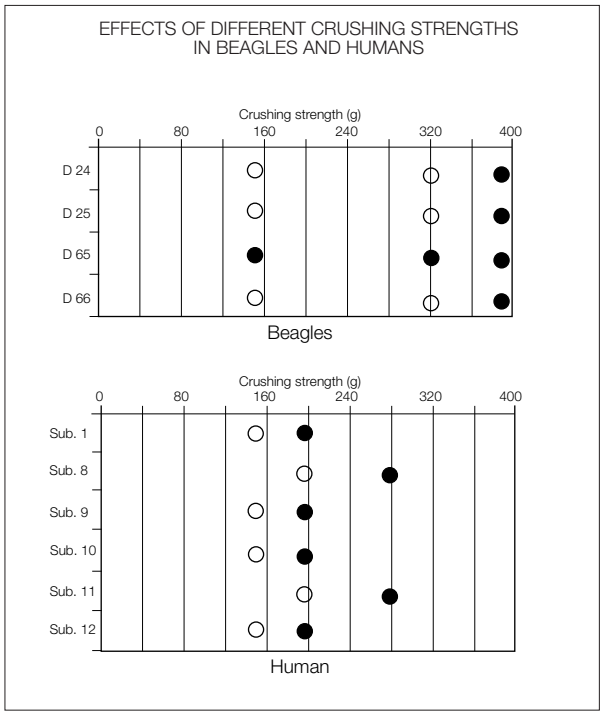


Figure 8.

the tablet breakdown, which was supported by the drug found in urine. Beagles are capable of breaking down even 320 g, although at 400 g the tablets remain intact. But in humans the maximum breakdown level is about 170 g, with a range of between 160 and 240 g. So I think there is a big difference in terms of crushing strength between humans and animals, and for human application we have to take that into consideration.

Bioequivalence study for formulation change during clinical study (1)
- Formulation changes: inevitable!!
- Dosage?
- Blindness vs easy identification

Table 12.

Earlier in my talk, I mentioned the bioequivalence study for formulation change during clinical study and stated that there are formulation changes during the development phase. In fact, these are inevitable because dosage is still being finalised, and the formulation has to change in line with dose changes. Blindness must also be assured during the development phase. On the other hand, once it is marketed the product has to be easily identifiable.

If we take the example of hypertensive drugs, where the usual final dosages are 5 mg and 10 mg. In fact, a range of doses — 2.5 mg and others — will have been tried out during the development stage. From Phase II onwards, the development scientists have to have a clearer idea, and for Phase III they have to be identical to the market image and to differentiate the size of the tablet, so that it is clear which one contains 10 mg, and which 5 mg, for instance.

During development, the western nations tend to use tabled-filled capsules in order to ensure blindness. But this is not the case in Japan, so we sometimes find we have identified different formulations which are actually the same.

Bioequivalence study for formulation change during clinical study (2)
Effective guide line
Approval of partial changes in approved items [Notificate N° 452, 31 May 1982 (partially revised, 18 July, 1988)]
Proposed guide lines
Approval of partial changes in approved items Bioequivalence study for different dosage
SUPAC-IR: guidance for industry
Immediate release solid dosage forms scale-up and post approval changes [Federal Register Vol. 60 (N° 230), 61638]

Table 13.

So what should be the basic rationale for formulation change in the course of the development-stage dose changes? The first guideline on the approval of partial changes in approved items was issued in 1982. It is currently undergoing revisions which will bring in proposals soon.

The proposed content is very similar to the comparable sections in the SUPAC guidance. But this is about approval of change at the post-approval stage — and, as Dr. Lesko stated, it is the changes at pre-approval stage which are actually more important for us engaged in R&D. How can we deal with these?

The US Food and Drug Administration plans to release new guidance on pre-approval changes this autumn, and we are greatly interested in the content. At this moment, there is a move towards global harmonisation in a number of pharmaceutical areas, and this leads us to expect that the new guidance will contribute to harmonization.

This concludes my talk about bioavailability.

I would now like to discuss the improvement of compliance. (*Table 14*)

Improvement of compliance
Gentle to the patients
- Taste masking
- Shape, size, hardness
- Direction
- Rapid disintegration in the mouth w/o water
Easy to handle at dispensary
- Easy to handle
- Easy to identificate
Stable in auto-dispenser (one pack dispensary)
- Stable at primal package (PTP sheet)

Table 14.

At first, let's focus on the gentleness to the patients. Granules or fine granules are popular dosage forms here in Japan, so the bitterness of the bulk has to be fully masked, and this is one of the big challenges for us. Products should also be of a proper shape, size and hardness. It is also important to reduce the frequency of administration from tid to bid and then once a day. Various pharmaceutical companies are competing in developing ways of producing rapid disintegration in the mouth without water, as this is a formulation that the public has readily accepted.

Then there is the aspect of improving ease of handling at the pharmacy. Products need to be easy to handle, easy to identify and stable within an automatic pack dispenser. These days, several different drugs are provided in one package, so drugs must be stable stored in an auto-dispenser. It can also be very difficult to maintain optimum storage stability at the dispensary when the air conditioner is switched off at night and the temperature or humidity rises. We really want to make use of a reliable automatic dispensing system, but this may mean taking the responsibility for ensuring that the dispenser, and the temperature control, are operating in optimal conditions.

Figure 9 illustrates different ways of taste masking, by powder coating, waxing, wax spray or granulation. The graphs indicate the time to dissolution in minutes which each method involves. Powder-coating granules, for example, do not disintegrate in the mouth but only disintegrate and dissolve after it enters the stomach. These are the kind of ap-

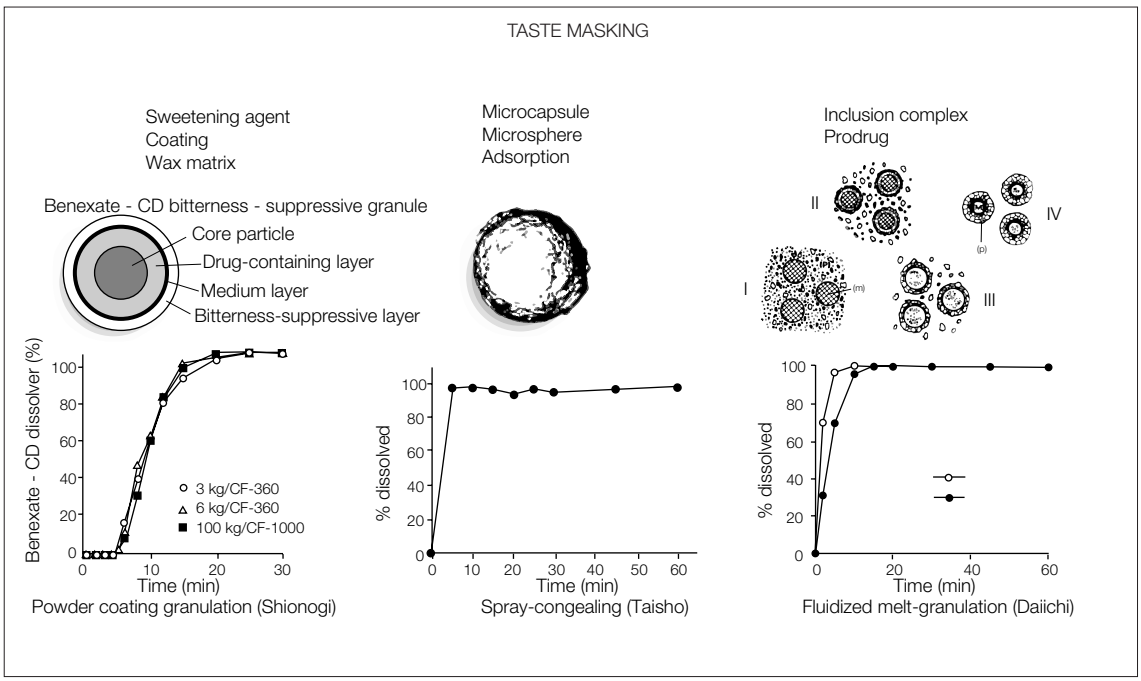


Figure 9.

Expert system for capsule formulation proposed by Prof. M.J. Newton
1. Physical & pharmaceutical properties
- Dosage, particle size, particle shape.
- Solubility including SUPAC classification
- Wetting properties, adhesion properties
- Melting point, powder bulk density
2. Information about compatibility/stability of the drug with respect to
- Excipients
- Moisture sensitivity
- Hygroscopicity
3. Excipient default list-user acceptance
4. Densification
- Granulation
- Granulation techniques available/acceptable
- Possibility of use of organic solvents
- Acceptability of solvents
- Acceptability of binders
- Incompatibilities/stability
- Moisture sensitivity in the terms of granulation
- Compression
- KAWAKITA-model
5. Miscellaneous
- Filling machine type
- Restriction of capsule size
- Restriction in maximum capsule fill weight

Table 15.

proaches under consideration as methods for improving taste. The development process is very complicated, however.

Computer application is the topic these days, and *Table 15* shows the input package list for the expert system for capsule formulation which Professor John Newton of London University has proposed. Professor Hashida's group is working on the evaluation of formulation design and also studying the possibility of using this expert system. As far as I know, the system is rather effective.

If the drug is not very complicated then there is some possibility that we can utilize Professor Newton's proposed system, but at this moment there are some differences in preference in excipients from one country to another. Professor Hashida's group is studying this point as well. Their findings are expected to be released very soon.

Thank you very much for your attention.

Professor Hashida: Thank you very much, Dr. Kusai. This concludes all the presentations.

Panel Discussion

Tokyo, Japan
July 15, 1997

Panel Discussion Tokyo

Professor Hashida: We are now moving into the last leg of our programme. We have heard the presentations and we will now have our panel discussion.

First, I would like to introduce the three specially-invited experts who have joined us here on the platform. They represent academia and the industry and also have an understanding of the regulatory issues involved. I will begin by asking each to speak for about 10 minutes, to give us their comments and opinions on the issues that have been discussed today, as well as any additional information that they may have. So without further ado, I would like to call upon Professor Sugiyama of the University of Tokyo, to put the academic viewpoint.

Professor Sugiyama, *Department of Biopharmaceutics, Faculty of Parmaceutical Sciences, University of Tokyo:* Professor Amidon, Professor Dressman, Dr. Lesko, thank you for your presentations. If I may, I would like to represent academia through my comments and questions. Broadly, there are three main points, which I would like to take up one by one.

The first comment concerns Professor Amidon's talk about predicting absorption in humans. Thank you very much — we now know it can be done successfully to a certain extent. My own department is working in a parallel area, on the prediction of first-pass hepatic metabolism. Hopefully it will be possible in the near future to integrate this with the work on gastrointestinal (GI) prediction, so that ultimately it will be possible to predict bioavailability. I would like to comment on how this might come about.

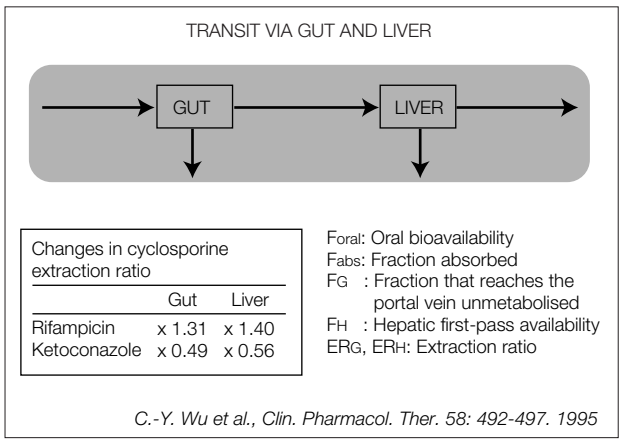


Figure 1.

As you know, drug comes into the GI tract, passes through the gut and liver and then is eliminated in the circulation. So first-pass metabolism is not just a function of the gut, but of the liver, too *(Fig. 1)*. *Figure 1* shows an example using clyclosporine.

Here I want to show you our study on a compound from Yamanouchi, YM796. I will not go into the details, but it is a preclinical study, where bioavailability is determined by changing the dose *(Fig. 2)*. From the slide, you can see that a low level

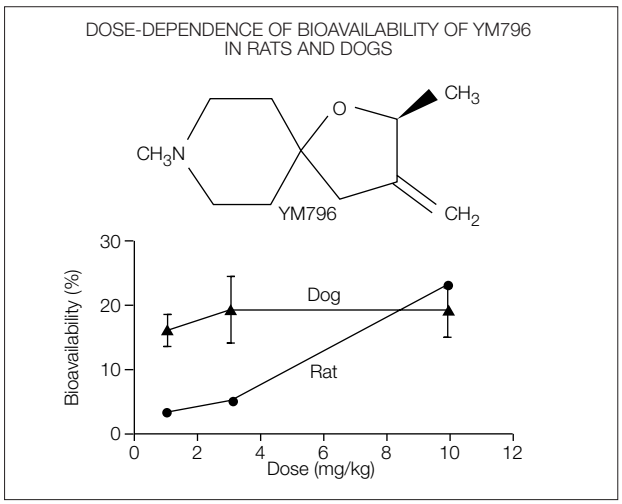


Figure 2.

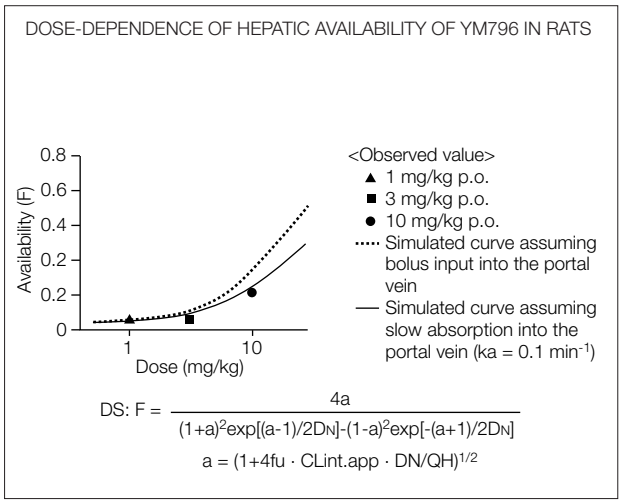


Figure 3.

of bioavailability was detected in rats at a low dose, while the overall results produce a non-linear progression. When kinetic analysis is carried out, it is clear that this low bioavailability does not represent poor GI absorption but is due to extensive first-pass hepatic metabolism.

What happens when we obtain this kind of result? Should we go forward into the clinical phase? It's an important question, because if there is low bioavailability in the clinical phase, there could be individual variations and that would be a problem. So we are now going to look at the possibility of predicting bioavailability through using microsome data for humans, dogs and rats.

Again we shall not go into the details, just use the dispersion model as such to track the dose-dependent changes in rats. The simulated curves shown in *Figure 3* represent the predicted values, calculated by partial differential equation. Using this approach, you arrive at a constant for an adequate GI absorption rate, from which dose-dependent bioavailability can be predicted to quite a successful degree.

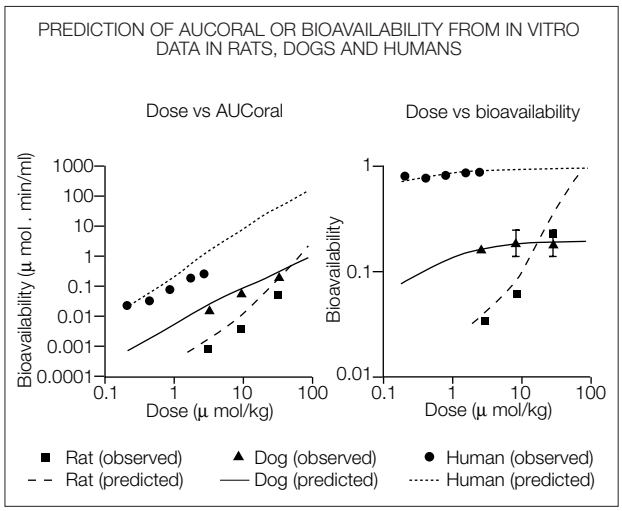


Figure 4.

The observed bioavailability in humans, dogs and rats, based on oral administration using microsome alone, is shown in *Figure 4*. If you compare the two — the predicted model and the observed data — the results for drug dose and biovailability are very high in humans. In other words, they are very close to Class 1 of the biopharmaceutical classification system, and can be predicted very well from the *in vitro* data.

I am not going to show you it today, but a similar prediction has been carried out using a cytochrome P50 isosyme expression sytem, where a similarly good prediction is achieved. GI absorption prediction of the type described by Professor Amidon and Professor Yamashita could be integrated with this, and I would like to ask for their comments later.

I'd like to comment on the clarification of species difference in GI permeability. Perhaps because of time constraints, Professor Amidon did not go into the species differences as much as he might have done. But I did see such data at a meeting of the Drug Delivery System Society and Professor Yamashita did touch upon species differences. I would like to comment on this area, since it could

become a big issue in the future, especially when carrier-mediated transport is present.

With regard to the influx process, the roles played by amino acid, glucose transporter, monocarboxylic acid transporter — which Dr. Tsedidas has worked on — and anion exchanger are already well known, as are the roles of MDR or MRP transporters. The species difference in these are important issues that will have to be addressed in the future.

Professor Amidon does have data, which I have seen, that includes carrier-mediated active drug transport in rats and humans, and there has been correspondence about this. We may have problems in the future with drugs transported by cell-surface carries in terms of species differences, and we will need to establish which types of transport media do not present a species difference. I think that kind of research will be required in the future.

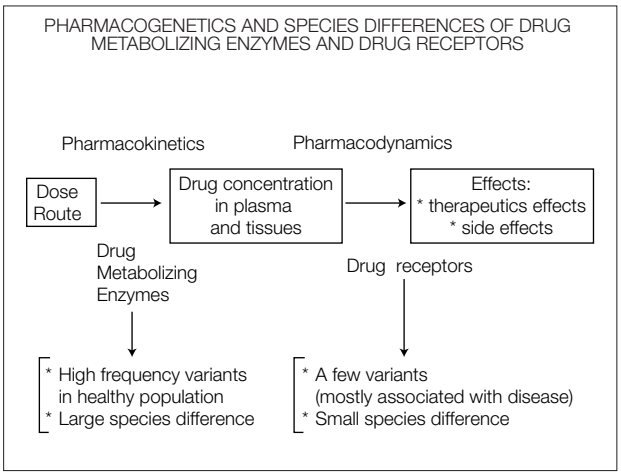
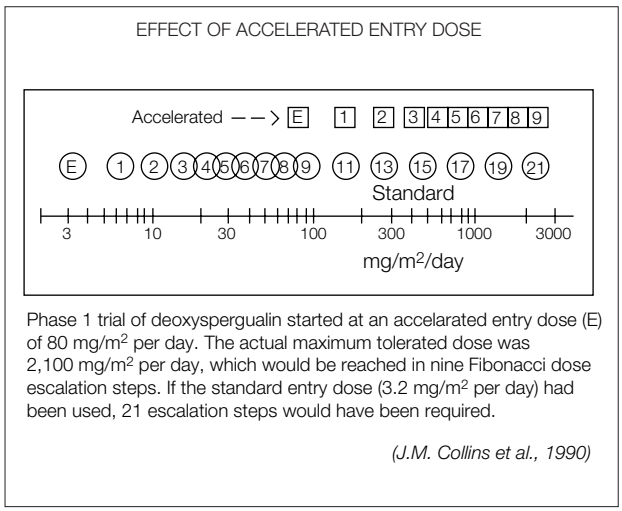


Figure 5.

I am sorry that *Figure 5* is complicated. It is one that Dr. Kalow of Toronto University presents. It represent the concept of asymmetrical pharmacogenetics. What it is trying to say is that drug receptors have small species differences whereas drug metabolzing enzymes produce larger species differences, and in order to argue this he is using Darwinism, or evolution of the species.

In vital protein species, where gene penetration is low, species difference is also low, while for enzymes like drug-metabolising enzymes, which are not vital, there is a large species difference. That is the argument. If that is the case, the species differences may be small for peptides transporters, because it is vital for the life.



Phase 1 trial of deoxyspergualin started at an accelarated entry dose (E) of 80 mg/m^2 per day. The actual maximum tolerated dose was 2,100 mg/m^2 per day, which would be reached in nine Fibonacci dose escalation steps. If the standard entry dose (3.2 mg/m^2 per day) had been used, 21 escalation steps would have been required.

(J.M. Collins et al., 1990)

Figure 6.

Last, but not least, my third comment. In the future there ought to be a method to predict non-linear GI absorption. If dose is escalated in the clinical phase of new drug development *(Fig. 6)* the non-linearity in the GI absorption makes the dose-escalation very difficult. It is because the drug concentration in the plasma and AUC is not proportional to the dose in such cases.

If this profile could be predicted, it would become critical to clinical studies. However, although I think the theoretical framework has now been established, a quantitative method has not. We do not have, for example, enough information about transit time, or the longitudinal distribution of a drug enzyme, or about how to predict the kinetic parameters. With so little information available at this point in time, how do we cope with this issue? I would appreciate it if Professor Amidon or Professor Yamashita could give their comments on this.

Dose escalation will produce an AUC when the drugs tested have the same toxicity between mice and humans, and *Figure 7* shows the results with anticancer agents in mice and humans. There is a cluster result with type I drugs, while type II show no correlation. This picture is not confined to anticancer agents.

All in all, then, it would appear helpful to accelerate the dose-escalation process, to establish a target AUC, and to approach the target AUC effectively *(Fig. 6)*. Ways of achieving the effective targeting of AUC are important, and hepatic clearance, GI absorption and other non-linear predictions could be a very useful methodology in the future. As far as I know there is no such methodology

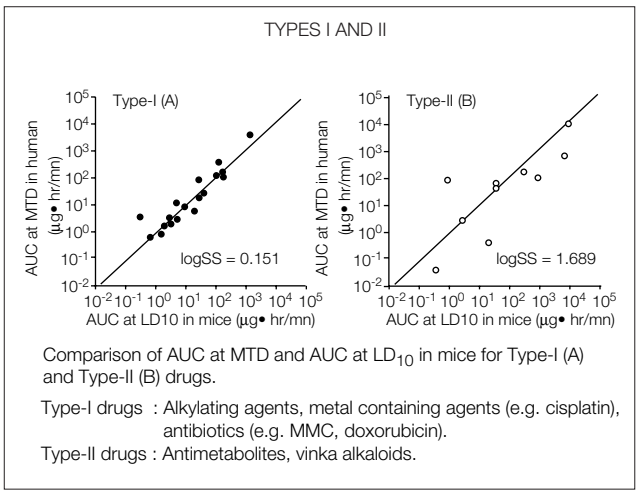


Figure 7.

as yet. I hope that all of you looking into the study of the GI tract will address these issues, too.

These are my comments and my questions.

Professor Hashida: Thank you very much. We would now like to hear from the industry. Our commentator is Mr. Norio Ohnishi from Fujisawa Pharmaceutical Company, who is an expert on regulation and is interested in globalisation issues as well.

Mr. Ohnishi, please.

Mr. Norio Ohnishi, *Director of Technological Development Laboratories, Fujisawa Parmaceutical Company*: Let me first express my gratitude for being invited to take part in this meeting, and also to Professor Amidon and to Capsugel for arranging the meeting. However, I am less well organised than Professor Sugiyama and have not prepared any slides.

Over two-thirds of the participants here today are from the pharmaceutical industry and associated companies. Therefore, I would like to refer to matters affecting pharmaceutical development activity, and to talk from the perspective not only of corporate research but also of international harmonisation.

Needless to say, the biopharmaceutic classification system (BCS) is important. Professor Amidon has told us about the rationale behind it, and about how the scientific basis of SUPAC-IR emerged from the BCS thanks to the efforts of the Food and Drug Administration. As far as SUPAC-IR is concerned — scale-up and possible changes of immediate-release oral dosage form are important matters, not only overseas but also in Japan.

Under Japan's current regulations, the full-scale manufacturing approval process requires validation predictions to be made. Auditing must also be carried out, and the industry is expected to show it is making efforts in this direction.

But on the question of guidelines, the reality is that we do not have guidelines in Japan comparable to those of the FDA, and we need to study them, implement them, and also prepare our own.

In common with previous speakers, I share the hope that the application of the SUPAC guideline will be extended to the pre-approval stage. I think Dr. Lesko mentioned that this is likely to happen this autumn, and that by the end of the year a further reference will be issued.

Anyway, if the pre-approval stage can be brought in, it will make the guidance even more important, particularly if it extends further back down the development line, to the preparation of the new drug application (NDA). This will inevitably produce various issues in the scale-up and process development phases that will have to be dealt with, such as the need to install appropriate equipment.

But if SUPAC is extended in the near future, it will be greatly appreciated. I hope it will happen: a guideline covering pre- and post-approval will be of great use to us.

If I may make a further comment during pharmaceutical development, in the course of changing the processes and formulations, we need to establish an *in vitro/in vivo* correlation. If there is one, we can work to it for the purpose of demonstrating bioequivalence.

Unfortunately, reliable *in vitro/in vivo* correlation is very difficult to establish. So this is why the biopharmaceutical classification system which Professor Amidon has proposed — the perspective, the philosophy, the approach based on the BCS — is indeed a significant scientific rationale for our activity.

Furthermore, if we look at this from the perspective of international harmonisation, pharmaceutical development in Japan has been growing significantly, particularly in recent years, and now needs to be moved on to a more global plane. This is the reality that most of the pharmaceutical industry and related companies in Japan can see.

At this juncture, the SUPAC guideline on immediate release oral dosage form is the forerunner of more to come from the guideline research and development activities going on in the US. Work on SUPAC-MR (modified release), SUPAC-SS (semisolid dosage forms), and also SUPAC ER (extended release) is either planned or already under way.

The work is not confined to formulations. Possible changes for bulk actives are also being considered, I hear, not only in the United States but also in Japan and Europe. If we can develop this draft guidance as a sort of tripartite harmonised guideline, it would be of great advantage to us. It is even a necessity, in view of the increasing trend towards global development, and will help us to make a stronger impact on international decisions in the future.

We need to consider how to bring together the overlapping areas of pharmaceutical process controls and pharmaceutical manufacturing, and we need to work towards a truly harmonised international guideline. Perhaps ICH, the international conference on harmonisation, could be utilized as an international forum for deliberations on these matters, and maybe SUPAC-IR will start us off in that direction.

But a real internationally harmonised guideline would be of great value to those working in the pharmaceutical industry and we will, of course, gain future benefit from such a guideline. I indeed look forward to the time that it will be to hand. That's my general comment.

If I can have one or two minutes for a further comment. Dr. Lesko explained that the SUPAC-IR guideline is formulated for an inventor drug, for application at post-approval stage. But there was a slide about the post-approval stage for generics which included reference to an abbreviated new drug application (ANDA) alongisde the NDA reference; next to NDA was listed ANDA post-approval change, suggesting that this falls within the range for generics. Were you referring to this as a possibility, or saying that it is already in force?

If that is the case, there would be a huge lag between the *in vitro* demonstration of the inventor drug's clinical efficacy, and the generic's post-approval change. So the question is, how applicable is this? It is something we need to discuss, particularly in relation to generic drugs.

My next point concerns Dr. Lesko's reference to level 2 changes within the SUPAC-IR guideline; that is, the likelihood of performance defects, and so on. Such a change would have an effect on the formulation quality. In relation to that, HP/HS dissolution of 50 per cent in 15 minutes is indeed very quick solubilisation.

I would suggest that a special process was used, since it takes up to 30 minutes for propanolol and metoprolol to reach 85 per cent dissolution. So I was wondering whether this part of level 2 will be modified to take this on board.

I may not have fully grasped the point you were making, so I would like to ask for confirmation. Thank you very much.

Professor Hashida: Thank you very much. Now I would like to ask Professor Watanabe of Nagoya City University to give his comments. He is here representing academia but also has a background in regulatory-related matters and development-related issues. Professor Watanabe, please.

Professor Watanabe, *Department of Biopharmaceutics, Faculty of Pharmaceutical Sciences, Nagoya City University:* Thank you very much for your kind introduction. I too would like to express my heartfelt thanks for being invited to this important symposium. I have been listening to the lectures since this morning and have learned a lot.

I am very happy to give you some comments.

Professor Hashida introduced me as a person who is well experienced in this field. At the Japanese pharmaceutical company I worked for, I was involved in new drug development for about 12 years, so the biopharmaceutical classification system seems very attractive to me.

The bioavailability and bioequivalence tests carried out in Japan are burdensome to many pharmaceutical companies, and I really hope that the BCS will lighten this load on the industry. I am very interested in the issues related to BCS and would like to see it working effectively.

In the course of my career I moved to Nagoya, where I served as head of pharmacy at the University Hospital for about five years, and so I fully appreciate the position of the end-user. I also worked as head of a pharmaceutical development team for about eight years, so I think that I can represent a broad range of interests. Let me make a few comments based on my experience.

The concept of BCS is aimed at simplifying the complexity of bioequivalence and bioavailability testing. This makes it very useful and very important. This being said, as a second point I would like to make two further comments, both related to variation.

AUC or C-Max are used in the evaluation of both bioavailability (BA) and bioequivalence (BE). However, in actual practice, when using AUC or C-Max we have to consider fully intra-individual or inter-individual variations, which seem to be closely related to the usability, efficacy and safety of the two indexes.

This would seem to be a further arena where the BCS could be valuable. In other words, we have to take variability into consideration when looking to expand the future use of BCS as a classification system. Permeability and solubility also seem to be very important factors.

The classification system should also take on board the fact that we use AUC and C-Max which are influenced by metabolic elimination.

Depending on the case — for instance, with highly accumulative drug products — some would argue that steady-state measurements are a good route to establishing the BE or BA. But this only works when accumulation is high and eliminated slowly owing to a rather long half-life.

So there is room for some kind of regulation to be applied where drugs with certain elimination characteristics are concerned. If so, pharmaceutical companies' burden will be lessened.

With regard to metabolism, of course absorption through the intestinal walls has to be considered, as well as the liver uptake. First-pass intake as well as intra-individual variation should also be taken into consideration, and the role of cytochrome P450 needs further study.

But I also think that SUPAC should cover additives. In the case of changes to the additives, then the SUPAC concept could be applied, and depending on the type of additives changed, it should be possible to omit some kinds of test.

I think that an extension into additives could make SUPAC — or rather, I mean the BCS — more effective in alleviating the burden on pharmaceutical companies.

I would now like to put forward a personal proposal. From the various opinions I have heard today, people seem to find it acceptable that the bioequivalence test is not required for high-permeability, high-solubility drugs, nor for soluble drugs.

Yet many would agree that the high-permeability, high-solubility type of drug is affected by the gastric-emptying rate — and it is well known that the gastric-emptying rate is affected by various factors, and so may be an important cause of intra-individual or inter-individual variation.

Do you think that to develop a drug by controlling dissolution is actually good for patients? If so, should it be categorised as pseudo class 2?

I am suggesting this as a possible idea, and would like to hear your comments on my proposal. Thank you very much.

Professor Hashida: Thank you very much. We will now move on to the panel discussion.

Having heard the proposals, questions and comments made by our three specially-invited experts, perhaps we could start by expanding on these. I would first like to call upon Professor Amidon, since several questions have been addressed to him. Would you start off the discussion?

Professor Amidon: I think the questions were addressed to me and to others, so I will bring in their help as we go along. I am not sure we will answer all of the questions, because I want time for audience questions. I will go through the important questions as I understand them from listening to the presenters, taking each speaker in turn.

First, Professor Sugiyama. I think that I agree with all of his comments. I think the possible need for correlations that are based on transport pathways or transporters when we are looking at animal to human, tissue culture to human, is essential. It will be essential to have mechanism-based correlations.

I believe the mechanisms of oral drug absorption are becoming much more understood but much more complicated, and there will be many advances in the future. So I think we cannot answer that question very well today.

In our studies at the FDA we have looked at very few carrier-mediated compounds in humans, so we have very limited data right now, based on only three compounds — alphamethyldopa, L-dopa, and a current study on cephalexin. I think that's it. So I hesitate to generalise.

Regarding non-linear absorption, that is extremely complicated. We view the reference permeability as just that — a reference permeability. The permeability probably should be determined at the low and high concentrations that you expect in the intestine, and perhaps *in vitro* studies or tissue culture studies can give you a good idea of whether non-linear absorption is important.

For many drugs, I think it is not too important, even though it may be one of the selection criteria we have for developing drugs. But I think that the non-linear absorption would be more complicated to predict and it requires further research. I guess I would like to have Professor Yamashita comment here.

Professor Yamashita: The question from Professor Sugiyama has been basically answered by Professor Amidon and I do not know if I can add to that, other than to say just a little on non-linear absorption. How far is the extent of bioavailability significant? Peptide transporters such as cephalexin and other drugs have a large capacity, as you all know.

When peptide substrate is present in large volume after a meal, absorption does not noticeably decline, and this applies when a drug dose is taken in a normal situation. Of course, in an *in vitro* experiment there would be saturation. But passing through the GI tract in the normal way, the full amount will be absorbed, although there might perhaps be a slight slow-down in the absorption rate.

We are talking about high-capacity peptide transporters and so far as the extent of bioavailability is concerned, I see no problem although, as Professor Sugiyama pointed out, we do have to look into the roles of influx and metabolism. I do agree that there ought to be more studies in these areas.

Professor Amidon: Next I would like to take the presentation by Mr. Ohnishi, and I think his questions were mainly directed to Dr. Lesko, regarding the SUPAC implications for generic drugs. He also referred to the time-standard — the 15-minute dissolution time-point — as being quite stringent and asked whether it could be relaxed to perhaps 30 minutes. So I think there are two questions here. Can you comment on that?

Dr. Lesko: Thank you. I think Mr. Ohnishi raised some excellent points in his commentary. I was happy to hear that our efforts in developing these guidances were well received, both scientifically and from a regulatory perspective.

When we first developed the SUPAC-IR guidance, we tended to be conservative because our database upon which the classification was based at the time was limited to perhaps 15 drugs from a permeability perspective and only six drugs in terms of the manufacturing research. So we tended to be a little conservative, partly because the database was limited by the small numbers of drugs.

This was a major step for the agency and indeed I think we have grown more confident, after seeing some supplements under the SUPAC guidance, that this dissolution specification for class 1 highly-soluble, highly-permeable drugs is in fact very conservative.

The question remains, however, what should that standard be? Our attempt to answer that is really part of the simulation work that we are carrying out at the agency. By simulating different gastric-emptying times and also simulating different percentages of dissolution over various time-frames, we are beginning to see what the sensitivity of the specification is with respect to comparative C-Max values. We're applying this especially to the C-Max values, since the impact on the extent of absorption is really negligible in terms of the specification.

So my anticipation is that in the revision of the SUPAC-IR guidance which we are about to begin, I can imagine a relaxed standard for highly-soluble, highly-permeable drugs, based on additional experience. I do think we can do better, and still maintain product quality for this class of drugs.

I should indicate, however, that the process of changing the SUPAC-IR guidance is probably not going to be complete by autumn 1997. I want to make sure that we do not over-promise on when we will complete this work, but it will most likely move on into 1998.

We are just beginning that revision and also as part of our revision of the SUPAC-IR guidance we are discussing the application of the principles of the guidance to the pre-approval period. We really do not see any valid scientific reason not to apply SUPAC's principles to pre-approval, so I expect that we are also going to look seriously at making that change in the second edition of the SUPAC-IR guidance.

Professor Amidon: Thank you, Larry. Mr. Ohnishi, do you want to comment?

Mr. Ohnishi: I have nothing special to add at this juncture, thank you.

Professor Amidon: I agree with what Dr. Lesko said, and that there are two areas that need further consideration in the very near future. One is the dissolution standard, the time to dissolution standard that will ensure bioequivalence. The other is the solubility definition, and the levels for high and low solubility — we have many pH-dependent drugs which are well absorbed and bioequivalent, and we need to capture a more relaxed solubility definition also.

I think we will see something about these matters in the BCS document in the next six months to a year, maybe by the end of 1997. But our first step is to be very conservative and then see — following input and comment, especially from development scientists — whether we can relax the guidance and arrive at a good documented validatable standard.

The third speaker, Professor Watanabe, has been a friend for many years and I very much appreciate his questions and comments.

His point, as I understand it, was that AUC and C-Max are probably the most important factors for arriving at the BA — bioavailability — and that bioavailability prediction is a bigger problem than the bioequivalence problem, yet the classification system has focused mainly on bioequivalence.

Extending the classification system to require additional metabolism and clearance data for the purpose of bioavailability prediction, I think can be extremely important for industry. But I think it is a slightly separate issue. We need the two components here, because bioavailability prediction I think is harder.

Regarding your comment on variability in gastric-emptying, I also very much agree with that. The studies on the bioavailability of propanolol, for example, which we did using propanolol immediate-release, averaged only about 20 per cent — they were hugely variable, because of variable gastric emptying. Therefore, presumably it is a drug with a wide therapeutic index and you can argue that that is not a good formulation, we should reduce the dissolution rate in order to reduce the variability because emptying variability is about 10-fold.

I think those are very important extensions for the industry and for drug product quality development, but we are not focusing on that in the bioequivalence regulation per se. Do you want to comment?

Professor Watanabe: No comment.

Professor Amidon: With that, I would first like to ask if any panel members want to comment... The discussion is now open to the floor.

Professor Yamashita: I have a question for Dr. Lesko. Well, you work together with Professor Amidon on the BCS, and you have Caco-2 cell systems data available to you. Do you think that there is a movement within the FDA towards using more data on Caco-2 cell monolayers?

Professor Amidon: An interesting question. I think the agency is looking favourably on the Caco-2 cell data from the standpoint of both applications that contain information using this model, as well as the research which Professor Hans Lennernäs has conducted at Uppsala.

My sense of all the data — and I know there have been some questions about mechanism of absorption relative to the value of Caco-2 cells — is that there seems to be a general agreement that, with passive diffusion, these cells look very good for predicting human absorption and permeability.

The problems come in with carrier-mediated and also paracellular absorption, in which the cell systems tend to underestimate effective human permeability. I saw some data at the Edinburgh conference recently which show that the correlation between Caco-2 and human permeability can be improved by the introduction of some scaling factors that would take into account the type of junction between the Caco-2 cells in the monolayers as well as the underdeveloped transport systems in these cells. So it seems like there is some potential here. To my mind, it's probably one of the more unresolved issues in this area.

But I hope before we come forth with the guidance on the BCS at the end of the year that we reach a little more clarity on this issue and are able to at least articulate for the industry what the current thinking is on the use of these cell systems, because clearly we need to have some well-established surrogates for human permeability.

Dr. Lesko: I will comment. In Professor Yamashita's presentation he made a very strong point about establishing validation procedures for tissue culture approaches and I agree that this is absolutely essential. But it will be difficult to achieve.

At the present time the biopharmaceutic classification guide, the BCS guidance, states that human data are not required to classify your drug — reflecting the fact that it is not so simple to develop a validated approach.

You would have to have a validated system correlated to the human database that we are developing at the FDA. There are many different laboratories and cell lines in the field, so the development of a validated approach is going to require considerable work and scientific input.

Nevertheless, the committee fully believes that it is possible for a significant number of drugs, but it is going to take some considerable effort and input to decide on a suitable validation approach.

Professor Dressman: I would just like to comment on the validation approach. The way that we validate our *in vitro* technique, which is actually an intestinal ring technique, is to use polyethyleneglycol 4000 as a negative control, mannitol as a marker for paracellular absorption, hydrocortisone as a marker for passive absorption, and 3-0-methylglucose as a marker for active absorption. I think that as long as we choose a range of compounds that can reflect the different transport mechanisms, and also include a negative control, that might be an acceptable approach.

Professor Amidon: I agree, and that is the approach we are looking at. We have a possible group of about 10 marker compounds. We are considering using marker compounds that are absorbed by the different mechanisms as we understand them today — paracellular, carrier-mediated, peptide transporter, amino acid transporter.

I am not sure what the selection will be, but several of the compounds you mentioned will be candidates. It may be that we would say: two of your control compounds should be selected from list A, one from list B, and so on. That type of approach will be essential.

Professor Hashida: With regard to Caco-2 related issues at the Edinburgh conference, I heard a presentation describing the validation work that is necessary in order to establish standard cell lines, and it appears that there are some groups working towards these goals in the United States. Do you know whether there are any groups moving towards establishing a standard method, Professor Amidon?

Professor Amidon: There is nothing at an official level. Of course, various companies, including some small ones, are trying to establish screening systems that are correlated with appropriate reference compounds for predicting absorption or permeability.

I am sure that the line that the FDA guidance will take will be to set a validation approach and leave it to the individual company to decide how it wants to generate that data. That is our current thinking. So if the companies you mention are developing a standardised approach, that would be very suitable, but other approaches would also be accepted. Larry, would you comment?

Dr. Lesko: Yes, I would agree with what Professor Amidon said. I am not aware of any widespread organisation or group trying to develop standards and validation of the Caco-2 cells.

The view we take at the FDA with the guidance is we try to emphasize the information that we want to get out of the test or out of the experiments, without prescribing a 'how-to' approach, or a basic set of instructions. So we tend to emphasize the value of information, and also the performance characteristics of the system that is producing the information.

So I expect that there will actually be flexibility in the way the information is generated, with the quality control built-in in the form of internal standards, as Professor Dressman and Professor Amidon have mentioned with the marker compounds, to get an estimate of how accurately the system is predicting the transport mechanisms.

I can also imagine a very similar validation to bioanalytical methodology, where estimates of precision and estimates of accuracy and so on might be utilized to try to gauge the quality of the performance of these test systems at the different sites.

So I believe it is a problem that can be resolved, although I think we do need to work together on the performance characteristics of the systems.

Professor Amidon: OK, I will make one comment, too. In support of *in vivo* studies, I would first say that the human jejunum is probably the gold standard — in order to do a human study you have to go through very rigorous protocol review and approval. When data based on a human study is submitted to the FDA they have been rigorously put through GLP, GMP and GCP procedures, so you

can look at a permeability number from a human experiment and know immediately what to conclude.

With other systems where there are more variables that can influence the permeability result, you will also have to establish a validation procedure, and that will take some more work and some more effort and we are at the early stage of a database for human data.

I believe that — if done carefully — animal and tissue culture methods can predict human results. But we still have very few data points and relatively few examples. So, for the foreseeable future we continue to need more human data; especially, I would say, if the compounds are carrier-mediated or if there is P-glycoprotein potential.

There are a lot of studies in tissue culture and in animals. There are few studies yet which really provide evidence on how important intestinal 3A4 and P-glycoprotein are *in vivo* in humans. They may be very important — but we need data, we need evidence, and that will take some time to establish. So I think *in vivo* human work is still going to be very important while we establish validated procedures for correlating with our database system.

Professor Hashida: We have time to accept some questions from the audience to any of the panel members.

Dr. Miyake, *from Fujisawa*: I am a development scientist working on final preparation forms. Today's discussion of biopharmaceutical science in terms of molecular was very informative to me, and based on that, how to evaluate a drug product was also interesting.

You talked about, Professor Dressman, *in vitro* studies, starting from the regulatory requirements and the bioequivalence approach. You then said dissolution can be simulated — simulated gastric fluid was a term you used — and you had a form and you said that 100 rpm was used and the volume held in a glass was different in Japan and the USA. And then, looking at BE from the patient's point of view, you said the in vitro dissolution test may contain something that is not a BE and that there ought to be a more sensitive detection method, like 50 rpm, which has become more popular today.

When Dr. Lesko was talking about the high-permeability, high-solubility classification, he said that whatever the formulation there will be no change in bioequivalence. However, if it is an exception to the class, or in a different class, if it demonstrates 100 rpm or some other rotation, a BE cannot be assured. Professor Dressman introduced some figures and perhaps 100 rpm was used, perhaps that was just a coincidence.

Now we have been exposed to this science, and I have a question to Dr. Lesko of the FDA. SUPAC introduces 50 rpm. Is this going to continue in the future or will there be changes depending on the situation? In the future, the focal point might perhaps move from apparent dissolution to bioequivalence considerations. If so, would there be any changes in the FDA approach?

Dr. Lesko: I guess the question relates to the next change in the SUPAC-IR guidance with respect to the stirring rate or the paddle speed or what have you. I don't know of any changes that we will be making in that area, the issue hasn't really come up and it hasn't been discussed, and that sort of leads me to believe that there is not any issue with what we have seen so far with the guidance.

So at this point I would have to say I really don't anticipate any changes there, although in the back of my mind I am thinking of another guidance, which is that dissolution IR guidance I mentioned and while I don't know off the top of my head, I believe there will be some further elaboration on the stirring speed and the media in that guidance. But it's not fresh in my mind to share that with you, at this point.

I do have a draft guidance with me and perhaps afterwards I can take a peek at it and see what is in there on the issue of stirring speeds.

Professor Dressman: Yes, I would like to make a comment on the question, also. I think an important question you raised is how accurately do the hydrodynamics in vitro resemble the physiological conditions.

Unfortunately, to date we have a lot of information about motility patterns, emptying rates and so forth in the stomach and in the small intestine, but no way have we really characterised the hydrodynamics in a pharmaceutically useful sense and likewise we haven't really characterised the hydrodynamics in the *in vitro* system till now.

At the moment, at the University of Frankfurt we are conducting experiments to look at hydrodynamics in paddle method and basket method, using the re-saturation of the medium with oxygen after de-aeration to study the hydrodynamics — how rapidly the system is stirred, and so how rapidly oxygen is brought back into the system.

Interesting to note in these experiments is that as you increase the stirring rate in the paddle system, you increase the hydrodynamic mixing as well, and so the effective stirring rate is a curvilinear relationship. With tbe basket, however, you don't really get any relationship between zero and 50 rpm and then there's a break, and then you get another flat response between 100 and 150 rpm, and then it starts to go up again.

So my feeling is that the basket method is particularly problematic in terms of trying to have reproducible hydrodynamics. It is very dependent on where you take the samples, as well.

So I think we have to characterise the in vitro system very carefully and then try to devise some methods for looking at this *in vivo* as well. One possibility here is to study *in vitro* hydrodynamics using ultrasound techniques. That should be theoretically possible.

Dr. Miyake, *from Fujisawa*: Thank you very much. As Dr. Kusai said, when I am studying new drugs, in the early stages of design preparation and formulation design, there is an absence of human data. The dissolution test has to be backed by scientific data, otherwise that makes it difficult for us to do our work, and I look forward to such scientific data on human beings in the future.

Mr. Mochizuki, *from Teijin:* I am Mr. Mochizuki from Teijin. Dr. Kusai and Mr. Ohnishi, my question concerning the SUPAC guideline is addressed to you.

I am involved in the clinical development of drugs, an area where the guideline is also important, as is the clinical trial. Dr. Kusai, you said that during clinical trials, changes in drug formulation do take place, and that during Phase I clinical study, bulk may be included in the capsule.

If the SUPAC guideline is applied to this situation, I think there is a level 3 change. A change of this magnitude would require validation of bioequivalence. So, as an approach during the clinical trial, how should we regard SUPAC? Is it considered as a reference, or should we take it as a regulation? Or does the approach differ depending on the phase of the clinical trial?

Dr. Kusai: To date, the thinking on SUPAC immediate-release is that it should be used as a reference, or for information. But, as I mentioned during my presentation, it is a post-approval guideline — which is unfortunate in terms of current Japanese need.

In the development stage, which includes clinical trials, there is no definite prescription to follow. So pharmaceutical development is faced with the question of how to deal with this situation.

Obviously, when the formulation changes, we have to know the volume or weight change of dosage form, and we need to bear in mind that although the key ingredients have not changed, the drug may have doubled in dosage, meaning that bioequivalence will change. Depending on the phase — I, II or III — changing the formulation after each phase will require a colossal number of BE calculations.

The most practical way to handle this could be to utilize the guideline up to early Phase II, knowing that at Phase III, or later, there will be a change of BE.

However, there could well be a need for drug modification around the time of late Phase II, most likely affecting minor ingredients rather than the key components. In the United States the guidance is intended for the post-approval stage.

Changes in formulation of class 1 drugs are clearly specified and a report is required later, but in the case of Japan, once the formulation is approved you cannot have a later change. If there is going to be a change, it will be post-approval of partial changes in approved items, and that is a different situation from US.

So we need to set aside what appears more rational to us in the Japanese industry, particularly in the earlier and later phases. Obviously the BE relationship will change although the ingredients would remain the same.

But as to what is to be applied at the experimental stage — whether BE will fall within class 1, or whether we could think in terms of dissolution — there is no specific procedure regarding that. And if we have a delay in the approval, this could really damage the company. So from now on, we need to be conscious of notifications from the authorities as part of the drug development activity. That is my personal view.

Professor Tsuji, *of Kanazawa University:* The presentations have concentrated on the BCS, and we fully understand its importance. The BCS is already important as far as BE is concerned, although it still needs to be developed so that in future it provides specific guidance on how to predict BA.

But in Japan, it is very difficult to carry out studies using humans, and therefore the focal point

of Japanese drug development at the moment concerns changes to class 1, 2 and 3, and the prediction of membrane permeability. Data from animal experiments are used to predict the human data, meaning that our predictions need to be made very specifically and clearly or we cannot predict permeability in humans.

Professor Amidon showed data indicating that human permeability is about 100 times that of the rat. That being so, our approach — of basing human permeability on predictions from animal data — gives rise to questions regarding the use of the BCS both at the preclinical stage and at the clinical trial stage. How should we look at the picture, how should we move forward? If you can comment on this aspect I would be very grateful.

Professor Amidon: In our laboratory the relationship between animal data — the rat, in particular — and humans, is actually almost one to one. The permeability for passive and carrier-mediated compounds in the rat jejunum is numerically identical to that in the human. For Caco-2 cells they are 100-fold less. So I think the animal data for permeability can predict human data very well.

In the guidance as we are developing it now, the classification system states the following: a drug can be classified based on fraction/dose absorbed. If the fraction/dose absorbed is greater than 90 per cent, it is a high-permeability drug.

One can determine fraction/dose absorbed in many cases from mass balance studies, results that are already available in pre-clinical development. So you can use your mass balance studies to determine fraction/dose absorbed. Probably mass balance studies, and maybe eventually the CMC data, might be enough to classify your drug.

Now, for some drugs mass balance is difficult because the drug goes all over the place. The guidance will probably require two or three pieces of information — mass balance and permeability in one or two animal and tissue culture systems. Eventually, as we establish the correlation between animal and human permeability, the animal permeability database will be the most important, I think. I emphasize 'eventually', as it still needs to be developed.

Meanwhile, because we do not yet have very many established correlations, we are basing our permeability on fraction/dose absorbed.

Dr. Lesko: I would just add to some of those comments because we run into this problem in the current situation with our SUPAC-IR guidance, where a firm doesn't have permeability studies conducted in humans and the question comes up, 'how do I classify the drug?'. Our reply is that you should develop supportive information that can come from a variety of sources, including the literature, or from studies that may have been conducted as part of drug development.

I can imagine supportive evidence being drawn from mass balance studies, or even discrete IV studies that may have been part of the Phase I dose-escalation studies, where actual absolute bioavailability could be estimated, and also from physical/chemical data that indicate a high permeability from measurements such as partition co-efficient.

I think we can also learn from past history with similar drugs in a given class, and build on a case-by-case basis the supporting evidence to call a drug high or low solubility.

Professor Dressman: I would like to raise a somewhat different concern about application of the biopharmaceutics classification system at the preclinical study level, and that is the classification of the drug into a high-solubility or low-solubility drug because, as you see from Professor Amidon's calculation, this depends on knowing what the dose is going to be. Unless you know what the dose is, you cannot determine what the dose number is.

This is a problem because when you are trying to determine what the dose in man is going to be, that's just an estimate and in speaking with people who deal with this kind of issue every day, the estimate may be out by a factor of 10 or even 100. This creates some problems in classifying a drug according to the scheme.

Would Dr. Lesko or Professor Amidon like to comment on that?

Dr. Lesko: I will comment, Jennifer. Clearly, if you need to guess, probably you could guess that 1 gram is going to be about the largest dose you are going to want to deal with, and today we heard that after 300 mg you have to go to multiple units and so Sankyo wants its doses at less than 300 mg. If you use 300 mg, you can then say, do I have a problem or not? Or do I have a problem at 3 mg or 0.3 mg?

The dose number calculation will tell you the range when you get into dissolution control and eventually into solubility control. Until you know the dose you can only say: in low dose we are OK, in high dose we are OK or we are not OK. So the dose number will change.

Our technical definition of dose number, though, is the highest strength, the dose used in the highest strength.

Professor Hashida: Last question please.

Professor Ogata, *Meiji College of Pharmacy:* I am Ogata from Meiji College of Pharmacy. Where a high-permeability, low-solubility drug can be well handled, the BE can be predicted by dissolution test and multiple conditions should be recommended.

But, based on my experience, in the case of a drug with low solubility, especially when solubility is extremely low, dissolution test data are not very reliable because they vary under the different physiological conditions. I have some doubts about their validity.

Surfactant can be added in some cases, to bring about a kind of dissolution. But these are artificial conditions. Is a resolution rate measured under artificial conditions valid?

This is my question. In a drug with high permeability and low solubility, I think some limit should be applied to solubility, but it should not be set at an extremely low level. Don't you think that we should set some limit to the low-solubility level?

Professor Amidon: I don't know if I would set a limit but I would agree that it is very important to have *in vivo* solubilisation and to reflect *in vivo* solubilisation in some way.

That is complex, but a number of systems that would include pharmaceutical lipid materials — bile salts, monoglycerides, fatty acids, emulsion systems — could be used to screen for solubilisation, and if your drug does not dissolve in anything, you should stop. No hope.

However, if it is soluble in some physiological-type solvents, then formulation can have a very big impact. If you have a very special situation, you may have to sample and do *in vivo* human experiments.

For example, in the case of the tube that we use for studying permeability, we collect the duodenal and upper jejunum fluid from a point above the proximal balloon, and we can evaluate either drug concentration emptying from the stomach, or we can evaluate drug solubility and precipitation right there in a human subject. If you have a very bad drug, human samples may be essential.

Professor Dressman: I would like to make a final comment about that. You mention that the addition of surfactants to the dissolution medium is an artificial system. Of course, we have native surfactants in the gastrointestinal tract: bile salts and lecithin. So the question is, how well do the artificial surfactants model the bile salt/lecithin effects on the drug?

They probably do not model bile salts-only effects on dissolution because bile salts form rather different micelles than do classical surfactants. Bile salt/lecithin micelles are a little bit more like the artificial surfactants in terms of their physical chemistry.

So I think there is a hope that by trying to look at the physico-chemical behaviour and solubilisation capacity of some different artificial surfactants, we may be able to come up with a useful surrogate system for *in vivo* conditions.

You also asked whether there is a case where the drug just has too low a solubility to be formulated orally and I would like to mention a couple of examples that I think are interesting. One is beta-carotene, which is an extremely lipophilic and extremely insoluble drug, probably less than one nanogram per ml. But this is a substance which we all know is absorbed from the gastrointestinal tract — though only when it is given with food, I have to say.

The second example is itraconazole. The intrinsic solubility of the free-base form is also less than one nanogram per ml and it is really only soluble below pH 1. This is probably not typical of gastric pH conditions for many people, you have to get down to about pH 0.2 for the dissolution to be good.

But through trying out different formulation techniques, Janssen managed to produce a formulation that is actually 50 per cent biovailable. The only reason that bioavailability is so low is that the drug undergoes first-pass metabolism.

So I would say that even if your drug has very poor solubility characteristics, it doesn't mean that you can't deliver it orally. You need to go to a special formulation, I guess.

Professor Hashida: Well thank you very much, I think that you might have more questions, but we are behind schedule, so I would like to conclude the panel discussion.

I would like to ask Professor Amidon to make the closing remarks.

Professor Amidon: Professor Hashida, I want to thank the participants for their comments, conclusions and support, as well as the audience for their comments and interest in the development of drug regulatory standards. I think today I feel that

the comments of the speakers and of the audience have been very supportive of this scientific forum for the development of regulations.

I think we are entering a new era in drug regulation in the US, Europe and Japan. The FDA's 1962 laws were formulated when our industry was actually fairly young, and now we have 30 years of accumulated knowledge that is in need of being incorporated into regulatory standards.

I believe that it is the scientific community — by which I mean academic, industry and regulatory scientists — that, through open discussion and presentations, can significantly impact world health in terms of the standards that we set. So I am extremely pleased with the interest of the pharmaceutical community in Japan and I look forward to future discussions, workshops and conferences, future interactions in developing international drug development standards, and I thank you for your comments and participation.

Professor Hashida: Let me add something. Today, we have discussed the biopharmaceutical classification system and we also had very extensive discussion on pharmaceutical absorption issues. I have actually nothing to add to the panel discussion, but I had a very, very good experience today, and there are two points I would like to make about that.

The first comment is — well, I think that I felt that this was a taste of American or Western culture. Every time people meet up, this leads to discussion, and out of this heated debate a system emerges, and people also get together to discuss possible problems with the established system. I think it is really an American approach that I experienced directly today, and I was very happy about that.

The second comment is related to something Professor Amidon said. Currently in the United States, at meetings of the American Association of Pharmaceutical Scientists and elsewhere, heated debate is going on between academia and government and industry, and here we are today, discussing such matters with those very representatives of the pharmaceutical industry.

Of course, we do have chances to discuss this kind of matter with regulatory people, but today we had a very valuable opportunity to listen to the opinions and presentations of those who are working at the forefront of these issues in the United States.

Lastly I would like to express my heartfelt thanks to our five speakers and to our specially-invited Japanese experts. Later, Mr. Daumesnil is going to make a few remarks, but I would first like to express my heartfelt thanks to Capsugel Corporation for giving us this kind of opportunity. My deep thanks go to Capsugel Corporation.

Professor Hashida: So this concludes the panel discussion. Thank you very much for your contributions, Professor Amidon and Professor Hashida, thank you very much. Now, as the representative of Capsugel Corporation, Mr. Roland Daumesnil is going to give us his closing remarks.

Roland Daumesnil, *Capsugel*: First of all on behalf of Capsugel I'd like to thank all our speakers and panel members for their contribution to this outstanding seminar on Biopharmaceutics Drug Classification system.

I also would like to thank you for your active participation as well as the translators who helped us to make this meeting a real two way communication seminar.

The format of this meeting with a limited number of speakers, a panel of experts from the industry as well as from universities permitted a frank and open discussion on this novel approach.

Since we started this series at Princeton in May 95, progress has been made. Not only in the number of participants from 60 in Princeton, 80 in Geneva, 100 here. But progress has been made in the fine tuning of the classification based on the participants' remarks and additional experiments.

As Professor Gordon Amidon mentioned at the beginning we are not only speaking about drug but also about the drug product which is the formulated product.

To make sure that all your remarks, comments and concerns are remembered, we are going to publish a booklet by the end of the year which will combine the lectures, questions and answers from the 3 symposia.

It has been an honor for Capsugel to sponsor such a scientific platform. I'm sure that with the remaining issue such as:

— Dissolution medium for poorly soluble compounds,

— *in vitro* prediction of human permeability,

— PK/PD correlation and formulation optimization,

— Non-linear absorption,

— Transporters,

— *In vivo/in vitro* correlation of hydrodynamics,

we will have in the near future additional opportunities to encourage the discussion and evolution of international standards to develop as Dr. Kusai said effective, safe and reliable drug products.

Indeed, we, Capsugel, will have additional opportunities to include these leading edge topics in new tools like we did last year with the inclusion of the SUPAC classification in the Expert System. A new system developed by the industry under the authority of Professor Michael Newton and sponsored by Capsugel.

Let me conclude this day by especially thanking Professor Mitsuru Hashida and Professor Gordon Amidon for having accepted to co-chair this outstanding seminar.

Last but not least, I would thank Sansel Oka and Norito Tabuko to have coordinated all the logistics for this event. A job well done.

Thanks again to all of you and see you again.

Closing remarks

Professor Hashida: Thank you very much, this concludes today's Capsugel Symposium. We are going to publish the proceedings of the three symposia very soon and we will send one to each of you, so please be sure to leave your name cards for us and also please do not forget to fill in the questionnaire. Thank you all very much for your kind cooperation — the panel experts and the speakers and everybody. Thank you.

Geneva

Switzerland

May 14, 1996

Geneva, Switzerland, May 14 1996

Opening Remarks

The bioavailability of a drug can be influenced by numerous factors. Formulations are intended to minimise these factors and provide dosage forms with maximum reproducible bioavailability. Unfortunately, even after formulation, the influence of some factors can still remain. The identification of the type of drugs involved, and the quantification of these effects provide problems for the industry and regulatory authorities.

To assist with the problem of product identification and evaluation, work has been undertaken on behalf of the FDA to provide a systematic approach. This has resulted in a biopharmaceutical classification of drugs to identify the evaluation procedures necessary when making formulation or processing changes. This approach was presented at a meeting of US companies in May 1995 at Princeton (New Jersey) where there was a full discussion of its implications.

Today's meeting has been organised with the aim of presenting this approach to a wider audience, to improve their awareness of the benefits and limitations of this drug classification. The format of the meeting, with a limited number of speakers, the inclusion of involved experts and extended time for discussion, is intended to provide the right environment for a frank and open discussion and a potential solution.

Professor Michael Newton, Chairman

A Biopharmaceutic Classification System:

Update May 1996

Professor Gordon L. AMIDON, Ph.D.

A Biopharmaceutic Classification System: Update May 1996

Professor Gordon L. Amidon, Ph.D.
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It has been approximately one year since the previous symposium presentation in Princeton, NJ, where we discussed the Biopharmaceutic Classification System (BCS) (1) and regulatory implementation. Since that time, interest in this approach to biopharmaceutic regulation of drug products has continued to increase. The biopharmaceutic classification system has been accepted as a useful approach to developing regulations by the scientific community as well as the regulatory community and is slowly finding its way into regulatory implementation. In particular, the SUPAC-IR (scale up and post approval changes) guidelines that were discussed at the last presentation have been released and include an early form of the biopharmaceutic classification system. The trend toward setting drug regulatory standards based on the biopharmaceutic classification system is increasing and there will be a dissolution testing guidance for immediate release solid oral dosage forms issued in June 1996 by the FDA that will include the biopharmaceutic classification system. A Biopharmaceutics Classification guidance is under development and the initial draft is scheduled for a January 1997 release.

(1) This approach to drug product regulation has been referred to as the Biopharmaceutic Drug Classification System (BCDS) or the Biopharmaceutic Classification System (BCS). However, since it includes the setting of dissolution specifications on the drug product, I will use the latter term in the report.

During the past year some of the questions that have been asked include the following: 1) how and when to classify a drug into its biopharmaceutic class; 2) how to define solubility limits and to assess variable gastrointestinal pH dependent solubility; 3) how to establish permeability correlations between tissue culture, animal and human models; 4) how to set dissolution limits, i.e., 85% dissolved in 15 min. I will briefly discuss these issues in the next sections. Not all of these issues can be adequately answered at this time.

This is due to the need for more investigations into the quantitative aspects needed for good guidelines. However, I think it is significant that the BCS serves as a basis to focus our attention on the key issues. I am certain that much more progress will be made over the next few years as a new more mechanistic based set of bioequivalence standards are developed.

First, with regard to classifying a drug product into its biopharmaceutic class prior to human data. It is certainly possible to establish permeability correlations between rat (perfusion or diffusion cell) and dog intestinal permeabilities, and/or Caco-2 cells grown in monolayers for transport studies, to the human permeability database that is being generated (See figure 1 for an example). However, it will be very important to establish some base-line drugs as key reference permeability compounds. I would suggest choosing that three drugs at least absorbed by the same absorption mechanism and having a higher, similar and lower permeability rela-

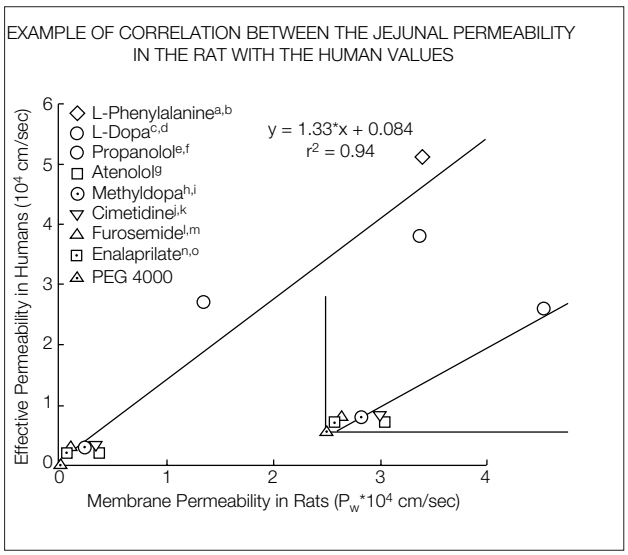

Figure 1.

tive to the expected permeability of the test drug, be used to bracket the permeability determination of a particular drug. The use of reference compounds is essential due to laboratory to laboratory variation in preparation, technique, methodology, etc. Analogous to HPLC, where it is not practical to obtain an absolute retention time for a drug, it is not practical to attempt to determine an absolute permeability. I think there should be significant flexibility so as to allow each laboratory to develop it's own specific techniques, within broad guidelines, and to validate them appropriately with reference compounds.

Regarding when to classify a drug, I see no reason why a drug cannot be classified at the IND stage based on physicochemical data and permeability preclinical data. Appropriate solubility and partition coefficient vs. pH profiles and one or more sets of permeability determinations in animal(s) (including validation of methodology with reference compounds) and/or Caco-2 cells would be sufficient to classify a drug. The cost of generating this preclinical data is small, since most of the physicochemical data is already included in the CMC section of IND/NDA applications and the permeability determinations would take one to two months. Many companies are already doing permeability determinations as part of their preclinical effort. Classifying a drug would then set the FDA bioequivalence standards that the product would have to meet for all subsequent development steps. This would accelerate development and reduce the cost of developing drugs. It could greatly reduce the number of *in vivo* bioequivalence studies currently performed during new drug development.

With regard to the solubility determination, the solubility for many drugs is dependent on pH as well as surfactants and hence will vary along the gastrointestinal tract. Thus we may need to have an intermediate solubility case, as presented in Table I below, where drugs are classified into high, intermediate or low solubility. Drugs whose solubility classification will change with pH in the physiological range would be classified as intermediate. This intermediate class of drugs would include many carboxylic acids and amines. In the case of the carboxylic acids, for example, the NSAID's aspirin, ibuprofen, naproxen, etc, we generally understand that they are very well absorbed. Consequently, classifying these drugs as low-solubility drugs may be too stringent. On the other hand, in the case of amines, these compounds might precipitate in the gastrointestinal tract, e.g., itraconazole, represents a most problematical class of drugs because it might variably precipitate in the gastrointestinal tract. The factors controlling precipitation (nucleation and crystal growth) in this very complex and time dependent environment are very difficult to reproduce and predict. *In vivo* bioequivalence studies may be required for this type of drug for the foreseeable future.

Table 1.

EXTENDED SOLUBILITY CLASSIFICATION

Class	pH = 1-8	V_{sol}
High	All	< 250 ml
Intermediate	Any	< 250 ml
Low	All	> 250 ml

In the case of the NSAIDs, with pK's in the 2-4.5 range they are clearly insoluble in the stomach and soluble in the intestine. Based on the proposed solubility definition in Table 1, the NSAIDs are interme-

diate solubility drugs. Since they are very soluble at intestinal pH (pH = 6.5 or 6.8 in USP SIF), being 3-4 orders of magnitude higher in the intestine than at gastric pH, it is expected that they dissolve rapidly in the intestinal environment (USP simulated intestinal fluid, SIF, pH = 6.8). It may be useful to set a rapid dissolution specification in SIF for compounds of this type. If the dissolution rate in the upper small intestine is rapid and the drugs are high permeability, they will be well absorbed and again gastric emptying, not dissolution, will be the rate determining step in absorption. This could lead to an intermediate solubility, rapidly dissolving product.

Regarding the cross species permeability correlations, we have performed some rat (*Figure 1*), dog and human correlations and have outstanding results to date. We are also in the process of establishing cross correlations with Caco-2 cells. I expect that the animal to human correlations will be excellent since the absorption mechanisms are qualitatively the same in these species. There may be some quantitative differences in the correlations for drugs absorbed by different mechanisms due to different membrane composition, different levels of expression of transporters and enzymes, and different surface areas in the different species. In the case of the Caco-2 cells, a cell line derived from the human colon, the transporters and enzymes as well as the intestinal mucin are present at lower levels in the tissue culture compared to the normal *in vivo* situation. I expect the permeability correlation to be the very mechanism of absorption dependent and the importance of the appropriate reference compounds to establish a correlation critical. I might add that the methodology used to determine the permeability in the dog is identical to the methodology we used for the human studies.

With regard to the dissolution limits and solubility specifications, I have discussed the solubility specification above. The dissolution specification recommended in the original publication, of NLT 85% dissolution in 15 min was based on 15 min being approximately the gastric half emptying time in the fasted state. This may be a relatively conservative specification and it may be possible to relax this time point to 20, 25, or 30 min, particularly for high permeability drugs. This, however, requires evaluation of a database of compounds and perhaps some simulations using gastric-emptying rate distributions in order to pin down the precise dissolution limits. I do believe that the dissolution specification as stated in the original publication is very likely too conservative.

With regard to a more general dissolution methodology, I would reiterate that flexibility in the dissolution methodology must be allowed, but of course this cannot get out of hand with a proliferation of dissolution devices. One should always start with the compendial dissolution apparatus and proceed to develop a dissolution test that will reflect the *in vivo* situation. This may be a multiple point, multiple pH test procedure and may include a media change or sequential methodology and surfactants. Consequently, this dissolution methodology will be significantly more complex than a dissolution methodology that would be used as part of a routine and comprehensive quality control program at a pharmaceutical manufacturing company. This more complex dissolution methodology would be used only in the case of supporting waiver requests from *in vivo* bioequivalence trials under certain regulatory situations.

The dissolution methodology discussed to date are 'product' dissolution profiles. When possible an intrinsic dissolution rate of the pure drug should be obtained. The general methodology requires making a tablet of pure drug (not always possible) and using the tablet dye in a rotating disk apparatus. This dissolution rate can be determined as a function of pH and surfactants. If the solubility vs. pH and the diffusivity of the compound are known, the intrinsic dissolution rate can be predicted with good accuracy. With the known or estimated intrinsic dissolution rate, the dissolution rate of the actual particle size in the product can be estimated, providing a theoretical 'product' dissolution profile. The difference between the product's theoretical and experimental dissolution rate gives a good idea of the degree to which the formulation is controlling the release rate of the drug.

In summary, progress on the biopharmaceutic classification system during the past year has been significant, particularly in the area of drug regulatory implementation. Some of the scientific questions surrounding this approach to classifying a drug and drug product require further quantitative studies in the area of human permeability determination, dissolution limits and connecting the oral input rates to plasma level variations. These are areas that are under active investigation today and I am certain that during the next several years we will see more refined and more quantitative standards set in this rapidly developing area of drug product regulation.

Human Permeability Determinations and *in vitro* and Animal Correlations

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Human permeability determinations and *in vitro* and animal correlations

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1. Introduction

The effective intestinal permeability coefficient of drugs in humans *in vivo* is possible to determine with a regional intestinal perfusion approach (1-2). Previously we have determined the effective permeability (P_{eff}) of several drugs with different physicochemical properties and transport mechanisms in the proximal jejunum in humans (1-8). Recently, the Department of Pharmacy, Uppsala University, started a research program together with the Center for Drug Evaluation, Food and Drug Administration (Rockville), Medical Products Agency (Uppsala), and School of Pharmacy, University of Michigan (Ann Arbor), where we have determined human P_{eff}-values for twenty drugs (9-10). During a time period from October 1993 to June 1996 we have performed 13 clinical studies at Uppsala University, where the human effective jejunal permeability of the following drugs has been determined; naproxen, metoprolol, ketoprofen, atenolol, furosemide, hydrochlorthiazide, carbamazepine, desipramine, α-methyldopa, (R,S)-verapamil, cimetidine, propranolol, amoxicillin and amiloride. These clinical studies were performed at the University Hospital at Uppsala University, and the chemical assays were done at the Medical Product Agency (MPA), Uppsala, and Division of Biopharmaceutics and the Pharmacokinetics, Uppsala University (9-10).

Studies of the *in vivo* permeability of drugs in different regions of the intestinal tract in humans are rare, due to the lack of a robust and reproducible intestinal perfusion technique. Earlier studies of drug absorption in man using the open or semiopen intestinal perfusion techniques have some drawbacks. These include entry of proximal and/or distal luminal contents into the test segment, the use of higher perfusion flow rates (10-20 ml/min) than normal jejunal flow (0.6 - 4.2 ml/min), and a low and variable recovery of the perfusion fluid (1-2, 11-12). A new technique for studies of drug absorption in man, based on a single-pass perfusion of a segment between two balloons, has recently been developed and validated (1-2). *Table 1* presents

Table 1. The validation criteria of the regional jejunal perfusion method in humans.

Mass balance of antipyrine across the intestinal barrier
Physiological sink conditions
Complete recovery of the non-absorbable volume marker ^{14}C-PEG 4000 in the outlet perfusate sample
The hydrodynamics can be described according to a well-mixed model
Molecular size selectivity of the jejunal membrane
Good prediction of the extent of drug absorption in vivo in humans from the P_{eff}-value
Carrier-mediated transport across the perfused jejunal segment

different experimental data that validate this regional intestinal perfusion approach for drug absorption studies in humans (1-10): (a) mass balance of the transport of antipyrine across the intestinal barrier (*Figure 1*), (b) physiological sink conditions of the drug concentrations between luminal and plasma compartments, (c) the hydrodynamics of the perfusion solution within the jejunal segment is best described by a well-stirred model, (d) and that the apical membrane in the jejunal mucosa has the ability to discriminate between different molecular weights and size in the range of 18-350. In addition, the functional viability of the mucosa was demonstrated by the rapid transmucosal transport of D-glucose and L-leucine from the regional jejunal segment, and a complete recovery (>95%) of PEG 4000 (a non-absorbable volume marker) in the perfusate leaving the jejunal segment (1-8).

In general, the macroscopic view of rate (mass/time) and extent (mass/dose) of drug absorption from the intestinal lumen *in vivo* includes: dose/dissolution ratio, chemical degradation/-metabolism in the lumen, luminal complex binding,

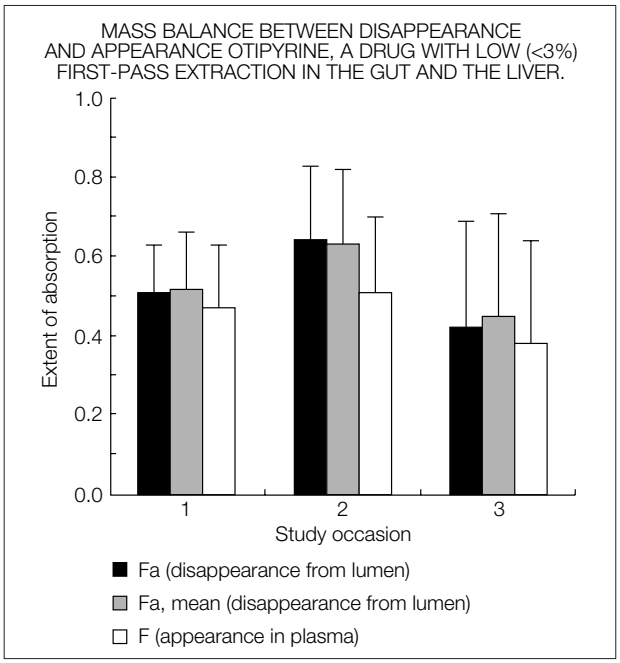

Figure 1. The mean values (± SD) of the extent of intestinal absorption of antipyrine calculated in three ways for each of the three experimental occasions (1, 2 and 3). The bioavailability of antipyrine based on peripheral plasma concentrations was calculated by using the deconvolution technique. At each study occasion the same 8 subjects participated (1).

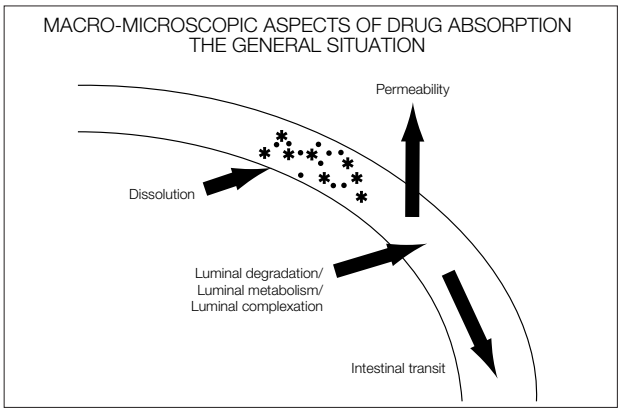

Figure 2. Macro- and micro-perspective of oral drug absorption which includes: dose/solubility ratio, complex binding, chemical and enzymatic degradation, intestinal transit and effective intestinal permeability. The theoretical discussion is based on mass balance on drug in the intestine. Permeability is a key variable in the overall absorption process.

intestinal transit, and effective permeability (P_{eff}) across the intestinal mucosa (*Figure 2*). The extent of drug absorption ($M_{(t)}$/Dose), i.e. the fraction of drug disappeared from the intestinal lumen during a certain residence time, assuming no luminal reactions, at any time t is:

$$\frac{M(t)}{Dose} = \int_0^t \iint_A \bullet P_{eff} \bullet C_{lumen} \bullet dAdt \qquad \text{(eq. 1)}$$

where A is the available intestinal surface area, P_{eff} is the average value of the effective intestinal permeability along the intestinal region where absorption occurs, and C_{lumen} is the free reference concentration of the drug in the intestinal lumen (14, 15).

From equation 1 and Figure 2 it is obvious that the effective intestinal permeability coefficient (P_{eff}) is one of the key variables controlling overall absorption rate and extent. Furthermore, it is a biopharmaceutical variable that it is possible to use regardless of the transport mechanism of the drug (15). The effective permeability includes the process of transport to the membrane (aqueous permeation e.g. diffusion and convection to the membrane), cell mucosa permeation, including mucin and membrane translocation processes (passive and/or active transcellular transport or passive paracellular

diffusion/convection), and perhaps transport through the cytosol, basolateral membrane, interstitial fluid and capillary wall to the blood (*Figure 3*) (1, 14-15). However, it is assumed that the permeability is dominated by the largest resistance, which is usually considered to be the apical brush border membrane (16). Drug metabolism in the cell cytosol

In parallel with these clinical studies in humans we have studied the permeability of some drugs and nutrients in three different commonly used preclinical permeability models; in situ rat perfusion of jejunum, Caco-2 model and excised jejunal segments in the Ussing chamber (18-19).

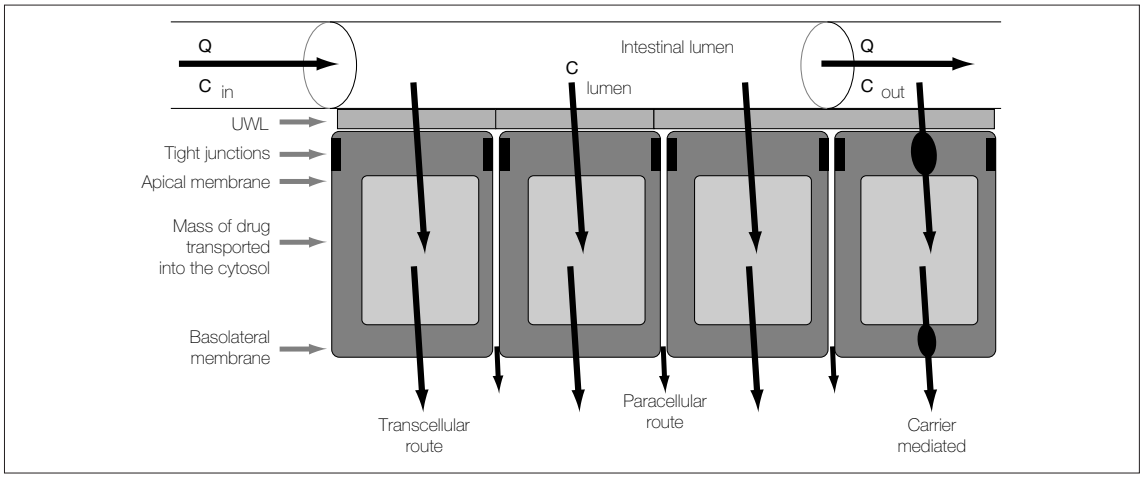

Figure 3. A schematic model of the different transport mechanisms that most drugs are absorbed with. The permeability is a key variable in the overall absorption process.

may influence the measured permeability through further maintaining sink conditions intracellularly. Carrier-mediated efflux mechanism(s) of a drug might decrease the value of the effective permeability coefficient, even if the passive permeability across the lipid membrane is high. These processes will certainly need to be accounted for in any detailed model of the drug transport mechanism(s) across the mucosal membrane. Furthermore, the effective permeability is measured at steady state in the perfusion system, so that the binding process that may influence (non steady state) drug permeation is quasi steady state and does not contribute to the measured permeability (15).

Other important research issues that can be investigated *in vivo* in humans by using the present perfusion approach are: (a) determine the first-pass effect of drugs in the liver, (b) drug metabolism in the intestinal tissue, (c) *in vivo* dissolution of drugs, (d) local pharmacological studies of drugs, (e) nutrient absorption, (f) biological mechanisms of different G-I diseases, (g) food-drug interactions, and (h) intestinal secretion of drugs and endogenous compounds.

2. Objectives

The long term goal with the human permeability project is to obtain quantitative values of the jejunal effective permeability coefficients (P_{eff}) in humans, in order to construct a database that contains the following qualitative categories regarding dose solubility (S) and effective permeability (P_{eff}); high S-high P_{eff}, high S-low P_{eff}, low S-high P_{eff}, low S-low P_{eff} (*Figure 4*). This human permeability database will be regarded as one part of the recently proposed biopharmaceutical classification system (BCS) for oral immediate release products (14). The major advantage of the BCS is that it will identify the controlling key variables regarding drug absorption from immediate release products, and thereby make it possible to classify drugs and simplify drug regulation. Furthermore, several studies are under process where the human permeability data are correlated to different preclinical perme-ability models, and as well-measured physico-chemical properties (log p, log D and hydrogen bonding potential).

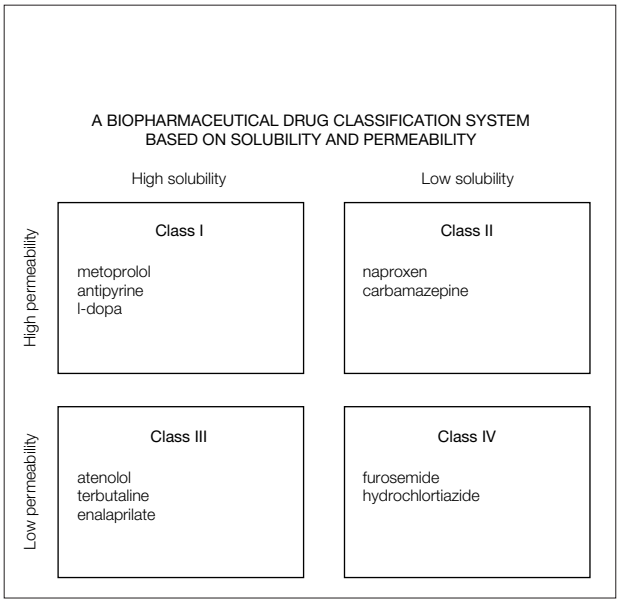

Figure 4. The long-term goal with the human permeability project is to obtain quantitative values of the jejunal effective permeability coefficients (P_{eff}) in humans, in order to construct a database that contains the following qualitative categories regarding dose solubility (S) and effective permeability (P_{eff}); high S-high P_{eff}, high S-low P_{eff}, low S-high P_{eff}, low S-low P_{eff}.

3. Human jejunal perfusion technique

In these human studies we used a new technique that has been developed in order to perform jejunal perfusion experiments in healthy fasted (10 hrs fasting) subjects (1-2). The perfusion instrument (Loc-I-Gut®, Synectics AB, Sweden) is a 175 cm long and sterile polyvinyl tube (external diameter 5.3 mm), with six inner channels and is distally provided with two elongated latex balloons, placed 10 cm apart (1-2). The tube was inserted and positioned in the human proximal jejunum under the guidance of a fluoroscopic technique. Air (24-32 ml) was inflated into the two balloons, creating a 10-cm long jejunal segment (*Figure 5*). The positioning of the tube usually takes 1 hour, and the perfusion rate is between 2.0-3.0 ml/min. A more detailed description of the positioning procedure and the perfusion technique can be found elsewhere (1-2).

4. Overall study design

The clinical studies were performed at Uppsala University, and were approved by the Ethics Committee at the Medical Faculty, Uppsala University. Each study part within this BCS research programme had a slightly different design regarding the number of successful perfusion investigations and

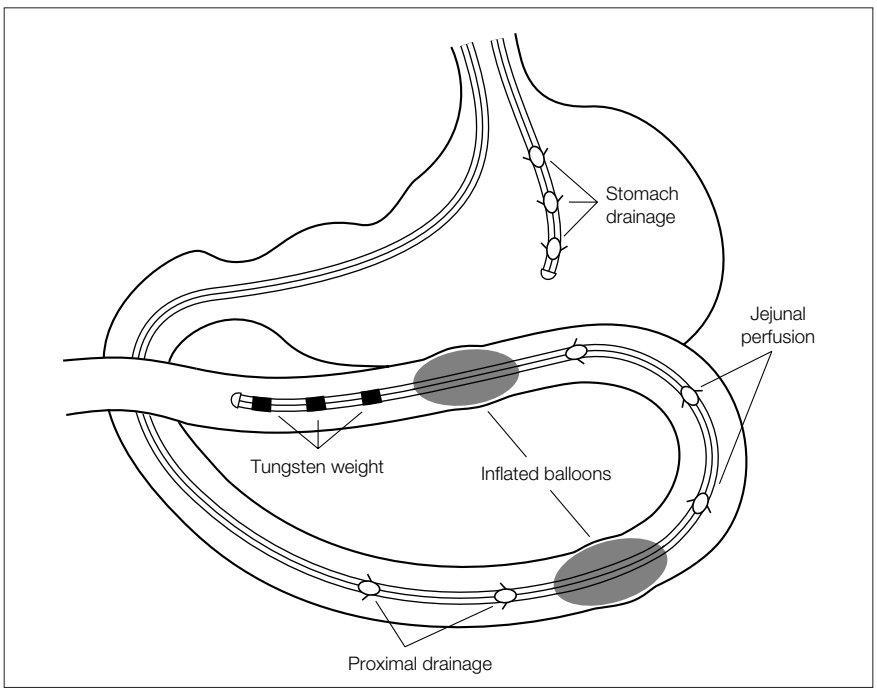

Figure 5. The perfusion technique is based on a double balloon approach allowing regional perfusion of the intestine. The balloons are filled with air when the proximal balloon has passed the ligament of Treitz. Gastric drainage is obtained by a separate tube.

the inlet concentration of each drug. All perfusion investigations were performed as a single-pass perfusion. Twelve of the clinical studies used a perfusion rate of 2.0 ml/min, and one used 3.0 ml/min. In general, the inlet concentration used should reflect the concentration following an oral administration. Therefore, the same amount of drug as a daily dose was dissolved in 250 ml, which is assumed to be a fairly robust estimate of the available volume in the stomach and upper small intestine to dissolve the drug. For low-solubility drugs we used a concentration that did not cause any precipitation during the perfusion experiment.

The perfusion solution was composed of Na^+(138 mM), Cl^- (53 mM), K^+(5 mM), phosphate buffer 63 mM (pH=6.5), mannitol 35 mM, polyethylene glycol (PEG 4000: MW 4000: 1 g/l). ^{14}C-labelled polyethylene glycol [^{14}C]PEG 4000 (Amersham Labs, Buckinghamshire, England) was added to the solution as a non-absorbable marker (2.5 µCi/l). The pH in the perfusion solution was 6.5. The outlet perfusate samples were quantitatively collected on ice at 10-min intervals, immediately frozen and stored at –20°C until analysis (–80°C when necessary). The permeability measurements were performed during isotonic conditions (270-295 mOsm l^{-1}) in the regional jejunal segment.

5. Investigation of stability and material adsorption

Incubation of each drug in the perfusion medium at 37°C for 180 min was performed as a standard procedure, and no degradation ofr any of the drugs investigated was detected. There was no adsorption of any of the drug to the catheters.

6. Chemical assays

The chemical assay of each drug was performed by GLP validated HPLC-methods at the Medical Products Agency (MPA), Uppsala, and the Department of Pharmacy, Uppsala University.

7. Theoretical section and data analysis

The starting point for analysing drug transport across the membrane wall of a tube, the perfused jejunal region, is the relationship between the mass entering and leaving the tube in equation 2:

$$dM / dt = Q_{in}C_{in} - Q_{out}C_{out} = Q(C_{in} - C_{out}) \quad \text{(eq. 2)}$$

where C_{in} and C_{out} are the inlet and outlet drug concentrations, respectively, and Q is the flow through the tube (*Figure 3*). The mass balance relationship can then be set to describe the transport rate of the drug across the tube membrane (absorbed mass) according to Fick's first law in equation 3 (14):

$$dM / dt = A \bullet P_{eff} \left(C_{ref}^{lumen} - C_{ref}^{blood}\right) \quad \text{(eq. 3)}$$

where *A* is the surface area of the membrane, P_{eff} is an effective permeability coefficient and the reference concentrations are on the two opposite sides of the intestinal mucosa C_{ref}^{lumen}, C_{ref}^{blood} (*Figure 3*). It is usually assumed that the reference blood concentration (C_{ref}^{blood}) is negligible in comparison with the lumen concentration, which has been directly shown to be valid for antipyrine in humans (1).

The effective jejunal permeability (P_{eff}) and other variables were calculated from the steady-state level in the perfusate leaving the intestinal segment. Equilibrium of the compounds of interest in the perfusate within the intestinal segment was achieved, when the concentrations of the solute and the ^{14}C-PEG 4000 in the outlet perfusate reached a plateau (at 60 min). The P_{eff} was calculated according to equation 4:

$$P_{eff} = \frac{Q_{in} \bullet (C_{in} - C_{out})}{C_{out} \bullet 2\pi RI} \quad \text{(eq. 4)}$$

where Q_{in} is the inlet perfusate rate, C_{in} and C_{out} are the inlet and outlet perfusate concentration of the drug, respectively, R is the radius (R=1.75 cm) and l is the length of the jejunal segment (10 cm). Q_{in} is the perfusion flow rate entering the jejunal segment, which is obtained by dividing the total volume entering the segment during a sampling period (10 min). The P_{eff} is calculated according to a well-mixed model (13). We have previously reported a residence-time distribution analysis, which clearly demonstrated that the hydrodynamics within the perfused jejunal segment were best described by a

well-mixed model. Based on that model analysis we used the outlet concentration as our reference concentration for the calculation of P_{eff} (1-10, 13). The net water flux (NWF) per cm of the jejunal segment was calculated using equation 5:

$$NWF = \left(1 - \frac{([PEG]_{out})}{([PEG]_{in})}\right) \bullet \frac{Q_{in}}{L} \qquad \text{(eq. 5)}$$

where $[PEG]_{in}$ and $[PEG]_{out}$ are the entering and leaving dpm/ml of ^{14}C-PEG 4000, respectively.

8. Effective human permeability of different drugs

At Uppsala University we have determined the effective permeability coefficients (P_{eff}) of a total of 25 drugs, and as well other compounds, in several clinical studies (1-10). More specifically, regarding the Biopharmaceutical Classification System we have performed 13 clinical studies, and determined the P_{eff} for 14 different drugs (9-10). Each human study includes 7-9 healthy human subjects. These human studies have been done within a clinical research program in collaboration with Center for Drug Evaluation, Food and Drug Administration, Rockville, The Medical Products Agency (MPA), Uppsala and the University of Michigan, Ann Arbor. The following drugs have been investigated at Uppsala University: naproxen, metoprolol, ketoprofen, atenolol, furosemide, carbamazepine, desipramine, α-methyldopa, (R,S)-verapamil, cimetidine, propranolol, amoxicillin, and amiloride.

The mean and individual values of net water flux (NWF) and the recovery of the non-absorbable volume marker ^{14}C-PEG 4000 were similar to previously published studies (1-10). The mean NWF throughout these studies was approximately 2.0 ml/h/cm, and ranged between 1.0-3.1 ml/h/cm. This secretory status of NWF corresponds to approximately 10-15% of the total perfusion volume passing through the segment, and is due to both fluid secretion and proximal leakage of intestinal fluids into the segment between the two balloons. The recovery of ^{14}C-PEG 4000 was on average more than 95%. The pH-values in the outlet perfusate were between 6.4-6.6 throughout all perfusion experiments. The osmolality in the outlet perfusate was between 265-295 mosm/l. However, a tendency to increased fluid secretion into the jejunal segment was observed when the diuretic drugs hydrochlortiazide and furosemide were studied.

The relation between human P_{eff}-values for different drugs (studied at Uppsala University) predicted well the extent of intestinal absorption (*Figure 6*). The values for the extent of intestinal absorption were obtained from published pharmacokinetic studies (*Figure 6*). The extent of absorption is defined as all events occurring from dissolution of the solid dosage form and to the intestinal transport of the drug into the intestinal tissue (across the intestinal mucosa), as described in figures 2-3. Furthermore, it does not include metabolic first-pass effects in the gut/liver and/or biliary excretion in the liver (*Figures 2-3*). It is assumed that the major absorption of these drugs occur in the proximal region of the small intestine when given as an immediate release product (*Figure 6*) (1-10). This

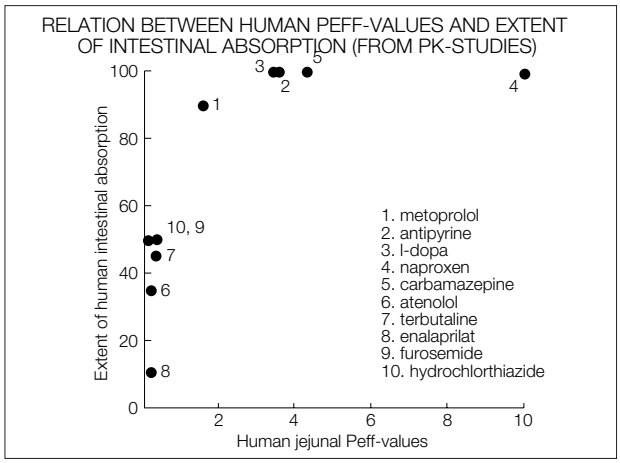

Figure 6. The relation between extent of intestinal absorption and the measured human jejunal permeability value.

means that the permeability measured in the proximal human jejunum is a good approximation of the permeability for the small intestine, regarding biopharmaceutical classification as a low or high permeability drug. Furthermore, based on the relationship in *Figure 6* the extent of oral absorption of drugs following oral administration is well predicted from the measured human P_{eff}-value, i.e., when chemical/enzymatic stability in the lumen as well as complexation/dissolution can be excluded as potential factors affecting drug absorption during the perfusion experiment (*Figure 2*). For instance, drugs with a high P_{eff} might have a low extent of intestinal absorption when administered as a high dose in relation to their solubility (14). It is interesting to note that a transformation of the permeability axis into a logarithmic scale results in a classification of P_{eff}-values of these drugs into two categories (low and

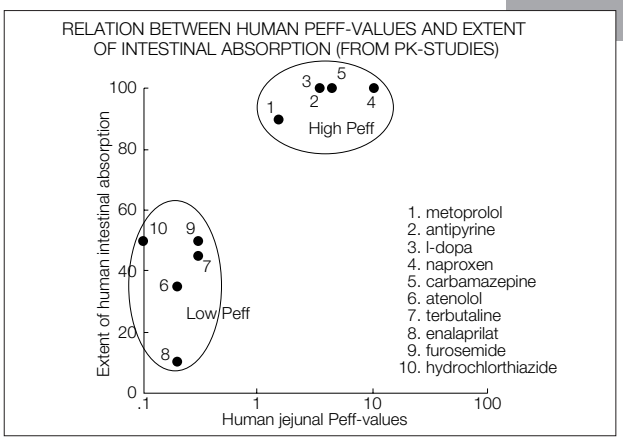

Figure 7. The relation between extent of intestinal absorption and the measured human jejunal permeability value.

high P_{eff}) (*Figure 7*). Furthermore, in *Figure 6* it is obvious that the critical permeability range for the border between the two categories low and high permeability is between 0.5-1.5 • 10^{-4} cm/s. Therefore, more clinical determinations of the effective jejunal permeability in humans for drugs in this range is crucial, in order to establish the limit between low and high effective jejunal permeability.

The measured P_{eff}-values of cimetidine at Uppsala and Michigan were about 0.3-0.4 • 10^{-4} cm/s, which clearly demonstrated that no difference existed between the two study sites.

The drugs shown in *Figure 6* are also classified in accordance with the proposed Biopharmaceutical Classification System (BCS) for oral immediate release products, i.e., based on the qualitative variables solubility (S) and permeability (P_{eff}). In *Figure 4* these drugs are divided into the qualitative categories regarding dose solubility (S) and effective permeability (P_{eff}); high S-high P_{eff}, high S-low P_{eff}, low S-high P_{eff}, low S-low P_{eff}.

Several attempts during the previous decades have been done in order to predict the passive transmucosal diffusion of drugs across the intestinal mucosa from the physico-chemical properties. The outcome of these predictions has shown various success. However, in this project we are currently working in a collaboration with the Division of Organic Pharmaceutical Chemistry, Uppsala University, where we are measuring the hydrogen bonding capacity, log p and log D, for about 30 drugs exhibiting a wide range of chemical structures. Thereafter we are applying a multivariant analysis of these physico-chemical properties in relation to human effective intestinal permeability, in order to establish the relation between measured physico-chemical properties and the *in vivo* estimate of human jejunal P_{eff}-values (*Figure 8*). These kind of relationships demonstrate the general to integrate aspects of drug absorption, as well other biopharmaceutic/pharmacokinetic variables, much earlier within the discovery and design process of new chemical entities.

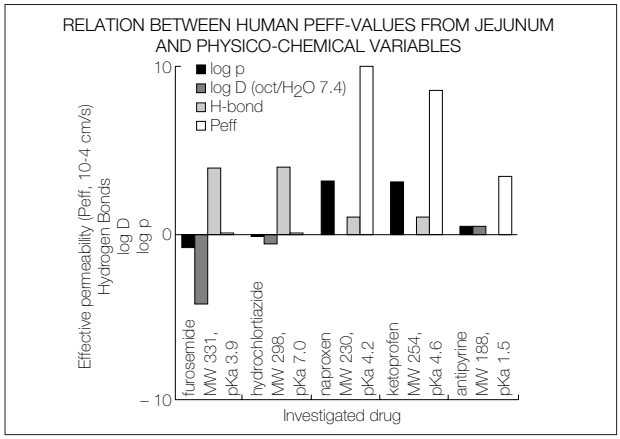

Figure 8. The relation between some physico-chemical variables and the measured human jejunal permeability value.

The biopharmaceutical classification of carrier-mediated drugs is well described by the permeability data obtained from three human perfusion studies for L-dopa, α-methyldopa and (R, S)-verapamil (3, 6, Lennernäs *et al.*, unpublished results). L-dopa and α-methyldopa have been shown to be transported by a carrier-mediated process (3, 6, 20, 24). The drug, α-methyldopa, is classified as a low permeability drug with a P_{eff}-value of about 0.1 x 10^{-4} cm/s at an inlet perfusate concentration

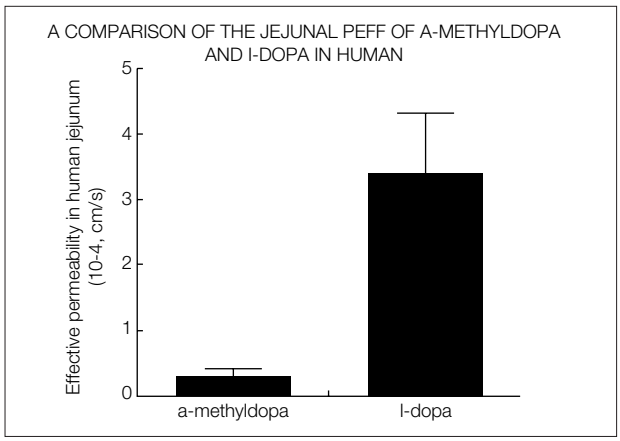

Figure 9. The effective jejunal permeability of α-methyldopa and l-dopa in humans.

of 1600 mg/l (6.7 mM) (*Figure 9*). This is approximately 30 times lower P_{eff} than L-dopa, which is 3.4 x 10^{-4} cm/s at a luminal concentration of approximately 2.0-2.5 mM (*Figure 9*) (3, 6). The lower transport rate of α-methyldopa compared to L-dopa is probably due to a lower affinity to the amino acid transport carrier. The lower affinity to an amino acid carrier and therefore a lower permeability coefficient, also means that the passive diffusion of α-methyl-dopa across the jejunal mucosa is low. The data in *Figure 9* illustrate that a small change in the chemical structure might give a marked alteration in the permeability for a carrier-mediated transported drug. In this case, it is most likely due to a very narrow structure specificity of the carrier-mediated transport mechanism for large neutral amino acids (LNAA).

The human P_{eff}-values of both, R- and S-verapamil, are similar, about 5-6 x 10^{-4} cm/s. These high intestinal permeability coefficients predicts a rapid and complete transport across the human jejunal mucosa of both enantiomers (*Figure 6*). Furthermore, it also indicates that the efflux mechanism, mediated by the P-glycoprotein(s) in the apical membrane of the enterocyte, might not affect the quantitative transport rate of (R,S)-verapamil across the human jejunal tissue at a luminal concentration of 375 mg/ml (0.8 mM). This concentration in the intestinal lumen is assumed to be relevant following an oral dose of 100 mg to humans (dissolved in 300 ml G-I fluids). Our clinical observation in humans clearly shows that not all compounds that are substrates for P-glycoprotein(s), directly will lead to a reduced bioavailability. However, more research is needed regarding the role of P-glycoprotein(s) in quantitative drug transport across the human intestinal mucosa (21, 28). For instance, the interplay between different factors is urgent to further investigation at different luminal concentrations. Factors of potential importance are: passive membrane diffusion, free concentration of the drug available for the transport protein, metabolism, affinity and transport capacity of the P-glycoprotein(s), involved. Moreover, it is essential to study the mechanism(s) behind inhibition and induction of P-glycoprotein(s) in the intestinal tissue. Fundamental knowledge of the dynamic mechanism of this efflux pump located in the intestinal mucosa will contribute to a better understanding of its role in biopharmaceutics/pharmacokinetics, i.e. intestinal absorption and bioavailability of drugs. It is also of special interest to investigate the potential inhibitory effect some pharmaceutical additives, detergents such as Tween 80, might have on the P-glycoprotein(s) *in vivo* (25).

Correlation to preclinical permeability models

In parallel with these clinical studies in humans we have studied the permeability of some of the drugs and nutrients in three commonly used preclinical permeability models, in situ rat perfusion of jejunum, Caco-2 model and excised intestinal segments in the Ussing chamber (17-19).

The effective permeability coefficients (P_{eff}) were determined using an in situ perfusion model in anaesthetised rats (thiobutabarbital Na^+) (17). The perfusion flow rate used was 0.2 ml/min, which was 10 times lower than that used in humans. The viability of the method was assessed by testing the physiological function of the rat intestine during perfusions. For instance, PEG 4000 labelled with ^{14}C is an established non-absorbable compound and was used as a marker for an intact jejunal barrier. Further validation of the model was obtained by investigating the carrier-mediated cotransport of Na^+/D-glucose. This Na^+/D-glucose cotransporter is a membrane protein that is crucial for the membrane transport of these two compounds. Antipyrine was included as a marker for passive transcellular absorption, and has been widely used in our human regional perfusion experiments. The P_{eff} of antipyrine is also used as an indicator of extensive changes of mesenteric blood flow (18). For passively absorbed compounds the rank order was the same in perfused proximal jejunal segment in both human and rat. The human P_{eff}-estimates

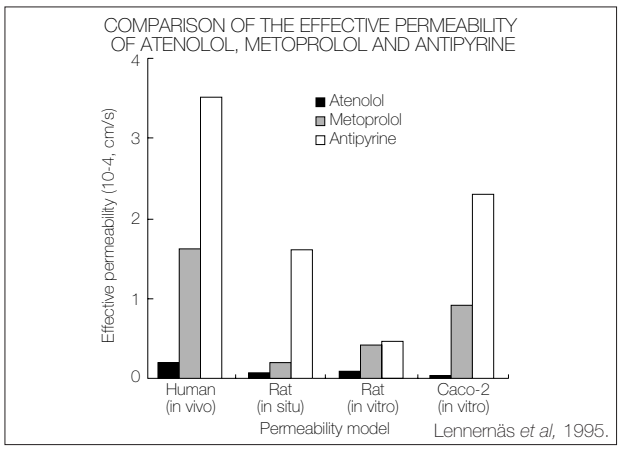

Figure 10. The effective permeability coefficients of three different model drugs in four different permeability models. These three drugs are transported by passive diffusion.

for all drugs absorbed by passive diffusion were on average 3.6 times higher in humans than in the rat, irrespective of the permeability classification of the drug (*Figure 10*). Plausible reasons for the lower value in the rat model are differences in effective absorptive area within the perfused segment, and/or species differences affecting partitioning into the membrane (K), diffusion coefficient (Dm) and/or diffusion distance (18). Carrier-mediated transported compounds, such as L-dopa and D-glucose, deviate from this linear relationship between the two models, which clearly demonstrates that each carrier-mediated transported drug has to be carefully investigated in order to find the accurate mechanism(s) and a scaling factor (*Figure 11*). Both human and rat P_{eff}-values predict the quantitative amount of drug absorbed *in vivo* in man very well, when given as a solution and/or IR-dosage form, i.e., when the drug is mainly absorbed in the proximal part of the small intestine (*Figure 6*).

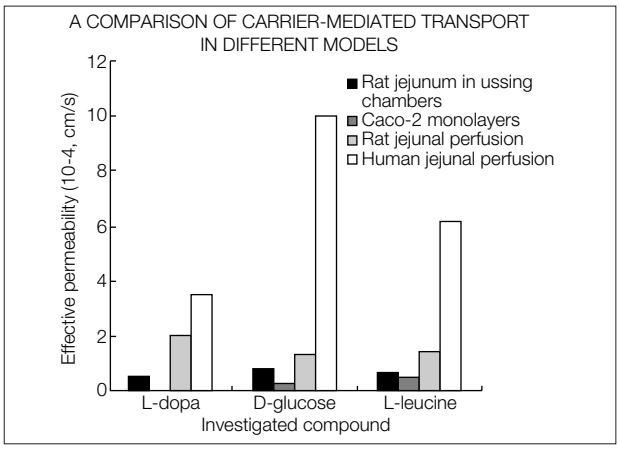

Figure 11. The effective permeability coefficients of three different model compounds in four different permeability models. These three compounds are transported by carrier-mediated mechanisms.

In the Caco-2 model the permeability coefficients of the rapidly transported drugs were dependent on the hydrodynamics (17). However, the true P_c-estimate for antipyrine of 2-3 x 10^{-4} cm/s was directly comparable to that obtained in the well-stirred *in vivo* situation in the human jejunum. Similar results were obtained for the other two model drugs for passive transcellular drug absorption, naproxen and metoprolol (17) (*Figure 10*). These results give further support to the hypothesis that the intestinal epithelium and not the adjacent unstirred water layer is the rate-limiting barrier to absorption of rapidly transported drugs (such as antipyrine, naproxen and metoprolol) (1, 17, 26). The permeability values of the low-permeability drugs, such as atenolol and terbutaline, were on average 50 times lower in the Caco-2 monolayers than in the human jejunum (*Figure 10*). The lower mean permeability in the Caco-2 monolayers might be due to a lower paracellular permeability of this colon-derived cell line as suggested by Artursson *et al*. in 1993 (23). Another possible explanation is the larger area available *in vivo* in humans as it is assumed that the absorption of hydrophilic compounds is so slow that the entire surface area of the intervillous space is exposed (27). Thus, the permeability values of hydrophilic compounds in the Caco-2 monolayers are closer to those seen in the human colon. We therefore conclude that the passive diffusion of drugs across the human jejunal mucosa *in vivo* can be predicted and classified in the Caco-2 model (*Figure 10*). The effective permeability values of carrier-mediated transported compounds like L-dopa, D-glucose and L-leucine were also much slower in Caco-2 cells than in human jejunum (*Figure 11*). For instance, the carrier-mediated transport rate of l-dopa was approximately 340-fold slower in Caco-2 monolayers than in human jejunum. However, we cannot exclude that these compounds were partly transported also by passive diffusion in the Caco-2 monolayers due to saturation of the carrier. Nevertheless, the results are in agreement with previous studies in Caco-2 monolayers which show that this cell line displays a variable and generally lower expression of carrier-mediated transport than seen *in vivo* (24). This is also consistent with the colonic origin of the Caco-2 cells. Prediction of carrier-mediated drug transport in humans based on data generated in the Caco-2 model will therefore only be possible after characterisation of each transport system, and subsequent introduction of a scaling factor to compensate for the different expression of the carrier in Caco-2 cells from that seen *in vivo* (17).

In a collaboration with Dr. A-L. Ungell we have determined the effective permeability coefficients (P_{eff}) for compounds transported by both passive diffusion and carrier-mediated mechanisms across the rat jejunal segment mounted in the Ussing chamber (19). The P_{eff}-values and their rank order were the same for passively transported compounds in the excised jejunal segment from rat (in vitro) and in human jejunum (*in vivo*). There was a high correlation between the two models when both low and high P_{eff} drugs (transported by pas-

sive diffusion) were compared. The human *in vivo* P_{eff}-estimates for all drugs absorbed by passive diffusion were in general about 6-7 times higher than in the rat (*Figure 10*). The carrier-mediated transport for D-glucose, L-dopa and L-leucine was approximately 15 times higher in the *in vivo* human model (*Figure 11*). The in vitro P_{eff}-values for the carrier-mediated transported compounds, might also be affected by the supply of co-factors which are crucial for an optimal function of the transport protein.

The extent of drug absorption in different species has been reported as illustrated in *Figure 12*. This figure demonstrates the well-known fact that small, hydrophilic, and passively transported drugs (at least to a major extent) are better absorbed in dogs than in other species such as rat, man and monkey. The physiological explanation underlying this observation is still unknown. A possible explanation might be the higher villus in the dog which might increase the available absorptive area for low permeability drugs (29). In another study we are currently investigating the interspecies permeability between man, dog and rat of permeability data generated by perfusion experiment (22). Preliminary analysis shows that different drugs have a lower permeability in rat and a higher permeability in dog (22). However, this issue is under further investigation.

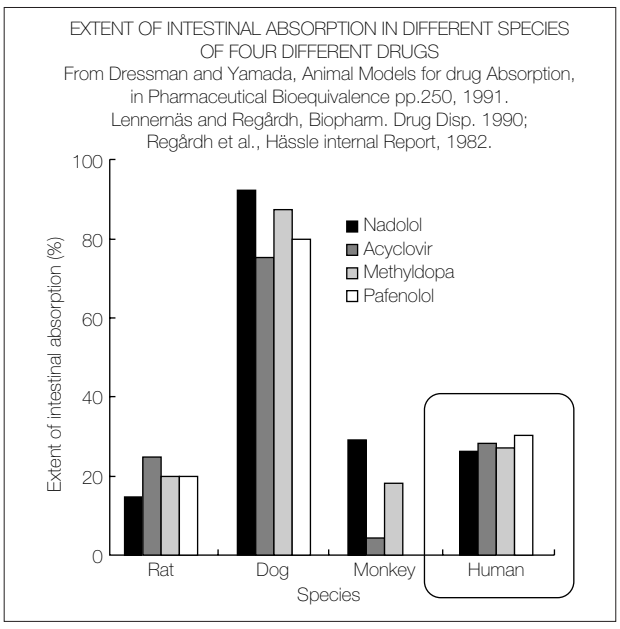

Figure 12. The interspecies variation in the extent of intestinal absorption of four incompletely absorbed drugs.

Conclusion

The regional human jejunal perfusion approach has been validated regarding several crucial aspects as shown in Table 1. One of the most important findings is the good correlation between the measured human effective permeability values and the extent of absorption of drugs in human from pharmacokinetic studies (*Figure 6*). We have also shown that it is possible to determine the P_{eff} for carrier-mediated transported compounds, and to classify them according to the proposed Biopharmaceutical Classification System (BCS) (*Figures 4, 6-7*).

Furthermore, it is possible to classify drugs according to BCS using preclinical permeability models such as in situ rat perfusion of jejunum, Caco-2 model and excised intestinal segments in the Ussing chamber (*Figures 10-11*). Especially passively transported compounds can be classified with high degree of accuracy. However, special care must be taken for drugs with carrier-mediated transport, and a scaling factor has to be used.

In order to standardise the permeability values from different laboratories we suggest that a number of well studied drugs should always be used to validate the method used. For instance, the three ß-blocking agents atenolol, metoprolol and propranolol could be used to facilitate inter laboratory comparisons regarding passive permeability estimates. Similar reference drugs must also be used when drugs with carrier-mediated transport are studied. It is also essential to further study the quantitative importance of efflux mechanisms by P-glycoprotein(s) in the apical membrane of the enterocytes.

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In vivo Bioequivalence Assessments

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In vivo bioequivalence assessments

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Introduction

I'm going to consider some important issues specifically in bioequivalence testing but very much downstream of the drug classification issue. I think this reductionist approach is very interesting, but I'm really coming from the other end, from the clinical end, of the significance and the rationale of bioequivalence testing.

Bioavailability & bioequivalence

— Do we know what we are doing? —

"… we continue to be confronted by the inappropriate and illogical criteria for BA and BE... it is time to completely re-examine the criteria for BE." L. Z. Benet (1992)

"One might assume that after about 15 years since the promulgation of the BA regulation in 1977, there are no open questions on performance and evaluation. This is far from reality..." W. A. Ritschel (1992)

"Yet there has been insufficient attention paid to rationale..., as most papers… discuss only methodology." L. B. Sheiner (1992)

"A matter that becomes clear ceases to concern us." Nietzche

This slide shows some quotations from a number of well-known philosophers — which encapsulate, I think, the fact that many of us remain uneasy about many aspects of the rationale of BA and BE studies. Methodology and statistics have been discussed *ad nauseam*, particularly the latter, but some fundamental matters remain unclear and are still of concern.

Pharmaceutics vs therapeutics
Pharmacokinetics vs pharmacodynamics

"At the beginning of the discussion... two apparently contradictory views were presented:

1. Since BA assessments are related to <u>therapeutic efficacy</u> …it would be preferable to measure <u>pharmacodynamic</u> effects related to clinical activity, in particular for drugs having numerous active metabolites with poorly defined pharmacological and pharmacokinetic responses.

2. Since BA assessments are related to in vivo evaluation of the <u>performance of drug products</u>, it is preferable to use <u>pharmacokinetic</u> data. In addition, since extent and rate are characteristics of the dosage form, these characteristics need not necessarily be directly related to pharmacological or therapeutic effects." L. P. Balant *et al* (1991)

Here is another quote, from a report of a "consensus" workshop held in 1989. However, although

this meeting managed to highlight a fundamental dilemma, unfortunately, it did not come to grips with it.

Thus, some consider that the reason for doing BE studies is to ensure *pharmaceutical quality*, whereas others see them as exercises in establishing *therapeutic performance* — the former would emphasise PK endpoints; the latter PD ones.

> *"...BA/BE testing is not a test for clinical efficacy* per se*, rather it is a biologic quality control, test."* W. A. Ritschel (1992)
>
> *"BE refers to the degree to which clinically important outcomes after receiving a new preparation resemble those of a previously established preparation."* L. B. Sheiner (1992)
>
> *"If two formulations are deemed BE... rate and extent of absorption are essentially the same when administered under similar conditions to human subjects. The key concept is that BE formulations should lead to the same therapeutic effect."* W. J. Westlake (1988)

More quotes... Ritschel the "pharmacist" and Sheiner the "clinician".

Westlake summarises the rationale for kinetic measurements as a surrogate for therapeutic effect — similar plasma concentrations should reflect similar effects. However, this does depend on how "similar" they are and, certainly, similar effects are not necessarily synonymous with similar plasma drug concentrations if we are operating near the top of the concentration effect relationship.

Metoprolol — Sandberg *et al* (1988)

	Conventional 100mg od	Conventional 50mg bd	Controlled -release 100mg od
AUC (nmol/l.h)	4625-	4532	3068
AUEC (% decrease ex HR x h)	261	321	282

This is illustrated here with some data for the beta-blocker metoprolol given as a conventional tablet either od or bd compared to an od CR formulation. PK data (relative AUCs) clearly indicate a lower BA from the CR product (greater 1st pass metabolism +- incomplete release?), yet no difference is found in the PD (AUEC). Clearly, PD are more clinically meaningful — but, unfortunately, all drugs are not beta-blockers and measuring clinically meaningful effects with any confidence is usually more difficult.

> Similar *in vivo* pharmaceutical quality indicates therapeutic equivalence, but the opposite is not necessarily true.

So, similar *in vivo* pharmaceutical quality indicates therapeutic equivalence, but therapeutic equivalence is possible without equivalent pharmaceutical quality with respect to release of drug from formulations. Should we worry if one product is only 79% as bioavailable as another if it is not even possible to differentiate the therapeutic effect of two doses of the same drug when we are at the top end of the dose-response curve?

Primary regulatory concerns:

Consequences of switching route of administration or pharmaceutical formulation
Bioavailability
— absolute
— relative

Consequences of prescribing different drug products or of switching drug products
Bioequivalence

Which brings us back to the rationale for BE studies. From a regulatory viewpoint, the primary concern must be for safety and efficacy with respect to developing and prescribing different drug products (relative BA) or switching such products (BE). However, there is also a responsibility to ensure the quality of formulations (as it effects drug release properties).

In my view, the distinction between these pharmaceutical and clinical rationales for BE testing has not been considered sufficiently. Having been trained in pharmacy, but holding a chair in clinical pharmacology I feel particularly schizophrenic about this issue.

The issue is compounded by ambiguities in the definition of BA which propagate through to the definition of BA. For example, the European CPMP in its 1991 guidance gave the following definitions…

Bioavailability (of an oral dosage form)

The rate at which and extent to which the drug substance or active moiety is delivered from a pharmaceutical form into the systemic circulation.

Bioequivalence

Two pharmaceutical products are considered to be equivalent when their bioavailabilities, from the same molar dose, are so similar that they are unlikely to produce clinically relevant differences in therapeutic and/or adverse effects.

International Harmonisation Meeting
Barcelona, 1991

The problems stem from the 3 key words "extent", "rate" and "active moiety" — leading to confusion over the choice of experimental metrics used to establish BE and of appropriate acceptance criteria.

"Extent"	assessing variability?
"Rate"	which metric?
"Active Moiety"	drug, metabolite, isomer?

So, for the rest of this talk I am going to consider each of these concepts in turn.

First a few words about "Extent".

"Extent" of what? Traditionally, the intention has been to assess the relative extent of actual drug "release" or "bioavailability" from two formulations.

"Extent"

Extent of drug "release" or "bioavailability"

AUC — a direct measure, but only under linear kinetic conditions

AUC — a measure of "exposure"

Fixed (80-125%) criterion
Pharmaceutical quality
Clinical exposure?

Under linear kinetic conditions this is very easy to do based upon the measurement of AUC — a direct metric for extent of release. However, if the kinetics of the drug in question are significantly non-linear, the estimation of extent of drug release from a formulation becomes a very difficult matter since AUC becomes a complex function of inherent drug kinetics as well as of the release characteristics of the formulation.

On the other hand, if we view AUC as simply a measure of systemic "exposure" rather than of "release", we focus on the clinical rather than the pharmaceutical rationale for BE testing. Clinically, we are interested in equivalent plasma drug levels as a surrogate for therapeutic effect, not the intrinsic release properties of the formulation — hence if safety and efficacy are the paramount regulatory issues we really do not need to establish similar "extent of drug release". This becomes a question of Quality Control rather than directly of BE assessment.

The other issue with regard to "Extent" is, of course, the acceptance criteria for BE. In this regard, a fixed 20% limit (80-125% for log transformed data) has been set as a universal guideline. It might be argued that this is not without virtue insofar as it attempts to reconcile both therapeutic and pharmaceutical requirements for BE. A mean 20% difference may or may not be significant in terms of mean clinical effect, but seems reasonable as a limit for product drug-release quality. However, even here I think clinical considerations should be

paramount in setting limits of clinical "exposure," based upon what we know about the concentration-response relationships of individual compounds. So, extent of systemic exposure not extent of drug release.

"Rate"— which metric(s) should we use and why? Traditionally, the assessment of "rate" in BE has relied on Cmax and tmax as metrics. This use again highlights the confrontation between clinical and pharmaceutical rationales.

Thus, while Cmax and tmax may have clinical relevance as surrogate measures of safety and efficacy, they are relatively poor indices of actual drug release rate (as indicated at least by a release rate constant), because of their contamination with other kinetic processes.

"Rate"

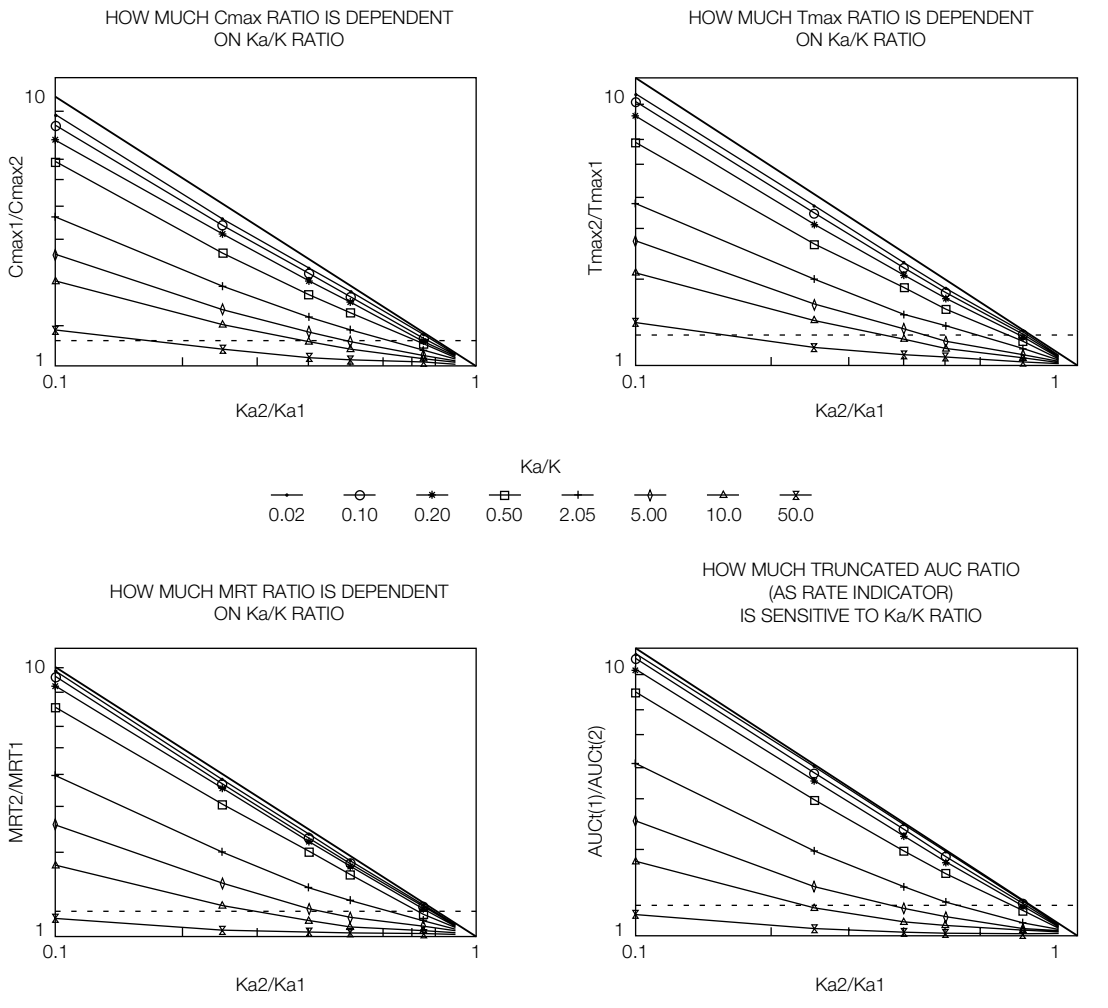
Cmax, tmax may have clinical relevance, but are insensitive to change in actual drug release rate

"Sensitivity" vs "variability" of indirect metrics

Cmax/AUC — normalises for "extent", but has little clinical relevance

There is no simple "rate" parameter which allows products to be compared for both pharmaceutical quality and clinical safety and efficacy

"Rate of exposure" — Cmax, Tmax...



This rather complex slide is based upon a computer simulation that we did to illustrate differences in the ability of various indirect metrics (Cmax, Tmax, MRT and partial AUC) to reflect differences in "true" rate, as expressed by ka in a single compartment model. This dependence is also calculated for different ka/k ratios — i.e. from fast to slow release products or from slow to fast eliminated drugs.

Take Cmax for example — the solid line indicates the ideal concordance between at maximum a 10-fold difference in ka and a 10-fold difference in Cmax for products 1 and 2. However, what we see is that in actuality a given change in ka is reflected in a much smaller change in Cmax, especially for fast-release products or slowly eliminated drugs (high ka/k). Thus, in the extreme case, a 20% difference (possible acceptance level) in Cmax may hide a 9.5 fold difference in ka.

Cmax is a very insensitive index of true "rate" — at least as expressed by ka — and is, therefore, a poor index of "pharmaceutical quality". On the other hand, it means much more clinically than an estimate of ka.

Furthermore, for a 20% change in Cmax this will reflect a variable (90-20%) change in ka as ka/k decreases from 50 to 0.1, thereby imposing a variable limit on pharmaceutical similarity depending upon both drug and formulation. Either way you look at it, fixing the same limits on Cmax for all drugs and all preparations makes no sense clinically or pharmaceutically.

For Tmax the sensitivity to a change in ka is still poor but, in this case, the sensitivity is worse for slow-release products or fast-eliminated drugs (low ka/k). MRT is the same way round as Cmax, but has no advantages with respect to sensitivity and is very sensitive to truncation. Partial AUC is better.

On the assumption that indirect metrics should provide estimates of actual "rate of drug release", the literature is full of nonsense. Thus, judgments about the relative performance of different indirect metrics invariably confuse the concepts of "sensitivity" and "variability", and make comparisons between metrics based upon a fixed acceptable limit.

Goalposts

For a 9-fold difference in ka when ka/k = 50, passing a -20, +25% criterion for C_{max} would be equivalent to passing a -67, +200% criterion for partial area AUC(t).

Clearly, if we are going to persist in using indirect indices to mark actual drug release (as opposed to being indices of clinical effect), the "goalposts" (acceptance limits) should move as a function of metric, drug and formulation.

Thus, for example, a 9-fold difference in ka when ka/k = 50 passes a 20 to 25% acceptance criterion for Cmax but would be equivalent to passing a 67 to 100% criterion for partial AUC…

A third point about "Rate". Professor Endrenyi in Toronto is a strong advocate for the use of Cmax/AUC as a "rate" metric because it normalises for "extent" of absorption, and is equally sensitive but less variable than Cmax as a measure of ka. However, Cmax/AUC has little meaning clinically with respect to safety and efficacy.

$$\frac{AUC_T}{AUC_R} = 0.8$$

$$\frac{C_{max\,T}/AUC_T}{C_{max\,R}/AUC_R} = 0.8$$

$$\frac{C_{max\,T}}{C_{max\,R}} \times \frac{AUC_R}{AUC_T} = 0.8$$

$$\frac{C_{max\,T}}{C_{max\,R}} = 0.8 \times \frac{AUC_T}{AUC_R}$$

$$\frac{C_{max\,T}}{C_{max\,R}} = 0.8 \times 0.8 = 0.64$$

Consider the case where the AUC ratio and Cmax/AUC ratios just meet a 20% acceptance criterion. If you do some simple algebra, the product of these ratios is in fact the Cmax ratio — which works out to be 0.64. Since Cmax is presumably more relevant clinically than Cmax/AUC — we have a problem.

In any case, how do you put acceptance criteria on Cmax/AUC (or indeed ka, if you could measure it) without referring them to clinically more meaningful measures such as Cmax and AUC anyway?

So, there is no simple "rate" parameter which allows products to be compared for both pharmaceutical quality (actual release rate) and clinical safety and efficacy. Tight limits on drug release will assure therapeutic equivalence, but the latter may be possible with wide margins on drug release.

We suggest that the ambiguity in the rationale for BE testing would be removed if the term “rate” were either deleted from the definition, or replaced with “rate of exposure” — which has no direct pharmaceutical connotations. Thus, apart from its value in calibrating in vitro dissolution tests, assessment of an actual *in vivo* drug release rate from a formulation (e.g. by deconvolution) should be seen as a product development and quality control issue and not as a part of the clinical regulatory assessment of the bioequivalence of 2 products.

Metrics used in BE should concentrate on those features of the plasma drug concentration-time curve which have clinical relevance. Depending upon the drug, these would include the traditional metrics such as Cmax and tmax, and their acceptance limits should vary with therapeutic index and the variability of the reference formulation.

Finally, the “active moiety” — what should we measure — drug, metabolite, isomer? Does the analyte have to be active anyway? Do we actually need a specific assay even?

Bio’89 —
Single-dose bioequivalence study (n = 27)

	AUC (2 one-sided t-test)	
Amoxapine	79	103
8 OH Amoxapine	93	101
7 OH Amoxapine	92	102

The problem is illustrated here with a single-dose BE study of amoxapine, an antidepressant, showing that the parent drug data for the test product just fails the BE acceptance criterion, whereas the data for two of its metabolites (less active) pass quite comfortably. Will the nasty regulator throw out the test product?

Extent — linear system

Drug:
$AUC = fa.F_H.D_{po}./CL$

Metabolite:
$AUC(m) = fa.fm.F_H(m).D_{po}/CL(m)$

Irrespective of analyte:

$$F_{rel} = \frac{fa_T.D_{po}R}{fa_R.D_{po}T}$$

To be consistent with my earlier suggestions about “exposure” — if the kinetics in the system are non-linear, it is essential to assess “extent” of BE on the basis of AUC values of active moiety. However, in a linear system, where AUC measures both drug exposure and extent of drug release, theory predicts that, irrespective of the activity of the analyte, the ratios of test to reference preparation AUC values for drug or metabolite are equally *sensitive* measures of BE.

This is because all kinetic parameters, other than the extent of bioavailability, cancel out for test and reference formulations. On the other hand, the various AUC ratios will not be equally discriminant of relative BA, because of differences in within-subject *variability* in the different clearance mechanisms which influence absolute AUC values, of each analyte.

It is generally accepted that within-subject variability in renal clearance is less than that in metabolic clearance. Therefore, for example, if a drug is converted into a single metabolite which is entirely excreted in the urine, intuitively it should be possible to appreciate that the metabolite rather than the drug AUC ratio should be more discriminatory in establishing BE.

Hence, even though a metabolite (or an optical isomer) may not have pharmacological activity, in a linear system its measurement may provide a superior index of relative BA of the “active moiety” with respect to statistical power than measurement of the “active moiety” itself. Equally under other conditions, variances in clearance may be such that the drug is more discriminatory than the metabolite.

Outcomes of simulated bioequivalence studies showing the likelihood of passing the acceptance criterion when the decision is based upon measurement of different chemical moieties (Acceptance criterion: 90% confidence interval of F_m within 0.80,1.25.).

Condition (CL_m/CL_R)	True F_m	D	M	D+M	D or M
Low for D & Low for M	0.85	98	29	29	98
	0.80-	6	4	4	10
Low for D & High for M	0.85	98	20	20	99
	0.80-	6	2	2	8
High for D & Low for M	0.85	42	83	42	91
	0.80-	3	4	3	7
High for D & High for M	0.85	42	37	37	63
	0.80-	4	4	4	8

D — a priori decision to use drug data only.
M — a priori decision to use metabolite data only.
D+M — requirement that both drug and metabolite data pass.
D or M — a posteriori decision to use drug or metabolite data.
(M data refer to main primary metabolite)

200 cross-over studies with 20 subjects.
$CL_R = CL_R(m)$ = 100 ml/min; Q_H = 1500ml/min: V = V(m) - 100 L: Dose = 1 unit
CL_{ml}/CL_m = 0.8; CL_{ml} (ml)/CL_m (ml) - 0.8
Coefficients of variation (inter; intra): CL_m s (0.40,0.15); CL_R s (0.15; 0.05); Q_H (0.10; 0.02)
Log (CL_m/CL_R): D = -1.0 (low) to + 2.6 (high); M = -0.06 (low) to + 2.4 (high)

F_{rel} = relative bioavailability (0.85 = bioequivalent; 0.80 - bioinequivalent); CL = clearance;
V = volume of distribution; Q = blood flow
Qualifiers: R = renal; int = intrinsic metabolic; m = metabolite; H = hepatic;
1 = primary metabolite; 2 = secondary metabolite.
CL_m = clearance to metabolite(s); CL(m) = clearance of a metabolite.

N.B. Differences between expected and reported likelihoods for the bioinequivalent case (F_{rel} = 0.80-) are inherent in simulation due to randomisation procedure and non-infinite number of studies.
Expected value for D, M and (D + M) is 5; maximum possible value for (D or M) is 10.

We have examined some of the outcomes theoretically by computer simulation. These simulations were based on a general, linear PK model, incorporating first-pass metabolism by both parallel and sequential pathways.

Four conditions — permutations of high and low CLint of drug and metabolite — metabolic/renal clearance ratios — assumption that variance in metabolic clearance > that in renal clearance. Numbers represent % of 200 replicate crossover studies in which BE was proven. Two situations — products

by definition equivalent (Frel = 0.85) and when by definition not equivalent (Frel just below 0.8).

Decision-making can be based on four alternatives: (1) A priori use of D data only to assess BE, (2) a priori selection of M data (under both these circumstances the D and M data are statistically independent), (3) The requirement that both D + M data pass, and (4) A posteriori selection of D or M data, whichever turn out best (Under this circumstance D and M data are not independent).

Note that when BE is set a priori, either D or M are more discriminant, depending upon the conditions. Choosing the better outcome between D or M increases the likelihood of passing, but requires that both D+M data should pass defaults to whichever of the D or M data are worse.

When bioinequivalence is set a priori, the consumer risk of wrongly concluding equivalence is acceptable when using D or M data in isolation. However, when selecting either D or M, the consumer risk increases to the extent that D and M data are correlated. Taken to its limit, this doubles the alpha error (the consumer risk) — but this can be side-stepped by simply halving the acceptable consumer risk.

"Active Moiety"
Extent of exposure:
Linear system — use analyte with lowest within-subject variance, irrespective of "activity"
Non-linear system — measure "active moiety"
Rate of exposure:
Measure "active moiety"

Conclusions with regard to "active moiety". With regard to assessing "extent of exposure" — if the kinetics of drug/metabolite disposition are linear, there is no theoretical objection to basing BE on measurement of the analyte with the lowest variance, irrespective of whether it is pharmacologically active or not.

Clinicians and regulators might feel "uncomfortable" about accepting BE based on measurement of inactive compounds. Nevertheless, the issue has practical implications with regard to increasing the statistical power of studies. Studies with large numbers of subjects are not just costly, they are ethically and scientifically questionable.

Incidentally, this choice of analyte applies not only to metabolites but to isomers. Whichever exhibits the least within-subject variability in disposition, whether it be one of the isomers or the sum of the isomers (non-chiral assay), will be more discriminant of BE in a linear system, irrespective of pharmacological activity or absolute plasma drug concentrations.

Chiromaniacs stress the absolute need for chiral assays in BE testing. Only if the kinetics of the system are non-linear is it absolutely necessary to measure the active species.

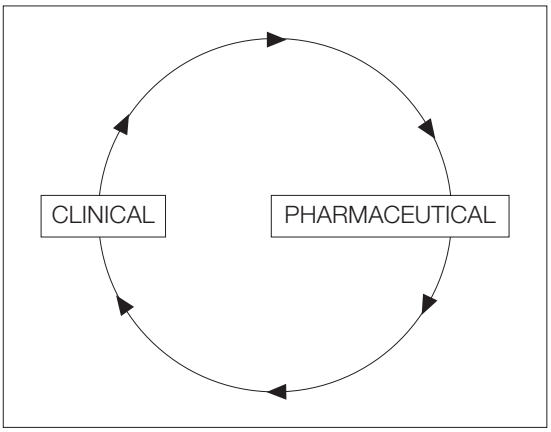
Bioequivalence
EC note for guidance: investigation of bioavailability & bioequivalence
Two products are bioequivalent… if their bioavailabilities (rate and extent) after administration in the same molar dose are similar to such a degree that their effect, with respect to both safety and efficacy, will be essentially the same.

In conclusion, then, I think we are moving towards a more rationale basis for the assessment of BE. This is the latest EC definition — note the focus on safety and efficacy — but it still mentions the extent and rate of BA.

Bioequivalence

Two products are bioequivalent if the rate and extent of systemic drug exposure after administration of the same molar dose are similar to such a degree that their effects with respect to both safety and efficacy will be essentially the same.

This is my proposal — emphasising safety and efficacy and exposure.



The assessment of BE continues to pose conceptual problems, not the least of which is that of reconciling both pharmaceutical and clinical concerns. General guidelines are difficult to formulate and often reinforce this vicious circle.

At the end of the day, each drug product should be considered with respect to what is actually known about its kinetic and pharmacological properties. We must define, or at least make much greater effort to define, a therapeutic classification as well as a biopharmaceutical classification.

Biopharmaceutic Classification System (BCS): a Policy Implementation Approach

Update May 1996

Lawrence J. LESKO, Ph.D.

Biopharmaceutic classification system (BCS): a policy implementation approach Update May 1996

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Introduction

The BCS is one of several inter-related research projects supported by the FDA in the area of product quality and drug registration since 1991. The purpose of supporting this research is to develop a firm scientific basis for regulatory decision-making as it relates to assuring the quality and performance of drug delivery systems. Product quality is one pillar of support for drug registration, the other pillar being the documentation of safety and efficacy of the active drug substance.

Product quality and performance is an important concern of regulatory authorities because over the lifetime of an innovator product there may be many pre-approval and post-approval changes in formulation, equipment, manufacturing process or site of manufacture. Regulatory authorities generally use either *in vitro* dissolution tests or *in vivo* bioequivalence studies to link the performance of the pivotal clinical trial dosage form to the currently marketed product. Furthermore, after patent expiration, there may be multiple manufacturers of a given product which are approved for marketing on the basis of *in vitro* dissolution or bioequivalence tests without further demonstration of safety and efficacy.

The first Capsugel Symposium on the BCS was held in May 1995 in Princeton, New Jersey, and a proceedings booklet was published by the sponsor. At the meeting, I discussed our initial thoughts on implementing regulatory policy based on the BCS and there were several key topics which were discussed by the participants:

1. What is the process for bringing research results to regulatory policy?

2. What are the unresolved scientific issues from an industry perspective?

3. What are the potential regulatory applications of the BCS?

Over the past 12 months, significant progress has been made in all of these areas. The FDA has established a public dialogue with representatives of the pharmaceutical industry and this has led to the issuance of the first Scale-Up and Post-Approval Change Guidance for Immediate-Release Oral Drug Products (SUPAC-IR) in November 1995. The SUPAC-IR guidance relied on the BCS primarily in defining the *in vitro* dissolution and bioequivalence requirements following a change in formulation. Furthermore, in June 1996, the FDA released a draft guidance on the Dissolution of Immediate-Release Oral Dosage Forms and this guidance utilized many principles of the BCS in defining dissolution specifications.

Currently there is an active BCS Working Group under the Biopharmaceutics Coordinating Committee (BCC) in FDA which is analyzing additional BCS research results and using these data to develop a draft BCS guidance for the pharmaceutical industry

and FDA reviewers. The BCC is a multidisciplinary oversight group that is responsible for integrating research results into regulatory policy. The BCC is also concerned with the training of reviewers and the education of industry on the principles and implications of guidances. The group is instrumental in implementing a guidance after it is finalized, resolving issues which arise in practise and revising the guidance as necessary. The draft BCS guidance is intended to be one of the foci of an April 1997 Workshop on *in vitro-in vivo* correlations sponsored by the American Association of Pharmaceutical Sciences.

Permeability determinations

Determining the solubility of a drug substance for the purpose of the BCS is relatively straightforward. In contrast, Professor Amidon, in his update, discussed a perspective on determining the permeability of a drug substance using a variety of *in vitro* and *in vivo* techniques. I agree with his suggestions and would emphasize flexibility in selecting a particular method in a given laboratory, with the understanding that the method is validated and includes an "internal standard" or set of reference compounds. Permeability studies are routinely performed early in drug development because, along with solubility data, classifying a drug based on biopharmaceutical properties allows one to predict how well the drug substance will be absorbed, and the significance of *in vitro* dissolution.

Potential applications of the BCS

The BCS Working Group has begun to explore future applications of the BCS in regulatory policy. It is intended that the SUPAC-IR guidance will be revised and two considerations have been as follows:

1. To allow greater changes in components and composition.

2. To extend the principles of SUPAC-IR into the pre-approval period.

Another application under discussion is the use of the BCS to waive *in vivo* bioequivalence requirements for certain drugs in the high permeability-high solubility class (HP-HS, Class I). Furthermore, a proposal was made by Doctor Aziz Karim in Tokyo, Japan at the FIP BioInternational Meeting in April 1996 to predict food-induced changes in the rate and extent of absorption using a classification system based on permeability and solubility. For example, Doctor Karim predicted that for drugs with low permeability and high solubility, the probable food-effect response would be decreased absorption unrelated to the fat content of the meal.

One of the major applications of the BCS is to set mechanistic-based dissolution specifications for immediate-release products. The intent, at the initiation of this research, was to move from a "one size fits all" paradigm of dissolution testing and specifications to a scaled approach to dissolution test conditions and requirements which are based on the biopharmaceutical properties of the drug substance.

The concept of moving from "one size fits all" regulatory requirements to more scientifically based requirements tailored to specific drugs or drug classes can also be extended to the world of bioequivalence testing. This idea was presented by Doctor Roger Williams at the FIP BioInternational '96 Meeting. Accordingly, the bioequivalence of some drugs can be determined by traditional use of plasma concentration-time data and the metrics of area-under-curve and maximum plasma concentration, with either single administration or replicate administration. In the latter case, the principles of individual bioequivalence might apply and acceptance criteria can be unscaled or scaled to the intrasubject variability of the test dosage form relative to the reference formulation. In other cases, e. g., metered dose inhalers, bioequivalence testing can be based on a pharmacodynamic response in light of the very low or unmeasurable plasma concentrations of the active drug substance. Still, in a few cases, comparative clinical trials may have to be used for bioequivalence when either pharmacokinetic or pharmaco-dynamic approaches are not suitable.

The BCS plays an important role in this hierarchy of bioequivalence test methods. One could imagine that for drugs that are both highly soluble and highly permeable, and whose formulations are rapidly dissolving (e. g., 85% in 15 minutes in simulated gastric fluid), bioequivalence studies could be waived in situations where they are currently required for regulatory decision making.

In summary, the BCS is an example of a collaborative research effort which has the potential for significant benefits to the pharmaceutical industry and regulatory agencies. Over the past year since the

first Capsugel Symposium on the BCS, we have made marked progress in further defining the mechanistic basis for the BCS. Certainly further public discussion of the concepts and applications of the BCS with regulated industry and academicians are planned before implementation of guidances or policies, and we look forward to those discussions. This research on product quality, like other FDA-sponsored research projects, is an integral part of a paradigm in the Office of Pharmaceutical Sciences which links basic and applied research to regulatory policy, and finally to review implementation and management in a meaningful and structured way.

Acknowledgments

I would like to acknowledge the contributions of Professor Gordon Amidon (University of Michigan) and Professor Hans Lennernäs (University of Uppsala), and their staffs, in providing the basic solubility and permeability information which supports the BCS; also, Doctor Tomas Salmonson and his colleagues at the Medical Products Agency in Sweden for their collaboration and support of the bioanalytical work associated with permeability studies ; my colleagues at FDA, Doctor Roger Williams, Doctor Vinod Shah and Doctor Ajaz Hussain who have worked with me to develop the regulatory perspective for the BCS; and finally, I would like to acknowledge Capsugel for creating the opportunity to discuss the BCS publicly with experts in the pharmaceutical and academic fields.

Drug Formulations: their Impact upon Drug Classification and *in vitro/in vivo* Correlations

Professor Jean-Marc AIACHE, Ph.D.

Drug formulations: their impact upon drug classification and *in vitro/in vivo* correlations

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For drug formulation it is compulsory to list, to know and to check, like a pilot in a plane, all the drug parameters required to obtain an active dosage form able to release its drug:

- at the right place (in the gastrointestinal tract for example),
- at the right time,
- in a sufficient amount so that drug is absorbed to reach its site of action.

These parameters are related to the:

- drug dissolution rate: particle size, crystal shape, polymorphism…
- drug absorption: type of absorption, site of absorption, pKa, gastrointestinal tract stability, adsorption on the surface of the intestine wall, first-pass-effect (FPE).

So, it is a good way which consists in studying systematically drug permeability in relation to its solubility. It is a necessary tool for people involved in drug dosage form elaboration but to what extent can the data obtained in such studies be used or can be interpreted to evaluate the performances of a dosage form like its bioavailability and/or bioequivalence to an innovator? This is the true question.

The determination of permeability in a single pH solution (6.5) and at a single site of the digestive tract (jejunum) (1) does not seem to be very compatible with the administration of drug formulations. We are going to raise some issues in this connection.

I - pH issues

a) The influence of the administered solution pH on gastric emptying and consequently, drug absorption

The first example is that of aspirin. Some years ago these were available on the French market many effervescent tablets which seemed to be pharmaceutically equivalent since they contained

- 350 mg aspirin,
- citric acid, sodium bicarbonate as main excipients and some others used as diluants or lubricants.

Almost all these tablets weighed 3 g and gave a complete solution after 3 minutes. Theoretically, these solutions must be bioequivalent (less than 15'-(1)). It has never been the case! (*Figure 1*) - and the differences were easily correlated with the pH of the administered solution. The acidic one gave lower blood levels of salicylic acid (at this time, it was not possible to evaluate the unchanged drug!) and delayed Tmax. On the contrary, the solutions, the pH of which was close to neutral (6.5 to 7.2) gave the highest blood level in quite half an hour! (2). The pH differences may be attributed to the amount of acidic or alkaline excipients.

This result is also close to the fact that low pH delays gastric emptying, high pH slows down this rate (3).

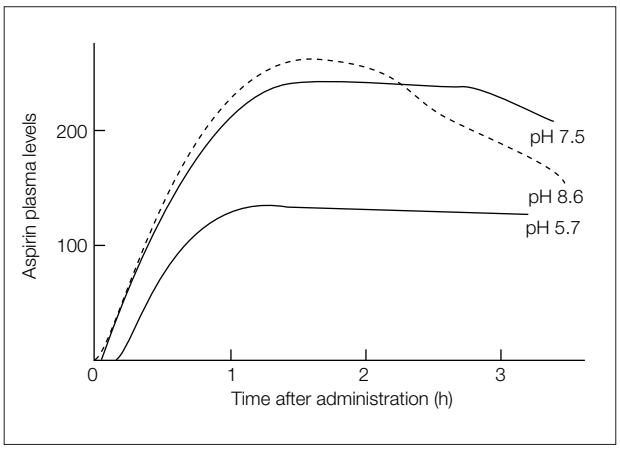

Figure 1. Influence of pH on aspirin absorption from effervescent tablets.

b) The volume of dissolution medium and pH

Adir and Barr described a special case: two tetracycline products showed no difference in average urinary recovery when given during the day (4). One product also showed no difference in urinary recovery when administered day or night. The other product however, had a significantly reduced extent of absorption during the night. The solubility and dissolution rate of tetracycline is smaller at higher pH and hence, bioavailability of tetracycline from solid dosage forms can be decreased at night when gastric pH increases and the volume of gastric fluid decreases. It was a "poor formulation" due to the presence of one excipient (that is not described in the paper!).

c) pH, dissolution medium and absorption site

This can be illustrated by furosemide. In the biopharmaceutical classification, it is the last class of drugs – Low Solubility-Low Permeability – with the G. Amidon's mention "that if I were in development and I got one, I would try to kill it because you are going uphill in all directions" (1). Some years ago, when it became possible to prepare generics of this drug, a lot of work has been made about these formulations that allowed to find specific pH for dissolution studies in vitro and *in vivo/in vitro* correlation predictive of blood levels. In a first step, it has been tried to determine what was the best in vitro pH dissolution medium to compare the dosage forms. From the partition coefficients (octanol/water) determined as a function of pH and solubility, it has been seen that drug solubility increased with the decrease of the partition coefficient value. So, the conclusion was that furosemide absorption was facilitated at low pH and by the contact with lipophilic surfaces of the intestinal tissue as opposed to gastric tissue. So, it has been assumed that the first part of the small intestine would be the most appropriate site for furosemide absorption, site where pH is between 4 and 5, the other pH would be critical, even if drug is fully and completely soluble but at the same time, it is in an ionised form (5).

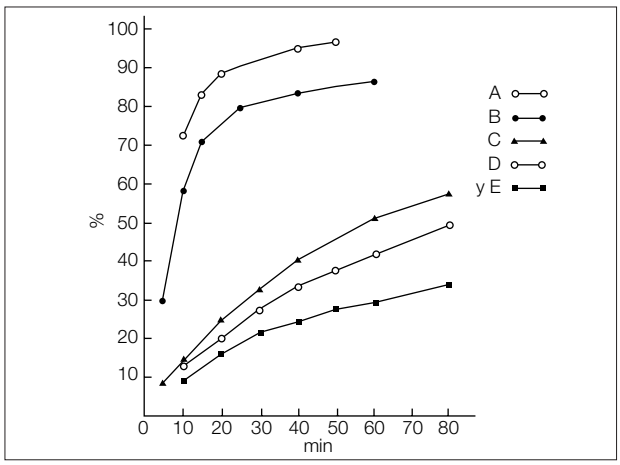

Figure 2. Dissolution profiles at pH 4.5 of 40 mg furosemide tablets (expressed in % from the drug amount dissolved).

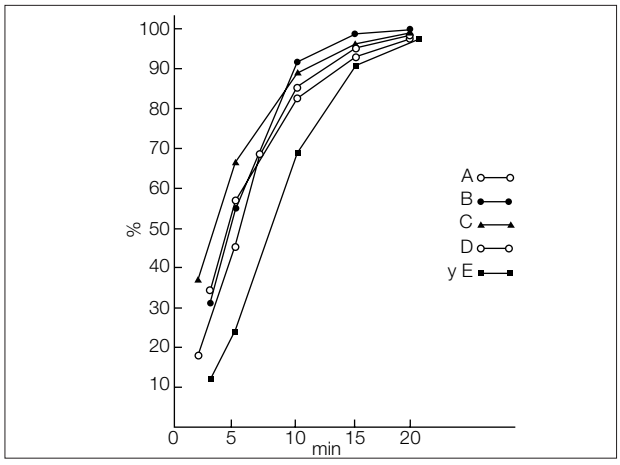

Figure 3. Dissolution profiles at pH 7.2 of 40 mg furosemide tablets (expressed in % from the drug amount dissolved).

Thus, the choice of a dissolution medium at pH 4.5 was decided and a lot of comparisons were made. *Figures 2 and 3* show the dissolution profiles of 5 products at pH 4.5 and 7.2: the discriminating power of the first medium is obvious. In a second step, 5 drug products were selected for an *in vitro/in vivo* study. The differences observed in vitro were detected *in vivo* (*Figures 4, 5*): one product that pratically did not release its drug in vitro, did not give any blood level.

Furthermore, from all these results and using a classical one-compartment model equation, it has been possible to simulate plasma level curves (*Figures 6,7*).

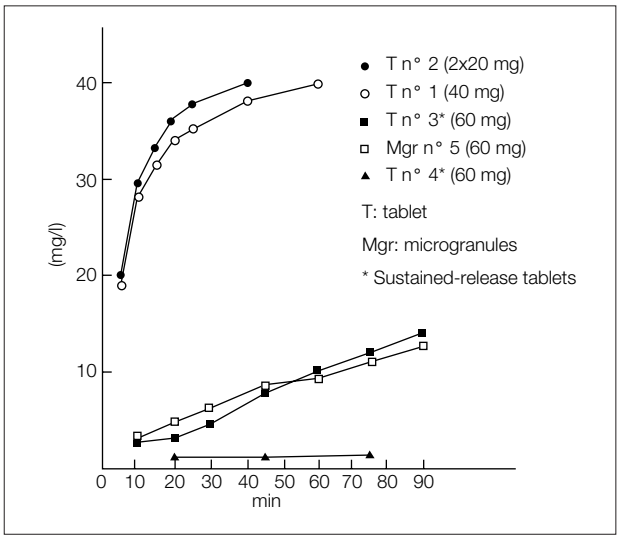

Figure 4. Dissolution profiles at pH 4.5 of 40 and 60 mg furosemide drug dosage forms (expressed in mg/l from the drug amount dissolved).

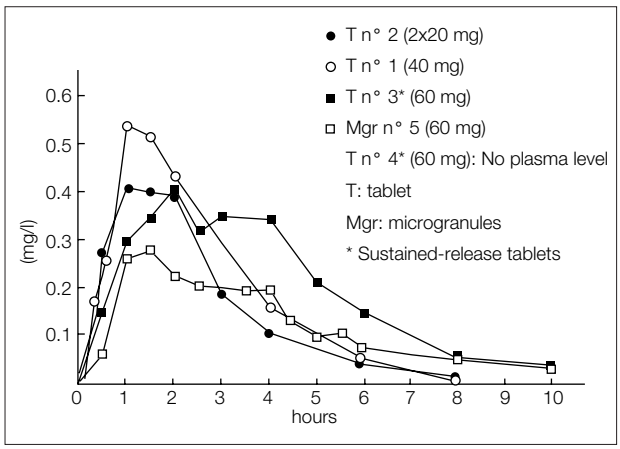

Figure 5. Plasma level profiles of furosemide after oral administration to volunteers.

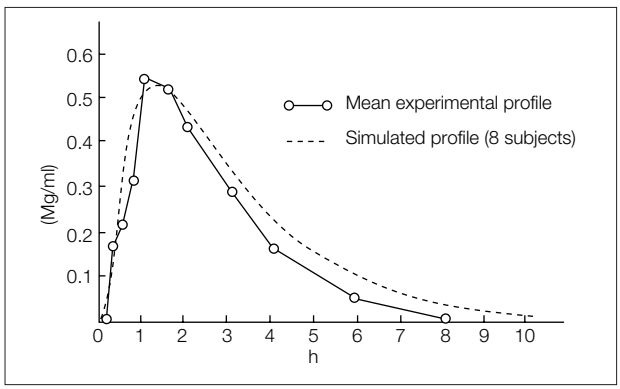

Figure 6. Plasma level profiles of 40 mg furosemide tablets.

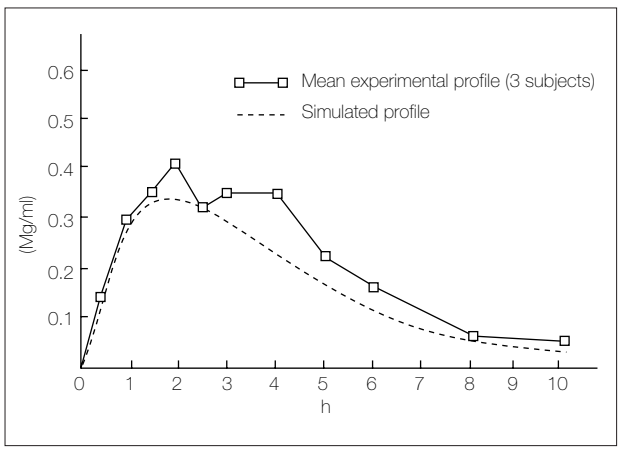

Figure 7. Plasma level profiles of 60 mg furosemide tablets.

The interest of pH 4.5 has been recently confirmed by the results of an international study sponsored by FIP and OLMCS Section: the acetate buffer (pH 4.6) as a dissolution medium seems to offer improved discriminating ability in drug release characteristics between products, but drug release appears to be longer than with the phosphate buffer (pH 5.8) (6) (*Figure 8*).

Two issues come from these results. The first one is the choice of a dissolution medium: is it more important to get a quick dissolution time without discriminating power or a longer one with a good discriminating power ? A dilemma! The second one is related to the classification of furosemide in the class IV (low permeability, low solubility) due to the fact that it was studied in a solution at pH 6.5 (fully ionised) and in the jejunum!

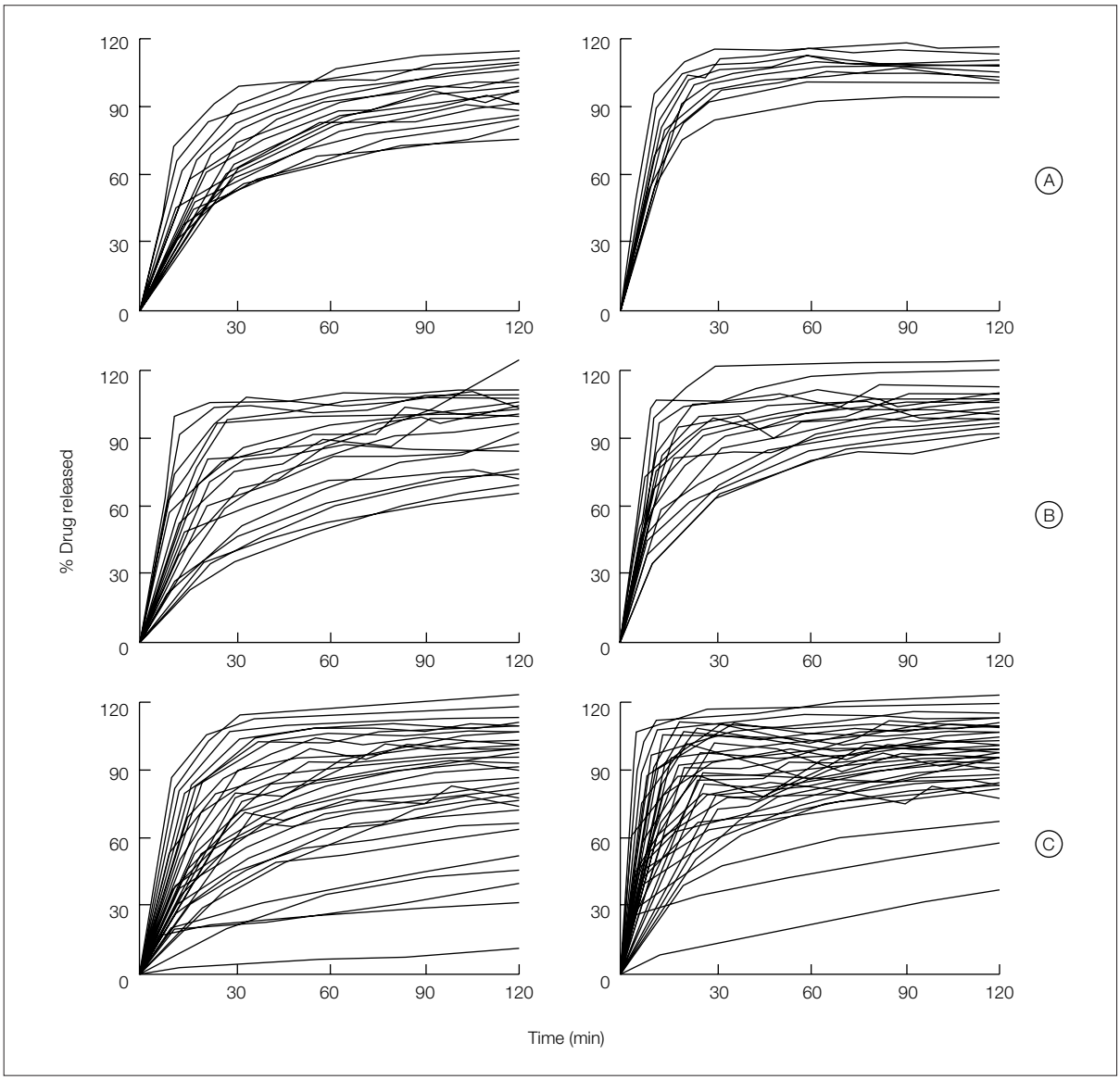

Figure 8. Dissolution Profiles. Drug release characteristics of furosemide products using acetate pH 4.6 (upper profiles) and phosphate pH 5.8 (lower profiles) buffers: A, Standard, Sample; B, Lasix (Innovator's) and C, other furosemide products.

II - Absorption site

Is the determined permeability at one absorption site convenient to every drug?

a) Prodrug absorption site

A good example: "glafenine": 4-(2''[β,γ-dihydroxypropoxycarbonyl]phenilamino)7-chloroquinoleine. It is 5 times more active than aspirin to pain and 10 - times as anti inflammatory. Its metabolism is particular because it is rapidly transformed into glafenic acid, which was demonstrated as the mechanism of action. So, glafenine is a prodrug and glafenic acid is the active moiety which is detected 15 minutes after administration of a single dose of 600 mg (7).

In vitro, the dissolution rate of glafenine from tablets was about 90% in 30 minutes in HCl 0.1N with the paddle at 50 rpm. A study demonstrated the bioequivalence of the innovator and the generic elaborated based on glafenic acid plasma levels. But, as for furosemide, it was demonstrated that the absorption site of glafenine was the first part of the small intestine because when administered in enteric coated hard gelatine capsules (8), which dissolution pH is close to 6.5, no blood level of glafenic acid was detected (the release of drug was followed by X-rays because the forms contained barium sulphate as a marker). But due to this special absorption and/or transformation site, it was impossible to prepare a prolonged-release dosage form whatever the various formula established: floating, swelling tablets, associated with gastrointestinal tract transit inhibitors (7).

b) Absorption site and pH of dissolution medium

Indomethacin is a good example for this issue. It is a well-known NSAIDs which was also studied with the same aim as glafenine: generic product and sustained-release dosage forms.

It was not really difficult to develop a generic at the laboratory scale but the scale-up to pilot and industrial batches was not really easy due to the use of an antistatic excipient, lecithin, and its incorporation technique in the drug excipient mixture. Furthermore, this drug presents some polymorphs, which can modify the dissolution rate. The absence of influence of the manufacturing process on polymorphous formation has still to be demonstrated.

The dissolution of the indomethacin hard gelatine capsules was complete in 20 minutes in a dissolution medium at pH 7.2 in which the solubility of drug is complete, while it is quite insoluble at pH 1.5 (9).

The determination of its absorption site with the same method used for glafenine showed that this drug is well absorbed all along the intestinal tract at an alkaline pH for up to 8 hours after the capsule opens. This fact allowed the development of a prolonged release dosage form, as hydrophilic matrix tablets which were bioequivalent to an OROS system, and an *in vitro/in vivo* correlation was established (10). Very recently, a work was published about Poly (D-L) Lactic biodegradable nanocapsules containing indomethacin in which drug absorption takes place in the last part of the small intestine (11). These data are well correlated with those already published (9-10).

c) Determination of the drug absorption site in the gastrointestinal tract

Many times, it is necessary to determine whether drug is absorbed all along the gastrointestinal tract. Jean Hirtz and co-workers from the Ciba-Geigy

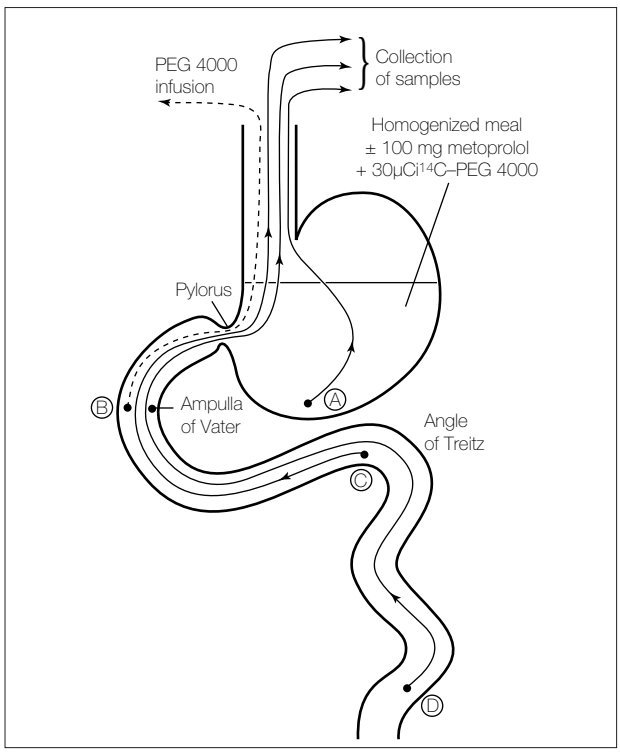

Figure 9. Schematic representation of the position of the tubes within the gastrointestinal tract. Distance from B to C = 20 cm ; distance from C to D = 30 cm.

Company made a lot of work about this subject. In order to develop various prolonged release dosage forms, this group developed in 1984-85 an intubation method with which it was possible to evaluate the drug absorption from the whole gastrointestinal tract of man. The principle of their method is similar to the one previously described by Gordon Amidon (1), with or without any balloon so that all the different parts of the gastrointestinal tract are able to be studied (*Figures 9, 10*). The luminal disappearance of drug was related to drug plasma levels (12).

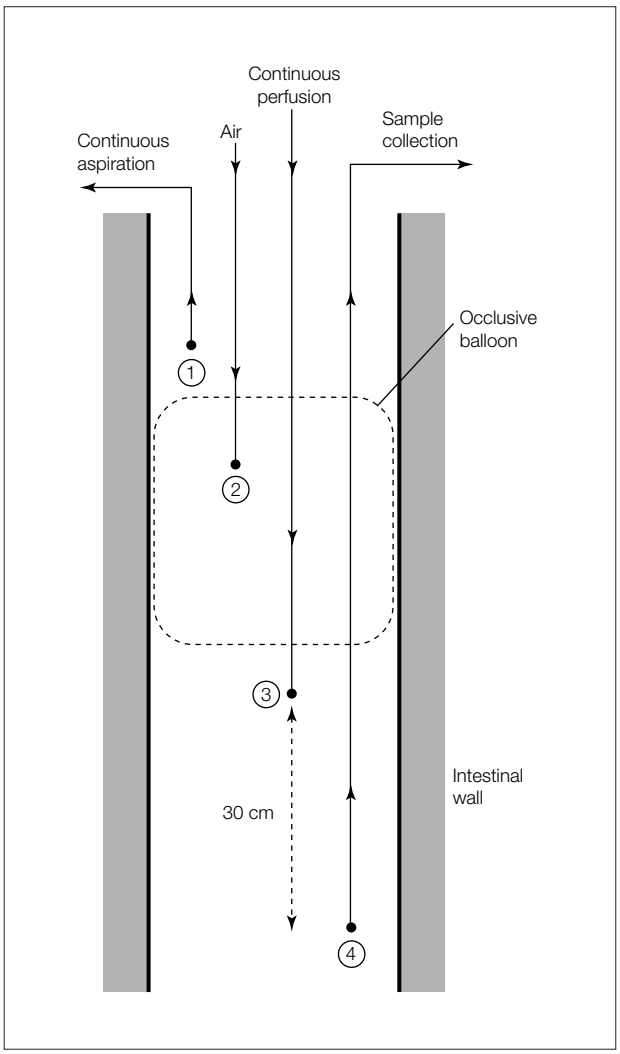

Figure 10. Schematic representation of tubes in the intestine.

They applied this method to diclofenac for which "some gastric absorption was established with the meal, but the plasma-drug concentration/time profiles, mainly reflected the process of gastric emptying" (13).

They also studied metoprolol for which no gastric absorption was demonstrated but a linear relationship between the rate of duodenal or jejunal absorption and the rate of drug delivery to the studied segment was established. In fact, this rate of delivery is directly related to the gastric-emptying rate. The absorption rates are the same in the duodenum and in the jejunum as well as in the ileum or caecum. So, a prolonged delivery system has been developed since the drug is absorbed all along the gastrointestinal tract (14-17).

The same results were obtained with oxprenolol: no gastric absorption was detected but 80% of the drug was absorbed from the duodenum and 80% of the rest in a 30 cm segment of the jejunum. But the AUCs were not related to the absorbed amounts determined by the decrease of drug concentrations in luminal fluid (18).

It is true that the Hirtz-Bernier's method used homogenised meals for drug administration to volunteers and they assumed that the gastrointestinal tract pH of the volunteers during experiment is quite natural but the amount of information coming from these experiments is really important. (14-17 and 19) The influence of food on drug absorption was also evaluated (19).

III - Modification of dissolution rate and/or solubility

Finally, formulations or some special modifications of drug can improve the dissolution rate (and sometimes, solubility) so that a drug could go from one class of the biopharmaceutical classification to another.

Two examples:

The first one is piroxicam: the drug belongs to the second class of the biopharmaceutical classification – Low Solubility and High Permeability. Using σ-cyclodextrine as additive, it is possible to increase the drug dissolution and absorption rate. This increases consequently bioavailability while the secondary effects decrease (20).

The second example is related to oxodipine, an analogue of nifedipine.

Oxodipine (OD), dihydro-1,4-dimethyl-2,6(benzodioxol-1,3-il-4)-4-pyridine-3,5-dicarboxylate-methyl-ethylester, is a calcium channel blocker of the 1-4dihydropyridine family.

This drug presents a low solubility and a slow dissolution rate. So, we tried to modify these parameters by preparing an OD-PVP (Polyvinyl pyrrolidone) complex with lauryl sulphate and a solid dispersion of amorphous OD in PVP. The dissolution of OD was improved and 80% was dissolved in 60 minutes. The comparison of pure drug, micronised pure drug and solid dispersion in vitro and *in vivo*, showed an improvement in solubility, dissolution rate and bioavailability (absorption rate and absorbed amount) (21) (*Figure 11*).

A good *in vitro/in vivo* correlation was also obtained between the percentage dissolved in one hour and the relative bioavailability of solid dispersion (*Figure. 12*).

At the same time, an absolute bioavailability determination showed that oral route presents first-pass-effect (FPE), the value of which is a function of the kind of drug administered: micronised drug or solid dispersion. It can be demonstrated that the variability of FPE (the amount of metabolised drug) is due to the saturation of metabolic enzyme systems.

Finally, a PK-PD study was conducted on diastolic pressure and heart rate: a good correlation was also established (*Figure 13*).

So, from all this information the development of a therapeutic system was initiated.

A step-by-step approach is used to calculate the plasma concentrations necessary to obtain a lowered blood pressure for 24 hours after administration.

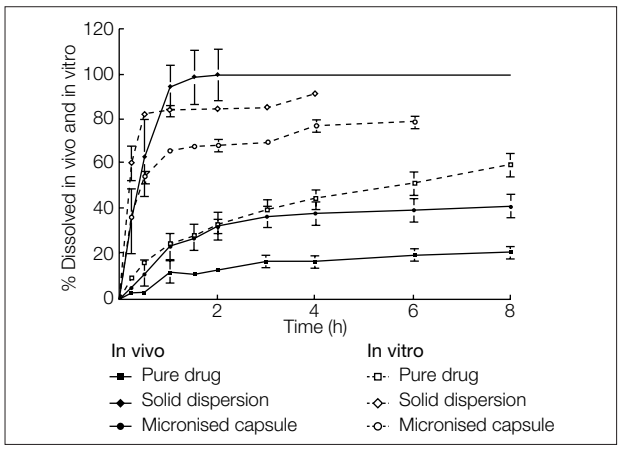

Figure 11. In vivo percent dissolved, determined by deconvolution, and in vitro percent dissolved obtained with the paddle method, for various formulations of OD (Mean ± SEM, n = 6).

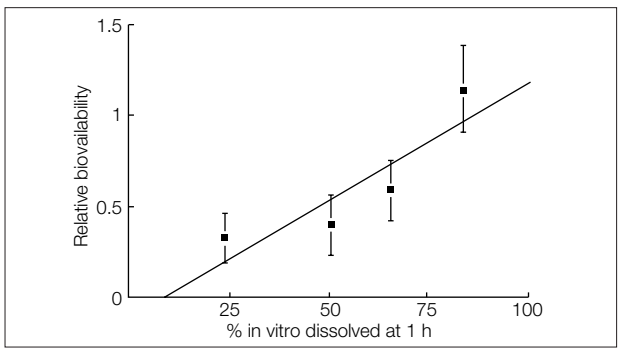

Figure 12. Relationship between in vitro percent dissolved at 1h and relative bioavailability of various formulations of OD.

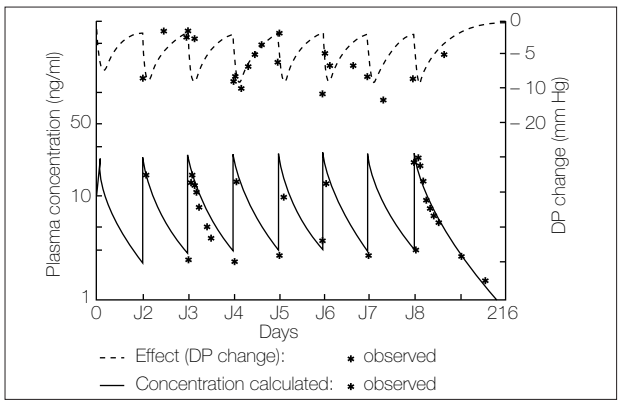

Figure 13. Simultaneous pharmacokinetic/pharmacodynamic simulation in healthy subject after multiple dosing (means from 6 subjects).

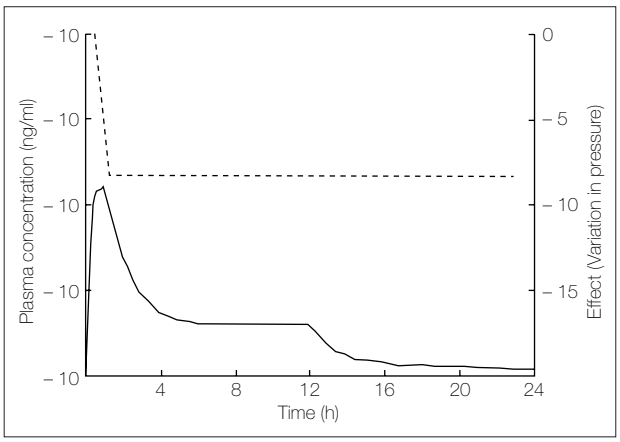

Figure 14. Theoretical plasma and effect profile of therapeutic system determined from pharmacokinetic/pharmacodynamic model.

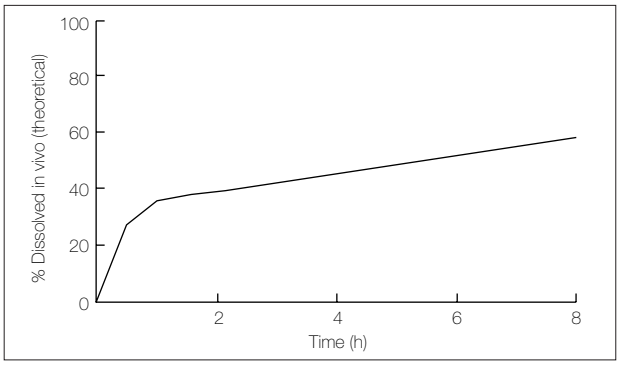

Figure 15. Theoretical in vivo percent dissolved determined from the theoretical plasma profile.

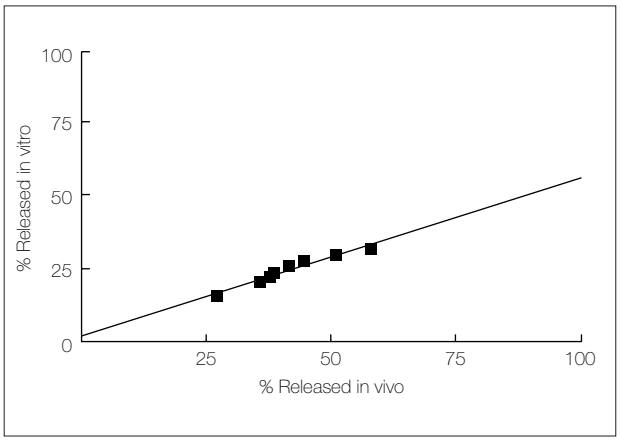

Figure 16. In vitro/in vivo correlation between in vitro percent released and in vivo theoretical percent released.

After administration of OD in patients, the maximum fall in blood pressure is 8.4 mmHg. corresponding to a plasma concentration of about 5 ng/ml. To obtain a high enough initial absorption rate to saturate the first-pass effect and ensure a sustained entry of the drug for long enough to maintain effective plasma levels, the absorption has practically to be in two phases, a first saturation dose with rapid entry to achieve high systemic levels followed by a second controlled-entry phase to maintain these levels.

The theoretical profile, represented in *Figure 14*, displays a plasma concentration peak of about 20 ng/ml. A level of 5 ng/ml is maintained for 12 h and the pharmacodynamic effect is sustained for 24 h.

From this theoretical *in vivo* profile, the *in vivo* dissolution profiles represented in *Figure 8* were calculated by numerical deconvolution using the per oral solution as a reference (*Figure 15*).

In view of *in vitro/in vivo* correlations, a modified release form presenting, under correlation-compliant operating conditions, in vitro kinetics identical to theoretical *in vivo* dissolution kinetics, should possess a plasma profile close to the theoretical profile and a therapeutic effect close to the optimum effect sought.

Various drug dosage forms were prepared and tested in vitro until dissolution kinetics compatible with the model were obtained. The form chosen was a two-layer modified release tablet consisting of a fast release layer (5 mg in OD-PVP dispersion) providing an initial rapid dissolution and absorption phase, and a slow release matrix (15 mg in OD-PVP) for subsequent controlled release of the active principle (22).

The in vitro dissolution characteristics of this form fit the theoretical model, as shown by the close linear relation obtained between percentage dissolved i*n vitro* and *in vivo* and the correlation coefficient r2 = 0.94 (*Figure 16*).

Six healthy volunteers weighing on average 69.2 kg and with an average age 23.7 years received the 5+15 mg prototype and a 20 mg oral solution per os in a single dose in random order. Blood samples were taken appropriately.

The results obtained showed a prompt plasma concentration peak at about 1 h followed by a short

decrease and then a steady level up to times 4 and 6 h. The maximum concentration obtained was 21.3 ± 6.6 ng/ml, the area under the curve from 0 to infinity was 138.6 ± 11.1 ng.h/ml and the relative bioavailability with respect to the solution was 105.9 ± 26.7. The results obtained were compared with the theoretical profiles by fitting the average plasma concentrations obtained on to the theoretical plasma profile, and fitting the average in vivo dissolution profile calculated by deconvolution with respect to the solution on to the theoetrical in vivo dissolution profile. These comparisons are illustrated in *Figures 17 and 18*.

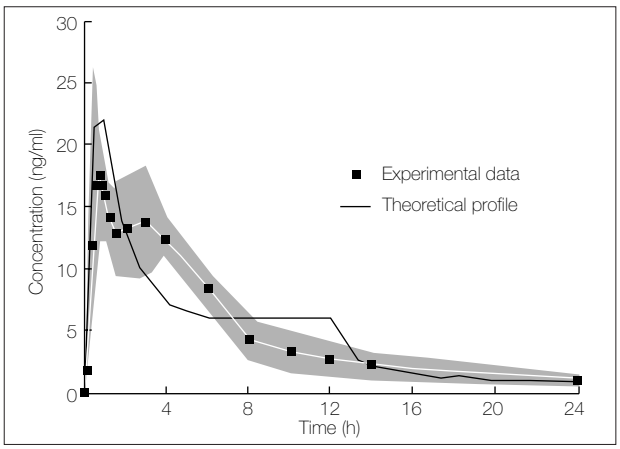

Figure 17. Comparison of theoretical plasma profile and plasma concentrations obtained after administration of a 20 mg prototype drug dosage form (Mean ± SD; n = 6). Shaded aera is established from the standard error deviation to the mean.

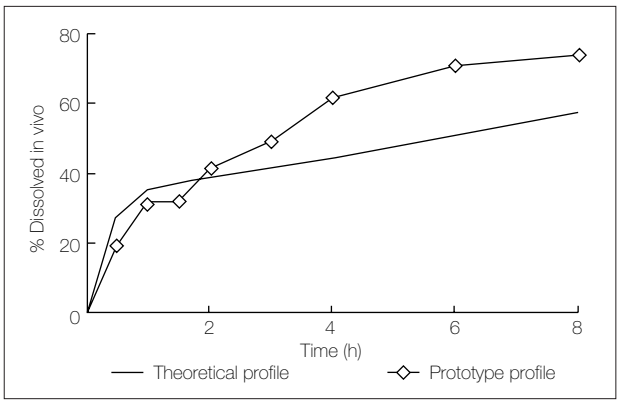

Figure 18. Comparison between the theoretical in vivo input and the experimental in vivo input determined by deconvolution from plasma data from the prototype drug dosage form.

The two-layer modified-release tablet displays a plasma profile and in vivo entry kinetics that correspond to the objectives set. The peak intensity is right, the absorption is first rapid, then controlled, the plasma concentrations are close to those required over a longer period, the entry kinetics are two-phase, and bioavailability is maximal.

Conclusion

All methods which can help the drug formulation are welcome by people involved in dosage forms development. They are all very good tools, but as a rule they are applied to pure drug and not to dosage forms where many elements may modify the in vivo or in vitro fate, but they give pre-approval parameters.

The biopharmaceutical classification belongs to this category of useful tool, but few drugs are studied today and furthermore they are "old well known drugs" of less interest for tomorrow dosage form development, except for special modified release forms.

Finally, the last point but not the least, today the in vitro/in vivo correlations are really possible and quite for every dosage form (conventional or modified release), and their interest is obvious to everyone, manufacturers or registration Authorities. The main issue is neither "how to do" nor "on what to do them" but WHEN! The best is at the first stage of development and not later, when it is always too late. So, in this way it will be possible to reduce the number of bioequivalence studies.

For post-approval, it would be necessary to study the dosage form engineering so that the manufacturing parameters will be managed and a change of manufacturing site combined with in vitro/in vivo correlations, and engineering would provide us with the way of a new kind of bioequivalence studies.

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Panel Discussion

Geneva, Switzerland
May 14, 1996

Panel Discussion Geneva

Professor J. Michael Newton: Due to personal events, Professor Breimer could not attend, and has been replaced by Professor Hans Junginger of the University of Leiden. Professor Henning Blume of the Zentrallaboratorium Deutscher Apoteker is here, and we have been joined by Doctor Tomas Salmonson from Sweden's Medical Products Agency (MPA) in Uppsala. So that is the new composition of the panel. Professor Hans Junginger will start the discussion.

Professor Hans Junginger, ***University of Leiden, NL:*** Thank you, Mike, for giving me the opportunity. It was completely unexpected, and a real breakfast surprise, but I will try to do my best. First of all, I would like to congratulate the organizer for this symposium because it is a multidisciplinary approach for academia. We have had a lot of lectures until now from people from academia and also one from regulatory affairs, but I think we should also speed up the discussion in order to give the third party — namely, the industry — this possibility and chance for discussion.

As Gordon already mentioned, we discussed some issues over breakfast, and I was challenging him because he made a statement and also he had his slide (with him). He was stating that if two drug products containing the same drug have the same permeability/concentration/time profile as the intestinal wall, they will have the same rate and extent of tract absorption, and I was saying could you even extend this definition to say, not two drug products, but if two drugs have the same permeability/concentration/time profile and so on, that we have an even broader definition so that you can compare drugs which have the same characteristics, and then going back to the classification, then perhaps you could have simpler tests if you could already classify a drug as belonging to category 1, 2 3 or 4. This is the first remark I have.

The second remark was I think I saw by Gordon that he was saying classification 4 may be predictable by in vitro dissolution rate. I was looking at a sheet of Larry, he was saying "No". My question is simply why is it also dissolution/dependent in case 2, but not in case 4? Why is it not possibly an in vivo/in vitro correlation? Basically it is a more general question, namely. To what extent, for instance, can a drug formulation overrule drug classification so that — by increasing solubility and if you have some penetration modifiers — a dosage form can come from a drug with low solubility and low permeability to a drug with a high solubility and at least an improved permeability?

Professor Henning Blume, *Zentrallaboratorium Deutscher Apotheker, D:* Yes, thank you very much. That was really an exciting symposium so far and we heard some interesting presentations and saw some interesting data. When I came to Geneva yesterday, late afternoon, I came being convinced of some, let me say, fundamental statements.

First of all, from my principle understanding, bioavailability is primarily drug product-related characteristics and not so far a drug substance parameter.

Secondly, a similar statement is true for *in vivo/in vitro* correlations, and has confirmed by the last speaker Professor Aiache, if also *in vivo/in vitro* correlations are not so much drug substance-related characteristics but are a more characteristics of the drug product.

Looking at the data from the University of Maryland, I was a little confused and I would like to come back to that problem in my remark. Also Hans Junginger said something in the same direction and that is really the basic question which we have to discuss in this conference.

The data for drug substances from class 1 — high permeability, high solubility — showed that even if dissolution was reduced to about 40 per cent, if I remember correctly, after 15 minutes, no differences in vivo occurred, and there are some options for an interpretation of these findings. One is, and that is what Larry Lesko mentioned in line with the philosophy of the biopharmaceutical classifications systems, that in such cases of drug substances which are highly soluble you will not find in vivo bioavailability problems.

However, I have personally some doubts. Doubts, because I know from cases on the German market — for example, verapamil immediate-release formulations and if possible I could show you later on the data to support my point of view — certain bioavailability problems, although as I heard (during the conference) verapamil is also a class 1 drug with high permeability and high solubility.

We found on the German market that of the group of 80 mg immediate-release formulations, or I would like to say, so-called immediate-release formulations, several products which dissolve the active drug ingredient to about 100 per cent within five to 10 minutes. However, there were some others which dissolve less than 30 per cent within 20 minutes and there is a bioequivalence investigation available showing that such two formulations differ in rate and extent of bioavailability. In this particular situation we have a class 1 drug substance, where drug products differ in dissolution and finally the bioavailability is different.

The basic question I would like to ask Doctor Lesko is, do you believe that the dissolution findings from the Maryland study reflect the situation in vivo correctly? Because that is a crucial question. If the dissolution methodology is not appropriate to predict the dissolution behaviour in vivo, your result is quite understandable. And to go one step further, what about controlled/modified-release formulations of such class 1 substances?

In these cases, dissolution is controlled by the dosage form and again if the findings of the University of Maryland, by use of an appropriate dissolution methodology are correct, I would expect no differences in vivo. But this would really surprise me. Thus, back to my basic statement at the very beginning, I still believe that also for Class 1 drugs dissolution is more important than just solubility, as dissolution is a characteristics of the dosage form, while solubility is a characteristics of the drug substance.

Doctor Thomas Salmonson, *MPA, Sweden:* I knew that I was expected to say something, since Gordon asked me to give a few comments from a more European regulatory position. I would like to explain why we, from a small regulatory agency put, from our perspective, a relatively large amount of work into a research program or a system like this. We have been delighted to cooperate with Gordon, Hans and the FDA because we believe that a problem exists both for you as the pharmaceutical industry and for us as regulators. However, my personal view is, and I think that it is shared by all regulators, that regulatory guidelines should be driven by scientific discussion such as this one today, not the other way round. And as you know, we have not gone as far in Europe as they have in the US when it comes to implementing or discussing specific utilization of these types of systems.

I will focus mainly on the situation within the European Union but I think that to a large extent it also applies to other countries outside the European Union. Now, why is it so important for us? I think previous speakers have elaborated a bit on this: ethics of course, economics, since in the end it is the patient who pays for all this and regulatory, which might seem a bit bureaucratic, but regulatory reasons actually contain the first two and some other issues as well, and I'll try to highlight that.

What we are talking about here, from my point of view, is transfer of clinical efficacy data from one dosage form to another one, and I guess just stating this shows that I share the same schizophrenic feeling as Professor Tucker. Being head of preclinical and clinical unit, I see this as mainly a clinical safety and efficacy issue, where we transfer data obtained with one dosage form to another, regardless of whether it is just a small or minor change, or a slow-release dosage form developed by a new company with a totally different concentration-time profile.

Now, depending on the changes of course, there will be different types of requirements, and what we

are looking for here is somewhere to put the divider between in vitro data and more costly — and more often, I am convinced, unethical — *in vivo* studies.

In Europe today we are in a situation where we are changing from an old to a new system. We have been sharing guidelines for a long time, suddenly we have to face the awful fact that we regulators have to come to the same decisions. And to put it jokingly, it is easy for a Swede to think that our decision should be accepted in e.g. France, while we hate accepting French decisions. And this is something that we have to learn, there is a need to have good scientific standards on which to base our discussions.

If we look in our guidelines they are not very helpful. In the European guidelines it states that bioequivalence studies should be carried out when bio-inequivalence may have a therapeutic significance. Therefore, bioequivalence studies are conducted if there is a risk of bio-inequivalence or a risk of pharmacokinetic failure or diminished clinical safety. This is very logical. No one would disagree, but it will not help you or us in our discussion with other regulatory agencies.

But the guidelines contain a little bit more than this and actually state when bioequivalence studies on new products may not be required, and give a few more details. I admit that they are relatively straightforward examples and most agencies would probably agree, that in these cases, there might not be a requirement for bioequivalence studies.

But it is the situation inbetween that is the problem. In some countries, there exists a list of compounds for which bioequivalence studies are not required. Other countries — more conservative countries like Sweden will say we require bioequivalence studies for all, generics for example unless the dosage form is dispersible tablets or pure water solution. So there is a need, and that is my conclusion, for the development of scientifically valid requirements as to when bioequivalence studies or in vivo studies are needed and it is of utmost importance that we, together, start discussing these matters and develop these methods.

The views that have been presented today, are one way forward. I am sure there are other ways as well, but we are interested to hear what your views are. Thank you very much.

Doctor Agnès Artiges, *European Pharmacopoeia*: As regards our European Pharmacopoeia point of view, we have to say that we are working closely and interacting with the CPMP and CVMP working group and the quality working groups, and we organize our work in order to answer the needs for standardization of methodology and general tests, functionality testing. So we also are very interested to have multidisciplinary exchange in order to describe tests which have a meaningful interpretation. If not, there is no interest, but it is clear that we have a big need in Europe, and I would say more than in Europe, on a worldwide level, to have a common general approach in describing the tests, the apparatus, the different parameters. So, I am ready to answer any question you have in this field.

Professor Gordon L. Amidon: First I'll comment to the panel committee members briefly, because I wrote some notes here. I don't think there is anything that is in fundamental disagreement. I believe, for example, with Henning Blume that the dissolution criteria are central, and a product criterion that you have to have.

The classification system helps in deciding when to expect a correlation or not to expect a correlation, but I believe that product characteristics are critical. I think with regard to generalising the Maryland Contract and the use of a very tight dissolution specification, which is one of the questions in the file here, that we have used, or I have suggested, that 85 per cent dissolution in 15 minutes would be considered rapid dissolution. That might be considered maybe very rapid dissolution by most standards. But that is because gastric emptying halftime is about 15 minutes.

I think that may be too short a time period, particularly for class 1 drugs which because of their high solubility and high permeability would be absorbed, most likely, throughout the upper GI, so that slowing down the dissolution rate for 30 or 45 minutes will not affect the AUC, particularly if the drug pharmacokinetics are linear. The data from the Maryland Contract is supporting that, that the dissolution specification may be relaxable under these criteria, and so… I think that is something to be considered. I am pleased that Larry has taken the heat from my suggestion of very rapid dissolution time… I think we start conservative, and then you obtain evidence and argument to decide how we should proceed.

The case we are shown with furosemide by Professor Jean-Marc Aiache, that's a very interesting example, you've certainly managed to pick out the real problematical formulation and delivery candidates and we have actually studied furosemide as well and I agree, that's a difficult drug.

I think one has to admit that the classification scheme will not fix everything, will not make everything simple. There are going to be drugs that are property-dependent, whose properties depend significantly on their pH solubilization position in the gastrointestinal tract and where, in fact, bioequivalence studies may be required.

I think with regard to Hans' comment about the generalization which I mentioned in my talk this morning, I think it is an excellent suggestion that the generalization — in fact, the physical principle — is not drug product-related, it is drug-related, and I think that is a very good point and I appreciate Hans' willingness to step in at a late date this morning.

Q: How did you select the reference concentration for the perfusion and what is the rationale for selecting only one segment of the small intestine?

Professor Hans Lennernäs: Well, the reference concentration is quite easy, we took the lowest clinical dose or what the MPA in Sweden allows us to use, and we divided that by 300 ml of this perfusion solution and that's the concentration we used. But of course, if you used a low-solubility drug… We had to use a concentration that was much, much lower, to be sure that we had the drug in solution when we performed that perfusion, and then the dose was much lower than a clinical dose, of course, but we had to be sure that we had a drug in solution.

And what is the rationale for selecting only one segment? First, this classification is based on an immediate-release dosage form. For many of these drugs, the absorption occurs in the upper part of the small intestine but of course, some of the absorption is occurring further down in the small intestine. But there's also a practical reason.

It is not possible to go down to ileum with this tube because then it is difficult to have the continuous flow that we usually have using this perfusion technique. Instead you might use an open perfusion system, which allows you to go further down in the intestine. However, one problem with an open system is that it will take approximately between 20-48 hours to come into the right position. With our regional perfusion system in jejunum it only takes an hour to come into right place. This means that it will take more time and require more work to use an open perfusion system for perfusion in the more distal regions of the small intestine. Furthermore, I think permeability estimates in the upper small intestine also provide us with a good prediction of the permeability in ileum in many cases.

Doctor Larry Lesko: Thanks. I'll just comment on some of the comments of the panelists, the comparative power, if you will, of an in vivo/in vitro correlation versus the drug classification system.

Looking back in time, I often view this classification system as a path to go down in the absence of an in vivo/in vitro correlation, particularly for the immediate-release products. I guess that, speaking in terms of assuring equivalence in the face of some change in that product, in vivo/in vitro correlation seems to be like a gold standard to me, that if it exists it is ideal to utilize in judging the significance of change relative to the resulting dissolution profile. I think the classification system comes into play primarily in the absence of that in vivo/in vitro correlation.

The other side of that is that, practically speaking, in the new drug applications we rarely see an in vivo/in vitro correlation for an immediate-release product. It's not that they perhaps can't be achieved, but they are not perhaps viewed as being beneficial in terms of submitting it to the regulatory authorities for later use in decision-making. Likewise, in even a modified release, up until about three years ago we saw in vivo/in vitro correlations in only about 10 per cent or so of our applications.

That is beginning to change now that there is more of a perceived regulatory value in terms of correlations with modified release. So I think, in terms of the power of correlation versus classification, that might be one comment.

Getting to Henning's comments on the UMAB and the data that came out of that, the dissolution curves that I showed for the panel on dissolution were primarily based on the USP dissolution test system in terms of the media and in terms of the conditions, and that was our starting point. What we found, though, was the differences in vivo in the various formulations that we prepared were not large enough in terms of AUC and C-max to develop correlations, no matter what we did to the in vitro test system. When we got into the low-solubility/high-permeability class — piroxicam, for example — we were able to develop rank order correlations by tinkering with the dissolution test system. But for Class 1 highly soluble, highly permeable, the bioavailability profiles between the various formulations were so close, we just couldn't develop correlations, no matter changing the pH of the dissolution test system or the stirring speed, or whatever. So, it was a case of we couldn't make a bad product for those highly-soluble, highly-permeable drugs.

Professor Gordon L. Amidon: I just want to add in to what Larry was saying. I said in my talk, but I think it is often overlooked, that if your dissolution for a high-solubility, high-permeability drug is less than 15 minutes, then it just means you have to do multiple points. In other words, what it is saying is that you have to control the profile, and maybe 15 minutes is too short, maybe it should be 30 minutes. But it is also saying that if your dissolution is very rapid, don't expect a correlation, don't bother, in fact you don't even need to do one. So I think there are some important inferences that I just want to emphasize, that are underlying what Larry is saying. If you have an in vivo/in vitro correlation then you have a standard, but I think that the classification will allow you to say, we don't expect a correlation.

Professor Henning Blume: No doubt, USP had a very important impact on the development of appropriate dissolution methods. However, I have some problems with the fact that, as far as I know, most of the methods are based on in vivo findings. Nobody knows what the differences in dissolution, evaluated using these methods, would mean for the in vivo situation. Therefore, I understand these methods as an appropriate starting point, nevertheless I strongly ask for in vivo support of these methods to show that they are "meaningful".

Moreover, I would like to comment on the 15-minute time point. You'll also find a similar requirement in the new FIP dissolution guidelines, not 15 minutes, our consensus was a requirement of 85 per cent after 20 minutes, which is quite similar. I was one of those who strongly supported such an early time point for dissolution specifications.

The background is that normally a single-point measurement is used for quality control of immediate-release formulations and, in accordance with data from the German market, our experience is that later time points — for example, after 45 minutes but even also after 30 minutes — are much too late from my understanding. You will hardly find differences between products if using a single-point measurement after 45 minutes.

In *Figure 1* (page 88), results of the German verapamil immediate-release products are shown. Obviously, they differ strongly in dissolution profiles. Some products release almost 100 per cent of the verapamil dose within 10 minutes, other only close to 20 or 30 per cent after 20 minutes. If a single-point measurement, after 45 minutes is used these differences in the profiles are not detectable. However, also after 30 minutes, only a few products may be detected as different in dissolution. On the other hand, and as I said earlier, between these products marked differences in vivo were assessed, although verapamil is a class I drug substance.

A second example, (*Figure 2* page 88) is that of glibenclamide. Also in this slide results of the German drug market are shown. There are products which dissolve the active drug ingredient to 100 per cent after five minutes, very quickly, while in other cases, only about 30 per cent are dissolved after 10 minutes. Again, if single-point measurements after 45 minutes would be used, one would not find any differences.

In this particular case, we have established an in vivo/in vitro correlation. For this purpose we selected some of the products out of the spectrum of in vitro dissolution profiles for a subsequent bioavailability investigation. There are marked differences in the rate and extent of bioavailability of these products, and we found a nice correlation between dissolution and bioavailability and between bioavailability, expressed as "early exposure" within the first three hours, and the reduction of blood glucose levels. This is the background why I am very much in favour of early time points to be used for single-point measurements in quality control.

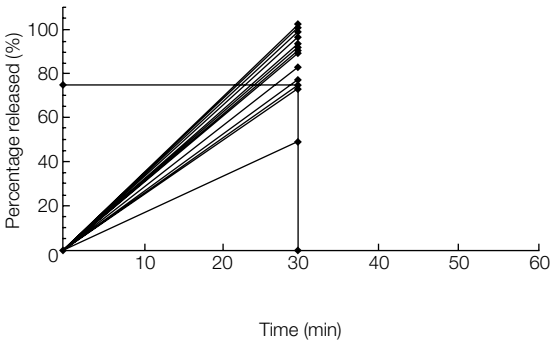
Professor Geoffrey Tucker: If I may add another dimension to the verapamil data. I think verapamil is a bad example in some ways, because it undergoes saturable first-pass metabolism. So the problem here may be simply that you have a rate of dissolution-limited metabolism, so it isn't a dissolution problem. And that's potentially one of the problems with the biochemical classification, that you're just looking at loss of drug from the lumen, you're not looking at the other side of the membrane, and with some drugs that becomes important, and the rate of dissolution is also an important factor in that context.

I think if you are going to do this, with a lot of drugs you are going to have to factor-in metabolism and its saturability, because we also now believe that there is a lot of cytochrome P450 in the intestine.

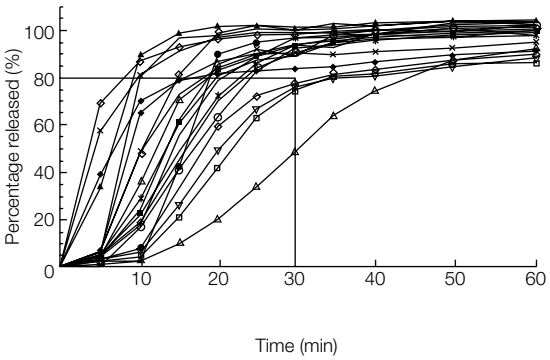
Professor Gordon L. Amidon: Isn't that what dissolution does? I mean, what you're saying is that if you control dissolution rates, you're controlling the rate of presentation to the intestinal mucosa for absorption, and also metabolism, because metabolism would be proportional to the concentration getting into the cell and the level of enzymes in

BIOPHARMACEUTICAL CHARACTERIZATION OF VERAPAMIL IR TABLETS

1-point measurements…?

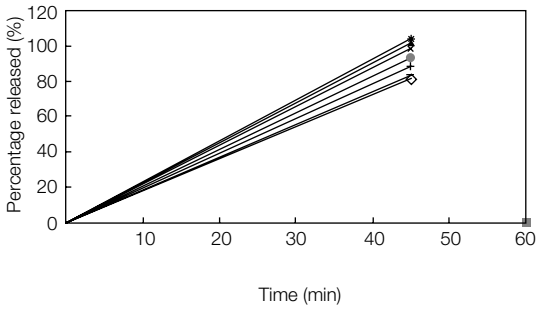


… or profiling?



BIOPHARMACEUTICAL CHARACTERIZATION OF GLIBENCLAMIDE TABLETS

1-point measurements…?



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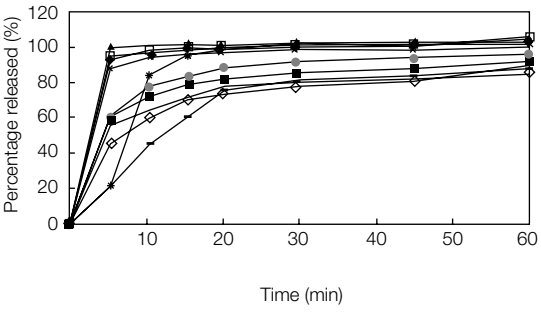

there. So, sure, controlling the dissolution rate means setting the specification for the dissolution rate as being more rapid than gastric emptying. Whether that is 15 or 20 minutes, I think that can be reasoned out, then the variability is due to gastric emptying.

If your product is slower than that, you have to be able to control the rate, otherwise you will see that variability and metabolism non-linearity could be apparent. So, then the media and methodology is critical and I think that opens up that whole issue for how we would develop a media methodology that would be reflective of the in vivo situation. I think we are in agreement, I think we are saying a lot of different data that is generally supportive of the value of classifying, plus then also obviously using dosage form descriptors; that is, dissolution.

Professor Geoffrey Tucker: But you've got to put the dissolution together with your knowledge about site-specific metabolism and saturability.

Professor Gordon L. Amidon: Yes, well, I'm not so sure for bioequivalence. You might be concerned about that for total bioavailability and the clinical pharmacology associated with the drug and metabolite ratio but if you just want to make sure your product is the same as the product used in the efficacy trial — the anchor formulation.

What you want to try and do is match it for bioequivalence, but if you are trying to design an optimal dosage form then I think all of those factors should be taken into consideration by the formulator.

Professor J. Michael Newton: I think you say at what point do you do these tests, at the early stage when the NDA comes in or are we talking about generics?

Professor Gordon L. Amidon: Larry, do you want to comment ? I think both.

Doctor Larry Lesko: Well, I guess I don't look at it as a generic new drug issue, if you will. I think once the innovator product is approved in terms of going to the market place, any subsequent changes either for that product or for changes later on in terms of post-approval changes, or as we move into the generic area, I think the issue becomes a product issue as opposed to safety and efficacy. So I think the principles we are talking about, in terms of assuring equivalence in the face of some change, apply equally to new and generic products.

Professor Jean-Marc Aiache: I come back to the point that Henning Blume said some moments ago about the in vitro technique using the Maryland studies. In my opinion, when we have a dispropensity between the in vitro/in vivo correlation, the first thing is to change the in vitro technique so that we can find either a real difference between the two formulations or demonstrate that they are not different. So, with all the techniques we currently have in different pharmacopoeia — the paddle, the flow through cell — we have the tools to do that and in our opinion I think that you agree with me that the flow through cell is really a very nice device to demonstrate either the similarity between two formulations or a big difference between two formulations, essentially if we change the pH every hour or every two hours, and so on. It is really a very important problem.

Professor Henning Kristensen, *Royal Danish School of Pharmacy:* I would like to give a personal comment and also another comment related to pharmacopoeia because I am the chairman of the clinical group of the European Pharmacopoeia and I have some viewpoints on the system in relation to the Pharmacopoeia. First, I wish to say that I heard a little about this classification system before I came here and generally I am very positive for it because I can see the possibility that Gordon, because of his sabbatical leave, has created some ideas and given some input which gives new thoughts and new rules of thinking in the pharmaceutical world, and that is very positive.

I think also that the pharmaceutical industry is more or less over-regulated today, and what we have heard from Doctor Lesko is that we can see some possibilities to loosen the system, or make it more flexible, to make life easier. But what we also see in the system is, for example, the 85 per cent/15 minutes discussion we have just heard again. I am very sorry about that discussion because it seems meaningless to me that we should make life easier for people by making a classification or specification based on 15 minutes. What Doctor Lesko says was fully satisfying and I agree completely with you and I also agree with you that one of the great issues here is that the absence of in vivo/in vitro correlations — we have these 12 classification schemes, so I feel very much in line with what the FDA representative has said.

As far as I can see, this has given us now a great input to think about formulation of drug substances. We have reasons to study, for example, dissolution testing not for pharmacopoeial purposes or quality control purposes, but for development purposes. I think we must make a distinction between what we are doing in the quality control department and

what we are doing for the development of a new product, and we have a stimulus here. We have it also in the occurrence of the many very, very low-solubility drugs, which gives us the need to develop strategies for the formulation of almost-insoluble drugs. I think you have pushed the wagon quite considerably here.

When it comes to the pharmacopoeia, I think we can do a great deal here to support the idea, which I really very much would like to do. What the pharmacopoeia can do is, for example, to go into the terminology we use. Some of the difficulties with the discussion of the 85 per cent/15 minutes is a question of terminology, because you call them immediate-release products. But what you are speaking about is not necessarily immediate release, it might be other types of products.

The pharmacopoeia can also make a good contribution in the development of testing methods. I agree with Jean-Marc in his opinion that we have good methods for the time being but maybe further methods can be developed and, in particular, the testing media — how to compose or develop the testing media. But I don't think the pharmacopoeia can make recommendations that with propanolol, for example, you don't need to carry out in vivo testing, it is not the purpose of the pharmacopoeia. I doubt even that a guideline from Brussels or the agency in London would be able to make such a recommendation.

What I see here is that we have a basis of thinking. We can, when we know enough about a drug, we can maybe classify it and have some pathway to follow in the development of the drug. I think also it's important for the manufacturers that you have a basis here for making changes in the composition, in the manufacturing methods, without too exhaustive testing and in vivo testing. But I am also sure that there will be quite a lot of opposition to the system in Europe, at least from manufacturers of pharmaceutical products, because they are afraid of the manufacture of generics. But the question concerns much more than generic development.

Professor Gordon L. Amidon: I very much appreciate your comments, Henning. I do not know the details of Europe and the European Pharmacopoeia like I do the USA and the USP. But your comments about quality control and having dissolution methodologies and media that serve different purposes I think would be an important step, that we could have a different methodology for a bioequivalence-type purpose versus routine quality control. One of the questions that I had here is that the media change in dissolution testing is difficult and not desirable.

The FDA is recommending multi-point dissolution tests in several media and I agree that that may be complicated and if your drug is not media-dependent you may have a strong case for arguing against needing to do media changing. So I do think the idea is to say we should use media change and we should enforce an elaborate methodology, that is a methodology we have confidence in, and then it can be relaxed if the drug properties are simple. If your drug in formulation is not pH-dependent, life could be a lot simpler. So I do think again that media change would be too complicated and unnecessary for some drug products. But that should be part of the regulatory package for that drug product, I guess.

Doctor Larry Lesko: Just a couple of quick comments. Prior to 1962 the FDA did approve products on the basis of in vitro dissolution. We defined at that point drugs that were not problems from a bioequivalence perspective. So there are some "pre-62 drugs", as we call them, in the market place, without the benefit of an in vivo bioequivalence.

Since 1962 we haven't approved any product without an in vivo bioequivalence study, so in a sense I often view the classification system as moving the US FDA to a more harmonizing position with other regions and other regulatory authorities in the sense that, for example, I think in Germany products can be approved on the basis of dissolution alone at some point, and products where bioequivalence testing isn't necessary are defined.

Similarly, in the World Health Organization document there are some criteria that are useful for defining when a bioequivalence study may not be needed for approving drugs in some countries. So I think the classification system is moving, from my point of view, from a very conservative position to a more harmonized position with other regions of the world.

Doctor James Swarbrick, *AAI, Wilmington, North Carolina:* I'd just like to support Larry Lesko in one of his earlier comments, that this shouldn't become a generic versus a new chemical entity conflict. But I think it's beholden on the regulatory bodies to ensure, again using Larry's terminology, that the anchor formulation is an optimal formulation. I think if that's taken care of at the beginning of the development process for the new chemical en-

tity then I think — not to put words into Geoffrey Tucker's mouth — I think some of his concerns about safety and efficacy would be diminished when the generic form came along. I think one of the major frustrations that some of us have who are involved in developing generic formulations is to formulate to a bad product, and that does nobody any good, and it's an anachronism.

Doctor Patrice Guitard, *Sandoz Pharmaceuticals, CH:* I don't want to restart the debate on your new single chemical entities and generics, but just to comment. When we start the development of the dosage form of a new single chemical entity we are sometimes working with 50 grammes, when you start with generics, you are working with kilos or tonnes. I think that it is not possible to do the same thing.

I have a question concerning the SUPAC, I think the name is post-approval. Why not pre-approval also? Because I think that when we have our anchor formulation, we continue the development and we have to improve it, and sometimes we have to make a slight change in the formulation, sometimes in the process. The daily question is: do we need bioequivalence, can we rely on dissolution? I think the extension of the SUPAC to the pre-approval will be praised by the industry.

Doctor Larry Lesko: Yes, it's a good point, and I think many people have asked that question. I have to say in the development of the SUPAC document it originally was a pre-approval and post-approval document and then as we rolled forward there were some concerns about the pre-approval area, and I think some of those concerns had to do with our field offices and compliance, rather than the offices within Rockville in the Center. So, to get the document to move forward, I believe we backed off from that pre-approval inclusion.

But as I mentioned in that one slide, that's something we are looking at right now and in my opinion — just a personal view of things — I don't see any difference in the changes that are allowed post-approval to those that are allowed pre-approval, and those changes in terms of magnitude are not much different than what was recommended in that AAPS/FDA USP workshop back in December 1991 or so. It's something we are exploring and I think that's a possibility for the next go-round on that SUPAC document.

Doctor Tomas Salmonson: Yes, I agree with Larry. Needless to say, in many European agencies today, the majority of all bioequivalence studies we see are performed by the so-called innovative industry, and a large number of those studies are actually done before approval. And it is frustrating to see that you have something that you would assume to be a class 1 type of drug, or a simple type of drug, where there are 14 bioequivalence studies cross-matching between various clinical trial formulations.

Now, it's also caused this huge risk, of course, that you're not able to establish all these links, and you run into at least delays when you develop your drug, when probably all these 14 studies could have done without them. So yes, I think this is a big value to include this type of thinking early on, and of course this requires that you obtain some of this information quite early on in the development.

Professor Gordon L. Amidon: I have to make a comment on that because I agree very strongly with what Tomas is saying. In fact, if I'm a formulator working in industry, one of the things you worry about is every time I make a change the company is going to make you go off and do a bioequivalence trial, when in fact it makes no sense to do that, and so I think this provides a rationale for when you should and shouldn't do one, a rationale that as scientists we can agree on and industry and regulatory authorities follow. I think it simplifies a lot of the pre-NDA and I think that the FDA is certainly being encouraged, and I would certainly encourage the FDA to think along those lines as well. But I am sure that Larry has mentioned that. Did you comment, Larry? Did you want to comment on this pre-NDA approach ?

Doctor Larry Lesko: Any more than I have?

Professor Gordon L. Amidon: No? OK.

Doctor Norman Orr, *SmithKline Beecham, UK:* We have heard a great deal about dissolution as a descriptor, I have not heard a single person mention, even hypothesize, what are the reasons why we get the differences in a dissolution. They basically fall into three separate categories: a subtle change in the chemical substance prior to secondary manufacture; or a subtle change in the chemical substance during the secondary manufacture, or some sort of interaction between the excipient, such as magnesium stearate coating the drug particles.

It alarms me that in the 25 years since the digoxin situation, which in a way focused everybody's attention on bioavailability, very, very little emphasis is actually put on trying to categorize the drug substance in the finished product. There are technolo-

gies and instrumentation that would allow us to actually do that, and I would be very interested in the panel's comments, and on that.

The second observation is over the anchor product being the optimal product. I think that puts a huge responsibility on, and is a huge disadvantage to companies trying to get products out fast. But, having said that, if you don't have the optimal product to give you higher dissolution, the opportunity for another product coming along using the same manufacturing process but an unintentional change,… danger to the patient must be there. As Gordon indicated, if you are working at the plateau right at the top of the formulation potential, and you can only have a less bioavailable product and not a more bioavailable product… I would be very interested to hear your comments.

Professor Gordon L. Amidon: Very quickly, Norman, I agree that characterizing the drug in the dosage form is not done nearly as well as it should be and that's where I think one should do intrinsic dissolution. You should know your particle size, your particle size distribution, you should look at the dissolution of the resulting formulation, there may be excipient effects, lots of things.

But when someone asks me to predict absorption in man, I'd ask him, can you predict your in vitro dissolution? No one does that, why not? You're right. There was a lot of work done in the '60s and '70s in what we call physical pharmacy that I think has kind of been forgotten, and we should perhaps resurrect that.

The other comment about the anchor formulation, I just don't think there's much we can do about that. I think the FDA has to accept what comes in as what the company offers and I think defending an optimal formulation can get very, very complicated. I fear that would greatly slow things down. Not that it shouldn't be a goal, I'm not arguing with the goal — it's just that I don't know how you could do it practically, that's the problem I would see with that, Norman. Maybe, Larry, you want to come in?

Doctor Larry Lesko: I guess the comments I would make are that the issue of the drug substance and the excipient interaction tend in my mind to come into play more in the pre-formulation area where those kinds of things are explored in terms of complexation or excipient effects — in terms of optimizing the formulation. I guess furthermore they might be viewed as being controlled within the context of the CMC (chemistry manufacturing control) specifications, whichever would be appropriate.

The other aspect is this anchor formulation concept and I think it's very critical in my mind that the efficacy/safety data is generated on an identified dosage form. What we are basically asking is that whatever marketed image or marketed formulation one goes forward with — in terms of changing bioavailability, or changing whatever — be linked to that formulation. If it isn't, then it seems like we're in a predicament, and that is to generate the appropriate labeling information on a formulation that's been changed from the one used in the clinical trial. That gets kind of complicated in my mind at that point.

Professor Gordon L. Amidon: To find the two most important questions and do them quickly and then I guess we get a few other panel members opinions and I think there's a couple of questions I won't get to, but if the individuals asking questions want to see me afterwards, that's fine, I'll be here for a while and I'll be happy to discuss some of the issues.

Q: Permeability studies done at one dose may not be sufficient, since the P 453A4 and/or pre-glycoprotein substrates can saturate at higher concentrations or demonstrate food effects. What concentrations should be used?

Professor Gordon L. Amidon: Well, that's tough decision. But I would take the normal dose range in human products of 1 milligramme to 1 gramme. Now, there are things that are less and things that are higher, but not many, so I would say, if you don't know what else to do, start there, in the intestinal volume of 250 ml (0.004-4 mg/ml)

But for classification, I recommend the lowest. Maybe that's not the best, but I am currently recommending the low concentration for the classification. But concentration-dependent permeability is an issue we have discussed with the FDA and Hans Lennernäs is going do some carrier-mediated compounds, he's also doing verapamil, so we are addressing that concentration-dependent issue, but there isn't anything specific yet.

Doctor Philip Smith, *SmithKline Beecham Pharmaceuticals, USA:* If you are looking at reformulations, and we know that formulation excipients can affect recycling or enzymes, then although you have classified it as a high-permeability, high-solubility molecule, you are going to miss the formulation effects.

Professor Gordon L. Amidon: In theory, I suppose, we could include the formulation components

or the other components in the formulation in the dissolution of those products in our specification. I think it gets complicated. In many cases, I guess, Phil, it wouldn't switch the classification, it just changes the operative permeability under the conditions of normal absorption and I think that's like, how do you convert your PKa into the real Ka under the ionic strength of the conditions, and whatever. So I think we are talking about an idealized reference number. The actual use of it would require this additional data. But I think that's not the part of the FDA nor the classification system.

Doctor Philip Smith: No, I think I disagree. If you have a molecule like verapamil, you do a low concentration, which you're assuming, you'll have a low permeability. Actually, you could have a low permeability.

Professor Gordon L. Amidon: That's correct.

Doctor Philip Smith: And you have good dissolution. When you then reformulate with an excipient that inhibits recycling or metabolism, you'll have a high permeability, an apparent high permeability…

Professor Gordon L. Amidon: The evidence for that, Phil, is in CACO-2 cells. I haven't seen evidence of that in vivo.

Doctor Philip Smith: What about cyclosporin in man?

Professor Gordon L. Amidon: Well, we are going to study cyclosporin, so we'll let you know…

Professor Geoffrey Tucker: Henning Blume just showed you some data that sort of proves it as well with verapamil. The reason for the differences in bioavailability are entirely metabolic, as affected by dissolution.

Doctor Philip Smith: I think all it means is you need to know more about your drug than just dissolution and permeability, you need to know something about how it is metabolized and transported. But you should know that by the time you get to that point, it's just that you should consider that…

Professor Geoffrey Tucker: And you've also got to know that quantitatively, in terms of relating the dissolution rate to that phenomena, and that's going to be difficult…

Professor Gordon L. Amidon: I think the low concentration that's expected, the low concentration that's expected to be presented to the gastrointestinal mucosa is the place I would start. That's also a more do-able concentration because you can get more drugs into solution that way. But you could present arguments where the adult intestine — the intestine is a very complex environment… we can't cover everything in a simple binary classification.

Professor Geoffrey Tucker: But it only takes one example to be wrong, and you've got trouble.

Professor Gordon L. Amidon: Wrong with what?

Professor Geoffrey Tucker: In terms of prediction. And you didn't do a bioequivalence study…

Professor Gordon L. Amidon: I think, if you are saying the dissolution rate, if the in vivo dissolution rate is the same for two products, and they have the same excipients and the excipients have the same dissolution rates…

Professor Geoffrey Tucker: What I'm worried about is how are you going to put the standards or the limits on those dissolution rates? How much of a difference is going to have an impact in vivo? That's the problem. How similar is similar? You've only got to get it wrong once, and then not do a bioequivalence study…

Professor Gordon L. Amidon: Certainly, for some drugs, I think, Geoffrey, there is no way round always requiring some kind of bioequivalence trial, human studies, because the complexity of the gastrointestinal tract is going to be too difficult for in vitro dissolution methods. Whether that is one-quarter or one-third of the drugs, I don't know. I think for another one-third of the drugs, I think doing bioequivalence trials could be considered unethical, because we're not testing the formulation. The test cannot discriminate between formulation differences. I think that is the other extreme.

Professor Geoffrey Tucker: I think we are still together. What we're saying is you need to know as much about the drug as you possibly can. It's not just dissolution, it's metabolism and everything else, and it's a case by case…

Professor Gordon L. Amidon: Of course. We're talking about bioequivalence-type regulation, but in terms of what you would want to supply and what would be required as part of the preclinical package, I don't know, I guess I'm not really prepared to comment about what I would do if I were developing a compound but I think you would want to do quite a bit.

Q: What is a better choice for solubility —

pH 6.5 minimum solubility over the physiological range?

Professor Gordon L. Amidon: I think that question comes from the fact that the jejunum average pH is about 6.5 and so therefore that's the region where drug is being absorbed. So the solubility at pH 6.5 is crucial from the point of view of drug absorption, because it's Pw•Cw, and that Cw is at 6.5. But drugs are always presented into a gastric environment first, and on average that is maybe 15 minutes, and so I took a conservative approach and used 0.1N HCL.

I think the dissolution media and the media change is saying that the dissolution media and methodology need to be considered more carefully and as I've suggested, the use of minimum solubility over the physiological pH range is probably too conservative and NSAIDs demonstrate that. We just have to determine on what basis can we relax it, and how far? So to me, it is a matter of looking at a database and deciding how far it can be relaxed.

Q: What is the variability associated with the permeability estimate in humans?

Professor Hans Lennernäs: The co-efficient variation is approximately between 30 and 60 per cent…

Professor Henning Blume: Between the subjects, or within?

Professor Hans Lennernäs: Inter.

Q: Can we really expect to get the same quantitative value of PF in humans as in animal models, when the physiology concerning blood flow, surface area and so on is so different?

Professor Hans Lennernäs: Of course, it is not expected to get the same quantitative value but, as we show in this correlation, there is a difference in the quantitative value between rat and man. However, the rank order is the same and the drugs falling definitely into two classes. It is hardly surprising that we don't end up with the same quantitative value for the rat model. Maybe if we talk about a dog model… But it is well known that hydrophilic compounds, or low permeability, might have high permeability in the dog model. That is another issue that we have to investigate further, I think.

Q: To be able to study the permeability of low-solubility drugs in early development vehicles, … using different vehicles in order to study this permeability.

Professor Hans Lennernäs: It is difficult in that way because you don't actually know the reference concentration. If you use, for instance, a vehicle that emulsifies the drug, what is the free concentration that is presented for the intestinal wall? So instead maybe it is better, if you have a low-solubility drug, to use as low concentration as possible, so that you know that the drug is in solution. In addition, if you are using some vehicle that is so aggressive that you increase the permeability from $0.1^{10\text{-}4}$ to $5^{10\text{-}4}$, then you really have an aggressive vehicle, I think. But I assume that is another big issue.

Doctor Larry Lesko: Can I go back to the verapamil story? Only a quick comment, because I think we have been looking for out-lyers to this classification system. I think they are useful to look at, and if any drugs present challenges, it's the 3-A4 pre-glycoprotein substrate drugs. But if I understood Professor Henning Blume's data, I think what he said is the product that showed 30 per cent dissolution in 20 minutes was bio-inequivalent to that which showed 100 per cent in five or 10 minutes.

But looking at the data another way, if those products that met the specification of 85 per cent in 15 minutes, I guess my question was, were they bioequivalent? That's really the test of the hypothesis here, and I think they were from the way you commented on that. I'm just trying to interpret your data, Henning, but I don't think it's an out-lyer in terms of the classification system if those are indeed bioequivalent that met the 85 per cent in 15 minutes.

Professor Henning Blume: Yes, I agree in principle. I think as long as the rate of input of two formulations is identical — also in those cases where first-pass metabolism is important — I would expect more or less identical plasma concentration versus time profiles. In so far, I am very much in favour of the classification system.

Nevertheless, there are other aspects which have to be taken into account. Therefore we follow a different approach in Germany. We have to decide in an Expert Commission at the German authorities on the question when are bioequivalence studies or a bioavailability study necessary on a case-by-case basis, and we have a system established which includes pharmacodynamic aspects which have to be taken into account as well as pharmacokinetic parameters, for example non-linear pharmacokinetics, high first-pass effects, low absorption and so on, and the physical/chemical characteristics.

However, although I believe that all these aspects have to be taken into account to come to a case-by-case decision, I think this biopharmaceutics classification system is very important in this context. But it does not solve all the problems.

Doctor Larry Lesko: Well, that's fair enough.

Q: Discuss applications, if any, of the biopharmaceutical drug classification of SUPAC for extended-release products.

Doctor Larry Lesko: I think what I can say is that the SUPAC-MR (modified release), as we call it, at the moment does not include any aspects of the biopharmaceutic drug classification system, but rather emphasizes the development of an in vivo-in vitro correlation as an alternative to a bioequivalence study.

Q: In cases where the disease state alters transit time and/or drug absorption — for example, inflammatory bowel disease — is there any rationale for performing bioavailability bio-product studies in healthy volunteers? What is the regulatory view?

Professor Geoffrey Tucker: For bioequivalence it doesn't matter if drug absorption is affected by disease; it is relevant if drug release is affected by disease. If disease affects pH, transit time or whatever it seems reasonable to do the study in the target patient group.

Michel Naze, General manager of Capsugel: It's a challenge for a non-scientific person to close a scientific meeting like this one. But in the light of these high-level presentations, I have to give you a post-performance approval and I think you get that from the audience, too.

I am also happy to hear that you left some issues open, so it is worth having another symposium in Japan, otherwise we won't have any questions any more. And all of us, we came here, very soluble, highly permeable this morning, but for those who lost their permeability this afternoon, you will have the proceedings of this meeting to refresh your mind and increase your permeability to what has been said here. And I guess some of you will go home with more questions after the meeting than before, but that is good, that's what science is for, so that we can keep on studying.

And for the organizers of the symposium, I have heard some very good news. If we could increase the solubility of the meals in the afternoon, at lunch, we would have no problem staying awake at the first symposium speech, because if we reach a high solubility within 15 minutes, your meal is gone before you swallow your dessert!

If you can't agree on drugs, maybe you can agree on some issues of food, but as we have to close this meeting, I must thank all the panel members and the speakers for their highly professional presentations and the issues raised and the answers given on all the questions.

Have a safe trip back home, and see you again in one of our other symposia. Thank you very much.

Princeton

NJ USA

May 17, 1995

Princeton, NJ. USA, May 17 1995

Opening Remarks

The organizers of this seminar intended to bring the proposed biopharmaceutic drug classification to an open public forum to give representatives of the pharmaceutical industry a chance to comment.

We wish to emphasize that no decisions will be made here today.

This is just a discussion, and our dialog will continue at the upcoming national meeting at the AAPS. Vinod Shah has a discussion group planned for November 8th 1995 in Miami. I wish to keep this seminar on a scientific basis. Dr. Amidon has told me that he is keen on receiving as many comments as possible from you.

Professor George Digenis, Chairman

The Rationale for a Biopharmaceutics Drug Classification

Update May 1996

Professor Gordon L. AMIDON, Ph.D.

The Rationale for a Biopharmaceutics Drug Classification Princeton, NJ, May 17, 1995

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Professor Gordon L. Amidon: I am honored to be here with this distinguished panel, all of whom have more experience than I do in this field. I think it is timely to begin a more theoretical approach with regard to the principles that we use to base regulations on, and also to talk about some of the potential implementation. I view this as an initial effort to get additional scientific discussion outside of the regulatory arena where there is often an overlay of issues that are difficult to unpack in the time frame that is allowed for a meeting.

The evolution of my thinking occurred in the following way: I took a sabbatical at the FDA and spent one year in the Parklawn Building. During that year I talked extensively with Vinod Shah with regard to dissolution, biopharmaceutics and drug properties – how these are used in the process of formulating decision rules, and making regulatory decisions. There was a constant struggle between the desire for a general set of guidelines and the reality of the system operating on an individual product basis. That led to the question: could we do anything other than operate on a product-by-product basis? That was the initial impetus for thinking about how we might be able to classify drug products.

I owe a lot of my thinking and early exposure to the dissolution requirements and their use for regulatory decisions to that sabbatical year. The FDA has supported much of the work, particularly human permeability and dissolution media, but also some of the solubility work that I am going to be talking about, and it is through that support of regulatory research that we have developed an approach upon which to make rational, scientific regulations.

The rationale is based on theoretical principles, and given the complexity of the gastrointestinal tract, it is best to limit our initial focus today to immediate release oral dosage forms. We have to concern ourselves with gastric emptying, gastric contents, fasted/fed state, pancreatic and biliary secretions, dissolution and solubilization, the actual lumenal environment, the transit which, depending on the drug characteristics and dosage form characteristics, may have a significant impact on rate and extent. Given the complexity of issues, what can we do to simplify regulation? The point of this approach to classifying drugs is that we can't solve all the problems but we can make progress and simplify some cases.

I want to point out some of the constraints associated with human dosage form performance. As an example, here are some textbook figures on daily fluid intake and output, so you can see what happens in the gastrointestinal tract (*Figure 1*).

We take in an average of 1,200 ml, and approximately 1.2-1.5 liters of saliva is added to that

per day. Two liters of gastric secretions, 500 ml of bile, and 1,500 milliliters of pancreatic secretions are also added per day, and then there are another 1.5 liters of intestinal secretion. Almost all of this is then reabsorbed, about 8 or 8.5 liters. 500 ml goes into the colon, with 350 ml being reabsorbed there. Of the approximately 9 liters that are processed in the upper GI, only 100 ml in volume is excreted per day.

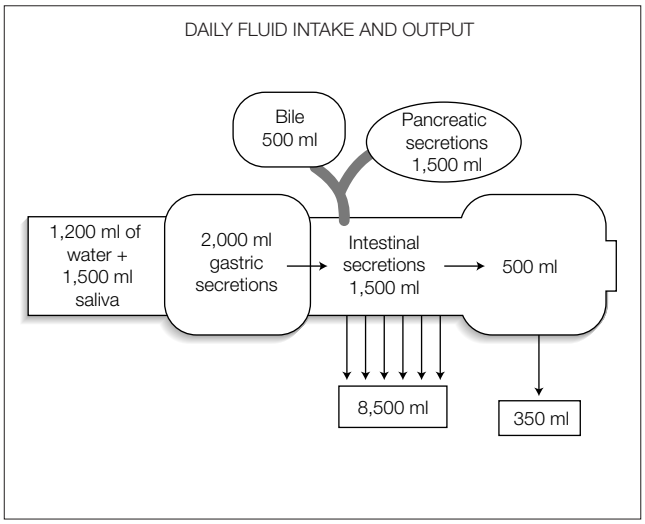

Figure 1.

If you do experiments and look at the upper GI, you'll see that it's a very complex, very efficient chemical reactor. The jejunum is about one-third to one-half of the intestine. If you cannulate the intestine of a dog at mid-gut, for example, and you give him a meal, almost nothing comes out. Everything is processed in about 50 cm or so of intestine.

Given this complexity and variability, how can we make progress toward simplification? One needs to develop an approach that asks what is controlling drug absorption. The bioequivalent definition from the Code of Federal Register deals with the rate and extent at which a therapeutic moiety or active ingredient is absorbed from the drug product and becomes available at the site of drug action.

Bioequivalent

CFR 21.320.1 (Definitions)
Bioavailability means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the *site of drug action*.

That is the legal definition. Now we all know that is impractical, and in almost all cases what we use, of course, is plasma level determinations.

On the other hand, the so-called Orange Book, which lists all of the drug products for which there are approved NDAs, doesn't actually state a definition of bioavailability, but puts it in this way: bioavailability describes the rate and extent to which the active drug ingredient or therapeutic ingredient is absorbed from a drug product.

Approved drug products

This term describes the rate and extent to which the active drug ingredient or therapeutic ingredient is absorbed from a drug product.

This is much closer to what one might want to utilize as a basis for a biopharmaceutics drug classification scheme.

In order to simplify and start to get a handle on first principles, we take an engineering view of how to define variables. Once we determine key variables, we use these lumped parameter models to do simulations, or correlations if the systems are too complex to simulate accurately. In a tube where we may have particles of drug dissolving, the lumenal contents are going to influence that, and the absorption rate will be determined by the permeability and (local) wall concentration (*Figure 2*).

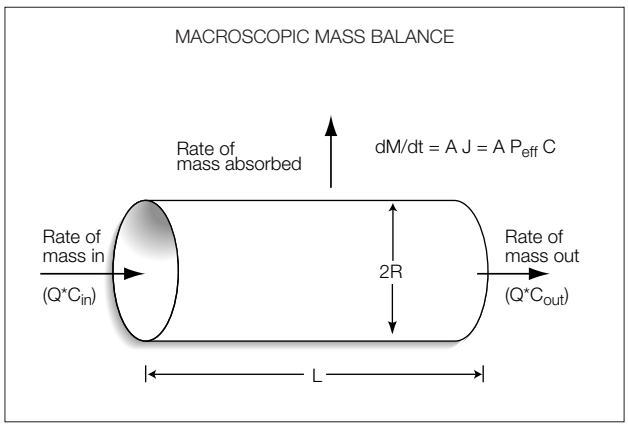

Figure 2.

That concentration is determined by the dissolution rate and environment or media. So, if there is a first principle for drug absorption, I think it has to be Fick's First Law applied to a membrane.

Fick's first law applied to a membrane

$$J_{wall} = P_{wall} \cdot C_{wall}$$

I would term this the first principle of bioequivalence: the mass absorbed per unit time per unit area. We are dealing with mass lost across the surface as opposed to a volumetric reaction. In that case you would have an absorption rate constant that would have units, time -1, whereas permeability is in centimeters per second or velocity. There is considerable analogy between chemical kinetic or mixing tank type approaches and tube approaches, but what they point out is that there are two main factors controlling drug absorption: permeability and concentration.

That underlying principle of drug absorption is what will lead to the system of biopharmaceutic drug classification. Concentration will be determined by dissolution rate, and the upper limit will be solubility. First, though, I will focus on permeability.

Just to show that I can still do Calculus 101, this is the solution to the previous problem. You add up everything over the surface area of the intestine; then, if you want to get the actual mass absorbed, you integrate that from time zero to t.

Rate and extent of absorption

Rate: $$dM / dt = \iint_A P_w C_w dA$$

Extent: $$M(t) = \int_t \iint_A P_w C_w dA dt$$

Total mass of drug absorbed

$$M(t) = \int_0^t \iint_A P_w C_w dA dt$$

This is the fundamental equation for predicting drug absorption rate and extent of drug absorption. The hidden complication is that I haven't listed some of the variables associated with permeability and concentration. In order to accurately predict what is going to happen, we need to understand the processes controlling permeability: space, time, and concentration dependence.

This equation converted to words is what I am proposing as the Principle of Bioequivalence:

If two drug products, containing the same drug, have the same permeability concentration time profile at the intestinal wall, they will have the same rate and extent of drug absorption.

That is getting close to the definition of bioavailability in the Orange Book, and it is nothing more than saying that if permeability and concentration are the same for two drug products you will have the same mass absorbed as a function of time. This is the physical principle, and the equation is the actual mathematical formulation.

There is a corollary, or maybe it should be caveat, because of the complexity of the world. The initial condition is an important determinant. From the point of view of drug dosing, the state of the gastrointestinal tract, the volume, pH and motility are going to influence the rate and extent of absorption. Consequently, since the gastrointestinal state of an individual varies with time, bioequivalence studies should be conducted in a suitable population and include a measure of intrasubject variability. Intrasubject variability, I think, is mainly a function of that variability in the initial gastrointestinal state.

I am now going to show some of the results of studies measuring human permeabilities which have been conducted under the direction of the FDA, working particularly closely with Larry Lesko and Vinod Shah. First the methodology. The methodology and the tube were developed at the University of Uppsala. The project involved in determining human permeabilities is done in a collaboration with Hans Lennernäs at the University of Uppsala. I will be showing data from both Uppsala and Michigan.

The tube is a multi-lumen tube, about eight different tube ports within a large tube (*Figure 3*).

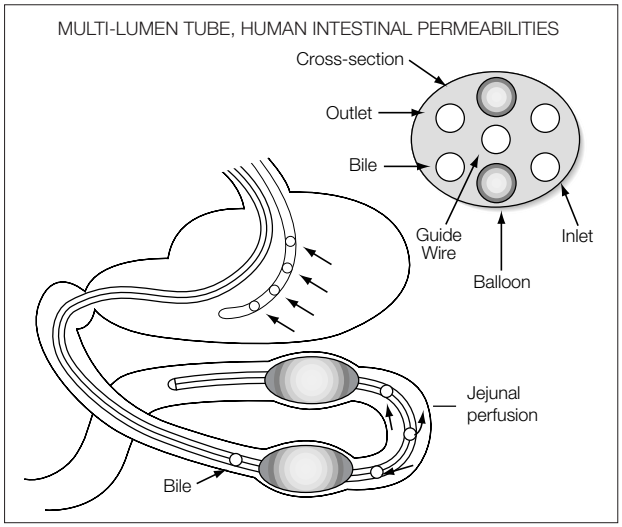

Figure 3.

Two of the ports inflate two balloons so we can confine the perfusing drug to 10 cm of jejunum. There are several ports for aspirating bile, because when you inflate the balloons you have to collect the bile. Then there is a gastric tube in-serted in order to aspirate the gastric contents continually during the two to three hours of human perfusion. The typical experiment would involve bringing subjects in around six in the morning, spending about an hour intubating them — we are presently about 80 percent successful at getting tubes placed in subjects — and then perfusing for about another four hours. You can take plasma samples if you want and continue extending the studies. About 20 percent of the time, the perfusion will stop during its course, perhaps the intestine crawls up over the tube and plugs one of the tubes, or a balloon breaks. If we are not able to aspirate fluid after about 20 or 30 minutes, we stop the study. There is a central port for the perfusing solution and two exit ports; so we perfuse 5 cm up and 5 cm down the intestine, which is similar to the fluid moving back and forth over short distances in normal segmental contractions in the intestine.

We typically use a low drug concentration. The drug must be in solution or the interpretation of permeability is more complicated, not only because of mass balance considerations, but because we are principally calculating permeabilities from the difference in the mass lost during perfusion between inlet and exit.

Standard perfusing conditions	
- Low concentration	
- Zero water flux	
- pH = 6.5	
Isotonic:	Glucose (10 mM), Phosphate Buffer, KCl, NaCl, Mannitol
Markers:	PEG 4000 (Non absorbable marker, cold) Phenylalanine (High P, nutrient) Propranolol (High P, passive) PEG 400 (Low P, passive)

Table 5.

We typically adjust and use isotonic solutions for zero water flux. We use pH 6.5, which is about an average jejunal pH. We also concomitantly perfuse nonabsorbable markers, a high permeability carrier-mediated nutrient, a high permeated passively absorbed drug, and then a low permeability drug; so we do assays on the drug plus four controls, so that we have internal controls during the perfusion.

Permeability analysis	
Design :	6-8 2 100 min. Periods each subject 4-6 Steady state permeability values each period
Analysis :	Well mixed Tube plug flow

I would view this as a reference permeability, because while conditions in the normal GI tract are quite variable, this is like a thermodynamic KA. Thermodynamic KA is only true with infinite dilution, and we never work there, so it is the same thing. We have a standard reference permeability. The actual operative permeability, under absorbing conditions, is more complicated. Nevertheless, this is a place to start. Then we would have to include concentration effects and permeability dependence of the intestine if we want to predict drug absorption. In the permeability determination we are basically monitoring mass loss over a segment of intestine, which is a function of inlet and exit concentrations.

The permeability calculation then says that the mass loss is due to surface area, concentration and permeability. Here we have a point that requires some note. In any approach you are going to have to define a reference concentration, because we are measuring inlet and outlet. Fick's First Law is a local law, only operative at each point in the intestine. If the concentration is changing across that surface, along the intestine, then we are going to have to pick some average or reference concentration. The only way to get around that is to have very defined hydrodynamics. You can do that with in vitro models, but in vivo, it means that we either have to assume that the reference concentration is, if it is well mixed, an outlet concentration, or, if it is plug flow, we use the inlet. You can also take an arithmetic mean.

Permeability determination	
$dM / dt = Q (C_{in} - C_{out})$ $= A \cdot P \cdot C$	
Reference Concentration	
$C = C_{out}$	Well mixed system
$C = C_{in}$	Plug flow system
$C = C_{avg}$	Arithmetic or log mean

The permeabilities calculated with these different reference concentrations are interchangeable, so it really doesn't matter which one you use as long as you recognize which you are using. You can mathematically calculate the relationship, because it is a function of two things you know — inlet and outlet concentration.

What we have shown through non-steady state tracer resident time studies is that in the case of the human intestine, the well-mixed approximation is probably better. In some work done early in my laboratories with Dr. I-Der Lee, we fit residence-time distribution models to human tracer studies. The kinetics of mixing are closely approximated by a mixing tank. Using the exit concentration is therefore probably the best approximation to the concentration at the intestinal surface during the perfusion. On the other hand, if you want to argue that we should use the inlet concentration, that is okay, too. It's a minor point, because you can calculate one from the other. I will show data calculated both ways.

It takes about 20 minutes or so to get to steady state during the course of a perfusion (*Figure 4*).

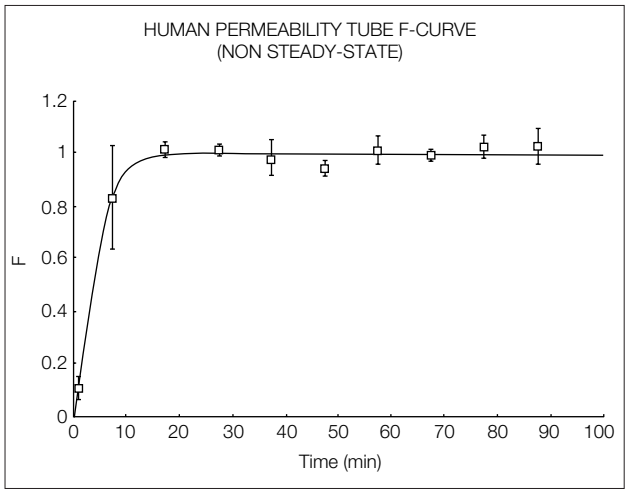

Figure 4.

When you start, there is some mixing, and it takes a while to see the increase in exit concentration. This was a non-absorbable marker, so it goes to one. In the case of a normal drug, you see the increase to steady-state, the time course of perfusion and the calculated exit and inlet concentration corrected for water flux (*Figure 5*).

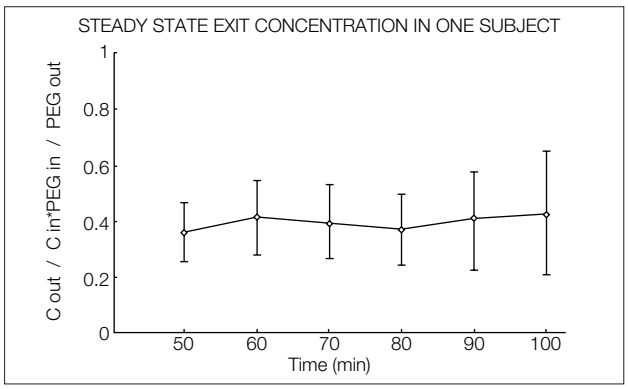

Figure 5.

If water is absorbed, you'll see a changing concentration even though there may be no mass absorbed, so you have to do a water flux corrected concentration.

I have shown the difference here between plug flow and mixing tank models. We chose piroxicam, a high permeability drug, to magnify the difference between permeabilities. I will focus on mixing tank because that appears to be the type of hydro-dynamics that most closely approximates what is occurring in this 10 cm of perfused segment. Since this is the actual permeability in different subjects, you can see the type of variability that we are seeing within subjects and between subjects (*Figure 6*).

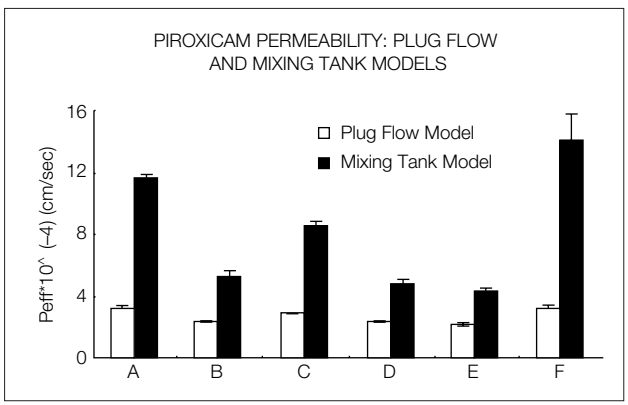

Figure 6.

This graph shows some of the data calculated using the two approaches.

Piroxicam, again, has a mixing tank permeability of around 10; propanolol, phenylalanine and then PEG-400, which is a poorly absorbed molecule, all have lower values (*Figure 7*).

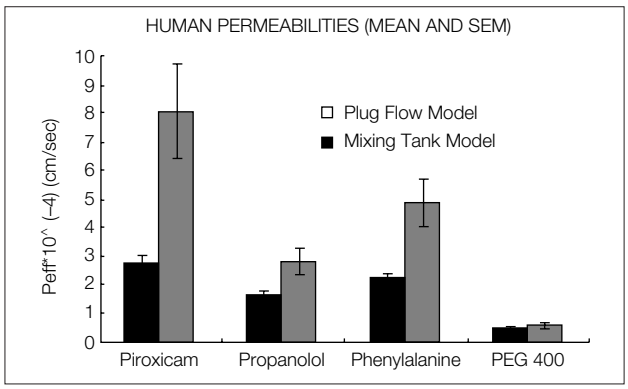

Figure 7.

These permeabilities for cimetidine, propanolol, phenylalanine, PEG were done on the same subject, with the same database, co-perfusing those drugs (*Figure 8*).

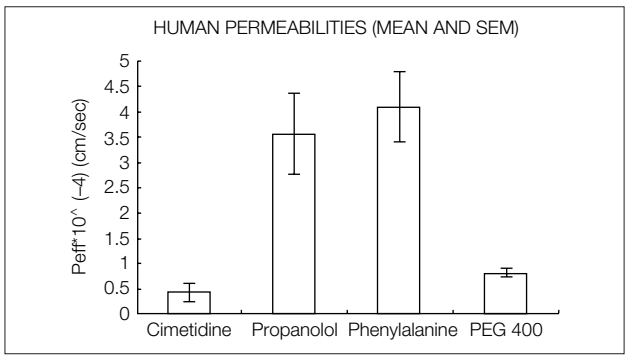

Figure 8.

So you can see the cimetidine reference permeability is about tenfold lower than that for propanolol. I think everyone would agree with that intuitively; permeability is low and bioavailability — fraction absorbed — is less than that of propanolol.

To give you an idea of the scale and scope of the project, I've provided a list of drugs that are being studied at Uppsala and at Michigan and then some reference compounds (Table 1).

Table 1.

PERMEABILITY DETERMINATION				
Uppsala University	P (prop)	S (prop)	Perm (cm/sec) (mixing tank)	
metoprolol	H	H	2.0 x 10	– 4
naproxen	H	L	8.0 x 10	– 4
atenolol	L	H	0.2 x 10	– 4
ketoprofen	H	L	9.0 x 10	– 4
furosemide	L	L	0.3 x 10	– 4
carbamazepine	H	L		
hydroclorthiazide	L	H		
desipromine	H	L		
α -methyldopa	L	H		
verapamil	H	L		
Ref. Compds				
glucose	H	H	10 x 10	– 4
antipyrine	H	H	3.5 x 10	– 4
l-dopa	H	H	3.8 x 10	– 4
enalaprilate	L	H	0.2 x 10	– 4
The University of Michigan				
piroxicam	H	L	7.8 x 10	– 4
propanolol	H	H	2.7 x 10	– 4
cimetidine	L	H	0.35 x 10	– 4
ranitidine	L	H	0.50 x 10	– 4
cyclosporin	L	L		
itraconazole	H	L		
acyclovir	L	H		
allopril	H	H		
Ref. Cmpds				
phenylalanine	H	H	5.1 x 10	– 4
PEG 400	L	H	0.75 x 10	– 4

At Uppsala, the drugs under study are metoprolol, naproxen, atenolol, ketoprofen, furosemide, carbamazepine, hydrochlorothiazide, disopromine, alpha-methyldopa, verapamil. At Michigan, piroxicam, propanol, cimetidine, ranitidine, cyclosporin, itraconizole, acyclovir, and allopril. The drugs are not so much the issue as a database covering a spectrum of drugs with differing solubilities and permeabilities. The basis for choosing the drugs in this list was coverage: each class getting representative examples. I will show the correlation in just a minute so that will be a little clearer. The reference compounds include glucose anti-pyrine, phenylalanine, PEG-400. At Michigan, we use propanolol as our internal standard for a high-permeability drug. At Uppsala they use antipyrine, which is not on the market in the U.S.

The goal is to obtain on the order of 20 permeabilities covering high and low permeability, high and low solubility in order to determine potential cut-offs for drug classification. There is no way to predict what cutoffs to use, given the complexity of the gastrointestinal tract, other than to generate a database and use that database as the basis for classification principles.

The graph of fraction absorbed versus human permeability covers the full range (*Figure 9*).

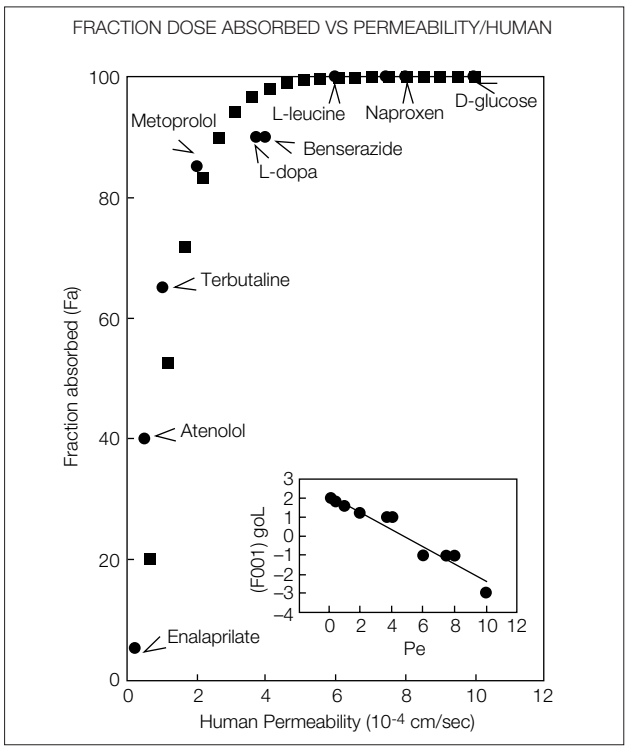

Figure 9.

You can see a poorly absorbed drug like enalaprilate, with very low permeability. If you want to pick a cutoff, I would say a permeability of around 1×10^{-4} cm per second gives you a potential drug, from the point of view of bioavailability, with a fraction absorbed in the range of 20 percent or more. What would be classified as a high permeability drug? Glucose, L. leucine, naproxen, piroxicam would be high, carrier-mediated l-dopa, metoprolol. We are currently studying chlorothiazide, hydrochlorothiazide, and furosemide which should be in the low range. So, we will cover a range of drugs going from high to low. Based on fitting an equation, that is doing linear regression on (a simple) exponential model for drug absorption, we can interpret the coefficient and calculate it out to intestinal transit time. The slope of the fitted equation calculates out to a transit time of about five hours, so the number is reasonable. While this equation is very simple, a simple exponential model, we can develop models to interpret the coefficients, and when you calculate those numbers out, they too come out to be reasonable, a transit time of around five hours.

With regard to good drug absorption, the relationship between the absorption rate constant and the permeability is just surface-to-volume ratio. Looking at the same segment of intestine as either a tube or a mixing tank, and taking the radius of the intestine to be about 2 cm, the surface-to-volume ratio is about one. Numerically, the absorption rate constant and the permeability are the same. In fact, the permeability then would represent a local absorption rate constant. The actual operative absorption rate constant during the dissolution and absorption could be more complex because of transit, that is position-dependent permeability, lumenal changes, activity of the drug etc. Another way of looking at good absorption is this: if we take 1×10^{-4} cm per second, that converts into an absorption rate constant of .36 reciprocal hours, and then absorptive half time of two hours. The relationship between permeability and absorption rate constant is qualitatively in agreement with what we know from the extensive pharmacokinetic database that we have.

With regard to a proposed definition, people would want a number defined or stated, but it is still too early in the process to say what should be considered a high or low permeability drug. The only way to make that decision is to have a database upon which to make that specification. However, if you take the previously studied drugs, which represent only about one-third of the selected drugs, you could calculate from that model, which fits the data quite well, that if you take fraction absorbed of 90 percent, you get a permeability of 3.28×10^{-4}. The proposal would be that a high permeability drug is a drug with a jejunal permeability greater than about 4×10^{-4} cm per second.

I want to emphasize that this is a proposal, based on looking at the science and saying that 95 percent is a reasonable fraction absorbed. I can't do more than that until we have more of a database, but I think we will eventually be able to state a permeability range above which there is high permeability and below which there is low permeability.

There may well be drugs that are close to the cutoff, in which case maybe there should be an intermediate class. I think we need the database and to see which and how many drugs are close to a cutoff point.

If we want to think in a binary classification scheme, then some drugs will obviously fall on the cut-off point and it may be difficult to classify those.

I am not proposing that this classification scheme will solve all problems. I think it can solve some, but there are still going to be borders and edges, situations where the real world is more complicated than a simple classification scheme can handle. The result will be that in some cases we can simplify regulation and in other cases we are going to have to perform bioequivalence tests because in fact the *in vivo* situation is complicated. Nevertheless, this permeability of 4 x 10^{-4} cm/sec. is a place to start. Many of the NSAIDs would fall in that range, and a fair number of amines. Those that are non-polar, at least in their unchanged form, would fall into that category. We are going to have fairly polar acids and bases, things like ranitidine, cimetidine, and some of the diuretics and betablockers that are going to be low permeability.

We do a perfusion under low concentration because we want to get a reference permeability. However, the other factor to bring in now is solubility and dissolution as the other principal variable controlling drug absorption. We are all familiar with mixing tank and tube modeling, particularly for pharmacokinetics or systemic kinetics. The added factor when it comes to modeling the gastrointestinal tract is the fact that we often introduce solid particles into the stomach, so we have to include the dissolution considerations.

The starting point in either case is the same.

In the equation to define low solubility drugs, Cs

Low solubility drugs

$$J^{max} = P_{eff}\, C_s$$

would be the solubility of the drug, and the product of Cs x permeability would be the maximal flux that can occur. This leads to the permeability-solubility classification proposal. Inside this mass balance relation, there is a fixed concentration, and if the permeability were fixed, the product would be constant. Then you just have the surface area of the intestine, so it is quite simple. The reality, of course, is determining solubility in what? Solubility is a complex phenomenon, and I want to provide some insight on how to approach that.

We start with a tube model. We want to consider dissolution of the particles, drug absorption and dissolution. We're working with a simple tube model including dissolution and absorption (*Figure 10*).

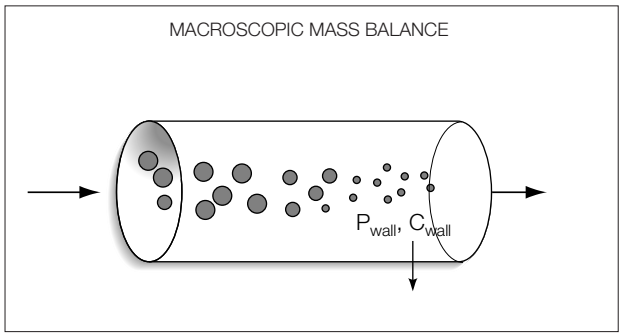

Figure 10.

What I want to point out from this equation is that when you scale it using standard engineering approaches to generate a dimensionless differential equation, then you only have to solve it once because everything becomes scaled by the parameters of the coefficients. In doing this we realized, of course, drug absorption number (or permeability), and drug dissolution number were obvious. We expected them, looked for them, but we found out in order to make everything simple we had to include a dose number.

Dimensionless differential equations describing total mass balance in the tube model

$$\frac{dr^*}{dz^*} = -\frac{3}{Dn}\,\frac{(1 - C^*)}{r^*}$$

$$\frac{dC^*}{dz^*} = Do \cdot Dn \cdot r^*(1-C^*) - 2An \cdot C^*$$

$$Do = \text{Dose Number} = \frac{M_o/V_o}{C_s}$$

We couldn't leave that out of the differential equation.

Figure 11 shows a typical profile for a high permeability drug. This profile for a high permeability drug (An=10) illustrates the sharp dependence of extent of drug absorption on the Dose and Dissolution Numbers when they are in critical ranges around one for a well absorbed (high-permeability) drug.

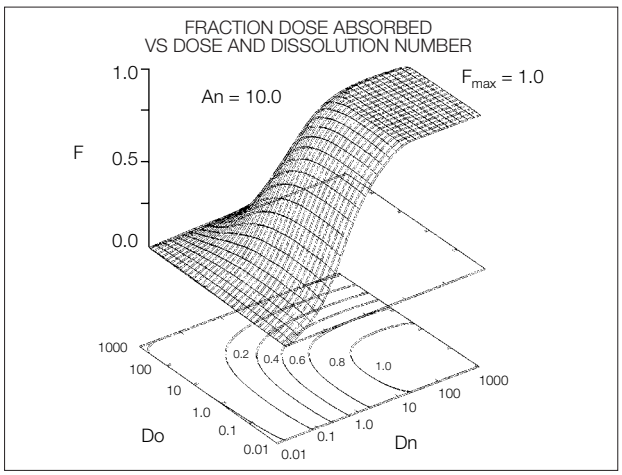

Figure 11.

It is also evident from the figure that at high dose numbers, the extent of absorption is only weakly dependent on the Dissolution Number. The limiting solution to dimensionless differential equations for the region is:

$$F = \frac{2An}{Do}$$

Dose is an often overlooked variable with regard to bio-availability and with regard to fraction dose absorbed. I think we all intuitively realized that dose is important. The differential equation tells us that dose is an important predictor of the extent of drug absorption for water-soluble drugs. I won't pretend for a minute that a simple tube model of the intestine is the final word, but what I will maintain is that any more elaborate model that more accurately reflects the mixing and dissolution, solubilization, and pH environment of the intestine, will include these parameters in that model.

These represent three of the most fundamental parameters, those which will remain part of any analysis. Solubility, as I point out here, is in the dissolution number, so we have dissolution as a function of particle size and solubility. Permeability we have already discussed. Finally comes dose number, which is a function of solubility, mass, and reference volume. We take a reference volume of 250 ml as a typical reference volume from the stomach. We know the volume effect is there – Peter Welling showed that 20 years or so ago when we were working together at Wisconsin – and so the answer is that the real world dynamics are more complicated. Nevertheless we pick a reference point, and I think on that basis we can then classify drugs in terms of dose number.

Solubility then actually comes in two places: dissolution number and dose number. You cannot get away from that; no model will allow you to remove those from the equations. With regard to interpretation, I will just point out that the absorption number, for example, is simply the ratio of the absorptive time to the residence time in the intestine, and the dissolution number is a ratio of the dissolution time and residence time in the intestine.

$$\text{An} = \text{Absorption number} = \frac{P_{eff}}{R} \bullet t_{res} = t_{abs} \bullet t_{res}$$

$2 \bullet \frac{P_{eff}}{R}$ = the effective absorption rate constant

$$\text{Dn} = \text{Dissolution number} = \frac{DC_s}{r_o} \bullet \frac{4\pi r_o^2}{\frac{4}{3}\pi r_o^3 \rho} \bullet t_{res}$$

$t_{res} = \pi R^2 L / Q$ = mean residence time

$t_{Diss} = \frac{r_o^2 \rho}{3DC_s}$ = time required for a particle of the drug to dissolve

All that is saying is that if you are going to predict fraction absorbed, it is not only a function of permeability but how long it spends in the intestine, so it is an absorption rate constant, or time constant, and a transit time constant. Likewise, dissolution is a dissolution-time constant and a transit-time constant. While there are a number of variables going into those dimensionless groups, in the simple case there are really only three variables controlling the

fraction absorbed. That, I think, is the significant import of a simple model in using a dimensional analysis approach.

I am not going to say the model will predict absorption. What we should do, however, is go back and look at a database to develop an empirical correlation. Some further comments regarding the model can be noted.

The particle dissolution assumed for that model is the particle dissolution model developed by Bill Higuchi where the dissolution rate is a function of the radius (*Figure 12*).

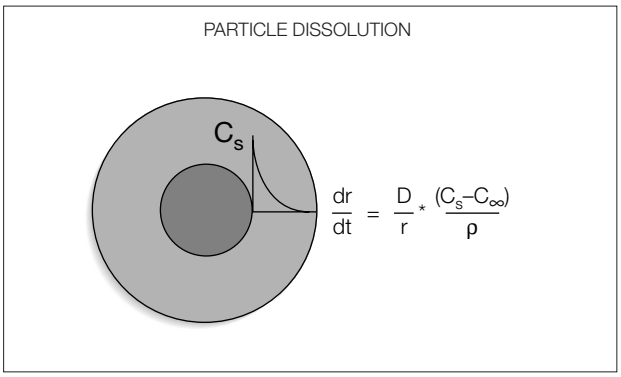

Figure 12.

That seems to be generally true for small particles, less than 30 or 40 microns.

We also have to consider solubilization in the gastro- intestinal tract. This is, of course, an item of major import for water-insoluble drugs. The most commonly considered situation is micelle solubilization, but of course the real world is more complicated because it is more like an emulsion (*Figure 13*).

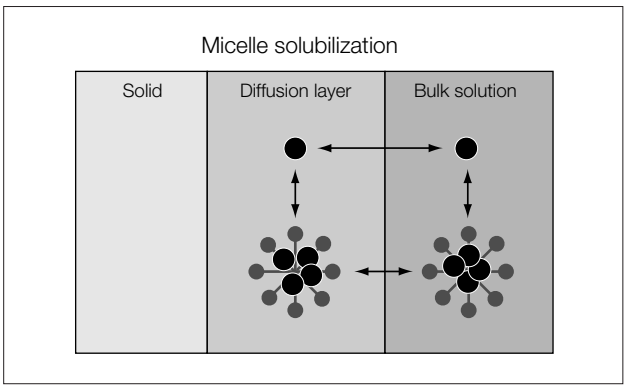

Figure 13.

What we have learned from many years of studies of surfactants, however, is that the dissolution rate enhancement is a function of two factors: amount of drug solubilized and micelle diffusion. Since the diffusion coefficient does not increase particularly rapidly with size, the solubilization factor is the dominant factor. I think that will carry over in vivo, but that's more than we can say today, except in selected cases.

We have been able to compile a table of some of the calculated parameters for drugs, based on dose, solubility, volume of solution, dose number, and dissolution number. Some of the drugs we've done that for are piroxicam, glyburide, cimetidine, chlorothiazide, digoxin, griseofulvin and carbamazepine (Table 2).

Table 2.

Dose number examples

	Digoxin	Griseofulvin
Dose	0,25mg	500mg
Solubility	0,024mg/ml	0,015mg/ml
Volume	250ml	250ml
Do	0,04	133

I want to focus on digoxin and griseofulvin because they represent the two extremes. Digoxin .5 mg dose, griseofulvin 500 mg dose have about the same solubilities of around 20 microgram per ml. If you calculate the volume required to dissolve the drug, you find it only takes 20 milliliters to dissolve digoxin while it takes 33 liters to dissolve griseofulvin.

If I were presented with these two drugs in development, I would clearly choose digoxin because 33 liters is a lot, whatever you take as your reference volume. Griseofulvin is a much more difficult problem. We can push Digoxin's bioavailability to 100 percent, but we don't know the bioavailability of griseofulvin in humans because there is no IV formulation. For dose number then, griseofulvin is dosed 133 times above what can dissolve in the stomach. One can also estimate dissolution numbers, though that clearly depends on an assumed particle size. If

you take a particle size of 25 micron, you can calculate dissolution numbers which range from very large like cimetidine, a high solubility drug, to relatively low like glyburide, a very low solubility drug.

Table 3.

CALCULATED PARAMETERS FOR REPRESENTATIVE DRUGS

Drug	Dose (mg)	C_s^{min} (mg/ml) [a]	V_{sol} (ml) [b]	Do [c]	Dn [d] (estimated intrinsic)
Piroxicam	20	0.007	2.857	11.4	0.15
Glyburide	10	0.0034	2907	11.6	0.074
Cimetidine	800	6.000	556	0.53	129
Chlorthiazide	500	0.786	636	2.54	17.0
Digoxin	0.5	0.024	20.8	0.08	0.52
Griseofulvin	500	0.015	33.333	133	0.32
Carbamazepine	200	0.260	769	3.08	5.61

a: Minimum physiologic solubilities were determined in the physiological pH range (1-8) and temperature (31.32).

b: Volume of solvent required to completely dissolve the dose at minimum physiologic solubility.

c: D_o = Dose/V_o/C_s^{min} . initial gastric volume. V_o = 250 ml.

d: Assumptions: r_o = 25 μm. D = 5 x 10^{-6} cm^2/sec. p = 1.2 gm/cm^3.<t_{res}> = 180 min (33)

Digoxin falls into a low dose and dissolution number range (Table 3).

Through micronization or solubilization, in one way or another, you can increase the bioavailability to essentially 100 percent, where you assume a high permeability drug limited by its aqueous permeability. On the other hand, griseofulvin is at 133. That's the range where I think we should develop a terminology for solubility limited absorption. The drug is very low solubility, very high dose. There is plenty of mass dose to dissolve and saturate the solution — it is a "white powder in, white powder out" situation, where the GI tract is saturated to such a great extent that it is no longer dissolution limited, it is actually solubility limited absorption. Formulation is going to have a very difficult time doing anything about that because of the high dose.

For high solubility drugs, permeability can be scaled to absorption number. We have to study a range of permeabilities. A high permeability drug like glucose is presumably an estimate of the upper limit or peak aqueous permeability, so that is what we have used in our estimates of absorption number and for our simulations for high permeability, low solubility drugs. Consequently, they all can go to 100 percent absorbed. If there is a high parameter limit to the solution for the differential equations, it would be this.

Dose number limited
F = 2An/Do
An < 10
Do > 20
Dose number greater than 20 may approximate the solubility limited region of drug absorption

If the dose number is greater than about 20, I think we can define that as a solubility limited region, because you are now putting enough of a dose in the intestinal tube to keep it saturated independent of surface area or micronization. Again, however, this is an area which requires more thought and more data to be able to determine when you are in a solubility limited versus a dissolution limited region.

I want to come back now to the classification implications. While I have talked about dose and dissolution number and that is the correct way to proceed from the point of view of simulation and predicting fraction absorbed, let's not forget that

Table 4.

Biopharmaceutical drug classification
• High solubility-high permeability
• Low solubility-high permeability
• High solubility-low permeability
• Low solubility-low permeability

Table 5.

IN VITRO-IN VIVO (IVIV) CORRELATION EXPECTATIONS FOR IMMEDIATE RELEASE PRODUCTS BASED ON BIOPHARMACEUTICS CLASS

Class	Solubility	Permeability	IVIV Correlation Expectation
I	High	High	IVIV correlation if dissolution rate is slower than gastric emptying rate. Otherwise limited or no correlation.
II	Low	High	IVIV correlation expected if *in vitro* dissolution rate is similar to *in vivo* dissolution rate. Unless dose is very high (see discussion).
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIV correlation with dissolution rate.
IV	Low	Low	Limited or no IVIV correlation expected.

permeability and solubility are the two key variables in determining what is controlling the oral biopharmaceutics of the drugs (Table 4).

Here are some of the implications I would point out for *in vitro/in vivo* correlations (Table 5).

In the case where we have a high solubility-high permeability drug, we would expect an *in vitro/in vivo* correlation if dissolution rate is slower than gastric emptying. Otherwise, limited or no correlation. In other words, this is a class where if you have a rapidly dissolving, high permeability-high solubility drug you do not expect a correlation between dissolution rate and absorption. Dissolution is not the rate-controlling step in vivo. Nevertheless we can regulate drugs based on insuring that the dissolution rate is fast enough.

On the other hand, of much more interest to pharmaceutical scientists are the low solubility-high permeability drugs where the *in vitro/in vivo* correlation is expected if in vitro dissolution rate is similar to *in vivo* dissolution rate. In order to reflect *in vivo* dissolution, you have got to know what is controlling in vivo, what *in vivo* variable is controlling your dissolution rate. You want to try to capture that in an in vitro methodology. What that means is that the in vitro methodology you might use to try to insure bioequivalence among your products for scale up or site change considerations might be different and more elaborate than your quality control dissolution methodology. Then you have the high solubility-low permeability drugs, like cimetidine, ranitidine. Because the permeability is low, that is because absorption or permeability is rate determining, we would expect limited or no correlation with dissolution rate.

I use the word "limited" in the sense that I know that if I take a low permeability drug, dissolution rate can be slowed down enough — even to zero — so that it is going to be the rate determining step. So, you may or may not get a correlation depending on the dissolution rate and permeability.

While that is important for controlled released dosage forms, for immediate release I think there are many cases where permeability is the limitation not the dissolution, and those drugs can be regulated more simply.

Finally, in the last class where you have low solubility and low permeability, you'll find very few drugs. My original thinking was that there would be no drugs in this class and that if I were in development and I got one, I would try to kill it because you are going uphill in all directions. In fact, though, there are some drugs where this class would apply, like a furosemide because of its particular solubility and pH permeability characteristics. I think the drugs in this class, though, would be relatively few.

At this point, I want to show physiological data to bring gastric emptying and intestinal pH into the

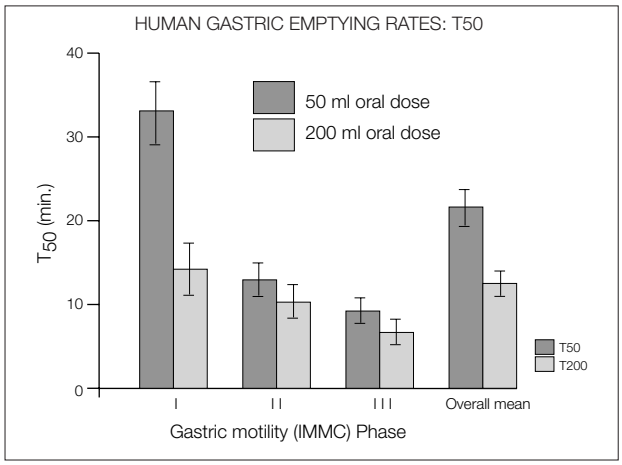

Figure 14.

classification scheme. While gastric emptying is a function of the motility phase in the fasted state, the average is somewhere between 10 and 20 minutes depending on the volume.

I'm frequently asked how rapid dissolution should be in order to insure that a drug product's absorption rate is gastric-emptying controlled, and

all I can say is I think it's about 15 minutes. We don't yet have a database and haven't done the underlying theoretical analysis to the point where we can quantify that type of cutoff more carefully. I believe today we can do that through knowledge of gastric emptying measurements, the distributions of gastric emptying and the corresponding implications, that is, the variability in gastric emptying and the corresponding expected variability and plasma levels. I think we will be able to define that in the future. If gastric emptying were much slower, we would have much fewer problems with dissolution, but obviously, that is not the case.

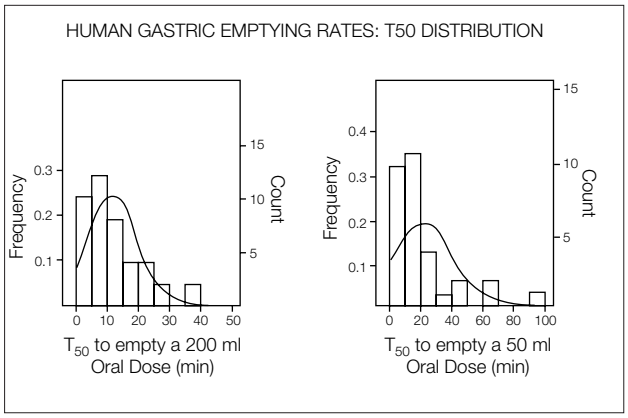

Figure 15.

The distribution of gastric emptying (*Figure 15*) is approximately truncated normal or log normal, but it appears through collecting a database of distributions that we can, in fact, do Monte Carlo or stochastic-type simulations and definite gastric emptying rate limits to set a dissolution standard.

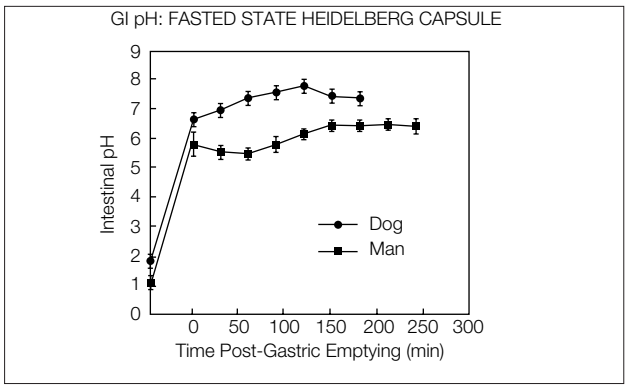

Figure 16.

Measurements of the gastro-intestinal pH using the Heidelberg capsule in human (*Figure 16*) show the pH going up to around 6 in the duodenum, dropping down to maybe 5.5 and then going up,

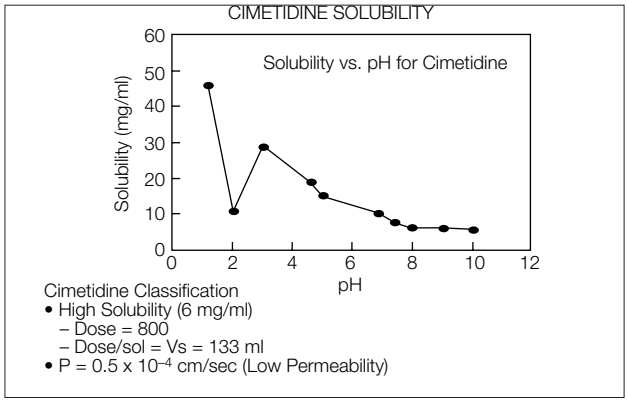

Figure 17.

presumably, in the jejunum to around 6.5. You could argue maybe it should be lower, but this is fasted state, so this is really measuring the pH as this capsule, is riding the contractual wave down the intestine. This is one picture of pH, only one picture of a fasted- state pH, but it does justify using around 6.5. The dog pH is about one unit higher, which I think is generally recognized.

If we take cimetidine (Figure17) it would be classified as a high solubility drug at this dose, vol-

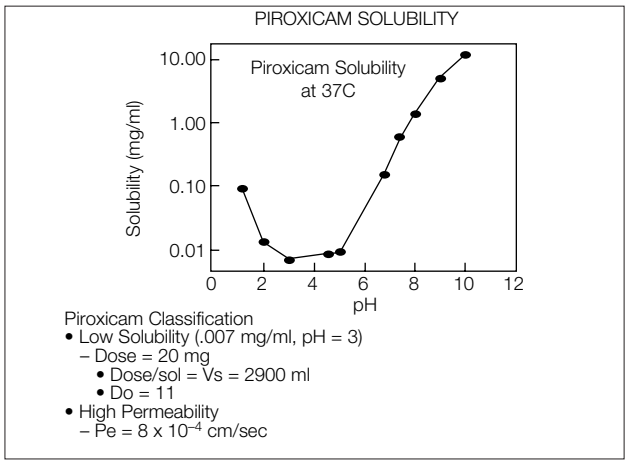

Figure 18.

ume of solution is 133 ml which is less than 250; it would also be a low permeability drug, based on a recently completed permeability study. On the other hand, Piroxicam, which has about a 7 microgram per ml solubility at pH 3, has a dose of about 20

mg, a dose number of 11, a volume solution of three liters, and we have determined its permeability to be around 8, so it would be a high permeability drug (*Figure 18*).

Piroxicam also indicates that solubility can be extremely pH dependent; Piroxicam has a pKa in the 6 to 7 range. What do we do in that case where we

Table 6.

EXTENDED SOLUBILITY CLASSIFICATION

Class	pH = 1-8	V_{sol}
High	All	< 250 ml
Intermediate	Any	< 250 ml
Low	All	> 250 ml

V_{sol} = Volume of water required to dissolve the highest human (single) dose.

are pH dependent? First, I will propose a definition for a high solubility drug. A high solubility drug is a drug which at the highest human dose is soluble in 250 ml of water throughout the physiological pH range. If pushed, I would say we could extend it somewhat. We could consider an extended solubility definition or classification, defining a low solubility drug as one that requires more than 250 ml to dissolve at all pHs (Table 6).

Then there is this intermediate range, where we have pKas in the physiological range. In those cases, we need to look at the drug more carefully to decide whether it should be classified as high or low solubility and how it should be determined.

To reinforce the classification and expected correlation in the case of high solubility-high permeability, we do not expect a correlation if dissolution is more rapid than gastric emptying. We would expect one if it is slower than gastric emptying, or if it is a controlled-release dosage form. Of course, that would be the best case for formulating controlled-release products. On the other hand, in the case of low solubility-high permeability, dissolution methodology is critical.

With regard to dissolution methodology, one of the things that we need to do is to think through in vitro dissolution methodology and how to use it as a better marker of *in vivo* performance. If your objective is simplicity in dissolution methodology, you are not going to achieve good quality control for *in vivo* performance for all drugs. Consequently, you are going to need to have some flexibility in dissolution methodology, at least if you want to use that as an indicator of *in vivo* performance. So, you may need two different dissolution methodologies. What I am talking about here is a more elaborate dissolution methodology that might be considered for scale up and site change situations (Table 7).

Table 7.

BIOPHARMACEUTICS CLASSIFICATION

Class	Solubility	Permeability	Dissolution
I	High	High	Single point if NLT 85 % Q in 15 min Multiple point if Q<85 % in 15 min
II	Low	High	Multiple point
III	High	Low	Same as Class I
IV	Low	Low	Same as Class II

Multiple Point Test: 4-6 points each test
Test 1: pH = 1, 2 hr., Volume = 250 ml
Test 2: Media Change at .5, 1, 2 hr. to pH 4.5, 6.5, 8.0
Surfactant media when required to achieve Q = 85 %, Volume = 900 ml

I am not a dissolution methodology expert, so I am only putting this out to stimulate thinking and discussion. The implications would be along these lines, though. For a high solubility-high permeability drug, a single point determination would be adequate if it is not less than 85 percent dissolved in 15 minutes.

This is not a rule, this is science. Fifteen minutes may not be the right number; we need a database to be able to tighten that up. Thirty minutes is probably too long, five minutes is much too short; we are defining that range. On the other hand, if it is slower than 85 percent in 15 minutes, then I think a multi-point determination is required and you must continue it until you get at least 85 percent dissolution. In the case of low solubility drugs, I think a multi-point dissolution methodology is required. Class III drugs should be the same as Class I, and

the low solubility-low permeability (Class IV) should be the same as Class II.

Multi-point dissolution tests should involve four to six points for each test. Test one would be pH 1, 0.1N HCL, and we would take points at .5, 1, and 2 hours in a volume reflective of the stomach: 250 ml. Test two would replicate test one and then incorporate a media change at .25, .5, 1, and 2 hours. A change at .25 is also discussible. This test should go to pH 4.5, 6.5 and 8, because if we look at human intestinal pH there is considerable variability, and you could use surfactant media when required to achieve 85 percent dissolution in a volume of 900 ml.

This is covering some ground that takes me away from my area of expertise with regard to dissolution methodology. I would simply like to propose that a multiple point dissolution test may be required, and that we must consider the media and media changes if we want to use it to more accurately reflect the *in vivo* situation. This would be a more involved and elaborate dissolution methodology than the usual USP methodology, which is more for quality control considerations. This methodology would only be required when you have to make a minor change like a site change. For a major change you may end up having to do a bioequivalence trial until we can guarantee that the dissolution methodology is reflective of all *in vivo* situations. We can't say that in vitro methodology is a good surrogate for *in vivo* performance under all conditions at the present time.

Some important issues remain concerning human permeabilities. We need the database, and it is being developed by the FDA in studies at Michigan and at the University of Uppsala. Over the next few years, we will end up with a database of perhaps 30 or so drugs in humans. That is going to be an exceedingly important database.

The question now is, do we have to do human permeabilities today to classify our drug? The answer is there is no other way because we don't yet have a database for insuring a correlation between animal and human. I would be inclined to use animal permeability results as a good correlate with humans and as a predictor of humans, but those correlations need to be established with data for drugs absorbed by different mechanisms — passive, carrier-mediated etc. — because transporters are somewhat different between animals and humans and paracellular versus transcellular. Those correlations will be determined over the next few years and this human database is going to be critical.

With regard to the *in vitro/in vivo* correlations, I think the dissolution standards need to reflect the *in vivo* situation, and we need to establish *in vitro/in vivo* correlations for representative drug products in each class. As we look at drug products and look at the controlling steps to classify the drugs, we will be able to look at in vitro methodology to determine how well that performs. Again, this is an operation of generating a database upon which to make decisions, and there is no other way to do it because of the complexity of the gastrointestinal tract. The basic principles are the place to start.

To conclude, the biopharmaceutics classification is based upon the fundamental variables, the first two variables to consider with regard to classifying drugs and then partitioning a set of regulatory standards. The advantage is that the classification scheme identifies the controlling variables and so, for example, if permeability is low or dissolution rate is very rapid, one would not expect a correlation with an in vitro dissolution because it is not the controlling process. This approach allows one then to compartmentalize drugs in ways that are rational. It can be used to simplify regulations, and that's the area where Larry Lesko will pick up to discuss how this classification could be used.

Biopharmaceutics drug classification and international drug regulation: a policy implementation approach

May 1995

Dr. Lawrence J. LESKO, Ph.D.

Biopharmaceutics drug classification and international drug regulation: a policy implementation approach ~~Princeton, NJ, May 17, 1995>~~ ??

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Dr. Lesko: Good morning. It's a pleasure to be here. I am pleased that the organizers invited me to represent the FDA at this symposium. I think it's terrific that the agency and its research program have access to the talent assembled in this room. It's a critical part of our process of moving research from the experimental stage over to the application stage in the regulatory world. I thank Capsugel for putting on this symposium. It's a very exciting topic and one that can have some significant implications not only in terms of U.S. regulatory standards but globally for product quality and formulation.

Whenever I talk about quality and formulation, I feel it's important to acknowledge that in this country we have a very high quality of formulations in the market place and anything I say today is not intended to imply otherwise. Both industry and the agency have done a terrific job to ensure that high-quality formulations are in the marketplace.

High-quality formulations lead me to another concept which will provide a theme for my remarks, and that is continued equivalence of formulations. The focal point of what I am going to say is the regulatory perspective on formulation quality and performance.

I want to acknowledge a few people who have been part of this research. Dr. Vinod Shah is with me on this trip. He has been instrumental in this research, as has Gerry Shiu who has done all the solubility determinations in his FDA laboratory. I want, also, to acknowledge the people in Sweden who have done a terrific job supporting this research from the international side. Gordon mentioned Hans Lennernäs. Tomas Salmonson and Jan-Olaf Walterson at the Medical Products Agency are doing a lot of the bioanalytical work involved in these permeability studies.

Within the FDA, we have a working group that interacts with the investigation sites and that includes people from across all the review divisions: Tom Ludden in the Biopharmaceutics Group, Alan Rudman from Chemistry, Suva Roy from Chemistry. So, this is truly an inter-divisional program within the FDA, and I think that makes it all the more exciting because of its widespread applicability.

If Gordon presented the technical side of the classification system, what I'll try to do is present the other side of the coin: the process and how we go about moving research information — technical information — into the realm of regulation. I've learned at the FDA that this is not an easy process.

In moving research from the data stage to applications, one has to consider all sorts of constituencies, not the least of which is our internal review staff. So, we have a path of consensus that we generally follow in implementing research and I'll talk a little today about some of the constituencies that come into play. Of course, this includes the trade associations, the pharmaceutical industries themselves, and international regulatory bodies.

People look to the FDA for what's going on, what's the next step in regulations. We have to take all that into account. With the change in administration in Washington we struggle a little bit with the politics of research and the politics of regulation. All of these things affect the world in which we work in terms of our research applications.

It's important to understand the process that we go through with research because it's a process of consensus. We have had so many changes in the Center recently that it becomes important to understand what is going on organizationally. Most of you already know about the changes in the new product evaluation side, the NDA side of the center. We have some new review divisions in the medical area. We're still undergoing some internal reorganization on the scientific side. If I were to divide the center into two worlds, on the one hand we have Mac Lumpkin's world which deals with the safety and efficacy issue of applications. On the other side, we have Roger Williams and his world of product quality, and that world deals with the scientific aspects of formulations. When it comes to things like the drug classification system, the challenge internally for FDA is to make sure there is horizontal communication about the impact of the work in the world of safety and efficacy and the world of formulation equivalence.

The way we handle that in the Center is with two policy coordinating committees, set up to provide that horizontal communication. These are also the coordinating committees responsible for the recommendation of regulatory policies to the center's top management. Among the current roster of coordinating committees, the one that most people are familiar with is the Chemistry Manufacturing Control Coordinating Committee. Under that committee are a whole range of working groups that study these issues and make recommendations through their coordinating committee for changes in regulatory policy. Medical Policy Coordinating Committee is starting to gain some momentum. But the one I want to talk about is the Research Coordinating Committee which is the conduit for the research we're doing with Gordon and Hans on the drug classification system.

The Research Coordinating Committee consists of individuals that represent disciplines of research which have been officially designated as focal points of research in the Center. The area that I chair is the area of Formulations Research. There are other areas: Clinical Pharmacology, Pharmacology, Toxicology, Methodological Research, etc. that each have their own groups doing either internal or extramural research.

The drug classification system falls into the purview of our Formulation Research Subcommittee. All the research we conduct that has potential regulatory significance follows the same path, beginning in research committee.

Today represents the second step. We are bringing a topic to the table to discuss with extramural experts assembled in this room. Other constituencies we deal with before regulations are impacted include the review divisions. It's important to get them to buy in. The trade associations are also a critical player here. Then we have a generic drug advisory committee where we tend to take unresolved issues for some input.

As we move forward, we have affiliations with organizations such as AAPS and the FIP where we gain access to the international scientific community. Through public meetings and workshops we can break into those types of discussions and bring the research forward. What we're doing today is a step in the process. There will be other steps, and the input that we get along the way is extremely critical as we get to the end of the pipeline where the recommendations for policy change go back to the CMCC for endorsement and also to the Center management for implementation.

The Associate Director of Policy is Jane Axelrad and the CDER management in this case are Roger Williams and Janet Woodcock. It's important to recognize that this is not ad hoc research but is part of a well-structured process.

I mentioned that this is a collaborative research initiative with Gordon and it comes under the umbrella of our formulation research. Formulation research is, in a broad sense, designed to provide a publicly available scientific data base to ensure consistent quality and performance of drug dosage forms. That gets to the heart of the question of tests and specifications. What do these tests do for us? What do these specifications mean in terms of quality? It challenges the current system to answer those questions and to see if we are doing an adequate job in ensuring quality and performance in the marketed products.

The data base falls into three broad areas. Much of the research we conducted at FDA is related to the CMC testing specifications: in terms of today's discussion, the in vitro dissolution area and the in

vivo availability area. The objective of this research — the regulatory pay-off — is very important and is one of the ways that research is evaluated at the Center. What does it do for the industry? What does it do for the FDA?

Research is intended to ensure the continued equivalence of the NDA clinical trial dosage form. You have to think back to the process we go through in drug product development. We have the IND studies, where we start out with some initial product formulation. The emphasis there is on safety and efficacy, and we have small studies to determine that. Then we go to the Phase 2 and 3 clinical trials. This is an area where formulations may change as the firm moves toward market launch material. We have to be concerned about continued equivalence as the development moves to that stage. We finally get into some bioequivalence within the NDA application. That process is then scaled up when market launch occurs, and then following market launch there are additional production lots and possibly some post-approval changes.

A lot of things are going on here. We know from the statistics within the Center that the formulation that's studied in the clinical trials often times is not the formulation that appears in the market after some scale-up and post-approval changes. Within the NDA world, there is an impact in terms of this continued equivalence once we get over that hurdle of safety and efficacy.

Now, when the patent for a given product expires, we move into the abbreviated new drug application world. One could think of an ANDA as the ultimate supplement. There is a change in site; there is a change in formulation. In terms of bioequivalence, one studies to document equivalence to the NDA material. They have their own scale-up market launch of those generic equivalents and then the production lots that may involve some post-approval changes. As you can see, the paradigm for equivalency of dosage forms is quite complex. One of the challenges in regulations is to assure that the patient who ultimately receives the product is clinically interchangeable with the patient who receives the product in clinical trials. That's the challenge in terms of regulations.

I want to give a little background to this project, because it is an integrated research initiative that has evolved over time. The first time I heard about the classification system was when Gordon presented this information at the December 1991 AAPS scale-up workshop on IR products. After that meeting, I remember thinking about regulatory applications and discussing the subject with others. There was pretty widespread uncertainty about the effects of scale-up and post-approval changes on bioequivalence. Even at that time there was a lot of excitement about this classification system as a way of honing-in on continued equivalence.

At about that time, we were getting under way with a manufacturing research contract at the University of Maryland with Dr. Augsburger. We asked Dr. Augsburger to participate in validating this classification system by stressing drugs in the various proposed categories: develop critical manufacturing variables for these products, push those variables to their limits, look at the changes in dissolution and see what happens in bioequivalence. When all is said and done, we studied six drugs falling into classes 1, 2 and 3 of the classification system. We conducted 21 bioavailability assessments. It gave us a very good feeling about the classification system and that it made sense in terms of continuing equivalence.

The SUPAC group was formed in April 1993. This was a critical step in the evolution of this type of research. This group had the responsibility to more clearly define for the industry what is meant in our federal regulations by major and minor changes. I was part of that group along with Hank Malinowski, Alan Rudman and Suva Roy. In addition to defining major and minor changes we changed the termi-nology to level 1, level 2 and level 3 changes. Another milestone was when we awarded a permeability research contract to Uppsala. Gordon and Hans coordinated their research and the Medical Products Agency in Sweden was excited to join us and was very helpful in this collaboration.

In November, 1994, we issued the draft SUPAC guidelines. Some of the tests and specifications for certain changes and formulations rely upon the drug classification system. This was the official introduction of the classification system into an FDA instrument that is intended to be used by the industry for guidance. We're putting some final touches on those guidelines at the moment because we got a lot of good comments from the industry and we're incorporating those into the final guidance.

I wanted to give a kind of cultural view of this research in terms of what we had in mind within the agency as we went about working with Gordon. First of all, we want to explore alternatives to the one-size-fits-all concept of regulation. In other words, when we have these regulations, why do we

apply them equally to all drugs and all dosage forms regardless of their biopharmaceutical properties? We wanted to ask the question: Is our regulatory operation as effective and as efficient as it can be?

Everyone knows what our work load is at the FDA: supplements, backlogs, etc. That's partly due to regulatory requirements. It would be a win-win situation if we could develop alternatives like the proposed drug classification system that would reduce the regulatory burden on the industry and reduce the regulatory workload for the FDA. The reality in the FDA is that in the absence of data, reviewers will make the most conservative decision. It's the safest, and probably the most prudent, path.

A second principle is that any research we got into with the classification system was intended to be general in nature. We wanted it to be applicable across the industry. This research fits very nicely into this concept because we look not at the pharmacological class of the drug but rather we focus on the science of its biopharmaceutical properties. I think that's a terrific direction that Gordon has taken on.

There is a world of other pressures in the FDA. We have something called REGO directives that we deal with as part of our regulatory life. REGO means reinventing government. President Clinton and Vice President Gore challenged the FDA and other agencies to look at all regulations to determine if they're really needed and ultimately to do a better job at a lower cost. That's the directive we got in the FDA. That has impacted research. We have sought to relax regulatory requirements wherever possible without sacrificing quality and performance. I think this research satisfies the spirit of the REGO directives. We have in fact positioned this research as one of the FDA initiatives and sent it up to Mr. Gore and Mr. Clinton.

Furthermore, the research contract with University of Maryland at Baltimore on immediate-release dosage forms suggests that the classification system is appropriate and in some ways may be even a little conservative. We looked at drugs in some of these biopharmaceutical classes; did some things with formulations; looked at dissolution and then looked at bioequivalence. This was some very hard data that supported a lot of the things that Gordon has suggested already. And, then finally, the expectation is well, what does all of this mean? And, what it meant to us was a chance to implement a biopharmaceutic classification system in a real FDA guideline that would have some impact in improving the way we do business and I think of it creating some advantages for the industry.

I think many people are familiar with SUPAC. But for those who aren't, I want to present the concept of SUPAC on scale-up and post-approval change. The philosophy of this document is that we wanted to define the magnitude of change, and we did, in three levels. Level 1 is change which is highly unlikely to have an impact on equivalence of that formulation. Level 2 is change which will probably have an effect, but we're not sure in terms of its impact on equivalence; and Level 3 is basically change that is sure to impact bioequivalence.

Then we set out to determine where these changes occur. They occur in composition; they occur in site; they occur in scale or batch size; they occur in equipment; and they occur in the manufacturing process. So, we defined where the changes would occur in the production of that product. Then the change was defined in a little more detail. The next question was to determine what we would require of that change to assure equivalence. Those requirements fall into several broad areas. There is the chemistry manufacturing control area, the compendial specifications, and the application specifications. This is a critical part of the document, and this is where the drug classification system came into play.

More relevant to what we're talking about today were the dissolution and bioequivalence requirements. We try to define that cascade of requirements for the respective levels of change. Finally, we thought about the filing requirements — how a firm would report those changes — and we were able to make some changes in what could be presented in annual reports and what would require a full supplement. That was the theoretical approach.

The CMC requirements principally involve meeting the application specs or the compendial specs and doing some accelerated long-term stability work on that changed product. Basically, however, the impact of the classification system was quite significant, particularly in the second level, where change may have an effect on equivalence. In trying to answer that question of if or when, we went to the classification system and began to sort out the requirements based on those biopharmaceutical principles. Individualizing requirements — getting data where it's needed and eliminating data where it's not needed — was the conceptual approach. We answered the question of whether a bioequivalence study was needed in terms of certain bio-

pharmaceutical classes. We didn't require it for every class but determined certain classes where the permeability or solubility may be a problem. That's the end product of that notion of individualizzing requirements.

As we continue our dialogue and look at the data that's coming in from Gordon and from Hans, we are now beginning to look out on the horizon. What else can be done with this information? What other pay-offs can be brought to bear on the regulatory process? This is where your input is important. This is why we're here. This is why the agency is interested in having this dialog, to learn what the issues are. Where else we can apply this type of research information.

In the area of in vitro dissolution, the IR dosage forms, we have a group which Dr. Shah chairs called the Immediate Release Dissolution Working Group. Its objective is to develop guidelines for the Center just like our stability guidelines that will define the test conditions for dissolution and specifications. That's a critical initiative, and it's underway. It has to go through a public process, just like this research. It identifies this tug of war that we have with dissolution that revolves around the question: What do you want it to do? The guidelines are intended to say when we want to function as quality control for the manufacturing process as opposed to acting as a surrogate for bioequivalence. I think that's an important distinction where the drug classification system can come into play to help resolve that difference.

There are other areas of application that we've talked about internally. I have to emphasize that these are only in discussion stages. We have to see more data, and we have to have more discussions to see a regulatory impact. We already have seen progress on our SUPAC document, but I can imagine extending that document, allowing for broader changes for certain classes of drugs. Maybe we can go beyond the current recommendations in the SUPAC document under certain conditions. We're exploring that as a possibility.

In the area of biowaivers, we now give waivers of lower strength products. But we often require that those lower strengths be qualitatively and sometimes quantitatively similar. However, I could imagine a flexible requirement based on the drug substance and its biopharmaceutic class. For instance, if the drug is highly soluble and highly permeable, the formulations are not qualitatively similar and the differences are not significant. Do we need a bio study on those lower strengths? That's the type of question we're looking at.

In food studies, we routinely require bio studies. We've talked about looking at our food study requirements both on the new drug side as well as on the generic drug side and asking questions: Do we need food studies in all cases where we currently do them? Does it make sense if we have a highly soluble, highly permeable drug with a broad therapeutic index (similar formulation except for minor change to require a food study)? That's another area we are exploring.

We're also looking into the allowable changes beyond SUPAC and the conditions under which those changes can occur. Finally, we're looking at the approval of drug products in a manner similar to AA drugs. AA is an old designation where drugs were approved on the basis of dissolution alone. There are some possibilities under certain conditions to maybe rethink that. If, for example, the drug is highly soluble, highly permeable with a broad therapeutic index, are there conditions under which we can approve a drug based on dissolution alone? I think it's worth asking.

To summarize for the lead-in to the panel discussion and audience participation, from my perspective, the questions are as follows:

1. Where do we go from here? I look at this as a process of information-gathering and advice. I am anxious to hear the comments on the research and on the policy implementation.

2. What are the issues for industry that result from the implementation of this classification system? Are there problems out there? Are there hurdles we haven't recognized?

3. In other areas of regulatory applications, what are the possibilities besides our SUPAC document? Where can we go in the future?

As I was sitting in the audience thinking about the title of my remarks, I knew the international component of the symposium needed to be addressed. I was going to say a few words about international or global standards for product quality. It's interesting that right now in Europe there is an FIP-sponsored symposium in which FDA attendees are participating on setting specifications, tests and test standards. That's one of the gaps in the international harmonization that we've seen through the ICH process. The ICH process has been very nice in terms of saying what needs to be done. But they often leave the interpretation of those tests and

specifications up to the regional regulatory agency. I think this research can fill a void by harmonizing with the European Union and the Japanese national health system, and by bringing together the regulatory agencies to set some uniform global standards for product quality.

We're also involved with the World Health Organization, which has as a mission to develop regulatory guidelines for smaller regulatory bodies. They put out some position papers and some documents. There is a close link between that document and the notion of a biopharmaceutical classification system. So there is a lot of opportunity and I think of all the research we are conducting within the FDA, this is probably one project that could represent the first inroads into international harmonization.

The next ICH process is coming up and there has been some discussion of including research as one of the pathways for ICH discussions. That's probably in recognition of the value of this research and the value of research in general when it's truly directed towards both the industry and the regulatory bodies that have oversight. Thanks.

Panel Discussion

Princeton, NJ USA
May 17, 1995

Panel Discussion
Princeton, NJ

Prof. John Wagner: First, I wish to say that I support Dr. Amidon's classification idea. If applied properly, it will aid biopharmaceutical research immensely. I have one comment about the theory application. Dr. Amidon and his co-workers applied their method to 13 sets of amoxicillin serum concentrations. The initial concentration (dose over volume of fluid taken with a dose) varied from 1.25 to 20 ml/m.

I plotted the model predicted fraction of the dose absorbed on the ordinate vs. the absorbed fraction of the dose absorbed on the abscissa. The correlation co-efficient was highly significant: P<0.001. But the large negative intercept of -23.5 indicates a significant bias of unknown source. I just want to comment about this. Maybe Dr. Amidon can go in and find out why there might be some kind of a bias like this. That's all I want to say. Thank you.

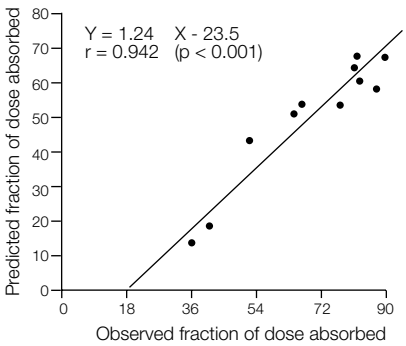
Dr. Gordon Amidon: Could you repeat the question?

Prof. Wagner: I didn't have a question. I just made a statement about your data. The only question I had, maybe you can investigate why there is such a bias? That's all.

This is model-predicted v. observed. He should get a line with the slope of one right through the origin.

Dr. Amidon: This is for amoxicilin as a function of dose?

Prof. Wagner: No, it's model predicted v. absorbed.



Plot of predicted versus observed fraction of dose absorbed using the amoxicillin human data of Sinko et al. [96]. The large negative intercept indicates a significant bias of unknown source.

Dr. Amidon: No, but the different data points are, it's all with the same drug. So, it's a different dose.

Prof. Wagner: Yes, that's right.

Dr. Amidon: And, the confidence factor on the intercept is what?

Prof. Wagner: Well, I didn't bring that with me but it's a highly significant intercept, put it that way. I don't want to make a big point of this... I just wanted to bring it up for you to consider later, OK?

Dr. Amidon: I'll just comment from that plot. Of course, predicting the fraction absorbed is model-dependent. You're dealing with non-linear permeability and where it's changing down the gastro-intestinal tract for a carrier-mediated drug like amoxicillin. I'm not making a case that the model predictions are accurate, because I think that's still too complicated. It's the correlation between the underlying variables and the database that we need to evolve. I think that shows an inadequacy in the model. I would readily admit that. We are using a fairly simple model when it comes to trying to predict fraction absorbed, but I think that's important for things like drug development. From the point of view of regulating drugs and establishing a correlation across permeabilities, I think it's a matter of getting enough data points to say we can define it.

Prof. Joseph Robinson: Gordon, first I want to congratulate you on bringing the focus back on the interface between physical chemistry and biology. I think that's an important statement.

Now, looking a little more carefully at some of the physical chemical aspects of the drug and relating that to performance, I think it's very important to comment that the drug classification system can be overwritten by the dosage form. So, even in your class 1, it's possible to modify it to the point where you have significant problems. I was a little concerned that the FDA contract includes only Class 1, 2 and 3 drugs and I wonder if it would be possible to incorporate some of those Class 4 drugs into the work Larry is doing to give a little bit of perspective, because it's those solubility-limited compounds that are often the largest problem. At the end of the day, you're still going to need lots of data to make this work and you're going to have to have some handle on metabolism and the full disposition of the drug. That's one of the concerns I had, Gordon. How well do you take into account surface metabolism in some of the classification that you're doing here? We are learning a great deal more about tissue and surface of the tissu, a case in point, metabolism. I wonder how much that would distort the model that you're dealing with, especially from a classification point of view.

I disagree with your comment that in Class 4 you would have limited or no IVV correlation. I don't know why you wouldn't. You're going to have low absorption, admittedly. Presumably, if you have something that is dissolution limited, you ought to have a correlatable system. Anyway, I've given you a series of questions to chew on. I am pleased that there is at least a willingness to get away from 'one size fits all'. Although it's at an early stage, I think it's to be applauded.

Dr. Amidon: I agree with what you said, Joe. 'Limited' will depend on what in fact is rate controlling and that's difficult to predict. In fact, yes, it could be dissolution-rate controlled and you might expect to see one in some cases for Class IV drugs. There is one Class IV drug we have come across for sure that was studied at Uppsala: furosemide which has pH dependent solubility and permeability. So, if we take the strict definitions, it would be low solubility, low permeability. There are probably some others. My initial thinking was there would not be very many drugs there. But we need to establish a database of drugs that we think are low permeability, low solubility. This approach says nothing about systemic viability and bioavailability because it does not include metabolism. Metabolism is something that occurs after the absorptive step and can affect the bioavailability and the variability.

Prof. Robinson: My comment was that your permeability coefficients could include metabolism.

Dr. Amidon: It could include metabolism. That's correct.

Prof. Robinson: It probably will, won't it?

Dr. Amidon: If there is surface metabolism, you would notice that as a high permeability. That's correct. And you would have to account for that. We are currently trying to study some drugs that are metabolized and assay the possible metabolites, like cyclosporin, for example. So we're trying to address that issue. We don't really know how much of a complication that might be for some drugs, but it probably will be.

Dr. Lesko: I just wanted to address the comment about the Class IV drugs. There's another issue that bothers me about that class in terms of regulation. In doing bioequivalence studies, we often made the leap that something shown to be bioequivalent in healthy volunteers would be bioequivalent in the variety of patient populations taking the drug. I think if there was a difference to be seen and there's not a lot of data in this area, we'd probably see the difference in that class of drugs. Cyclosporin is a drug in that class for which the absorption changes as you move through different patient populations. So in pushing the envelope on this classification system, that would be a case where I'd be very concerned and need some data to look at it.

Dr. Peter Welling: Many of the issues have been raised already by my colleagues. I would just like to add a couple of things that always concern me when we talk about *in vitro/in vivo* correlations. Where do you set standards and specifications on in vitro dissolution and apply them to the *in vivo* situation? For example, if you establish a correlation, which is difficult at best, how do you set the limits of your correlation to say whether or not the two products will be bioequivalent *in vivo*? That will need to be addressed as these meetings evolve. I certainly endorse Joe's comment that we are talking about formulations here, not about drugs. Discussing data on drugs in informative but, even for a rapidly dissolving high permeability drug, formulation can play an important role.

Dr. Amidon: Of course formulation can have an effect. What we're trying to do, Peter, is to find regions where the effect is not significant from the point of view of requiring a bioequivalence trial. If the plasma levels and their variation are not measuring something related to the formulation, then how can we justify doing the study. So the goal is to define those regions. But I agree with you. The result has to be based on data and looked at to see that it works. In the end, because of the complexity of the systems, the drug products and the gastrointestinal tract, we need a database to stand on.

Dr. Lewis Leeson: I too want to congratulate Gordon for doing some very, very fine work. He has taken concepts that we've heard about for a period of time, such as partition coefficients, and he's expanded them to permiation values. He's actually gone ahead and done them. He's not looking at partition coefficients in hexane and making all sorts of conclusions about how it's going to behave in man. He's measured the more meaningful things in man.

On the other hand, I also agree with Joe. It is so good to see physical chemistry coming back. The whole concept started off as what used to be called Physical Pharmacy. Over the years, the biological aspect has taken over so strongly that the physical chemistry started to disappear. I see it coming back and I congratulate Gordon for this.

I hope, however, we don't go the other way and forget the biological aspects. As I've said at many meetings, we need both pieces of information. We need the pharmacokinetics of the drug and we need the physical chemistry of the drug and the formulation. From what I heard Gordon say, hopefully our goal is at least a universal dissolution specification for every drug. It doesn't necessarily have to be cross-drug, but it certainly should be within drugs. That's the hope. You're obviously not going to set a specification based strictly on partition coefficients or even using the *in vivo* measurements Gordon made. We're going to have to have a quality control specification. Hopefully it will be one that has *in vivo* meaning.

That's the second level of correlation. The first levels are what Gordon is doing by looking at in vitro and *in vivo* data and making some decisions about how this product is going to perform based on his evaluations of the four drug types. However, let's get pragmatic. We need a quality control tool. We have one today. It's called in vitro dissolution. There are two approaches to that. There are those who say in vitro dissolution is a quality control tool which has nothing to do with bioavailability. My answer to that is if it's a quality control tool that doesn't relate to bioavailability, what quality are you controlling?

What's needed, in my opinion, is the second approach – a good in vitro *in vivo* correlation where one can look at the in vitro dissolution and have an idea of how that product is going to deliver the drug to the body *in vivo*. I think the best way to do it is to do some sort of input rate determination such as the Wagner Nelson equation. Tie that in with some in vitro measurement. Now, for in vitro dissolution, we always start out with biological conditions. We look at 37 degrees, pH 7.5, 50 RPM. In reality, we can start there and go on to try to find a good correlatable set of conditions. The conditions can be almost arbitrary if that's all that's going to work. But if the relationship exists, you have an in vitro measurement that will tell you how that product is going to perform. That's why you need this quality control tool, and that can be tied in well with what Gordon has been talking about.

I think you can develop correlations for all four classes. I agree with Joe that Class 4 can be done. Class 1 can be done by modifying the input rate, which also lets you find out where dissolution becomes rate controlling. However, the thought of saying 85 percent released in 15 minutes scares me. Because you're at a very steep section of your dissolution curve and it wouldn't take much to fail – 10 or 15 seconds can kill you at that point. But developing the correlation, looking at a poorly releasing version of a highly soluble or highly absorbed drug, allows you to find exactly what your dissolution data is telling you. I think we have to tie those things together.

I have some other points. When we're talking about a correlation which our colleagues at the agency can use I again remind you that all correla-

tions are not equal. The USP committee defined three levels. Level A, the one which can be used as the surrogate, is the one we ought to consider. Levels B and C concern me as surrogates.

Dr. Amidon: Lew, I don't think we're in disagreement. I was saying that if dissolution is rapid for a Class I drug, then one point is enough. In fact, doing more points is problematical, as you point out. If dissolution is slower, then you have to do multiple points. So I don't think we're in any worse situation. But there are some cases where it can be rapid enough, and in those cases I would argue that there would be no correlation with dissolution rate.

Dr. Leeson: In those cases you simply have to be faster than a certain rate, I agree.

Dr. Amidon: So it's still a very valuable regulatory tool which can simplify things in some cases. There isn't anything magical about 15 minutes. It's got to be thought about and worked at a little more.

Dr. Leeson: I'm afraid people might come away from here thinking that's the new term. I know you put a lot of caveats in what you said, but I don't want people going out and thinking that's the new specification, 85 percent in 15 minutes. Because I can see everyone running back to his or her company and making that announcement. It happens all the time.

Dr. Digenis: We're collecting questions now. I'm going to ask the panel members to accelerate their comments. There's one short question from Dr. Robinson.

Prof. Robinson: This is a very important point with regard to what I'm saying versus regulatory implementations. Larry pointed out clearly that there's a long regulatory process. On the other hand, this is the forum to gather input to start getting it done correctly. If we wait until the end to speak up, it's too late.

Dr. Lesko: I want to clarify the distinction that I tried to make with regard to dissolution requirements in the FDA. A product has to meet USP requirements. We hold to that as a quality control test of the process of making that product. If the product is not undergoing any change, why would I expect it to be bioequivalent if it met a USP specification. On the other hand, when we talk about a biopharmaceutical classification system, we move into the world of change. We need to ask a different question. When the firm has changed a site or a process or a formulation, the question then is whether the USP specification is enough to assure equivalence.

Prof. Robinson: Is it telling you the true story?

Dr. Lesko: Yes. The answer in terms of visualizing this research is that it isn't telling you the true story. For a change, we need more information. A single point for a Class 1 drug, or a multiple medium, multiple profile for the Class 2 drug, or something like that. So the issue of no change versus change in formulation is an important distinction in my mind.

Question & Answer
Princeton, NJ

Q: What is the role of chylomicrons in the absorption of drugs with high permeability and low solubility?

Dr. Amidon: The components which are synthesized in the cell can in fact be one of the routes out of the mucosal cell, into the interstitial fluid, and then, depending on the partitioning into the chylomicrons, may play a significant role in the systemic availability. The chylomicrons themselves are not transported across the brush border of the mucosal membrane, so they would have little impact on permeability. They could have some impact if the drug process of absorption is always a diffusive one. Even though in all the pharmacokinetics we write K x C, the reality is if it were diffused, it would be K or P x Δ C. Δ C is there even if we don't include it. So the Δ C means there is a sink condition someplace. We discuss that a little bit in the paper. To the extent that the sink condition on the plasma side is maintained, sink conditions will in general lead to higher permeability and higher flux. I don't think it would have an impact on a classification scheme because it would still be classified as a higher permeability drug. The actual operative permeability *in vivo*, that's more complicated. There are many factors affecting a permeability.

Q: If there's limited in vitro and *in vivo* correlation data for IR products, which impact do you see for the industry on products using dissolution data for QC tests only?

Dr. Lesko: First, on the part of that question dealing with *in vitro/in vivo* correlations, we rarely see them at the agency for IR products. We don't require them, and I think they can take a considerable degree of effort to achieve. In fact, only recently have we begun to see those types of correlations for the extended release products. Getting back to reality, we don't require, and don't see in the application, the *in vitro/in vivo* correlations for IR products. That's one of the motivating factors for the research that we're working on with Gordon.

In lieu of those correlations, we have to ask more under the conditions of change in the dissolution test. What we're trying to do here is define extensions from a single point USP dissolution test for those sets of conditions where it's required in terms of the formulation change. I don't think any of the dissolution requirements we talked about today for Class 2, 3 or 4 drugs are intended to be for routine quality control. They're intended for situations where you're trying to determine equivalence after some change in the product in one of those aspects we've talked about. For QC tests, I don't see any change from what we now do for the IR products.

Q: To what extent has the permeability been studied at other sites of the GI tract? Could this answer the bioavailability of the amoxicillin?

Prof. Wagner: Only if, for instance, Gordon studied it and the drug was absorbed in the ileum. That may effect it. But this is a correlation of model predicted versus observed, and that correlation theoretically says the line should go through the origin and have a slope of one. If it doesn't, there's something wrong. If the data are nonlinear, then the

model should be nonlinear, or vice versa. If the model is nonlinear, the data will be nonlinear. I don't really see that as an explanation. There's some reason, and I'm sure Dr. Amidon will come up with a reason after he gets home and starts studying the problem.

Dr. Amidon: I agree, John. When you're doing predictive versus observed, it should be a straight line through the origin in one. No doubt about that. I don't think the point of that paper was to develop an accurate model for prediction. That's a separate issue, and an important one from the point of view of drug development. I think it's a secondary issue for this meeting. But in the end, to have a good model, you have to have a straight line through the origin.

Prof. Wagner: Some of the additional questions here indicate the experiment set allows the determination of drug disappearance, not the determination of drug absorption. A plasma profile is needed to confirm drug absorption.

Dr. Amidon: I would just rephrase, though I agree with the point. Systemic availability is an important determinant of the biopharmaceutics, and you should know that about all drugs. When we're talking about bioequivalence and changing formulations, though, the nature of the question changes: If the plasma level variability is due to something other than the formulation, should you be doing a study? We're trying to define that. Systemic availability is obviously a key factor for drug development and the biopharmaceutical properties. For bioequivalence, we're trying to separate and untangle that, so we are focusing on drug absorbed and factors controlling drug absorption. If one wanted to take the analysis to include metabolism, if it were not the surface or brush border metabolism but cytosolic and liver metabolism, then we could also include that if the permeability concentration profile is the same in the model, they will not only have the same rate of penetration into the mucosal cell, they will have the same rate of metabolism. Now that's saying a lot. If they're surface or luminal metabolism, it's a different factor. That has to be separated out. If you have, for example, a pro-drug that an ester has metabolized in the brush border, you better be following the metabolite too. Those considerations have to be included.

Prof. Wagner: There are so many drugs that are highly permeable. However, they are either metabolized or have active metabolites. What does permeability mean for them?

Dr. Amidon: If they're high permeability, and the high permeability tend to be the more nonpolar drugs, they'll tend to be more highly metabolized. If you look at the plot in the data we have so far, the drugs on the slope actually tend to be less metabolized, more polar drugs. That's nice because the bioavailability fraction dose absorbed tends to be closer; they're not highly metabolized and you don't have to worry about hepatic elimination. What it means is that if a drug is classified as a high permeability drug, then when you want to make a site change or you want to scale up, you may be able to request a waiver from a bioequivalence trial on the basis of its classification, because the changes you've made in the formulation are not going to impact the absorption of the drug.

If you take, for example, propanolol, which we have studied, the IV curves are virtually superimposable. The oral curves are all over the place. Its absolute bioavailability is around 20 percent. Now, if that drug product disintegrates and dissolves rapidly, what are you measuring when you measure plasma levels? The variability has nothing to do with the pharmaceutics of the formulation. So doing the study doesn't make objective scientific sense. I think we can define high solubility, high permeability classes of drugs under certain conditions so that we can simplify regulation.

Q: I have run a bioequivalency study on a highly soluble, highly permeable drug using two tablets simply changing the vehicle for administering the tablet from water to orange juice. This resulted in a 20 percent reduction in bioavailability. Clearly, dissolution rate in this case was meaningless. Using the new guidelines would have missed this important observation. Are there any other examples for IR products where dissolution does not predict the equivalency?

Dr. Amidon: I don't think this is a dissolution problem. I see it as something in the orange juice interacting with the drug, making it less than fully bioavailable. The best way to find out is either to run dissolution in orange juice, or simply study the physical chemistry and possible binding of the drug with it. I don't think any in vitro test will predict that a drug is going to interact with something in another vehicle that you've never studied. But I don't think any dissolution test would have predicted this unless you ran it in orange juice.

Dr. Leeson: Can I comment briefly on that? The work of Bailey recently is showing tremendous changes in absorption of opine in grape juice as an example of an unsuspected but nonetheless profound interaction which dissolution would not have revealed. This is clearly a drug-food interaction which is beyond the limits of what we are trying to do.

Prof. Wagner: Somebody asked if we should have two sets of dissolution requirements when a drug is known to have a significant food effect on bioavailability. I did a lot of food studies long before they were common. A lot of antibiotics have profound food effects, a lot worse than most people think. Doctors are still prescribing penicillin and tetracycline to be taken with food. Well, I showed if you eat a steak meal and take tetracycline, the absorption is 50 percent. So I don't think it requires two sets of dissolution data, but you have to be very cognizant of the effect of foods. Put it in your labeling.

Dr. Digenis: I want to say something myself. In a paper that we published a few years back in the Journal of Clinical Pharmacology, we showed that if you give food 30 minutes after you administer erythromycin on an empty stomach, you can reduce its bioavailability by 50 percent. Dramatic, just as John said.

Q: For a combination product, if the components are not in the same class, what do you do?

Dr. Lesko: Let's imagine a combination product that has a highly soluble, highly permeable drug in combination with a low solubility, high permeability drug. My initial reaction is to think about the consumer risk of a bioequivalence study following a change in that formulation. My feeling would be that we have to base the decision on the ingredient that is in the low solubility, high permeability class. To go the other way would involve too much risk for the consumer in terms of inequivalence or lack of interchangeability. However, on the other hand, there may be some leeway in that bioequivalence study if the active ingredient that would be measured was not a highly soluble, highly permeable drug. I could imagine something like that. I can't imagine not going with the more stringent requirements for that type of combination.

Q: How many drugs have you looked at that have a poor fit to the model?

Dr. Amidon: If you're asking about fitting fraction absorbed versus permeability, which is not really the direct point of what we're discussing today, I think it's extremely important in drug development and you want to be able to assess that early on. But you've got to add the metabolism component because the two organs are in series. If the drug is not secreted in the bile and changed, the correlation appears to be quite good with regard to fraction absorbed. But if the drug were secreted in the bile, it may be problematical. We can probably say scientifically that if the drug is uncomplicated in terms of metabolism, then the correlation would be expected to be very good in virtually all cases. But that's not the direct point of the discussions today. We're trying to understand and develop a basis for the biopharmaceutics properties that are going to influence absorption, and we want to be sure that they're the same within some criteria.

Dr. Karl DeSante: Larry, you presented this process by questioning how we're going to get all these developed. You have a lot of steps in your process. Are we going to have to do every one of those steps? Do you need the advisory committee input if you have a workshop going on? I'm not trying to short circuit anything you're doing, but it sounds like a very elaborate process for something that everybody is saying we need. Since we need to develop data, how can we start developing the data faster rather than wait until we get through all the steps in the process.

Dr. Lesko: That was a good question, Karl. I didn't clarify it. I tried to represent the options that we have as we move down the regulatory pipeline. In many cases we don't need all those steps. It depends on the particular research and the particular issue. That full set of steps, including an advisory committee meeting, isn't necessarily needed for this research. We didn't go through all those steps for our SUPAC document, for example. We went through some of it, interacting with the trade associations in the industry and getting out there at the annual meeting. That was sufficient. I think everybody felt comfortable with the change. People were happy with the outcome for the most part. I think that process worked well. In fact, I think that's a model for the way things should work. I would move this research down that pathway, but not do anything more than we need to do.

Dr. Kevin Johnson, *Pfizer:* I just had a comment I wanted to make. I'm pretty comfortable with neutral compounds and maybe even acids. Bases really scare me. I've seen a few of them where they're highly soluble at the pH in the stomach and possibly precipitate as they exit the stomach. It's hard to determine whether dissolution may impact the bioavailability of those compounds. I wondered if you had any comment on those cases?

Dr. Amidon: Yes. I think that may be the most complicated class-type of drug for pharmaceutical regulation. To address that, we are studying itreconizole, with a pKa around 3-4, solubility is high at pH = 1. It's a terrible drug to study. It absorbs to the tubing. The methodology is problematical. We have an approved protocol, but we're not sure it will work. We're trying to work through all of those details. I don't know what the answer is, but we may have to go to surfactants in the perfusing media. I think

that amines with pKa in the range of 2-6 or 3-6 are just complicated because they would be soluble in the stomach and precipitate. And then the question is if they re-precipitate and crystallize *in vivo*, I think it could be quite complicated. I think that's going to end up being a case where we're going to have to say we have no choice but a bioequivalence trial. But at least I think we've defined the problem. One of the reasons for suggesting a media change is that it could partially account for that. I don't in any way believe it's going to reflect *in vivo* until we understand more what might be controlling the precipitation and crystal grown *in vivo*. So, I think that's a class of drugs that are going to remain complicated.

Dr. John Cardinal, *Great Valley Pharmaceuticals:* I think it's important there's an effort here to provide some rationale as to when bioequivalency studies are required. It's a recognition that a negative result of a bioequivalency study is not always the result of the formulation. I'd like to see some recognition that it may not be the formulator's fault when a bioequivalency study comes out negative.

However, I'd also like to add two points. Your wall permeability numbers only vary about a factor of 10 from what I could see. Somewhere around .5 x 10^{-4} or 6, 7 or 8 x 10^{-4}. So the range isn't all that great. That means determination of the P-value is going to be critical to this discussion. I think that there needs to be some careful attention paid to that.

The next part is going to be digging into this correlation and understanding the dissolution test. I'm wondering if the agency is planning to take a look at a way of doing the dissolution test with respect to these correlations, because that's going to be critical in understanding where we go from here. You've had an effort to identify the theoretical part and you've had an effort to evaluate the effect of formulation on bioequivalence. Is there going to be a regulatory effort to identify a dissolution test that may be more predictive of the *in vitro/in vivo* situation than we've had up to this point?

Dr. Amidon: We have currently studied only oral products, so there already is a pre-screening. All the low permeability drugs have been sent back. If we take a low permeability drug like enalaprilate, that was available for study because it was in IV form, so it was convenient. If you go from enalaprilate to a piroxicam, it's a hundred-fold. Quite steep, and that steepness is an interesting scientific issue. We're working through that.

The permeabilities I think can become quite small for some drugs. We're just prescreening because we're using drugs only available for study in humans. We could certainly study low permeability drugs that you have INDs for in Phase I trials, and help identify that part of the curve. But we're limited by available drugs.

Dr. Lesko: I think there's two swings to the pendulum here. On one hand we have the USP dissolution test, which we're somewhat uncomfortable with as a measure of continued equivalence in cases of a change in formulation. On the other side is the question why not require some sort of correlation? I don't see any initiative under way to require any *in vitro/in vivo* correlation from a regulatory standpoint. But I think what the classification system does is fit in between that by requiring profiles where they're deemed necessary as opposed to a single point where that might be acceptable. So I see this as a middle ground between those two extremes.

The second thought that came to mind when you asked the question was whether there is a way to look back into the files to validate the database when we finish the initial development. One of the initiatives I'd like to see us get into is looking into our FDA drug database and see how the classification would have worked out had we applied it in those instances. We can do that where we've had supplements and where we've had bioequivalent studies required and where we've had change.

Dr. Cardinal: How do we get to the point of starting to understand and interpret the changes in the dissolution test beyond quality control? If we start looking at four and six point dissolution tests, we have to ask when the change becomes significant. Because if you're going to require it, the next obvious question is when did the change become significant and how do you determine that?

Dr. Lesko: That's a tough question.

Dr. Cardinal: There are times that we look at the traditional quality control tests, at three points, and we get a change of 10 or 20 percent. What does it mean? At what point does it become significant?

Dr. Lesko: We struggle with that now.

Dr. Cardinal: Ultimately, it seems that's in the eyes of the beholder.

Dr. Lesko: Currently it may be in the eyes of the beholder, but we're trying to make more sense of that.

Dr. Cardinal: I understand that. But I'm saying that in turn begs the question of how to bring some sense to this dissolution test.

Dr. Lesko: This is why I have urged that we develop the correlation, and modify these formulations to determine what it means *in vivo*. That way, you

can simulate your bioavailability data. Many people are doing it with extended release. With the proper effort, I think it can be done with immediate release, to see what these changes in dissolution are actually doing. If they stay within some figure like 20 percent, which is the number now for bioequivalence intervals if a generic company runs against you, then it isn't a major change and you don't have to do the study.

Prof. Robinson: Let me play the devil's advocate here. You can take a biostudy and get an absorption rate constant out of that. So you already have a database that speaks to the issue of how well a drug is absorbed with certain assumptions, and you know something about the solubility dissolution behavior. So you can already make some judgments without the more definitive work that Gordon is doing. The concern I have is that everybody's going to dash out of here and contact Gordon or Upsula and say we've got to do our human studies because that's the only data that's going to make any difference. You do have absorption rate constant data.

At this stage, if you have permeability data from humans, there should be enough to do some animal correlations to look for scaling factors. I assume that's down the road. But I guess at the end of the day you are still going to be faced with what you've always been faced with. You're going to have to make a decision about whether you use permeability coefficients or absorption rate constants. There are assumptions in both of those as to how clean they are and what they represent, so you're still going to have that terrible decision. I'm not sure that any amount of data you collect will ever resolve that.

Dr. Amidon: Certainly there is a mathematical relationship between absorption rate constant and permeability, but the absorption rate constant is more complicated and includes more of the metabolism, so I think it's more difficult to interpret. That's why we're focusing back on permeability. But even permeability isn't without complications in some cases. You can't get everything. But I think permeability brings it back to a perimeter that is responsible for the drug leaving the gastrointestinal tract and entering the absorbing surface. That brings the focus to the absorbing process, and removes the other systemic availability variability issues. It's a step in the right direction, but it's still not clean.

D**r. King-Chiu Kwan, *Merck Research Laboratories:*** I'm a little bit concerned about the suggestion of trying to pull the rate constant from a bioequivalence study in man. Assuming that one could do it, that is still not a permeation. That's a measure of the rate of loss from the lumen. You didn't make the corrections for bioavailability.

Dr. Lesko: That's my point, Chiu. At this point in time, the differential in absorption through the intestine and the fact that he's measuring a rate of loss means he's not really measuring absorption. So the quality of the number is about the same in both cases. I'm applauding what Gordon is doing because he's eventually going to get to the point where he has a much better number. At this point in time, though, the agency has a number that's probably equivalent in quality in terms of the absorption versus permeability coefficients.

Dr. Kwan: Like everybody else, I'm applauding the effort to try to understand and predict bioavailability based on physical chemical principles. For historical purposes, we have to achieve constant bioavailability so that in time we should be able to reduce the need to do bioavailability studies. For that purpose, I was wondering if you have done things like riboflavin or thiamin, where the initial issues of bioavailability were based, and in what class would the water soluble vitamins be placed in your classification system?

Dr. Amidon: First, the answer is no, we haven't studied that type of drug. One of the reasons is that selection of drugs has other overlays. The drugs I would like to select as a scientist are not always the ones I'm allowed to study. Riboflavin is not a very critical drug, so why should we put resources into studying riboflavin, when studying something else is more important. To answer your question scientifically, on a carrier mediated drug where the permeability would be concentration-dependent, we would still take the low concentration on a first order estimate of permeability as our reference standard, but then say this drug is more complicated because it's carrier mediated. That's what's happening with the B-lactam antibiotics like amoxicilin with the data that John Wagner showed. It's complicated to do the simulations because of its nonlinear absorption. With those, though, one would need the permeability profile and the concentration dependence along the gastrointestinal tract in order to do a prediction. That's complicated. We can't do that yet.

Dr. Lesko: Just a couple of comments on some of the other things that have been discussed. Getting back to the question about dissolution profiles, we do that now in a rather anecdotal way. We eyeball profiles and decide if they're different or the same. We want to move away from that. That's one of the limitations of our SUPAC document. It didn't define how you compare profiles in dissolution. I can imagine looking into the future that there's going to be some methods for comparing dissolu-

tion profiles. But we recognize that as a limitation at this point.

I want to re-emphasize where we are in the initiative. I wouldn't want to encourage anyone to read too much into this at the moment in terms of a regulatory payoff. The SUPAC document will become final. That's the position in terms of applicability of this information. I don't want to extrapolate much beyond that until Gordon and others have said we have the data and the thought process within the agency to move that into the regulatory world.

I'd like to ask Gordon a question. In terms of everyone running home and starting studies like this, have you done any work attempting to correlate your permeability constant with something like a partition coefficient? It's almost too obvious a question. I'm sure you've thought about it. What have you found?

Dr. Amidon: Hans Lennernäs and I are both doing that with our data. We have some abstracts on rat-dog and dog- human correlation. But these are with 3, 4, 5 compounds. The acquiring and establishment of human data is a slow process. I believe that we will validate those correlations within the next few years and that it may be possible with problematical drugs like high nonpolar, highly metabolized drugs to use preclinical data to classify the drug.

Q: When a drug is inactive, but has an active metabolite, how do we classify it?

Dr. Amidon: The classification has to be based on the drug that's absorbing into the mucosal cell. If you look mechanistically, that's the key step. Subsequent conversion to an active metabolite is not part of the absorption process. So I would propose that the actual parent drug in the administered dosage form is the drug upon which to base a classification. Now what if the drug is a pro-drug and unstable in the lumen or metabolized in the brush border. I can't answer that right now without thinking about it and having some more data.

Q: The industry hears anecdotal evidence about the FDA UMAB initiative which suggests a large proportion of drug performance *in vivo* is unpredictably unaffected by formulation changes. Will these data be published, and are we making change controls more complicated than necessary?

Dr. Lesko: Dr. Singh and Dr. Augsburger are in the audience if anybody wants to talk about specifics of that database. To our surprise, that's what we did find in the contract that we did at Maryland, taking a wide variety of drugs with different biopharmaceutical properties and different methods of manufacture and making what we thought were changes up to and beyond the limits of what a firm might do in real life. We found that we would affect dissolution significantly and those products *in vivo* turned out to be bioequivalent. I think there are some interesting lessons to be learned from that. It gets back to what Lou has said about dissolution test design and it gets back to the drug classification system where you expect or don't expect dissolution to play a role in *in vivo* bioequivalence. The papers from that work are drafted and will be sent in for publication.

The SUPAC document was successful getting through FDA because of the data we had from that contract. Without that database we would not have gotten SUPAC to a consensus point.

Dr. William Robinson, *Sandoz:* I have a question on poorly soluble drugs as they relate to the conduct of the *in vivo* study. For poorly soluble drugs, I assume that you're formulating to some degree to get an emulsion and the particle or droplet size of the emulsion could alter your measurement of permeability. How are you planning to deal with that?

Dr. Amidon: We're working that out now, but that's certainly true. In fact, cyclosporin is one of the model drugs, and we're trying to figure out if we can do it because it does absorb to the tubing. We've got to look for metabolites. We probably have to use some components similar to those in the IV form in order to keep it in solution and reduce absorption. That in turn will alter the permeability estimate. If we know the solubilization I think we can account for the concentration adjustment. We also can validate the methodology in animals, rats and dogs. The nonpolar, high permeability, low solubility drugs are experimentally problematical with this methodology. The most problematical thing is the tubing absorption. We're working out methods to do that. One of them might be to go to an open tube design where you have less tubing than you do with the closed tube design. We have to work that out. One of our current activities is developing procedures for measuring permeabilities for water and soluble drugs. That's an ongoing effort.

Dr. Irwin Lippman, *Whitehall-Robbins:* I was thinking about the permeability in ileum versus the permeability in jejunum and whether you found compounds that may vary greatly one from another. When you classify a compound based on one part, might it fall into another class if you considered it through both parts?

Dr. Amidon: Yes. Certainly for some drugs that would be true, probably even for some of the drugs that we've studied. The polar drugs have very low colon permeability. There are differences in the ileum in humans vs. animals. You see that with some of the H2 antagonists and with carrier-mediated compounds. In humans, though, there's much less of a database because it's much harder to study the ileum. Maybe you could not study it properly with the closed tube method we're using now. You'd have to go to open tube and intubate overnight. I would say there's very little database at the present time. And that's why we refer to the jejunum as the reference permeability, focusing mainly on immediate release. Because that's the first step we can take. For controlled release or concentration dependent permeability, there needs to be some structure probably put under the classification to account for that. The real world is more complicated and we don't have the answers yet.

Q: What are your thoughts about therapeutic index in the biopharmaceutical classification?

Dr. Amidon: I think the therapeutic index has more to do with the variability and plasma levels in your specification limits. I think that's broader than just the classification. A high therapeutic index, high solubility, high permeability drug should be the easiest to regulate.

Dr. Lesko: I think that's a good point. When we put the SUPAC document together, solubility, permeability and therapeutic index came into play in our considerations. And if some of you remember our 1993 Generic Drug Advisory Committee Meeting on dissolution, one recommendation was to incorporate therapeutic index into our thinking on the drug classification system. So we went ahead and did that. In the SUPAC document for a Level 2 change, a change that's possibly going to impact equivalence, we break drugs down into narrow and broad therapeutic index and that triggers different requirements in bioequivalence. So it does come into play, particularly with the composition component section of change.

Prof. William Barr, *Virginia Commonwealth University:* A couple of comments on permeability. First of all, it's regional. We have done some work on amoxicillin as published in CPT and found that its permeability differs tremendously as you go down the GI track. When you get to the colon, it's absolutely zero. We intubated the colon and found out that in the proximal and distimal parts of the colon, you get absolutely zero absorption. If you give the drug very slowly, you get absorption as you get down to the ileum. So obviously it is saturable, highly dependent upon the position. When we look at permeability, we're looking first of all at position and we have to realize for some drugs, particularly saturable or carrier-mediated drugs, that may be different. So that's going to complicate the problem.

Secondly, the permeability coefficient makes the assumption of a sync condition in the cell. There's at least two factors which control that sink condition in addition to permeability. One being cellular metabolism and even cytozolic. A number of years ago we did some studies looking at disappearance of drug from the lumen in a drug that was highly metabolized by good formation in the cell. If you gave it a low dosage, you got a different model than if you gave it high doses. That's clearly going to be another saturable process that you have to determine what level you do the drug at.

Finally, the other process is blood flow. If you get a drug that's highly lipid soluble in which there's a high permeability coefficient, ultimately the upper limit will be blood flow. That's probably why we reach a saturation in the permeability coefficient.

Dr. Amidon: I agree with all of those statements. Your methodology has shown some of the permeability dependency for some drugs more clearly. The requirements may vary by absorption mechanism.

Regarding your second question, the apparent, calculated permeability is for drug loss. Contributors to drug loss are included in that permeability. If you then want to go to a molecular cellular membrane interpretation, since we've ignored the concentration on the sink side, that's going to influence the interpretation of permeability. For many of the high permeability drugs, it's not going to matter. It won't impact on the classification very much. If you look at where the cut off may be, it would be around metoprolol, perhaps. Call it somewhere between two and four; they tend to be less metabolized, so I think we have less of a problem. The brush border membrane is the rate determining step. A significant fall off in concentration and sink conditions is a good assumption.

Dr. Munir Hussain, *DuPont Merck:* I wonder about the numbers you showed on permeability, since most of our work is with animals. Do you have any correlation be-tween those permeability numbers in humans vs. animals?

Dr. Amidon: Yes. Both at Upsula and Michigan. We have done ongoing rat, dog and human studies for selected compounds. In our case, for example, if I take the permeability fraction absorbed plot in rats that was published eight or ten years ago, the curve overlays pretty well the fraction dose absorb per-

meability for humans, with an almost completely different set of drugs, since NIH is interested in different drugs than FDA. Now we're putting the data together. We have studied rats and dogs for some beta-blockers. Numerically they're within a factor of two or three, so they're close. It's going to depend on the absorption mechanism, paracellular, transcellular, carrier, passive. I think there will be some separation depending on the mechanism.

Q: The problem with that would be permeability numbers so narrow it would be difficult to judge if the drug is going to be bioavailable or not. What does three times mean? Could three times differentiate permeability versus impermeability?

Dr. Amidon: For metoprolol, maybe. For piroxicam or naproxen, probably no. However, we have to firm up those correlations and make it fairly tight. We're not there yet. This meeting is about discussing not only the science, but the regulatory import in doing the science in an early stage so we can think about all these issues.

Q: As the FDA looks at the tons of data in its files on failed BE studies, is it looking for outlyers and challenging the paradigm?

Dr. Lesko: I think we are talking about a new paradigm of assessing equivalence. Unfortunately, we don't have a ton of data on failed biostudies, but the most data we have in the Center in the Office of Generic Drugs is on the multi-source products. Unfortunately, they're all passed biostudies. We're looking in our files for confirmation or outliers of this paradigm. I think it's not unreasonable to say that if people have data that either confirms or validates this paradigm we might be very interested in seeing it. I think we all would. If we can access that data in a way that everyone is comfortable with, then it would be a wonderful way of moving this process along more quickly.

Dr. Amidon: Larry mentioned there is some effort at looking retrospectively at a database. One of the largest databases is Dr. Henning Blume's ZL (Central Laboratory) in Germany which is funded by the Pharmaceutical Society. It's a pharmacist's laboratory. He probably has the most extensive database, and he's agreed to work with us so we can try and look retrospectively at dissolution and bioavailability to see how it works. In the end, we have to hold that up the goal.

Dr. Digenis: Why limit to 250 ml fluid for solubility? There is about 9000 ml fluid in the GI tract. At rest, the stomach of a human has about 50 ml capacity. Dr. Amidon was very careful in saying 250 ml, but then he pointed out a time. Time is very important because the gastric emptying rate of water is only 12 to 13 minutes. So 250 ml is a reasonable amount when we consider gastric emptying, which is the key particularly with highly water soluble compounds.

Dr. Amidon: One has to pick a reference. If you look at the analysis, you come out with having to pick a reference volume because that's part of the differential equation no matter how simple or complex your description of the process. And so you pick a reference volume. I showed you the range because we have to pick something to start. So I say, well if it can dissolve in a glass of water that you take with a bioequivalence trial, then it's a soluble drug. And if it's soluble at all pHs you might agree with that. You might argue that may be too restrictive. That's almost certainly true. Drugs less soluble than that can dissolve sufficiently and be a hundred percent bioavailable. That would be part of the retrospective database searching to decide where one should draw the limits. I've argued for what I think are conservative limits that I feel are safe in terms of definition for high solubility high permeability drugs.

Dr. Digenis: I think that 250 ml is good for is one or two of your classes. It could be argued that the 250 ml is too restrictive for the other classes. The best piece of real estate for absorption after the duodenum, which is a short organ, about 25 centimeters, where nothing stays more than eight minutes, is the jejunum. The first 70 centimeters of jejunum appears to be very important. Time is very important also. If it's in solution, the drug is going to clear out from the stomach rapidly, in 12 to 13 minutes. In the next 70 centimeters, you probably have a residence of about two hours. That is reasonable with 250 ml. Things get to be cloudy where the drug is very insoluble. I don't think we have enough data to answer the question then.

Dr. Amidon: There's nearly 10 liters per day processed. It's not all present at one time.

Dr. Digenis: That's why I mentioned the time factor as very important. If we're going to assign a volume, we have to assign a time factor.

Dr. Surendra Mehta, *Warner-Lambert/Parke Davis:* When you talk about compounds which are solids and especially the basic compounds, and you start changing the dissolution media, especially when it reaches stage 5 through 8 when the compound is very soluble, the formulation would make a difference because it all depends how that compound precipitates out the rate of nucleation, the rate of dissolution. So that pH profile becomes awfully difficult. It's tough enough to get a dissolution media for certain drugs.

Dr. Amidon: Drugs that precipitate in the GI tract are going to be the most complicated. I don't think there's any way around that. We may never find a way to avoid doing a bioequivalence trial because it's too complicated to mimic in vitro.

Dr. Leeson: Someone asked me about my four commandments and I couldn't remember what they were, but I did write them down. These were probably designed for extended release dosage forms, but I think a couple of them apply to immediate release. First, correlations are dosage form dependent, not drug dependent. If you change your drug, especially with an extended release dosage form, the correlation may change completely. You can't have one set of specifications for every extended release product. Second, correlations are not always possible. I certainly have examples where we could not develop an *in vitro/in vivo* correlation. I think other people have, too. Third, the decision of developing a correlation is not the job of the FDA, nor is it the job of the USP. It's the job of the company. If they decide they want to put the effort into developing the correlation, that's their business. However, if they don't do it, they're going to have to live with the consequences when they make changes. That's their decision. A lot of companies would rather do the bioequivalency study at the time. They don't want to be bothered with anything else. Finally fourth, if a Level A correlation exists, the agency should allow it to be used as a surrogate for bioequivalency.

Dr. Welling: I have debated this topic with Gordon Amidon and Larry Lesko for the past three or four years. I have acted as their resident skeptic. I feel that the task of using a very simple, highly controlled system to try to predict a very complex, uncontrollable system is awesome. The conversations we have heard today reflect the enormous difficulty of trying to get a simple test to predict or represent an extremely complex phenomenon. Attempting to address and confront this problem is a noble task. I am still a skeptic, but I think that what they are attempting is impressive and potentially extremely useful.

Dr. Amidon: I actually learned pharmacokinetics from John and Peter. I come from that school, but I was reluctant to do much with it until recently. I tried to stay in pharmaceutics and formulations, oral delivery and that arena. Ultimately, though, I was captured by the idea of combining these two issues. During a sabbatical year at the FDA, I talked with Vinod and other scientists there about how we could simplify things. I had little idea of the complexity of the issues.

There are some cases where, with additional data, we can simplify things. The counterpoint of that is that if someone says doing these human studies makes no sense because you're not measuring anything related to what you're trying to test, how can we as scientists defend that to the public? It's not defensible. What we need to do, then, is remove the politics and business overlay on the issues. That's where this conference helps. I see some additional forums to help flush out these issues, both for the science and the regulatory implementation. Based on the input here, I'm sure that if we've made some mistakes, we'll hear about it. I'm looking forward to that, because I want to know what the problems are sooner rather than later. I want to thank Capsugel for the opportunity to initiate this open forum.

Dr. Digenis: Thank you Gordon. We've heard today about human permeability, solubility in dose, and other important issues. We have to be appreciative of the efforts that you've made to bring back physical chemistry to biological systems. I want to congratulate the FDA representatives who were courageous enough to come here and answer all the questions, actually the barrage of questions. We're most appreciative of both of you (Drs. Amidon and Lesko) for agreeing to make your presentations and for the patience you've showed in answering all these questions.

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