Biopharmaceutics Classification System: an industrial experience

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Joseph R. Robinson, University of Wisconsin, USA: We'd like to turn now to the next presentation, the Biopharmaceutics Classification System: an industrial experience by O.H. Chan and H. Bockbrader, of Parke-Davis. The speaker will be Dr Chan.

Dr O. Helen Chan, Parke-Davis, Ann Arbor, USA: Thank you for your introduction, Dr Robinson. I would like to thank Dr Vince Lee and the organizing committee for inviting me to speak here at my birthplace, Hong Kong. The title of my talk is, Biopharmaceutics Classification System: an industrial experience.

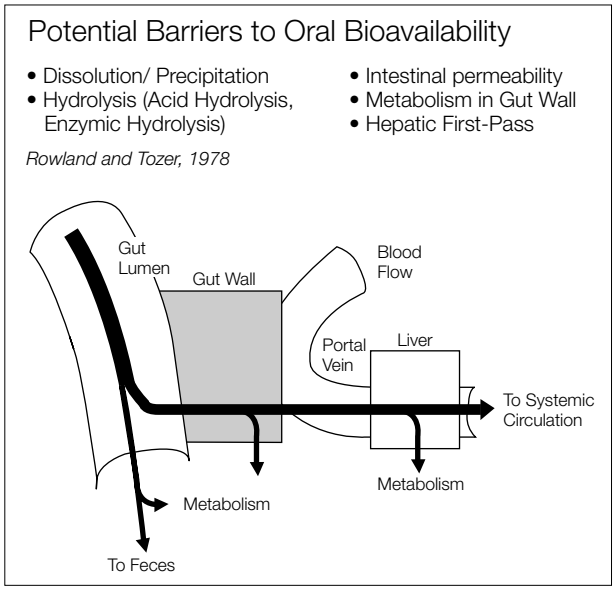

Figure 1.

I would like to acknowledge my colleagues, Dr Howard Bockbrader who provided me with the majority of the data, and Dr Jack Cook for his contribution to the discussion.

Figure 1 must be familiar to many of you. It shows the potential barriers for solid oral dosage forms. The barriers that the dosage form has to overcome before it can reach the systemic circulation involve dissolution or precipitation in the GI (gastrointestinal) lumen, instability in the GI tract, and permeation through the gut wall. And after that there is a first pass at the liver. If the compound itself is stable in the GI environment – in the lumen or in the gut wall – intestinal absorption is affected mainly by dissolution, solubility or permeation.

The candidates for biowaiver based on BCS are compounds that fulfil five qualifications. They have to be immediate-release solid oral dosage forms. They cannot be drugs with a narrow therapeutic index. The formulation has to dissolve rapidly, and the compound itself has to have high solubility and high permeability.

Figure 2 is one that I borrowed from Ajaz Hussain of the Food and Drug Administration (FDA). It explains the rationale for Class I compounds that may qualify for a biowaiver: when the dissolution rate is much greater than the gastric emptying, dissolution is not likely to be rate-limiting.

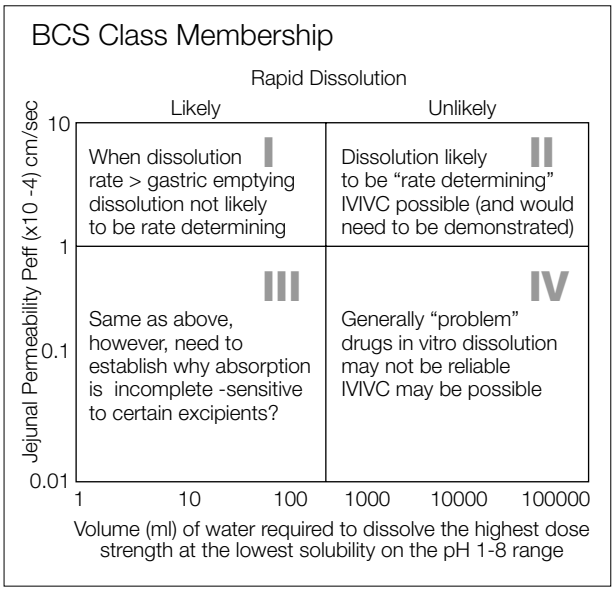

Figure 2.

Today I am going to show you two case studies. The first concerns a compound that we believe belongs to Class I, and where we think that we may be able to get a biowaiver; at least, we're formally going to request for one. I'll also present to you another case study, on a Class III compound, where we actually obtained a biowaiver before there was a BCS draft guidance.

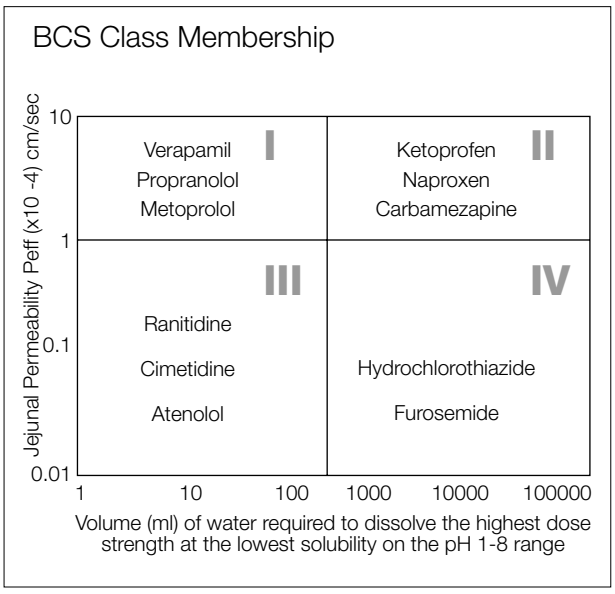

Figure 3.

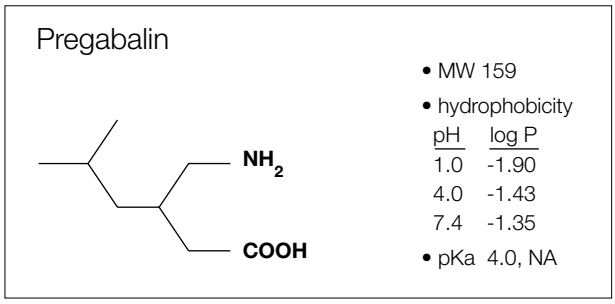

Figure 4.

We accept, of course, that candidates for the biowaiver be in immediate-release dosage form. But we believe that it is reasonable to include in the biowaiver controlled-release or modified-release dosage forms where one can demonstrate IV/IVC (*in-vitro/in-vivo* correlation).

Figure 3 shows several examples of compounds that belong to each class. I would like to draw your attention to metoprolol, which is a high-permeability/high-solubility compound that the FDA suggests as a potential internal standard, and which we did use in one of our case studies.

Figure 4 is our first case-study example, pregabalin. Pregabalin is being developed as an analgesic, anti-convulsant, and anxiolytic. It is a small polar molecule, with a molecular weight of about 160, and the log P is negative at all physiological pH levels. It has two ionizable groups, the pKa of the carboxylic acid is about 4.0 but the one for the

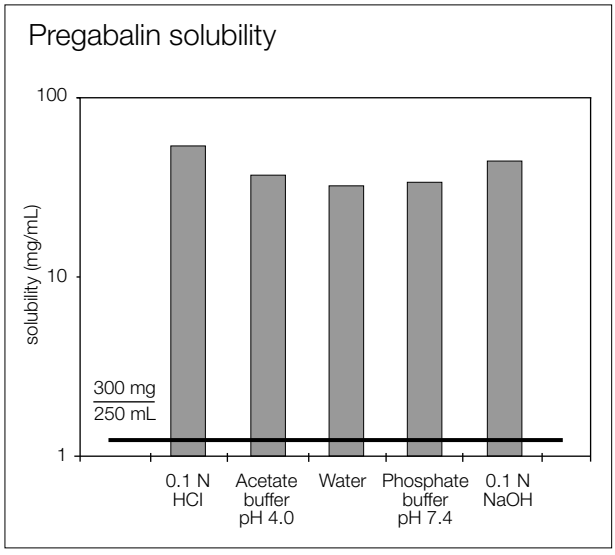

Figure 5.

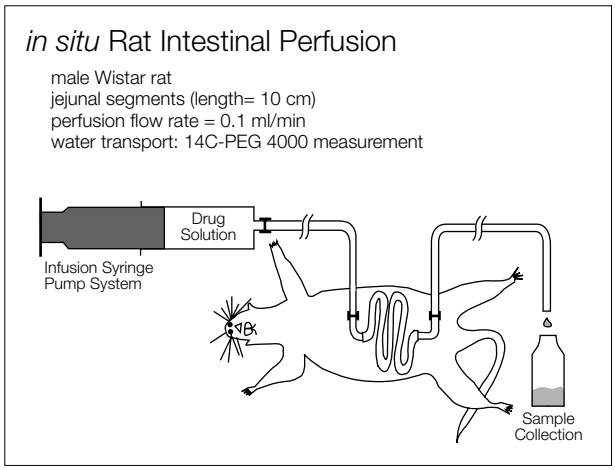

Figure 6.

amine is not determined, although I think it's about 11. It is an isobutyl GABA in structure, i.e. gamma aminobutyric acid.

We determined all solubilities at equilibrium *(Figure 5)*. For pregabalin, it is pH-dependent, going from 0.1 normal hydrochloric acid (HCl) to 0.1 normal sodium hydroxide, with the solubility being lowest in water and the phosphate buffer, pH 7.4. At all pH levels, the solubility is much higher than the highest-dose strength divided by 250 ml, which is the guidance requirement. So it is a high-solubility compound. Note that this was a log scale.

Figure 6 indicates the model we used to determine permeability. It is an *in-situ* rat intestinal perfusion model where we perfused the compound at the proximal end and measured what came out from the distal end. As long as the compound is stable in the GI tract, what is not coming out from the distal end at steady-state can be safely assumed to be absorbed. Besides perfusing the drug, we also perfused the internal standard, metoprolol, as well as a water transport marker, simultaneously.

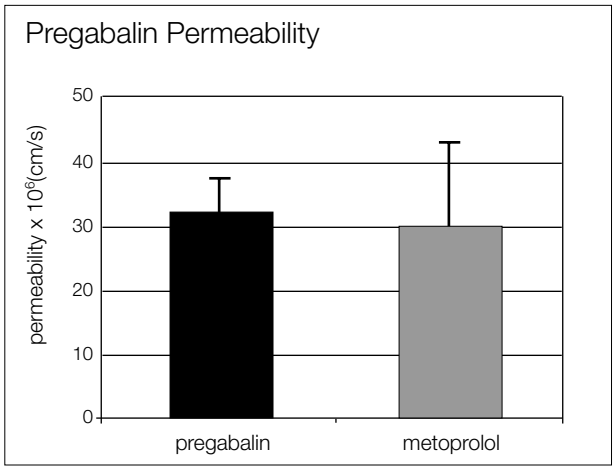

Figure 7.

Figure 7 shows the research results for pregabalin. The permeability of pregabalin is pretty high; it is fairly comparable to the permeability of metoprolol, the high-permeability internal standard that we used. So from this Figure we can tell that pregabalin is a high-permeability compound.

We also examined the relationship between permeability and the fraction absorbed in humans *(Figure 8)*. The fractions absorption of the reference compounds are either from the literature, or were determined experimentally by our company. With the value of permeability that pregabalin has, it is predicted to be about 90 percent absorbed in humans.

The solid curve on the Figure is the correlation for the rat intestinal perfusion model. Although I have not presented the Caco-2 data here today, the correlation curve is the dotted line shown on the Figure.

When we determined the bioavailability in humans, the oral bioavailability was 90 percent,

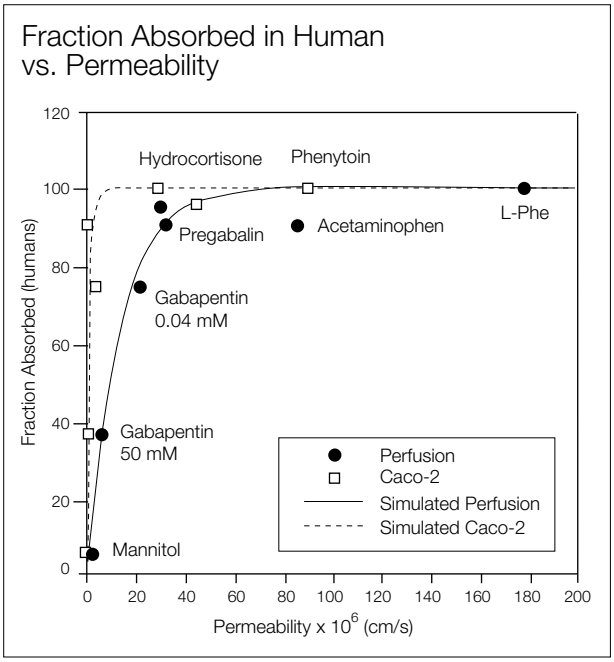

Figure 8.

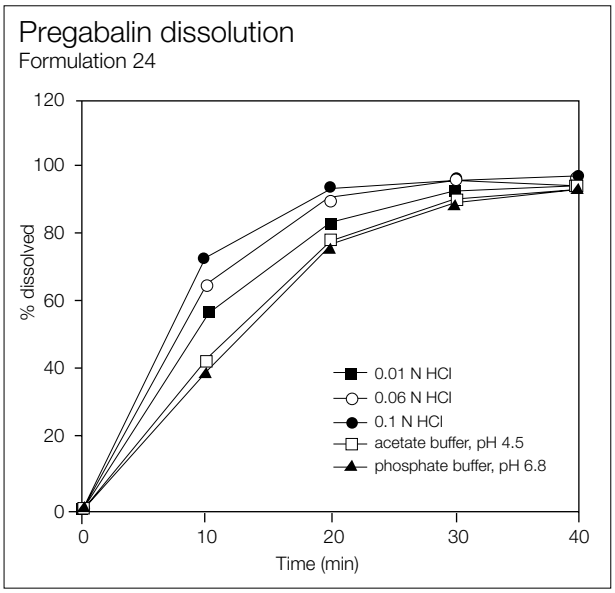

Figure 9.

which is exactly what we predicted. From our work in humans, in single-dose pharmacokinetics (PK) we found that the PK is linear over the dose range of 1-300 mg, and in multiple-dose PK it is predictable from the single-dose data.

We determined the stability under some very extreme conditions – 16 hours at 80° Celsius – and found that pregabalin was stable in water (0.47% degradation) and also at 0.1 normal HCl (3.23%). But at 0.1 normal sodium hydroxide it is not as stable (32.2 percent), although this may not be relevant in the GI environment.

For dissolution we used USP Apparatus II, 900 ml, at 50 rotations per minute. Dissolution was found to be rapid in all the dissolution media that we used *(Figure 9)*, and that means that it is more than 85 percent dissolved at 30 minutes, as defined by the guidance.

The dissolution media we used included several HCls, (from 0.01 to 0.1 normal), acetate buffer, pH 4.5 and phosphate buffer, pH 6.8.

Figure 9 constitutes the dissolution profile for formulation 24.

We actually have four formulations, numbered 7, 8, 23 and 24. Seven, 23 and 24 are all content-proportional, whereas formulation 8 contains identical inactive ingredients to the rest, but is not content-proportional. This is a Level 3 change, and so it requires either bioequivalence testing, or the demonstration that we don't need to test for bioequivalence *in-vivo*.

We found similar dissolution rates between these formulations, as determined by the F2 test – between 50 and 100. We also found that formulation 8 was bioequivalent to a solution, and that formulations 7 and 8 both have similar bioavailability compared to each other *(Figure 10)*. So we are planning to ask the FDA for a biowaiver for formulations 7 and 24. These two are the products that we would like to market, and the others were pivotal formulations.

With regard to the rationale for a biowaiver, we have formulations that have identical inactive ingredients, although they are not content-proportional, and we have a highly-soluble, highly-permeable and rapidly-dissolved product. That means that it is a Class I product. Based on this we expect bioequivalence, and so we believe we may qualify for a BCS biowaiver.

Meanwhile, the interactions we have had so far with the FDA indicate that the guidance is not yet accepted by all reviewers, since it is still a draft at

Pregabalin bioequivalence

Formulation	Reference	Comment
50-mg formulation 23	25-mg formulation 7	Similar dissolution
100-mg formulation 24	25-mg formulation 7	Similar dissolution
100-mg formulation 24	100-mg formulation 8	Similar dissolution
100-mg formulation 8	100-mg solution	bioequivalent
25-mg formulation 7	100-mg formulation 8	Similar bioavailability
25-mg formulation 7	100-mg formulation 8	biowaiver
100-mg formulation 24	100-mg formulation 8	biowaiver

formulation 8 : not content proportional, identical inactive ingredients.

Figure 10.

Gabapentin Stability

4 weeks at ambient temp		% degradation at 60°C			
solvent	% degradation	solvent	15 min	30 min	120 min
water	0	water	< 0.2	< 0.4	< 0.4
buffer pH 1	< 2				
buffer pH 4	< 1	buffer pH 4	< 0.2	< 0.4	< 0.4
buffer pH 7	0	buffer pH 7	< 0.4	< 0.4	< 0.6
buffer pH 10	~15	buffer pH 10	< 0.5	< 2	~ 6

Figure 11.

this point. *Post conference notes. The guidance became official August 2000.*

The next example we have is gabapentin. Gabapentin is also a small polar molecule, just like pregabalin, and it has the same GABA structure, with a cyclohexyl ring. It has two ionizable groups, with a pKa of about 3.7 and 10.7 respectively.

Figure 11 shows the stability of gabapentin. We found that at ambient temperature for four weeks, gabapentin was stable in water or in a buffer with pH range of 1-7, but not at pH 10. At the extreme condition of 60° Celsius, we found that gabapentin was stable in buffer 4 and 7 for up to two hours, but not so stable in pH 10.

The solubility of gabapentin in 0.1 normal HCl, water and 0.1 normal sodium hydroxide is pH-independent *(Figure 12)*. At all pH levels, we found that the solubility was much higher than the highest dose strength, 800 mg, divided by 250 ml. So this is a high-solubility compound.

Using the same in situ rat intestinal perfusion model *(Figure 6)*, we found that the permeability of gabapentin was concentration-dependent. At the higher concentration of 50 millimolar, permeability was a lot lower than at the low concentration of 0.01 millimolar *(Figure 13)*. At either of these concentrations, we also found that the permeability was lower than the internal standard, prednisolone, which is more than 90 percent absorbed. So gabapentin permeability is concentration-dependent, and it is a low-permeability compound.

The correlation curve in *Figure 8* show that gabapentin, at 0.04 millimolar, is predicted to be about 70 percent absorbed in humans, and at the higher concentration, 50 millimolar, about 35 percent absorbed. So, at either concentration, it is a low-permeability compound.

Figure 14 represents data from *in-vivo* studies in humans. Single-dose findings are indicated by the diamond shape, and agree with the predictions,

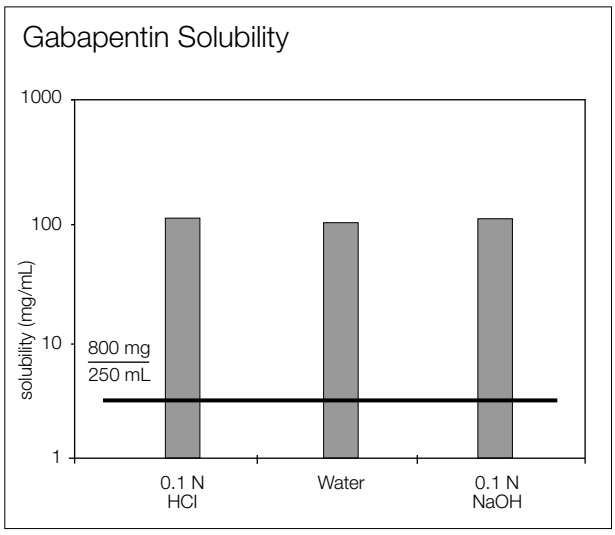

Figure 12.

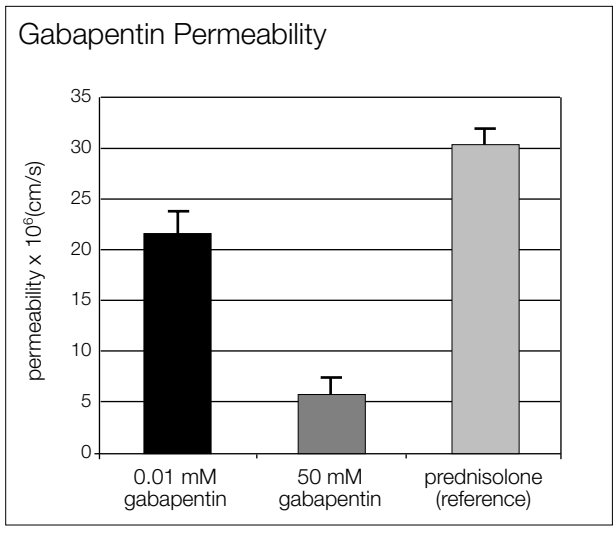

Figure 13.

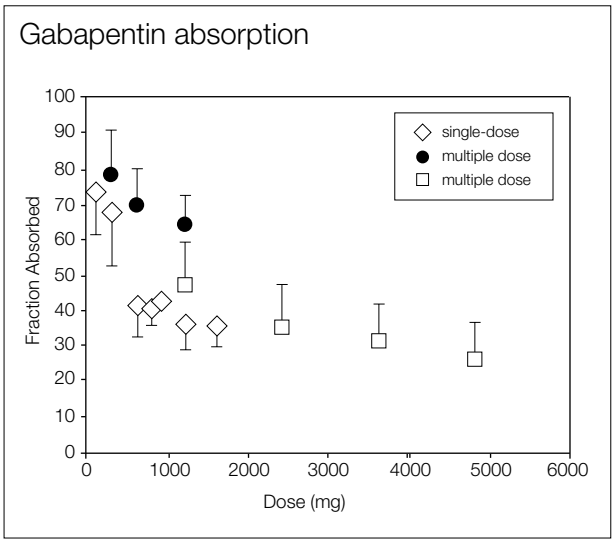

Figure 14.

with approximately 70 percent absorbed at a low dose and about 35 percent at the higher dose. The circles and the triangles are what result from the multiple doses. With both the single-dose studies and the multiple-dose studies, there is a dose-dependent absorption.

Figure 15 shows the dissolution methods used for gabapentin, with the same apparatus as for pregabalin. We have two types of formulations, capsules and tablets.

Gabapentin Dissolution

- USP Apparatus II, 50 rpm, 900 mL
- Dissolution is pH independent

capsules	**tablets**
water	water
0.06 N HCl	0.06 N HCl
phosphate buffer pH 7.5	acetate buffer pH 4.5
	phosphate buffer pH 6.8

Figure 15.

We found that the capsules from Freiburg dissolved very rapidly, more than 80 percent in 10 minutes; we had only one time-point for the 300-mg and the 400-mg capsules From Vega baja *(Figure 16)*. All three of these capsules were fairly rapidly dissolved, about 90 percent in 20 minutes. The three types of tablets -- the 600-mg tablet from either Morris Plains or Vega Baja, or the 800-mg tablet from Morris Plains -- did not dissolve as rapidly

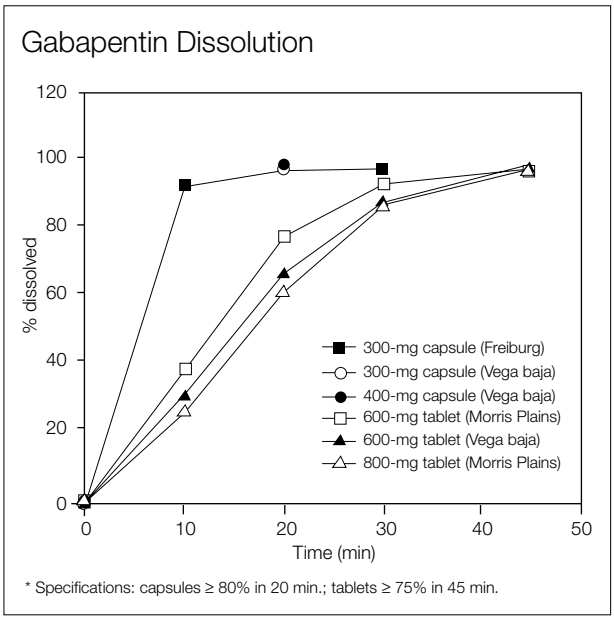

Figure 16.

as the capsules, although they still dissolved very rapidly as defined by the guidance, about 85 percent at 30 minutes.

Figure 17 is a summary of some of the bioequivalence studies carried out on gabapentin. The 100-mg capsules and the 300- and 400-mg capsules are all bioequivalent to the same-strength solution. The tablets from Morris Plains were bioequivalent to the capsules and the 600-mg tablets from Baja were also bioequivalent to two 300-mg capsules. What we were requesting was a biowaiver for the 800-mg tablet.

I mentioned earlier that the tablets did not dissolve as rapidly as the capsules, although both still dissolve rapidly as defined by the guidance. What I'm going to show is that dissolution rate does not matter very much for this compound. *Figure 18* is a simulation. The circles represent the actual data for the 800-mg tablet, the broken lines are the various simulations. Clearly, the compound is completely dissolved, regardless of whether the dissolution rate is 50 percent, 25 or 17 percent.

Figure 19 gives the concentration-time profile in humans. The circles are the actual observed data for the tablet. The dotted line is not very clear, but it represents the 50 percent dissolution rate. If the dissolution rate is only 50 percent of the original, or if it is 25 percent (as shown by the line with short dashes), you can see that in either case the

Gabapentin Bioequivalence

Formulation	Reference	Bioequivalent
4x100-mg capsule	400-mg solution	Yes
300-mg capsule (Vega Baja)	300-mg solution	Yes
400-mg capsule (Vega Baja)	400-mg solution	Yes
600-mg tablet (Morris Plains)	2x300-mg solution	Yes
800-mg tablet (Morris Plains)	2x400-mg solution	Yes
600-mg tablet (Vega Baja)	2x300-mg solution	Yes
800-mg tablet (Vega Baja)	2x400-mg solution	biowaiver

Figure 17.

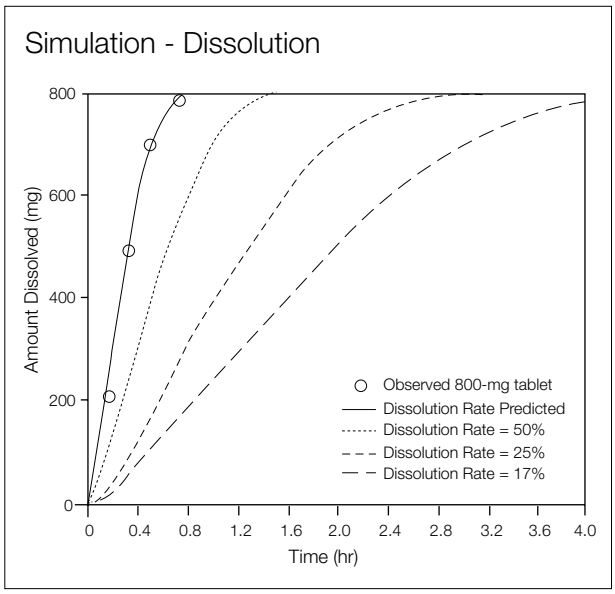

Figure 18.

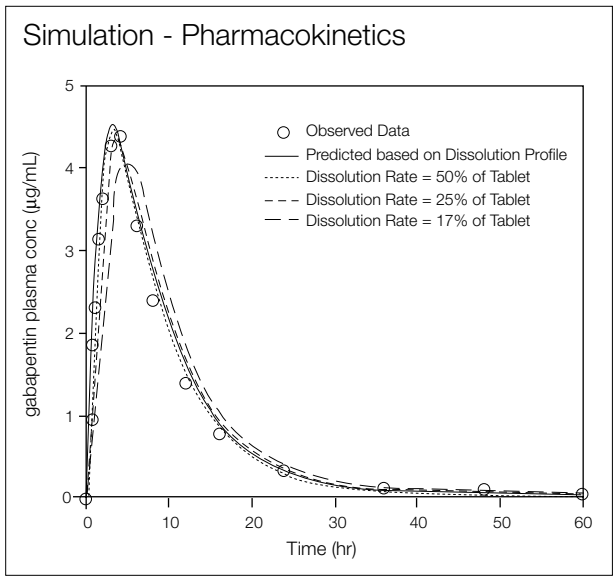

Figure 19.

concentration-time profile does not change very much. When the dissolution rate is only 17 percent of the original, as shown by the line with long dashes, that's when the concentration-time profile demonstrably changes. So what we can conclude is that if the dissolution rate of the product is between one-quarter to one-half of the original dissolution rate, the concentration/time profile is only minimally affected.

With gabapentin we also know that the concentration dependence is probably due to a carrier-mediated transport that's saturable, and the carrier is a system L large neutral amino acid transporter. In the case of gabapentin, since it is a highly-soluble compound with low permeability and dissolves rapidly, the rate-limiting step is the permeability, not dissolution.

Gabapentin Biowaiver

- If 800-mg tablet (Vega Baja) achieved dissolution specification of ≥ 75% in 45 min
  ➡ expect bioequivalence
- Biowaiver granted
- BCS biowaivers could be safely extended to Class III compounds

Figure 20.

So when we asked for the biowaiver, our thinking was that if the 800-mg tablet could achieve the dissolution specification, we should expect bioequivalence *(Figure 20)*. In fact, we were granted a biowaiver, and this was before the BCS draft guidance was published.

We also conclude that even though the guidance on biowaivers only allows for Class I compounds,

we think that this is a good case for demonstrating it can be safely extended to Class III compounds, because the compound is not dissolution-rate limited, it is permeability-limited.

In summary, what I have presented to you are two case studies. Pregabalin is a Class I compound where we think we have a good case for obtaining a biowaiver. The second example, gabapentin, is a Class III compound, which is not a class that is currently provided for by the guidance for biowaivers – and yet we indeed obtained a biowaiver. Thank you.

Roland Daumesnil, Capsugel AG, Switzerland: Now for some questions – but before we start, let me just say to my colleague, she's talking about Warner-Lambert's two most important products for the next few years. We are expecting both of them to be blockbusters.

Professor Gordon Amidon, University of Michigan, USA: They changed them from capsule to tablet, though, Roland, so... Helen, one point, first I would just clarify the term 'biowaiver'. You are waiving *in-vivo* bioequivalence. I think saying 'waiving bioequivalence' is dangerous. We're being more precise in the language.

Dr O. Helen Chan, Parke-Davis, Ann Arbor, USA: Yes, it's waiving the *in-vivo* bioequivalence studies. Thank you for your correction.

Professor Gordon Amidon, University of Michigan, USA: The guidance was published in January 1999, the draft form was available in the fall of 1996, so it took that long to get it through the FDA, almost three years. I think your example's a brilliant one with gabapentin, low permeability/high solubility -- as long as the dissolution is fast enough, and it clearly is. You're saying 30 minutes is good enough and I think we believe that, but we need data to show it. I think the concern is we're certain that if you slowed it down further, at some point you would have a problem.

Dr O. Helen Chan, Parke-Davis, Ann Arbor, USA: Yes, if you slow it down further it is not just permeability-limited, it is also dissolution-limited. I agree.

Roland Daumesnil, Capsugel AG, Switzerland: Another question please? Tom.

Tom: Could you comment a little bit on the difference between the Caco-2 model and the *in-situ* perfusion model you used for permeability studies?

Dr O. Helen Chan, Parke-Davis, Ann Arbor, USA: Yes. The question is the difference between Caco-2 and the *in-situ* perfusion model. For many compounds, I believe that if you achieve the correlation curves that I showed you (Figure 8), you can use either model.

But what we have found in practice is that with some compounds -- for example, pregabalin or gabapentin – somehow, Caco-2 has a lower permeability than *in-situ* perfusion and, comparing that permeability to the reference compound, you would assume that it is a low-permeability compound. In fact, it may not be.

So what I'm saying is that the Caco-2 model can give you a false-negative and sometimes we know why – sometimes it's because of the expression of the transporter – but sometimes we do not know why, yet. Also, to use it for the guidance purpose, since the Caco-2 is an *in-vitro* model you have to demonstrate that it is not a carrier-mediated transport compound, because you don't know whether the expression is comparable to *in-vivo* or not. So I would say the rat perfusion model is a safe bet.

Professor Gordon Amidon, University of Michigan, USA: Just a quick comment about the Caco-2 cells. I think the FDA will allow Caco-2 cells but you have to use, like, 20 standard compounds, you really have to characterize your system with reference compounds. But at least in principle they will allow Caco-2 cell data to be used in the assessment of high and low permeability.

Dr O. Helen Chan, Parke-Davis, Ann Arbor, USA: Yes. Actually, with either Caco-2 or the perfusion model, you have to have 20 reference compounds.

Professor Gordon Amidon, University of Michigan, USA: The *in-vivo* system is probably more accurate overall, but…

Joseph R. Robinson, University of Wisconsin, USA: Thank you, Gordon, thank you very much, Dr Chan. We are now at coffee break time. I want to thank all three speakers in this morning's presentation. Please be prompt and reassemble at 10.30 for the next half of this morning's session. Thank you.