

Reducing the Time to Develop and Manufacture Formulations for First Oral Dose in Humans

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The authors discuss approaches to delivering formulations for first-time-in-human dosing.

The advantages and disadvantages of various formulation types and a work-process flow chart are presented to help formulation scientists select an appropriate formulation that can minimize the required resources and rapidly deliver a functional formulation for clinical testing. The data needs for each type of formulation and alternatives such as microdosing and chemical in capsule in bottle-type approaches are also discussed.

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In the early stages of pharmaceutical development, product development can be approached using two basic techniques: The exploratory formulation approach favors the use of the simplest possible formulation that is consistent with the clinical goals of early-phase safety and proof-of-concept studies, and the commercial formulation approach advocates a clinical formulation that is a functional progenitor of the desired commercial formulation (see Figure 1). Both methods have their merits and demerits. A simple exploratory formulation may result in the development and clinical testing of a formulation that is unusable beyond the clinical trial phases because of a physical or chemical instability or a manufacturing process that is not amenable to large-scale production. However, the exploratory formulation approach offers the fastest way for the formulation to enter the clinical trial phase, which in turn may lead to the rapid screening of several potential drug candidates. Similarly, this approach may allow the rapid demonstration of the proof-of-concept of a therapeutic approach or platform.

Some clinical reasons to use exploratory formulation approaches are when the drug

- is a humanized monoclonal antibody or other biologic
- shows variations in clearance between species
- has challenging bioavailability issues
- shows enzyme inhibition or drug interactions
- is an easily labile pro-drug
- is being evaluated at microdose levels.

Other logistical reasons may include poor predictability of efficacy models and a lack of clinical sites with well-trained dosage form dispensing staff.

In the commercial prototype formulation approach, the product development team plans for success or assumes that the probability of success is much higher than failure. This kind of reasoning encourages the front-loading of significant resources to produce a formulation that is similar to the expected commercial formulation. This approach has the merit of potentially speeding up development in later stages of clinical testing by reducing or eliminating the need for bridging bioequivalency studies. It may also allow speedier delivery of stability, validation, and launch batches. The commercial formulation approach is particularly suitable for second-generation compounds in a therapeutic class that already have an estab-

lished platform. Situations also may arise in which the molecule may require nontraditional formulation approaches such as modulated-release or solubilized dosage forms. When complex formulations are used, resources should be invested earlier in the development process to allow sufficient time to deal with any challenges in the design of a marketable version of the formulation.

In reality, however, the number of compounds dropping out after early clinical studies is much higher than at later stages of clinical development. Furthermore, the commercial formulation approach is significantly more time- and resource-intensive than the exploratory formulation approach. In practice, the formulation strategy is always decided by the project team on the basis of collected scientific and business information. The exploratory formulation approach is probably more commonly used in the industry than the commercial formulation approach because the simplest possible formulation is developed in the early stages of clinical development, and manufacturable formulations are designed at later stages of development. Recently, equipment has become available that allows a manufacturer to automatically fill a pure active pharmaceutical ingredient (API) into bottles and capsules gravimetrically, which will undoubtedly further reduce the time to deliver simple formulations for use in the clinic.

The recommendations and guidelines outlined in this article may allow the rapid development of the following formulation types for use in first-time-in man (FTIM) studies: chemical in bottle (CIB) for reconstitution or resuspension, chemical in capsule (CIC), ready-to-use (RTU) solution, RTU suspension, formulated capsule (includes semiformulated binary blends in capsules), formulated tablet, and a hybrid dosage form—chemical in capsule in bottle (CICIB).

In this article, the term *first time in man* is not meant in the literal sense of formulations that are used only in the very first study in which a molecule is clinically tested. The term describes formulations used in any early clinical studies conducted during Phase I safety, pharmacokinetic, or proof-of-concept evaluations. This definition does not necessarily preclude the use of simple formulations such as CIB for Phase II clinical efficacy studies. However, such situations are less likely, except when the size and scope of the clinical studies are unusually small as in the case of orphan drugs. FTIM has also been known as *first in man* (FIM), *first dose in man* (FDIM), and *first dose in human* (FDIH). This article will use the term *FTIM*, which will mean only FTIM formulations for oral use.

FTIM clinical studies may have the following characteristics:

- moderately high failure rates
- unknown human pharmacokinetics of the compound being tested
- fewer human subjects and minimal duration of the clinical studies
- a significant effect on the drug design process.

FTIM formulations have unique demands. Often, the clinic will require considerable dosing flexibility and a potentially

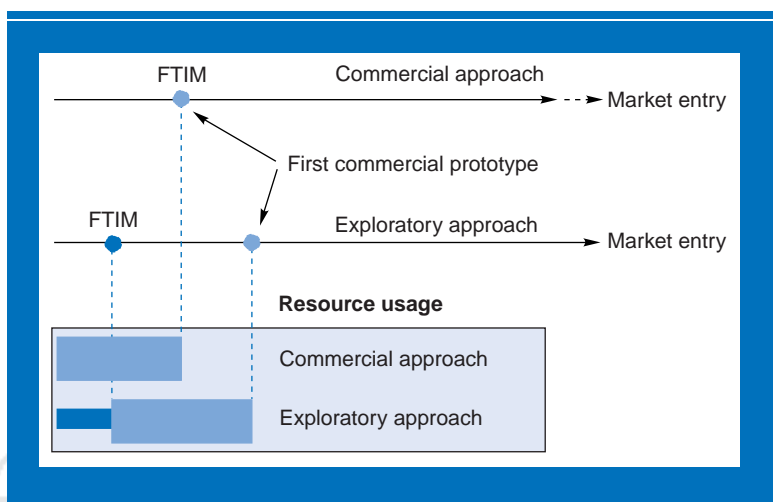


Figure 1: Exploratory formulation approach versus commercial formulation approach.

wide dose range. The problem may be compounded by the limited availability of the API for formulation and analytical development. Furthermore, the purity and micromeritic properties of early lots of an API may not be representative of the API from the commercial manufacturing process. These factors complicate the ability to minimize the time between the first good laboratory practice (GLP) animal studies and the first clinical dose. Challenges and data needs for various types of FTIM formulations are listed in this article and can serve as comparative decision-making tools for project teams and formulation development subteams during the development of a new chemical entity (NCE). Individual projects may have various constraints that may necessitate approaches that are contrary to this discussion. However, the authors hope that this report will stimulate further discussion and serve as a useful starting point from which to narrow down the list of possible choices for development.

FTIM formulation decision tree

A flow chart for FTIM formulation decision making is shown in Figure 2. Traditionally, it may have been practical to conclude that if there is no reason to “front-load” (e.g., for a high-solubility or high-permeability drug), the first choice would be to use a pre-existing toxicology formulation for oral FTIM dosing, assuming that it is safe and suitable for human dosing. If the molecule presents physicochemical or biological challenges, the formulation approach chosen will depend on the required or desirable degree of dosing flexibility as outlined in the scenario shown in Figure 2.

A solution or suspension made for toxicology studies may present difficulties when adapted for use in the clinic. Conducting a large clinical study (e.g., a Phase II study) using a liquid formulation may not be convenient. Furthermore, liquid formulations must have demonstrated physicochemical and microbiological stability and must also have acceptable dose uniformity. The simplest alternative to using an RTU suspension or solution from a toxicology program is to fill the dry chemical directly into a bottle (CIB) and reconstitute it as a so-

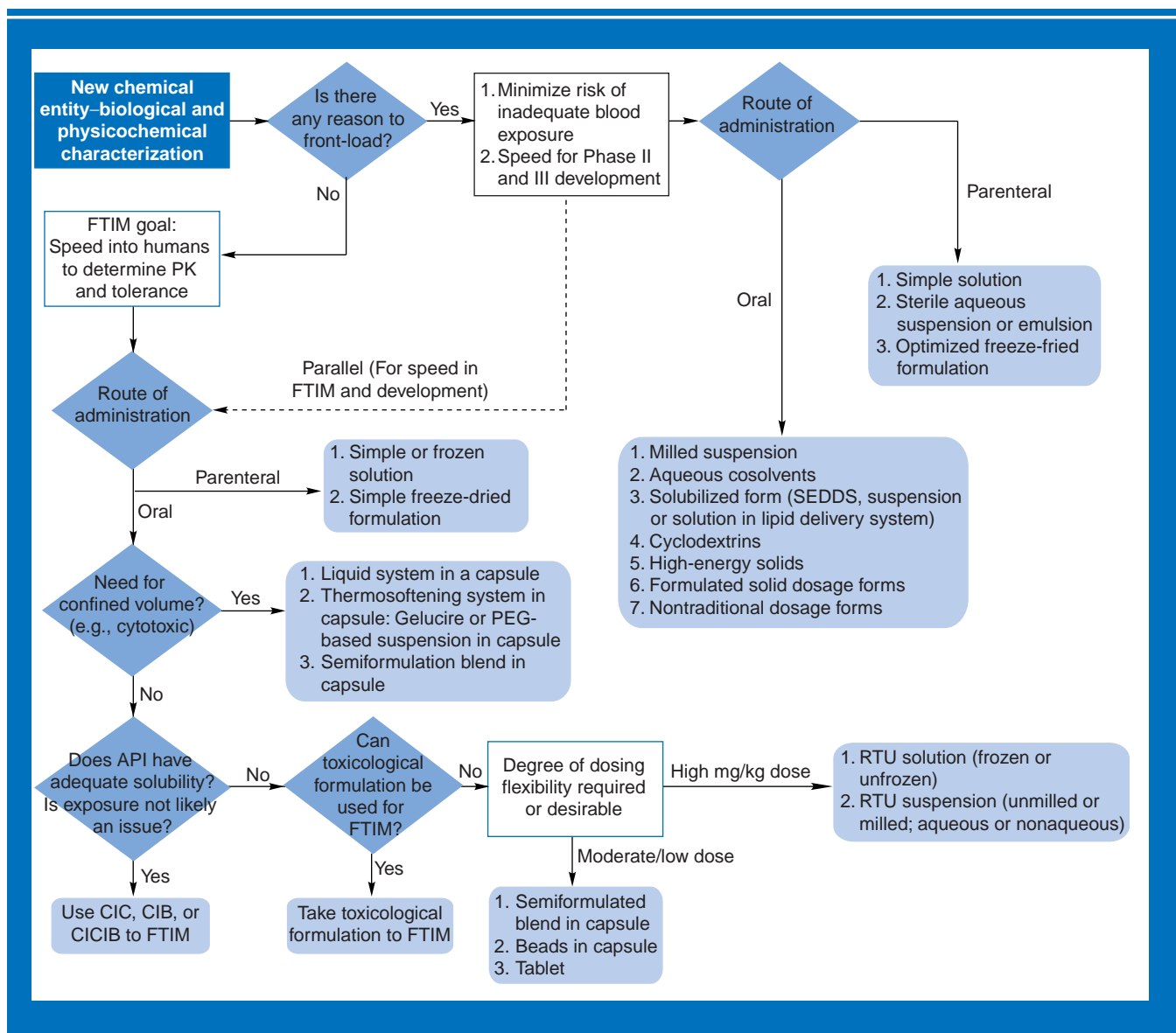


Figure 2: FTIM formulation decision tree.

lution or suspension at the clinical testing site. This method could present its own set of difficulties, especially in instances in which solution stability of the chemical is poor and if multiple dilutions are required to achieve the desired dose. Again, this type of approach is not suitable for larger clinical studies.

A similar but alternative approach to CIB is to prepare doses by weighing the chemical directly (gravimetrically) into capsules (CIC). Until recently, this dosage form (as well as CIB) suffered from the disadvantage that the capsules (or bottles) had to be filled by hand in a slow, tedious, and potentially error-prone process, which led to the assumption that CIC dosage forms could be used only for small clinical studies in which a few capsules could be filled by hand. Traditional capsule-filling machines cannot be used for CIC because they use volumetric means to measure a dose, and CICs usually require the formulation of the API to make them amenable for filling on such machines. Manufacturing a granulated formulation is often difficult in the early stages because of the limited amounts of chemical available for development as well as the need to expend formulation and analytical resources to design and test

the product. Table I lists the typical equipment required for manufacturing FTIM dosage forms.

The traditional approach of selecting a toxicology formulation as the easiest way to reach FTIM dosing might have to be revised because of new equipment that has recently become available. This equipment can be used to gravimetrically fill the chemical into bottles or capsules either automatically or semi-automatically, which allows pilot-scale production (i.e., from a few hundred to a few thousand) of CIC or CIB (or CICIB) without the need to formulate the chemical and may represent the fastest way to FTIM dosing. Some initial capital investments may be required for gravimetric filling technologies, but this could be offset by the considerable productivity gains that could be achieved. As this technology becomes more widely adopted, liquid formulations may be favored even less in the future. Gravimetric powder-filling machines have the potential to greatly reduce the time and resources required for delivering FTIM dosage forms to the clinic and may also support large clinical studies.

With the availability of gravimetric capsule-filling machines, CIB and CIC dosage forms can become the first choice for FTIM

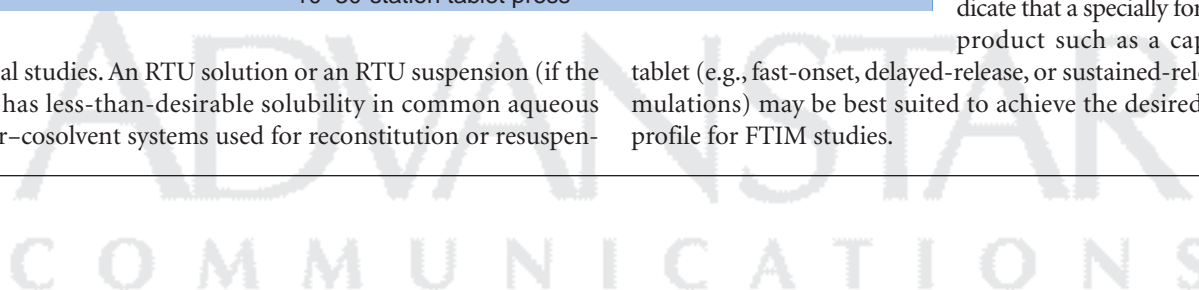
Table I: Typical equipment for FTIM dosage forms.

FTIM dosage form	Equipment and processing parameters
CIC (or binary blends)	Manual individual capsule weighing and checking Manual tray filler (individual weighing required) Automatic or semiautomatic gravimetric capsule fillers
CIB for solution or suspension	Back weighing of tared plastic or metal container to determine the actual amount transferred to a bottle Dispensed in bottle by weight
RTU solution	Manual: stirrer bars, dedicated glassware, masterflex pump, etc. Dispensed in bottle by weight
RTU suspension	Manual: high-shear mixing (e.g., Silverson) or low-shear propeller mixer, dedicated glassware, peristaltic pump, etc. Dispensed in bottle by weight
Formulated capsule (wet granulation)	Dosator or dosing disk-type capsule-filling machine Manual tray filler (used mostly for blinding tablets but can be used for placebo filling)
Tablet (direct compression)	Impact or cone mill, V-blender or equivalent, 10–30-station tablet press (ability to use large equipment is very dependent on API availability, and in most instances API will be limited during the FTIM sequence)
Formulated tablet (wet granulation)	Low-shear or high-shear granulator, tray dryer or fluid-bed dryer, impact or cone mill, V-blender or equivalent, 10–30-station tablet press

clinical studies. An RTU solution or an RTU suspension (if the drug has less-than-desirable solubility in common aqueous buffer-cosolvent systems used for reconstitution or resuspension

of the CIB at the clinic) formulation may be the next best choice. The solution or suspension may be the same as what is used in toxicology studies. If the toxicology formulation is untenable because of factors such as poor physical or chemical stability or the need for a large number of doses, it may be necessary to specially formulate a nonaqueous RTU solution or suspension.

If the size of the clinical study is large and dosing flexibility is not the overriding concern, formulated capsules or tablets may prove to be the most practical FTIM dosage form. Physicochemical information or animal bioavailability data may also indicate that a specially formulated product such as a capsule or tablet (e.g., fast-onset, delayed-release, or sustained-release formulations) may be best suited to achieve the desired plasma profile for FTIM studies.



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Data needs for FTIM formulations

Some physicochemical data are typically required to decide the type of FTIM formulation that is best suited for a particular NCE. Additional data are needed depending on the type of dosage form chosen for FTIM studies. Some recommendations of the type and sources of these data are shown in the sidebar, "Data requirements and points to consider for FTIM formulations," for each of the different FTIM dosage forms. Depending on the dosage forms identified for development, additional information may be required to establish and support a shelf life, identify an appropriate container system, establish necessary procedures for proper dosing in the clinic, and define necessary handling and storage conditions.

Advantages and disadvantages of various FTIM formulations

Table II lists the commonly used oral dosage forms for FTIM studies and their relevant pros and cons. On the basis of the pros and cons of each dosage form, and assuming the availability of appropriate gravimetric filling machines, the preferred FTIM dosage forms (in order of speed and convenience) are

- CIB. The chemical may be reconstituted at the clinic using water for injection, commercially available buffers, fruit juices, or any other specially prepared solvent or cosolvent system approved for human use.
- CIC. Simple filling of milled or unmilled chemical into hard

gelatin, hydroxypropyl methylcellulose (HPMC) (Celcaps, Shionogi Qualicaps Co. Ltd, Yamato-Koriyama City, Japan), or Pullulan capsules (NPCaps, Capsugel, Morris Plains, NJ) by hand or an automatic or semiautomatic gravimetric capsule-filling machine.

- CICIB. This atypical approach involves placing one or more CIC units into a bottle for reconstitution as a solution or suspension in the clinic.
- RTU solution. This formulation consists of a simple or solubilized solution of the API in water, buffers, or cosolvent systems. The solution may or may not contain a preservative and may be supplied refrigerated or frozen. Ideally, this would be the same as the formulation used in GLP animal or toxicology studies.
- RTU suspension. This formulation consists of an API suspended in a suitable liquid vehicle. The formulations may contain other excipients that are necessary for physical, chemical, and microbial stability. Ideally, this would be the formulation used in GLP animal or toxicology studies.
- formulated capsule. This type of formulation usually involves a granulated blend of drug but could also be a simple blend of the drug with suitable excipients filled into gelatin capsules. The formulation is typically filled volumetrically on semiautomatic or automatic machines.
- formulated tablet. This type of formulation usually involves compression of a granulated blend of the drug with suitable

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excipients. At low drug doses, tablets compressed from a direct blend of the API with suitable excipients may also be acceptable. The formulated product usually must have important attributes such as machine processability and the ability to release the drug rapidly and completely.

New technologies for filling APIs into capsules

Commercially marketed capsule dosage forms are usually manufactured using capsule-filling equipment designed to volumetrically measure a dose of the pharmaceutical powder before filling it into a capsule. Such capsule-filling equipment may use either the dosator principle (e.g., MG capsule fillers, MG2 S. p. A, Bologna, Italy) or a dosing disk-type mechanism (e.g., H&K capsule fillers, Robert Bosch GmbH, Waiblingen, Germany). The volumetric approach is favored in large-scale production because it can be conducted rapidly with high-speed machines. To make the API amenable for the volumetric filling of capsules in these machines, one must formulate the API to make it free flowing, which usually involves the blending of various excipients with the API and may also include subjecting the powder blend to a granulation process to increase the particle size. The formulated product is expected to possess a high degree of homogeneity so that each volumetrically measured dose will contain the expected amount of drug within statistically determined margins of error. The process of formulating the API is usually time- and resource-consuming because it involves test-

ing the compatibility and stability of the chemical with the excipients. In addition, formulation scientists are required to design a process for the reliable and reproducible manufacture of the granulated API, which must meet the desired attributes of content uniformity and drug release from the dosage form.

Early clinical studies usually require supplies that number from a few hundred to a few thousand doses. Traditionally, filling APIs into capsules or bottles for early clinical studies has been performed by manually measuring and filling the required dose into capsules or bottles. This procedure can be awkward, tedious, repetitive, and prone to operator weighing errors, which may result in incorrect dosing.

Recently, new equipment has become available to automate these tasks and rapidly weigh powders into capsules or bottles with a high degree of precision. Examples of companies providing these equipment solutions are

- Autodose SA, Geneva, Switzerland: markets various models of semiautomatic machines that can fill one or multiple powders into capsules, bottles, well plates, vials, tubes, and other containers.
- FillPro Inc., Golden, Colorado: markets models for semi-automatic or automatic filling of powders into various types of containers, including capsules.
- Meridica Ltd, Melbourn, United Kingdom: markets a semi-automatic model for capsules and vials and a fully automatic model exclusively for capsule filling.

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Data requirements and points to consider for FTIM formulations

Chemical in bottle (CIB) for dilution at time of use

- Use solid-state bulk drug stability data at an elevated temperature (dry and elevated relative humidity) to support the stability in the bottle
- Generate stability at room and elevated temperature conditions in the bottle to be used in a clinical study
- Consider using only an exit assay test instead of a formal stability study
- Complete antimicrobial testing on a bulk drug.

Dilute to solution (CIB solution)

- Use any pre-existing solution stability data (GLP toxicology formulation)
- Generate stability at room and elevated temperature conditions in buffer system, if different from GLP toxicology formulation
- Recommend single use with 6-h limit of use (no preservative would be required)
- Demonstrate dosing accuracy (e.g., deliverable dose in clinic).

Dilute to suspension (CIB suspension)

- Use any pre-existing suspension stability data (GLP toxicology formulation)
- Generate stability at room and elevated temperature conditions in suspension system, if different from GLP toxicology formulation
- Recommend single use with 6-h limit of use (no preservative would be required)
- Demonstrate dosing accuracy (e.g., deliverable dose in clinic).

Chemical in capsule (CIC)

- Use solid-state bulk drug stability data at an elevated temperature (dry and elevated RH) to support the stability
- Generate stability at room and elevated temperature conditions in capsule and clinical bottle system
- Consider using only an exit assay test instead of a formal stability study
- Complete antimicrobial testing on a bulk drug.

Ready-to-use solution (RTU solution)

- Use any pre-existing solution stability data
- Use GLP toxicology formulation if possible
- Generate antimicrobial effectiveness test data on solution
- Generate stability at room and elevated temperature conditions in solution system, if different from GLP toxicology formulation
- Demonstrate dosing accuracy (e.g., deliverable dose in clinic)
- Recommend using clear bottles (easier to visualize solution properties in clinic)
- Protect from light if needed. Amber glass bottles may be an appropriate option.

Ready-to-use suspension (RTU suspension)

- Use GLP toxicology formulation if possible
- Use any pre-existing suspension stability data (GLP toxicology formulation)
- Generate antimicrobial effectiveness test data on suspension
- Generate stability at room and elevated temperature conditions in suspension system, if different from GLP toxicology formulation
- Demonstrate dosing accuracy and resuspendability (e.g., deliverable dose in clinic)
- Recommend using clear bottles (easier to visualize suspension properties in clinic)
- Protect from light if needed. Amber glass bottles may be an appropriate option.

Formulations (tablet, capsule)

- A wide range of typical product performance attributes. Formulation scientists or analysts are generally responsible for characterizing the dosage form.

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Table II: Pros and cons of common FTIM formulations.

FTIM formulation	Pros	Cons
CIB for solution or suspension	<ul style="list-style-type: none"> High dosing flexibility Only API stability plan required Fastest development activities (solution) Least resource requirement (solution) Low API requirement No drug load or unit concerns Few analytical activities (solution) 	<ul style="list-style-type: none"> Taste could be an issue Manual process (possibility of using automatic powder-dosing system to speed up manufacturing) Reconstitution should be acceptable at clinics Withdrawal volume to be verified Possible need to bridge studies for solution Dosing flexibility may be an issue for multidose suspension
CIC	<ul style="list-style-type: none"> Useful for high- or moderate-solubility compounds No taste problems No excipient compatibility testing needed A major potential advantage is the ability to easily accomplish blinding for clinical studies 	<ul style="list-style-type: none"> Low dosing flexibility Possible drug load or unit concerns For FTIM and proof-of-concept studies only More time-consuming than CIB in case of manual filling Stability plan for API and finished product required May not be applicable to moisture-degradable drugs
Semiformulated or formulated capsule	<ul style="list-style-type: none"> Automatic manufacturing process could be applied Moderately complex development activities for binary mixture formulations Compatibility with excipients could be useful for further development activities (i.e., beyond FTIM and proof-of-concept studies) 	<ul style="list-style-type: none"> Drug–excipient compatibility must be evaluated Possible drug load concerns Some analytical activities required Not applicable to moisture-degradable drugs More-complex formulations require more activities and longer time
RTU solution or suspension	<ul style="list-style-type: none"> Automatic process could be applied No drug load or unit concerns 	<ul style="list-style-type: none"> Preservative might be required Taste or smell could be an issue Not applicable to moisture-degradable drugs Some development and analytical activities required Redispersability may be an issue (verification activities) in case of multiple-dose unit
Formulated tablet	<ul style="list-style-type: none"> Automatic manufacturing process may be applied (see also cons) Compatibility with excipients could be useful for further development activities (i.e., beyond FTIM and proof-of-concept studies) Potential full-development formulation 	<ul style="list-style-type: none"> Higher development effort than capsules More API required for development and clinical batches Difficult to obtain a small number of consistent tablets with automatic operation Taste or color masking may require coating, which would increase of the development complexity

These machines use a gravimetric filling approach—a dosing head delivers the powder into a final container placed on the balance, and a feedback system stops the dosing when the target weight is reached. Additional features in the feedback system may be present such as a variable dosing speed to achieve better filling precision—sensitivity or powder-behavior self-learning software. The availability of these machines makes CIC, CIB, and CICIB options more desirable as FTIM formulations.

Microdosing

An innovative approach gaining interest in preclinical development is the possible use of subactive doses for human clinical studies. This microdose approach can provide preliminary information about pharmacokinetic and possibly even toxicological data about NCEs. These studies also can be conducted very quickly if the same lot of API (manufactured using current good manufacturing practices) is used for both the GLP toxicology studies and the microdose clinical studies. This ap-

proach can combine stability testing and analytical methods development for GLP toxicology and FTIM studies.

Before the availability of gravimetric powder-filling machines, the only feasible formulations for the rapid delivery of supplies for microdose studies were CIB (for reconstitution) or RTU liquid formulations. Even with CIB formulations, one may have to dilute the solution at the clinic after reconstitution to achieve low doses because the doses for such studies are usually in the sub-milligram range, which poses difficulties in filling small amounts of API directly into a capsule or bottle with a high degree of precision. The only way by which capsules could be used in a microdose study would be to bulk the drug by formulating (or semiformulating by direct blending) the API and to hand-fill the formulations into capsules or to machine-fill them using a pilot-scale production machine. However, this approach could potentially involve considerable development time and resources. Gravimetric powder-filling machines that can precisely and accurately fill small quantities (≥ 0.1 mg) of API into capsules in an automatic or semiautomatic manner may provide the means to quickly manufacture CIC supplies for microdosing.

CICIB

An atypical approach to FTIM formulation is the CICIB dosage form for reconstitution in the clinic as a suspension or solution. This approach involves filling a chemical in an HPMC or Pullulan capsule and subsequently placing the capsules in a bottle in which the capsule shells and their contents may be reconstituted. The reason for using HPMC or Pullulan capsules instead of gelatin capsules is that gelatin dissolves only at $\sim 37^\circ\text{C}$, whereas HPMC and Pullulan capsules dissolve at room temperature. Pullulan capsules are not yet approved for pharmaceutical use, but they may gain regulatory acceptance in the near future. The CICIB approach may have some advantages such as

- multiuse dosage form, which can be used as both CIC and CIB
- high dosing flexibility (by using one or multiple capsules in a bottle)
- low API requirement (no formulation work required)
- ease of microdosing if reliable gravimetric powder-dosing systems are used
- low error rate, no spillage or leakage of chemical
- automatic blinding of clinical supplies (bottle may contain an empty or filled capsule), except if the suspension or solution after reconstitution is colored.

Conclusions

Selecting the right approach to FTIM dosing can help reduce the overall timeline for drug development. In this article, the authors have summarized the various widely used and less-common approaches to FTIM formulation development and the relative advantages and disadvantages of these approaches. The authors hope that this summary will be a useful starting point for discussions within product development teams to select the most appropriate formulation for FTIM dosing. **PT**