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The field of solid-state chemistry of drugs encompasses many scientific disciplines and is crucial for preclinical drug development.

Designing a molecular delivery system within a preclinical timeframe

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An understanding of solid-state chemistry, including polymorphism, can reduce the time to filing an investigative new drug (IND) application. Obtaining a stable formulation for IND studies is crucial and must be the focus of much of the early solid-state chemistry research. Simple formulations such as a chemical substance in capsule (CIC) – the chemical substance can be crystalline or amorphpous – are preferable for the IND trial and the solubility/dissolution rate has an important role in manufacturing IND clinical supplies. Two fast-to-IND flowcharts are presented here for exploratory IND and conventional IND. The utilization of quality by design and process analytical chemistry (PAT) concepts at an early stage will lay the foundation for the accelerated development of the medicines that are successful in the IND trials.

Introduction

The field of solid-state chemistry of drugs encompasses many scientific disciplines and is crucial for preclinical drug development. The aim of this review is to show how knowledge of solid-state properties can reduce the time to preclinical trials, reduce errors and ultimately reduce costs. A secondary goal of this review is to suggest how quality by design concepts can be implemented even during the preclinical phase of drug development. The general approach will be to demonstrate how an understanding of the supramolecular structure of the solid state can result in better design and control of drug performance within preclinical time frames.

This review should be read with the following caveats in mind: (i) The field addressed is broad and changing and only some of the most important issues are addressed. Space will not permit detailed discussion of all of the topics, concepts and definitions used. Additionally, discussion of the analytical methods is abbreviated. The interested reader is referred to one of the major books in the field for a more detailed discussion of these topics [1,2]; (ii) The timelines presented here can probably only be achieved if no problems are encountered and all necessary resources are committed to a single project. Thus, it would be very difficult for these timescales to be met across all programs in a pharmaceutical company.; (iii) In reality, a flowchart describing the timeline for each development project would need to be developed to identify potential bottlenecks and pitfalls; and (iv) For simplicity, the timelines shown are based on the assumption that a sufficient

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amount of material is delivered to start all activities. In reality, small-size batches of material are often made before the larger investigative new drug (IND) batch and these batches can be used in initiating salt selection, form screening, formulation evaluation, toxicological formulation development, toxicological dose ranging investigations and other relevant studies.

Solid-state properties of active pharmaceutical ingredients (APIs)

Solid pharmaceuticals exist as polymorphs, solvates or in non-crystalline (amorphous) forms, collectively described as solid forms. Polymorphism refers to the different crystal structures in which a compound can crystallize. Polymorphs [1,2] are characterized by a wide range of methods including their crystallographic space groups and unit cell parameters. The term is usually reserved for materials with the same elemental analysis. Solvates are crystal forms that contain either stoichiometric or nonstoichiometric amounts of solvent. However, the FDA uses the word polymorphism to include solvates and non-crystalline (amorphous) forms. Amorphous forms are forms that lack long-range order. Because amorphous materials lack long-range order, their X-ray powder diffraction patterns are devoid of 'sharp' Bragg reflections characteristic of crystalline materials.

APIs can often also be converted into salts and/or cocrystals. Salts are formed when equivalent amounts of an acid or a base are reacted. A cocrystal is a multicomponent crystalline system containing at least two different molecules. In solvates, salts and cocrystals the active molecule (drug or active ingredient) exists in the presence of another species. In most cases, crystalline salts, cocrystals or solvates are of primary interest. In recent years there has been a resurgence of interest in cocrystals because these materials, like salts, can alter properties including dissolution rates and bioavailability [3,4].

Liquid crystals and plastic crystals, also referred to as mesophases, are solid materials with an order intermediate between that of a liquid and that of a crystal. They have imperfect long-range orders of orientation and/or position. Because of that, they can be fluid like a liquid and they can have anisotropic properties like crystals. Whereas the plastic crystals have a predominating positional order, the liquid crystals have a predominating orientational order. Operationally, most pharmaceutical mesophases are birefringent and give an X-ray diffraction pattern with one low angle peak and a halo.

Each of these different solids (polymorphs, solvates, amorphous forms, salts, cocrystals and liquid crystals) contains the same active moiety. Typically, solids must dissolve to exert their action. Thus, both solubility and dissolution rate are important parameters related to bioavailability. In many respects, the different solid forms represent different molecular (or supramolecular) delivery systems for a drug. The solubility and/or dissolution rate difference between these various molecular delivery systems can vary by a factor of 10^6.

Materials with such a wide variation in solubility or dissolution rate have a wide variation in biological activity. For compounds such as ritonavir, the amorphous form is bioavailable and is an effective drug, whereas the crystalline form is dramatically less bioavailable and, hence, is devoid of activity. Although the solubility difference between the crystalline and amorphous form of ritonavir is not known, Hancock and Parks [5] suggest that such solubility differences can be as large as 1000. For phenytoin, the sodium salt is 10 000 to 100 000 times more soluble than the free acid. Additionally, nonpolar salts such as the pamoate salt (e.g. imipramine pamoate, hydroxyzine pamoate) have been used to design controlled release dosage forms. Cocrystals can also show significantly different solubility and bioavailability but rarely as large as salts [4].

TABLE 1

Examples of properties of a compound that depend on structure differences

Solubility	Water uptake (deliquescense)	Solid-state reactivity
Hardness	Optical and electrical properties	Physical stability
Cleavage	Color	Chemical stability
Density	Thermoanalytical behavior	And so on

TABLE 2

Examples of areas where control of solid form and size distribution are important

Yield	Milling	Dissolution
Filtration	Mixing	Suspension
Washing	Tableting	Lyophilization
Drying	Flowability	

For early development and first-in-human studies, the choice of the solid form can greatly influence the exposure of the organism to a drug. It is also important to know what solid-state form of a drug is present in the formulated dosage form to interpret clinical results properly. Finally, a variation in the solid-state form present could result in an unacceptable variation in clinical blood levels.

The solid-state form can also influence both chemical and physical stability. Studies of hydrocortisone *tert*-butylacetate and prednisolone *tert*-butylacetate [6,7] and dihydrophenylalanine [8] show that different crystal forms of these substances have different chemical reactivity. For example, the hexagonal crystal form of both hydrocortisone *tert*-butylacetate and prednisolone *tert*-butylacetate oxidizes in the solid state, whereas the other crystal forms of these two pharmaceutical compounds are chemically stable. Tables 1 and 2 summarize the different properties of different solid forms.

An in-depth understanding of the solid-state chemistry of drugs as it relates to preclinical development begins with a statement of several general points:

- Drugs must be synthesized and handled in preclinical drug development
- Most drugs are used in a crystalline form
- Crystals are held together by intermolecular forces
- The arrangement of molecules in a crystal determine its physical properties
- The physical properties of a drug can affect its performance

Solid-state properties of APIs in drug formulations

The solid form of the drug substance can have an important effect on the morphology, shape, flowability, syringeability, filterability, tableting behavior, and bulk density ('handleability') of the drug. The tableting behavior of plate-shaped crystals would differ from

that of needle-shaped crystals. Additionally, a suspension of plate-shaped crystals can be injected through a small needle with greater ease than one of needle-shaped crystals. Furthermore, the shape and size of the particles is generally related to the internal crystal structure, the growth kinetics, and the method of crystal formation. In favorable cases, the crystal structure can be used to predict the shape of the crystallized product. The shape in turn relates to bulk density as well as formulation, manufacturing and patents.

The ritonavir story illustrates a recent example of the importance of transitions among crystal forms. In 1998, Abbott experienced a catastrophic example of the physical instability of a drug product [9,10]. Up until 1998, Abbott had successfully manufactured hundreds of batches of the life-saving AIDS drug ritonavir. These batches were formulated by dissolving ritonavir in polyethylene glycol/ethanol/polyoxyethylene/other components in a soft-gelatin capsule. In the spring of that year, batches of the soft gelatin capsule started failing dissolution specifications. Abbott quickly established that these failures were caused by the crystallization of a new, previously unknown, less soluble polymorph of ritonivir from the formulation. This new polymorph (Form 2) had about half of the solubility of the old form in the formulation and was supersaturated in the formulation. Ultimately, Abbott had to withdraw the soft-gel product from the market and reformulate in a soft elastic capsule. The pharmaceutical literature is full of other examples of transitions among crystal forms (see [2] and references therein). Such transformations, because they affect solubility, can complicate first-in-human trials and toxicological studies.

One of the practical areas encompassed by the field of solid-state chemistry of drugs is the area of stability testing. Stability tests are conducted on all drugs to determine whether the drug will degrade or change during clinical trials. For first-in-human studies, only a short stability study is needed. For an IND, the applicant must show that the drug formulation, whatever it might be, must be stable during the IND study. Likewise, it is important to show that the drug remained stable during the toxicological investigations. It is helpful to be able to predict the stability of formulations very early in preclinical development to avoid problems and reduce development time. In cases of instability there is a need to develop a preliminary understanding of the solid-state reactions of drugs in terms of the molecular details of the reactions. Of particular interest is the determination of the parameters that can result in the retardation of the solid-state reactions of drugs and thus render drugs stable enough for initial trials.

Analytical methods and tools for API and drug product analysis

In recent years, several powerful analytical methods have been developed. These methods allow a rapid and precise determination of the solid-state properties of a material. In several respects, our ability to determine solid-state properties within the preclinical timeframe and design a preclinical dosage form with optimum properties for its intended purpose is based on the powerful new methods that have developed.

X-ray diffraction

X-ray diffraction remains the best method for determining solid-state properties. Both single-crystal and X-ray powder diffraction are widely used. X-ray powder diffraction allows the direct determination of the crystallinity of a material and in favorable cases the crystal structure, true density and unit cell contents. During screening, most scientists believe that X-ray powder diffraction is the best method for determining the number of unique forms. In favorable cases, X-ray powder diffraction can result in a complete determination of the structure of the solid and the determination of the crystal packing relationship among individual molecules in the solid. This knowledge is often crucial to understanding and predicting/anticipating the solid-state chemistry of drugs.

X-rays are diffracted from crystals according to the Bragg equation: $n\lambda = 2d\ \sin\theta$. The peaks produced by diffraction from imaginary planes in a crystal are called Bragg peaks. The diffraction angle of Bragg peaks, θ, depends on the d-spacing of the planes in the crystal. Thus, different crystals with different d-spacings give different diffraction patterns. Because of this, the X-ray diffraction pattern is considered a fingerprint for the crystalline phase present.

In recent years, several powerful algorithims for comparing X-ray patterns have been developed. Bates and Ivanisevic at SSCI [11,12] developed an algorithm on the basis of hierarchical cluster analysis that allows a rapid comparison of the diffraction patterns from samples crystallized in several ways, including samples crystallized using robot-based equipment and well plates.

This algorithm also carries out indexing and determination of the unit cell parameters. In most cases, the true density can be directly determined from the unit cell parameters. Burger and Ramberger [13,14] showed that the true density could be related to the thermodynamic stability of the material with the most dense form (closest packed) being the most stable form at zero Kelvin. This is called the density rule and is estimated to hold ~80% of the time. Of course, the most stable form will not spontaneously convert to any other form and thus is the desired form for development. This means that, in favorable cases, the most stable form can be determined during the screening/analysis process. Finding the most stable form during the screening process can greatly facility fast to IND procedures such as those described in this review.

Solids can also produce diffuse scattering [15]. For amorphous and disordered solids, only diffuse scattering is produced. For systems with intermediate order between crystals and amorphous, a mixture of diffuse scattering and Bragg peaks is observed [15]. Diffuse scattering provides important information on the local order of the system. This was first recognized by Debye in 1915 (as discussed by Egami and Billinge [15]). However, studies of diffuse X-ray scattering did not expand until modern computers became available. Egami and Billinge's book entitled 'Underneath the Bragg Peaks' provides an excellent review of the power of this method for disordered and complex materials [15]. Bates and co-workers have also developed algorithms for the analysis of amorphous and disordered organic solids [16,17].

These methods have led to important insights into the short-range order of disordered and amorphous drugs. For example, Bates, working with David Grant and Agam Sheth, was able to show that one polymorph of piroxacam when ground maintained the same short-range order that was in the parent form [16]. A second polymorph, when ground, lost the short-range order of the parent. Not surprisingly, the disordered form that retained the short-range order of the parent recrystallized back to the parent. By

contrast, the disordered material from the other polymorph did not crystallize to the parent but instead produced a third form.

Vibrational spectroscopy

Both infrared and Raman spectroscopy are very useful for the analysis of solids because they can be performed without the dissolution of the sample [1,2]. For infrared spectroscopy, several techniques and methods of sample treatment are useful including diffuse reflectance, KBr pellet, Nujol mull, attenuated total reflectance (ATR), and microscopy. Raman spectroscopy is rather insensitive to water bands and also can be taken in glass containers. By contrast, infrared spectroscopy is often dominated by even a small amount of water and cannot be measured in glass containers because of the Si–O vibrations absorptions. Raman microscopy is an extremely powerful technique, having a spatial resolution of 1 micron or less.

Vibrational spectroscopy is extensively used for the analysis of solids both as bulk drugs (drug substance, API) and in formulations and drug product. Vibrational spectroscopy can be easily used to analyze polymorphs, solvates, amorphous forms, salts, cocrystals and liquid crystals. When vibrational methods are combined with chemometrics to analyze mixtures, very low detection limits can be achieved.

Solid-state NMR

Solid-state NMR is another powerful method for the analysis of solids [1,2,18]. The analysis of pharmaceutical solids using cross polarization magic-angle spinning nuclear magnetic resonance spectroscopy (^{13}C CP/MAS NMR) offers access to otherwise elusive information. This method can differentiate between polymorphs, solvates, amorphous forms and mesophases and is particularly useful for mixture analysis. It is a bulk technique that requires little sample preparation. It is possible to analyze a tablet by simply cutting it into smaller pieces and placing it in the probe. Solid-state NMR can also be used to determine the mobility of specific functional groups or atoms. In some cases, this mobility is proportional to the reactivity of these materials.

Mapping and imaging

Mapping and imaging are rapidly advancing methods for formulation analysis [19]. Raman and infrared mapping, as well as Near Infrared (NIR) imaging, are also important methods of analysis for solids and mixtures. Additionally, Raman microscopy has been used to analyze small amounts of samples crystallized in robotic crystallization studies.

In favorable cases, Raman microscopy can determine the solid form of particles in the one micron range or smaller. It is also possible to utilize imaging to provide a visual picture of the homogeneity of blends and the nature of formulations. In many cases a color enhanced image of the distribution of all components in the formulation can be obtained. These technologies provide an analytical method for the direct analysis of the formulation used for the IND study.

Analysis of phase I (first-in-human) formulations

A crucial aspect of examining and understanding the solid-state properties and polymorphism of the material within the preclinical timeframe is to understand the formulation. The methods outlined above, especially in combination, can almost always provide the needed information within a day or two on small amounts of sample.

Basic stability concepts

The stability of a solid pharmaceutical compound is of paramount importance. The drug must be stable during its transportation and administration. For this reason accelerated stability studies are needed.

Instability is classified into two general types: physical and chemical. Physical instability results in the transformation of a solid pharmaceutical from one form to another. Chemical instability involves reactions in which chemical bonds are broken or made. Chemical reactions involve 'intrinsically unstable molecules'. For this reason the development scientist usually knows early on that the molecule is chemically unstable. Additionally, the types of reactions involved (e.g. oxidation, hydrolysis, rearrangement and so on) are usually known. In favorable cases, these reactions can be prevented using proper storage conditions and packaging.

The classic review by Paul and Curtin [20] provides a basis for understanding the physical and chemical instabilities of pharmaceuticals. This review establishes that solid-state reactions involve a four-step mechanism:

(i) *Loosening of molecules at the reaction site.* It is reasonable to assume that molecular loosening facilitates the next step, molecular change.

(ii) *Molecular change.* This step is similar to the corresponding solution reaction where the bonds of the reactant are broken and the bonds of the product are formed.

(iii) *Solid-solution formation.* During the early stages of the reaction, a solid solution of the product in the starting crystal is formed at the site of reaction. However, after the concentration of the product reaches a certain point, the product will separate.

(iv) *Separation of product.* This step gives new crystals, either randomly oriented or with an orientation governed by the crystals of the starting material. This last case is termed a topotactic reaction and will be discussed below.

Thus, molecular loosening is required for an API or formulation to be unstable. Conversely, it is possible to eliminate instabilities by preventing molecular loosening. For example, milling can disorder a solid, resulting in a reactive material. By avoiding milling or doing 'cold' milling the development scientist can sometimes avoid instabilities.

In some cases, water is the cause of molecular loosening. Water mobilizes groups on the surface of crystals and in the amorphous state. For amorphous materials it has been established that water dissolves in the amorphous phase and increases the mobility of the system. Water also lowers the glass transition temperature (the temperature at which an amorphous solid becomes a rubber) of an amorphous solid. By lowering the glass transition temperature, mobility is enhanced. In such cases, it is best to avoid exposure of the drug substance and drug product to moisture. Molecular mobility is also the fundamental cause of phase transitions between: (i) polymorphs; (ii) solvates of different stoichiometry; (iii) an unsolvated form and a solvated form; and (iv) amorphous and crystalline forms.

For crystallization, as described above for ritonavir, a new crystal form appears. Another type of physical transformation involves slurry conversion. In this case, one form converts to another in a slurry. In these cases, the most stable form grows and the less stable form disappears. Crystallization processes require enough molecular loosening for the molecules to repack in a new crystal form.

In summary, for preclinical studies, it is important to establish that the drug substance is stable for its intended use, which is a first-in-human clinical trial. This is generally accomplished by collaborating with HPLC experts who often do some forced degradation studies for a preliminary validation of their method and to make sure there are only small amounts of unknown impurities present in the first-in-human batches. Armed with this information, the drug development scientist can usually quickly determine the stability of the API. If the instability cannot be prevented, special packaging and/or storage conditions should be investigated as a means of reducing degradations or transformations. For example, a material that is chemically unstable can be stored at dry-ice temperatures sealed in foil pouches and administered almost immediately after removal from the container.

Preformulation and formulation concepts

A group of scientists at Abbott and Pfizer published an important review on reducing time to develop first-in-human formulations [21]. The centerpiece of this review is a flowchart that is shown in Figure 1.

There are several key decision points in this flowchart. Some of these decision points require experimental information and others are philosophical. The key decision points are:

Key decision point 1

Should the formulation and solid-state work be front loaded? A front-loaded formulation program as shown in the flow chart is a program that: (i) involves doing enough formulation studies to minimize the risk of inadequate exposure; and (ii) speeds phase II and III studies. A front-loaded formulation study will typically be more expensive and more involved than the alternative, which is focused on speed.

Key decision point 2

Route of administration? The route of administration and the dosage forms are key questions in both the fast and front loaded route.

Key decision point 3

Is the drug high potency? This decision point is important because usually it is more difficult to ensure content uniformity for formulation methods for highly potent drugs because of their relatively low drug substance load.

Key decision point 4

Does the API have adequate solubility? This is a key decision because it will determine what kind of formulation can be used.

Key decision point 5

Can the toxicological formulation be used for the first-in-human formulation? This, of course, would simplify the first-in-human formulation work.

The exploratory IND concept

In recent years, as the sensitivity of analytical methods for measuring blood levels of drugs and biomarkers has increased, the concept of an exploratory IND (first-in-human study) has developed. Often this study would involve microdoses. In keeping with this concept, in January 2006 the FDA issued a Guidance for Industry entitled 'Exploratory IND Studies'. This guidance states: 'Existing regulations allow a great deal of flexibility in the amount of data that needs to be submitted with an IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility and often provide more supporting information in INDs than is required by regulations.' The agency issued this guidance in response to the Critical Path Report and it is aimed at increasing the number of drugs that reach the market by increasing the number of first-in-human clinical trials that can be performed with the same expenditures. In other words, the guidance is intended to reduce the cost of drug development without increasing the risk.

The guidance contains a section entitled 'Clinical Trials to Study Pharmacologically Relevant Doses'. This section outlines IND studies that are not intended to find the maximally tolerated dose of the candidate. It states that 'repeat dose clinical trials lasting up to 7 days can be supported by a 2-week repeat dose toxicology study in a sensitive species accompanied by toxicokinetic evaluations'. This section is accompanied by a flow chart to outline the approach. The section also states 'The confirmatory study could be a dedicated study involving repeat administrations of a single dose level approximating the rat NOAEL [no-observed-adverse-effect level] calculated on the basis of body surface area.' Finally, the guidance states that each candidate should be tested for safety pharmacology and geneotoxicity. The guidance recommends that this data can be used to select starting and maximum doses for the clinical trials according to a table provided. A redrawn flowchart is shown in Figure 2.

Timeframe for toxicological studies

It is important to determine the fastest preclinical timeframe to address the question: what is an effective model for examining solid-state properties (polymorphism) within preclinical timeframes? This is because these timeframes will determine the time that is allowed to examine solid-state properties, polymorphism, without delaying development.

There are several FDA guidances that bear on the question. One important document is entitled 'M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals' (July 1997). This document states that the goals of nonclinical safety evaluation are to characterize the toxic effects with respect to target organs, dose dependence, relationship to exposure and potential reversibility. The document also states that safety pharmacology is a separate study aimed at assessing the effects of the drug on vital functions including cardiovascular, central nervous and respiratory systems. These studies can be conducted as additions to toxicity studies or as separate studies. Table 1 of the document states that the 'minimum duration of repeated dose toxicity studies is 2–4 weeks in rodents and 2 weeks in nonrodents'. This information suggests that the fastest a toxicity study

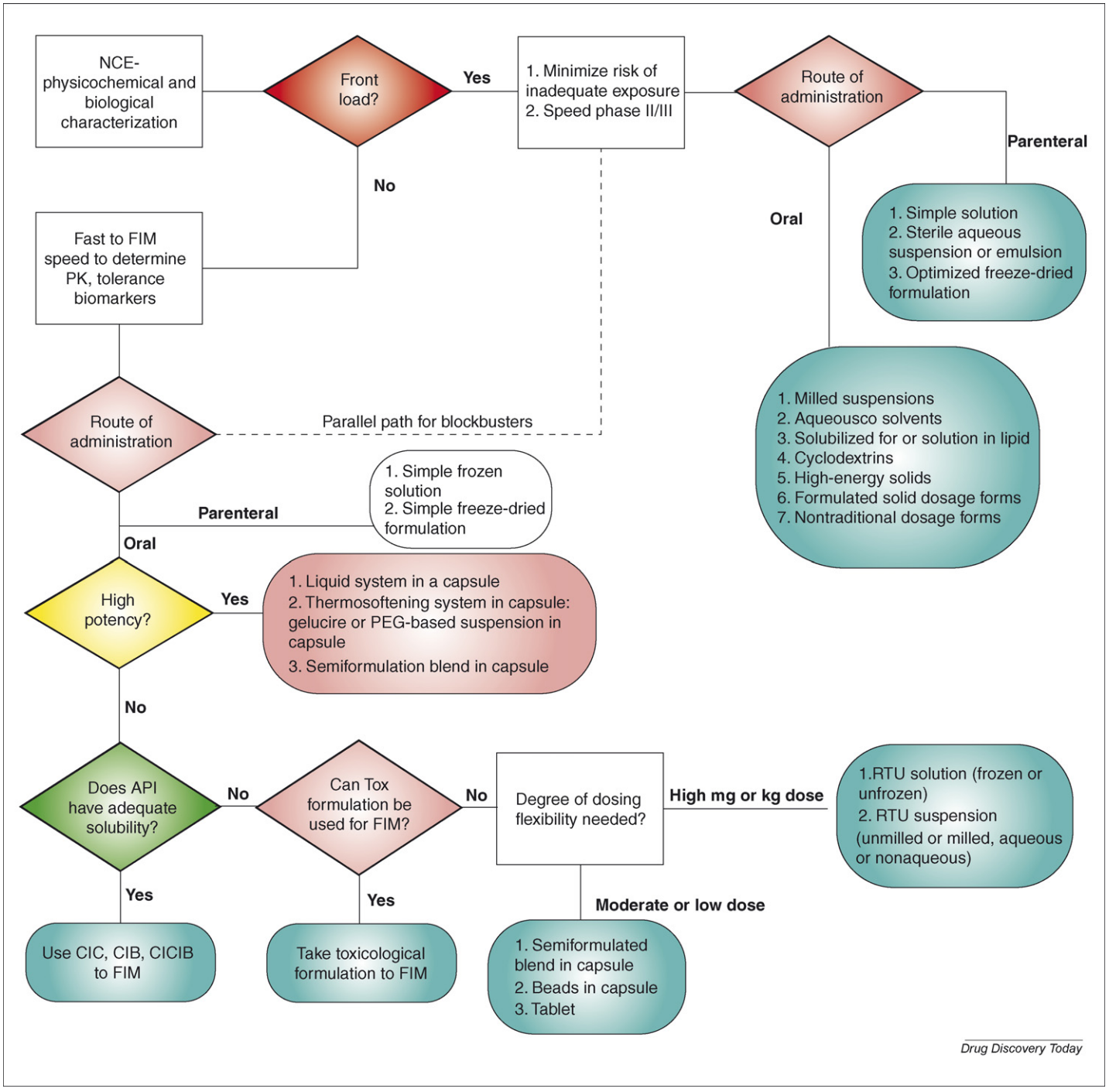

FIGURE 1

Formulation and preformulation work aimed at reducing the time to first-in-human clinical trials [21]. Abbreviations: FIM, first-in-man; NCE, new chemical entity; PEG, polyethylene glycol; PK, pharmacokinetics.; RTU, ready to use.

could be completed is four weeks. Because some time will be required to evaluate the data, a more realistic estimate of the shortest possible time for toxicology study is six weeks.

Another important FDA document that relates to the time for preclinical trials is the recently issued 'Guidance for Exploratory IND Studies' (January 2006). This document, which is discussed above, suggests a strategy for exploratory IND studies. The guidance contains an interesting section entitled 'Clinical Trials to Study Pharmacologically Relevant Doses', which states that 'repeat dose clinical trials lasting up to seven days can be supported by a two-week repeat dose toxicology study in a sensitive species accompanied by toxicokinetic evaluations'. More detail is provided in a flow chart (Figure 2). This flow chart shows a 2-week toxicology study in a rodent species to establish NOAEL and then a 'confirmatory' repeat dose toxicology study in a non-rodent. This repeat dose study could be as short as two weeks. This flow short also suggests that a realistic estimate for the shortest possible time for toxicological study is 6–8 weeks.

The extensive evaluation of toxicological data might be required to ensure that the drug is safe for administering to

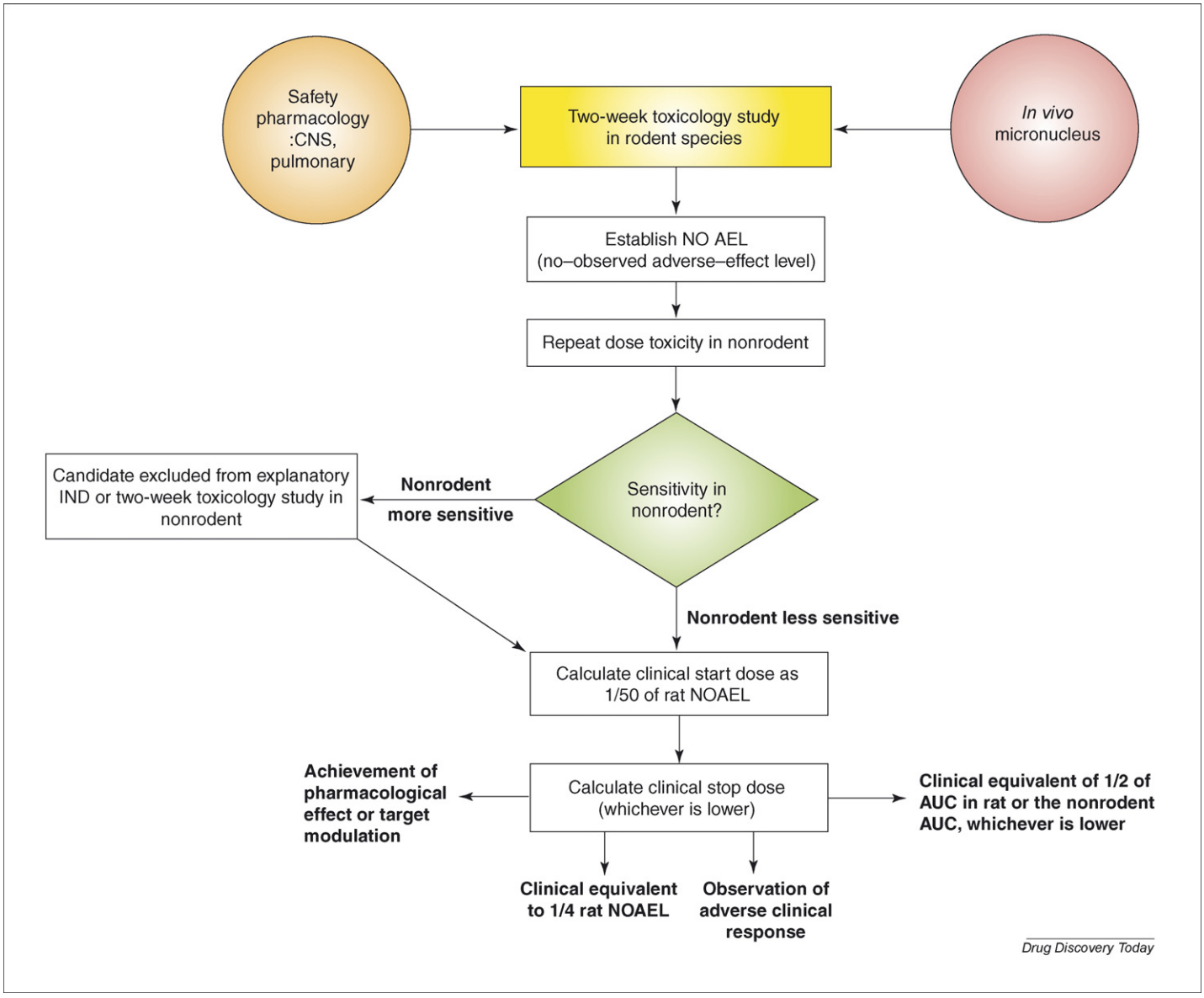

FIGURE 2

A flow chart describing the exploratory IND concept of the FDA. Abbreviation: AUC, area under curve.

humans if there are any unusual findings. In such cases, the time frames outlined would need to be extended. Conversely, if there are no unexpected findings, a review could be accomplished quickly, especially if it involved multiple reviewers.

Timeframe for examining solid-state properties and preparing a first-in-human product (clinical trial samples)

As discussed in the previous section, a six-week timeframe is the fastest possible timeframe for toxicological studies. In fact, it is likely that toxicological studies will take significantly longer than six weeks. Nevertheless, it is instructive to consider the extent to which solid-state properties can be examined in this timeframe.

Table 3 shows a timeline for a six-week examination of solid-state properties. For this scenario, it is assumed that the IND clinical trials will be performed on the same lot used for the toxicological studies. It is also assumed that chemical in capsule (CIC), chemical in bottle (CIB) or chemical in capsule in bottle (CICIB) formulations will be used.

Week 1: During this week, a fast screen to try to find the most stable form and possibly one or two stable salt forms is carried out. Approximately 100 mg of material should be used for this study. This fast screen should use both automated and by-hand approaches.

Week 2: During this week, the data from the fast screen are analyzed and the two best forms selected. Material is recycled and 10–40 mg of each form is prepared.

Week 3: During this week, the solubility of the forms is determined and some analytical characterization is carried out. Additionally this solubility is used to determine the final formulation: CIC, CIB or CICIB. The solubility of the final form in various vehicles for human administration is also examined. The initial toxicological data are also evaluated. It might be necessary to use multiple evaluators and even work two or three shifts to accomplish this review.

TABLE 3

Timeline for a 12-week study of solid-state properties, preparation of clinical trial material and initiation of exploratory IND trial

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Submit IND	Week 8	Week 9	Week 10	Week 11	Week 12[a,b]
Tox track	Tox. formu-lation	Rat and dog studies determine NOAEL		Evaluation			Prepre IND						
CMC analytical track	Purity assay - partial validation		Physical charac-teristics	Impurity profile		Prepare IND & QA review	Prepare IND					Prepare C of A	
CMC form and formulation track	Fast screen (including salts)		Scale up two best forms	Solubility & prepare initial CIC formulation	Stability study	Prepare IND & QA review	Prepare IND		Crystalliza-tion optimization	Scale up crystalliza-tion	Prepare CIC, CIB or CICIB formulation		
Regulatory track	Begin IND identity structure	Continue IND preparation; add data as available				Complete IND	Complete and submit IND						

[a]Contingency.
[b]Following contingency week, begin IND clinical trial.
Abbreviations: CMC, chemistry, manufacturing and controls; C of A, certificate of analysis.

Week 4: During this week, the formulation is prepared and a brief stability study under a few conditions (e.g. 80°C) is carried out to determine stability. This study will include ground materials because milling might be used to reduce particle size. Additionally, initial studies aimed at scaling up the crystallization are performed. It is very helpful to use online methods of analysis during these studies. In this way, the particle size and solid form can be determined as the crystallization is taking place.

Week 5: During this week, the crystallization method developed in week 4 is attempted on a slightly larger scale and, if successful, the entire lot is crystallized using the procedure developed during week 4. As in week 4, it is advisable to use online methods to verify that the solid form and particle size of the crystals is appropriate. If possible, a general crystallization method is developed that will allow the synthesis of the desired form from a variety of lots of API (drug substance).

Week 6: The crystals are harvested, dried and formulated into CIC, CIB or CICIB formulations. At this stage it is important to pay particular attention to the solid form produced and its particle size. If necessary some particle size reduction will need to be performed. As shown in Table 3, it is necessary to prepare doses of ~1/50 to 1/4 of the rate NOAEL. For a NOAEL of 1 mg/kg this would be doses of ~1.4 mg up to 17.5 mg. The solid form of the API in the final formulation is verified using one of the analytical techniques listed above. Additionally, the usual studies of purity, content uniformity and dissolution are also performed. These studies can be done as clinical trials are ongoing. Other formulations could be used but would take longer. During this week the evaluation of all of the data (including toxicological data) is completed and the IND is written, which will require multiple scientific reviewers, QA auditors, and writers.

Weeks 7–10: During this timeframe, clinical supplies are manufactured. This involves recrystallization of the initial lot on a large scale and manufacture into clinical supplies (CIC, CIB or CICIB). It is important to realize that the recrystallized lot would be expected to be 'cleaner' (have fewer impurities) than the original lot. This must be confirmed before manufacture into clinical supplies. Similarly, the finally clinical supplies must be 'cleaner' and equivalent to the lots used for earlier studies. In no case could the clinical supplies have higher bioavailability than that allowed by the toxicological studies.

If a formulation more complex than CIC, CIB or CICIB is required to achieve reasonable blood levels then the toxicological formulation can be used. If this is not possible, then it will be necessary to add at least one week to the timeline to design and manufacture the new formulation. Additionally, if problems of any sort are encountered then longer times might be needed.

It should be apparent that to file an IND in the timeframe outlined, an informatics backbone will be required. This backbone will allow instant entry of all data needed for the IND. The backbone will also allow QA of data as it is entered, avoiding the need for extensive QA at the end of the process.

Conventional IND concept

In some cases, it is more appropriate to bypass an exploratory IND and simply go directly to a conventional IND. In most cases this means that enough toxicological studies have been done to justify higher doses in the first-in-human trials. These higher doses are determined from animal studies, at which one is expected to see therapeutic effects. Table 4 shows a timeline for carrying out a conventional IND study.

This timeline shows that by merging solid-state-form discovery, formulation design and first-in-human manufacturing into the same team it is possible to submit an IND in 13 weeks and begin an IND 17 weeks following the delivery of a lot of drug substance (API).

This timeline allows more time for:

- Solid-form discovery and selection
- Scale-up
- Crystallization optimization
- Formulation design
- Manufacturing

TABLE 4

Timeline for an 18-week study of solid-state properties, preparation of clinical trial material and initiation of conventional IND trial[a]

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13		Week 14	Week 15	Week 16	Week 17	Week 18[a]
Tox track	Tox. formulation	Rat and dog toxicological studies				Evaluation							Prep. IND						
CMC analytical track	Purity assay; partial validation				Physical characteristics		Impurity profile				QA review, prep. IND, and contingency		Prep. IND					Prep. C of A	
CMC form and formulation track	Fast screen (including salts)				Scale up two best forms		Solubility and prepare initial CIC formulation		Stability study		Crystallization optimization	QA review, prep. IND	Prep. IND	Submit IND	Crystallization optimization	Scale up crystallization	Prep. CIC, CIB or CICIB formulation		
QA and regulatory track	Begin IND identity structure	Continue IND prep; QA review and add data as available										Complete IND	Complete and submit IND						

[a] Following Week 18, begin IND clinical trial.

It is important to realize: (i) This timeline shows general timeframes. In reality, a timeline would be constructed for each compound on the basis of the information provided with the lot of API delivered to the IND team; (ii) as with the previous flowchart, it will probably be necessary to have several scientific reviewers, toxicological reviewers, QA personnel and regulatory writers to achieve the timeline outlined in Table 4.

Merging solid-form discovery and formulation in a preclinical timeframe

A key element of the strategy to reduce the time required for preclinical development is to link solid-form discovery with formulation, formulation design and manufacturing. This strategy involves:

- Focusing early on discovering the most stable form
- Determining the solubility of the most stable form
- Setting the first-in-human formulation development strategy on the basis of this solubility
- Merging solid-form discovery with the formulation design and development and with first-in-human manufacturing into the same cohesive team

This strategy involves performing a fast polymorph screen as soon as possible after the candidate is selected. Once the screen is completed the most stable form is identified and a decision on the formulation is made immediately:

- Is the form soluble enough to be used as a CIC or CIB?
- Is the form insoluble and can the toxicological formulation be used for first-in-human studies?
- Can some other liquid formulation be used?
- Can an amorphous formulation, a salt formulation, a cocrystal formulation or liquid crystal formulation be used?

Thus, the first-in-human formulation and development strategy could involve any of the following:

- Solid formulation of the most stable form
- Suspension formulation
- Liquid formulation based on toxicological formulation
- Salt formulation
- Cocrystal formulation
- Amorphous formulation or liquid crystal formulation

The solid formulation would preferably be a CIB, CIC or CICIB. The CIB formulation would be suspended in solution and administered. However, such suspensions must be stable and are inconvenient for a large clinical trial. An alternative is to weigh the chemical into capsules and administer the capsules. Equipment that will perform this filling operation is available. Additionally, it might be possible to improve the flow of the chemical (drug) in these machines by making a simple formulation with a flow aid. Such simple formulations are within the timeframe of the studies proposed above. The CICIB approach involves placing one or more CIC dosage forms in a solution, allowing the capsule shells to dissolve and administering the solution.

In recent years it has become clear that amorphous formulations can achieve solubility and blood levels that are much higher than conventional formulations that involve crystalline materials [2,5,22]. Thus, for insoluble compounds it might be judicious to explore the use of amorphous formulations to achieve higher exposure. A fast abbreviated screen for amorphous formulations can be performed by adding only a week to the timeframe of the study. In this case, studies will need to be done to establish that the formulation is stable enough for clinical trials. An alternative strategy is to use the toxicological formulation or a soft-gel formulation.

Once the clinical trial material is manufactured, it is analyzed for purity, impurities and solid form. The purity and impurity analyses are done using conventional HPLC. The solid form can conveniently be determined using solid-state NMR or X-ray powder diffraction. Solid-state NMR is particularly attractive for dosage forms involving capsules because the entire capsule can be placed in the instrument.

The work done during this IND stage provides valuable information for the next steps. It will provide answers to the following questions:

- Can the form selected reach adequate blood levels?
- Is the form selected stable under clinical trial conditions?
- Will the form selected be stable under more extreme stability conditions and will the form be stable enough to provide a two-year shelf life?
- Did the form show reasonable processability?

If the answer to these questions is yes, then this would suggest that the form selected **{AU:OK?}** could be used in subsequent clinical trials. If the answer to any of these questions is no, then this would suggest there should be continued searching for a better form for future clinical trials.

If a suitable form cannot be found, then formulation approaches will be needed to 'correct for' the deficits of the solid form. Of course, the solid form with the best combination of properties is selected. However, this form might not have all of the properties required for robust manufacture. For example, if the best solid form still has poor flow properties then a granulation method would be developed to mask these undesirable properties.

As more material becomes available, it is important to confirm the choice of the form discovered for the first-in-human trials or continue the search for a better form. Thus, in cases where the initial first-in-human trial is successful, a more complete solid-state study will be performed. The focus of this study will depend on the answers to the questions above. For example, if the form is hygroscopic and cannot be stored above 70% relative humidity then a search for a new form with equivalent solubility and stability but reduced hygroscopicity would be initiated.

Formulation design, quality by design in preclinical timeframe

How can quality by design be carried out in the preclinical timeframe? Companies that are successful in applying quality by design to the preclinical timeframe will be able to reduce risks and regulatory problems later in development.

Moheb Nasr of the FDA developed a quality wheel for several of his presentations. Figure 3 shows a modification of this wheel to emphasize the important aspects of product design and process development for the preclinical timeframe. Quality by design is defined as 'designing and developing manufacturing processes during the product development stage to consistently ensure a predefined quality at the end of the manufacturing process.' In the inner part of the wheel the most important aspects of preclinical drug development are emphasized. Product design involves determining the optimum solid form as outlined above and designing the dosage form (usually CIC or CIB) for this solid form. Then the process for both preparing this forms and the formulation are designed. In the preclinical timeframe simple processes are used so this step should be straightforward. The performance of the designed process is assessed both before and after the process is carried out. The work before the manufacture of the first-in-human product is aimed at predicting any design flaws in the process design. The work following the manufacture of the first-in-human product is an assessment of how the process design worked. Finally, the product performance is assessed both on the basis of the blood-level data and also on the analytical studies carried out.

FIGURE 3

Quality-by-design wheel for early preclinical development (after Nasr). Reproduced from http://www.fda.gov.

Even in this preclinical timeframe it is possible to define a preliminary design space. The design space is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases, design space can also be applicable to formulation attributes. Working within the design space is not generally considered as a change of the approved ranges for process parameters and formulation attributes. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. The design space will form the foundation for the design space that will be included in the pharmaceutical development report as defined in the ICH Q8 document (Guidance for Industry: Q8 Pharmaceutical Development, May, 2006). This section 'is intended to provide a more comprehensive understanding of the product and manufacturing process for reviewers and inspectors.' This section will be particularly crucial in convincing the FDA that the product described in a subsequent new drug application is low risk and designed for quality.

PAT in preclinical development

Process analytical technology (PAT; a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of assuring final product quality) can be applied to the preparation of the API and the final drug product. Especially important is the monitoring of the solid form of the API and the particle shape and size during the final crystallization process. Several sensors are available for this task and can provide important real-time information. During the past couple of years, numerous powerful analytical instruments have been developed

(e.g. Online Raman spectroscopy, Online NIR spectroscopy and X-ray powder diffractometry) that are capable of real-time monitoring and controlling of a crystallization process or solid-state transformation process [23–26]. It is especially important to use these sensors for this early crystallization work because less is known about the crystallization process. Additionally, if the sensors detect problems during the crystallization then it is possible to stop the crystallization and develop an improved method to prepare the proper API. Clearly, data obtained during the development phase are necessary to explore the 'design space' for optimizing crystallization conditions.

Solid-state forms might also undergo phase transformations during the different steps of process to produce the final dosage form because the drug substance will be exposed to elevated temperatures (e.g. drying and extrusion), high relative humidity (e.g. wet granulation and spray drying) and/or high sheer forces (e.g. milling and micronization). This might result in a conversion of an anhydrous form into a hydrate, crystallization of non-crystalline material or conversion of a thermodynamically metastable crystal form into the stable one under ambient conditions. Again, powerful analytical instruments, the most prominent of which to date seems to be near infrared spectroscopy, have been developed for monitoring pharmaceutical processes such as blending or drying of granules [27].

Conclusions

This review provides a model for addressing solid-state properties, polymorphism, within the preclinical timeframe. We recommend the combination of two main approaches: (i) the use of modern tools for determining solid-state properties and (ii) a strategy that merges polymorphism studies, formulation and clinical supplies manufacture into a single administrative group. This combination will reduce the time to first-in-human clinical trials. Tools for accomplishing this goal include methods for fast screening that combine automated systems and by-hand approaches and sensitive analytical methods including X-ray diffraction and spectroscopy. Another important part of this strategy involves preparing clinical trial material that is stable and for this reason formulations involving crystalline API in a capsule or bottle are preferred. A third important component of this strategy is to take no longer to determine the solid form and formulation than it takes to do the toxicology study. In this way, the solid-state properties work is never on the critical path. Finally, the scientific studies outlined in this proposal will lay the foundation for a process and product prepared using Quality by Design principles as outlined in the recent ICH quality guidances. In this way major regulatory challenges can be met at the same time as performing research that reduces time to market.

References

1 Bernstein, J. (2002) *Polymorphism in Molecular Crystals*. Oxford Science Publications
2 Byrn, S.R. *et al.* (2000) *Solid State Chemistry of Drugs* (2nd edn), SSCI Press
3 Childs, S.L. *et al.* (2004) Crystal engineering approach to forming cocrystals of amine hydrochlorides with organic acids. molecular complexes of fluoxetine hydrochloride with benzoic, succinic, and fumaric acids. *J. Am. Chem. Soc.* 126, 13335–13342
4 McNamara, D.P. *et al.* (2006) Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. *Pharm. Res.* 23, 1888–1897
5 Hancock, B.C. and Parks, M. (2000) What is the true solubility advantage for amorphous pharmaceuticals? *Pharm. Res.* 17, 397–404
6 Byrn, S.R. *et al.* (1988) The crystal structure, solid-state NMR spectra, and oxygen reactivity of five crystal forms of prednisolone tert-butylacetate. *J. Am. Chem. Soc.* 110, 1609–1614
7 Lin, C.T. *et al.* (1982) Solid-state photooxidation of 21-cortisol tert-butylacetate to 21-cortisone tert-butylacetate. *J. Org. Chem.* 47, 2978–2981
8 Ressler, C. (1972) Solid-state dehydrogenation of L-1,4-cyclohexadiene-1-alanine hydrate to L-phenylalanine. *J. Org. Chem.* 37, 2933–2936
9 Bauer, J. *et al.* (2001) Ritonavir an extraordinary example of conformational polymorphism. *Pharm. Res.* 18, 859–866
10 Chemburkar, S.R. *et al.* (2000) Dealing with the impact of ritonavir polymorphs on the late stages of bulk drug process development. *Org. Proc. Res. Dev.* 4, 413–417
11 Byrn, S.R. (2005) Regulatory aspects of x-ray powder diffraction, Part I. *Am. Pharm. Rev.* 8, 55–59
12 Byrn, S.R. (2005) Regulatory aspects of x-ray powder diffraction, Part II. *Am. Pharm. Rev.* 8, 137–141
13 Burger, A. and Ramberger, R. (1979) On the polymorphism of pharmaceuticals and other molecular crystals. I. Theory and thermodynamic rules. *Mikrochim. Acta* 2, 259–271
14 Burger, A. and Ramberger, R. (1979) On the polymorphism of pharmaceuticals and other molecular crystals. II. Applicability of thermodynamic rules. *Mikrochim. Acta* 2, 273–316
15 Egami, T. and Billinge, S.J.L. (2003) *Underneath the Bragg Peaks: Structural Analysis of Complex Materials*. Pergamon Press
16 Sheth, A. *et al.* (2005) Local structure in amorphous phases of piroxicam from powder X-ray diffractometry. *Cryst. Growth Des.* 5, 571–578
17 Bates, S. *et al.* (2006) Analysis of amorphous and nanocrystalline solids from their X-ray diffraction patterns. *Pharm. Res.* 23, 2333–2349
18 Tishmack, P.A. *et al.* (2002) Solid-state nuclear magnetic resonance spectroscopy: pharmaceutical applications. *J. Pharm. Sci.* 92, 441–474
19 McGeorge, G. (2004) Combining Raman spectroscopy and microscopy to support pharmaceutical development. *Am. Pharm. Rev.* 6, 96–99
20 Paul, I.C. and Curtin, D.Y. (1973) Thermally induced organic reactions in the solid state. *Acc. Chem. Res.* 6, 217–225
21 Hariharan, M. *et al.* (2003) Reducing the time to develop and manufacture formulations for first oral dose in humans. *Pharm. Technol.* 27, 68–84
22 Law, D. *et al.* (2003) Ritonavir–PEG 8000 amorphous solid dispersions: *in vitro* and *in vivo* evaluations. *J. Pharm. Sci.* 93, 563–570
23 Wang, F. *et al.* (2000) An investigation of solvent-mediated polymorphic transformation of progesterone using *in situ* raman spectroscopy. *Org. Process Res. Dev.* 4, 391–395
24 Starbuck, C. *et al.* (2002) Process optimization of a complex pharmaceutical polymorphic system via *in situ* raman spectroscopy. *Cryst. Growth Des.* 2, 515–522
25 Norris, T. *et al.* (1997) Determination of end-points for polymorph conversions of crystalline organic compounds using on-line near-infrared spectroscopy. *Analyst* 122, 549–552
26 O'Sullivan, B. *et al.* (2003) *In situ* monitoring of polymorphic transitions. *Org. Process Res. Dev.* 7, 882–997
27 Davis, T.D. *et al.* (2004) *In situ* monitoring of wet granulation using online x-ray powder diffraction. *Pharm. Res.* 21, 860–866