Organic Process Research & Development

Regulatory Highlights

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Regulatory Highlights for August 2011−January 2012

■ PHARMACEUTICAL COCRYSTALS

The U.S. Food and Drug Administration (FDA) have released a new draft guideline on the Regulatory Classification of Pharmaceutical Cocrystals. Cocrystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice, and may offer advantages in terms of improved bioavailability or processing characteristics. Although there has been intense interest in these solids and much research over the past decade, until now no regulatory paradigm exists governing cocrystal forms. So far, no cocrystal drug substances have received regulatory approval (although it is likely that some substances officially designated "salts" are in reality cocrystals). This new guideline outlines the FDA's current thinking on the subject.

The interesting point is that the agency intends to treat cocrystals as "dissociable API-excipient molecular complexes", fully analogous, for example, to an API incorporated into a β-cyclodextrin excipient in formulations (e.g., to enhance drug bioavailability or stability, or to mask taste). The only difference is that in a cocrystal the molecular association occurs within the crystal lattice. Thus, the cocrystal would be regarded as a *drug product intermediate*. This means that a cocrystal form of an existing API would not be a new drug substance but rather an alternative formulation. (In contrast, a new salt form is a different drug substance.) This designation should be welcome to prospective cocrystal manufacturers and developers, as it relieves them of the burden of additional testing. In practice, however, the cocrystal would be prepared by chemical procedures in an API plant, so it seems counterintuitive to refer to it as a drug product intermediate, and this may give rise to difficulties in practice.

When submitting new, or abbreviated, drug applications ((A)NDAs), the applicant should determine whether, in the crystalline solid, the component API and coformer compounds exist in their neutral states and interact via nonionic interactions, as opposed to an ionic interaction. If there is a negative pK_a difference between the components, it can be assumed that no ionization takes place. However, where ΔpK_a lies between 0 and 3, some spectroscopic evidence would be expected, to indicate the degree of proton transfer. The applicant should also demonstrate that the API dissociates from the coformer (excipient) prior to reaching the site of action. The draft guideline is available from the FDA Web site (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281764.pdf). Comments are invited.

■ APPLYING ICH GUIDELINES TO CMC REVIEW

The FDA's Office of Pharmaceutical Science has issued a new policy (MAPP 5016.1, 2 Aug 2011) on applying the principles of ICH guidelines Q8−Q10 to the review of the Chemistry, Manufacturing and Control (CMC) sections of new applications. Because the number of applications and supplements containing Quality by Design (QbD) approaches has increased over the past few years, there is a need for agency reviewers to consistently implement the relevant guidances in their reviews. Reviewers should ensure that applications contain at least the minimum information on pharmaceutical development described by ICH Q8(R2), including details of the Quality Target Product Profile (QTTP), Critical Quality Attributes (CQAs) of the drug product, drug substance and excipients, selection of an appropriate manufacturing process and of a control strategy. An application should contain information that conveys an understanding of the development of the drug product and its manufacturing process, identify those aspects that are critical to product quality, safety and efficacy, and provide a justification for the control strategy. Applications may also include information on enhanced knowledge of the product and process which can be used to support more flexible regulatory approaches; in such cases reviewers should determine whether this enhanced knowledge is sufficient and ensure that, where real time release testing is proposed, the associated methodology is included in the specifications. Applications are expected to contain risk assessments (ICH Q9), each of which should be evaluated during the review. In addition, the reviewers themselves should take a scientific and risk-based approach when reviewing the application, evaluating the risks to product quality and the ability of the control strategy to suitably control those risks. The reviewer may choose to conduct an independent formal risk assessment using the tools provided in ICH Q9 to aid with this evaluation.

In a related move, FDA have contracted an independent consultant to evaluate current industry adoption of QbD, and the findings are summarized by senior FDA directors (Winkle and Nasr, *Pharm. Technol.* **2011**, *35*(9), 60−64). Unsurprisingly, the study found different levels of maturity in terms of QbD adoption and has identified four broad stages of maturity: novice, pilot, rollout, and fully implemented. Only manufacturers of new drugs (as opposed to generics and biologics) are classed as fully implemented, and only 22% of these have this status. At the other end of the spectrum, among generic manufacturers 40% are classed as novice, i.e. still skeptical about the value of QbD. In conducting its research, the team discovered 10 key challenges related to QbD adoption:

- Internal misalignment
- Lack of belief in a business case
- Lack of technology to execute
- Concern over alignment with third parties
- Inconsistent treatment of QbD across FDA
- Lack of tangible guidance for industry
- Regulators not prepared to handle QbD applications
- Lack of confidence in promised regulatory benefits
- Misalignment of international regulatory bodies
- Perception of current interaction of FDA with companies not being conducive to QbD

Several options were provided to encourage and accelerate QbD adoption, including policy development and changes to

Published: February 27, 2012

dx.doi.org/10.1021/op300032j | *Org. Process Res. Dev.* 2012, 16, 545−549

internal and external change management. The FDA directors do not indicate how far these suggestions will be pursued but do say that they "plan to spend the next 5 years focusing on putting QbD into consistent practice, including ensuring the clarity of our vision, message, and aspirational targets and timelines; clarifying expectations and benefits of QbD within FDA and industry; and ensuring a broad codification and guidances".

To encourage greater use of QbD among generic manufacturers, the FDA's Office of Generic Drugs (OGD) has published an example of a fictitious pharmaceutical development report (ANDA Module 3 Quality 3.2.P.2) for a modified release tablet formulation. (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf) The purpose of the example (161 pages) is to illustrate the types of studies ANDA applicants may use as they implement QbD in their development process and to promote discussion on how OGD would use this information in review.

DRUG MASTER FILES

In November 2011, FDA's Arthur Shaw presented a webinar on the U.S. Drug Master File (DMF) system. DMFs are a means of communicating Chemistry, Manufacturing and Control (CMC) information to the agency in support of drug applications, while maintaining the confidentiality of the DMF holder's proprietary information. The FDA requires such CMC information for drug products, drug substances (APIs), novel or unusual excipients, and some packaging materials. A DMF is usually not necessary for compendial excipients, or for drug substances used in older "over-the-counter" (OTC) products, which are marketed without prior approval by FDA under the OTC monograph system (e.g., aspirin). DMFs are usually submitted by "third-party" manufacturers, i.e. not the applicants themselves, and are most commonly used in connection with generic drugs. For new molecular entities, all the CMC information should normally be submitted as part of the NDA itself, even if the drug substance is manufactured by a third party. The exception is for a new formulation of a previously approved drug, where the drug substance information can be submitted in a DMF if it is manufactured by a third party. The DMF holder is normally expected to be the actual manufacturer of the material.

The presentation outlines the procedures for submission of a DMF to the agency, and for referencing it in (A)NDAs. It gives details of technical and administrative requirements, timelines, and links to appropriate regulations and guidances. The recorded webinar may be viewed at https://collaboration.fda.gov/p84453591. Alternatively, a PDF of the slides (64) is available from www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM279666.

REGULATORY STARTING MATERIALS

Barbara Scott, a reviewer in FDA's Office of Generic Drugs, offers some advice to DMF holders in a recent article (Designation of Regulatory Starting Materials in the Manufacturing of Drug Substances: Impact on ANDA Review Time. In *Pharm. Technol.* **2012**, *36*(1), 63−66). She notes that ANDA submissions have now reached staggering numbers, which in turn has led to longer review and approval times. In many instances the ANDA applicant references a DMF that contains the API information; it is important that the DMF holder understands the impact of starting material designation on the ANDA review time. The holder's decision on how far back in the synthesis to go before designating the regulatory starting material is impacted by the cost of CGMP compliance, publishing proprietary information, and the necessity of reporting any future changes to the process that might involve outsourcing. Increasingly, DMF holders define a key intermediate as the starting material and outsource the synthesis of that intermediate without due consideration to quality. This leads the agency to request additional information, thus prolonging the review time. A number of cases are presented where the proposed starting material would—in the author's view—be considered unacceptable. In one case, this is because the starting material is only one synthesis step removed from the final API; in another the starting material contains all of the API's chiral centres. In a third example, the racemic form of the API is proposed as the starting material, and the "synthesis" consists only of resolution and purification steps; "this would be unacceptable even in cases where the racemate is a drug substance in and of itself". Molecules that contain potential genotoxic structural elements in intermediates anywhere along the synthetic route require extra care in managing impurity profiles and the corresponding risk. A proposed bis-anilino compound is here considered unacceptable as a starting material, as there is no information on how the preceding nitration step is controlled or how subsequent (potentially genotoxic) impurities were removed. Some pointers regarding starting materials derived from fermentation, or from plants or animals, are also given.

My own impression is that this reviewer's approach is overly inflexible; it appears to conflict with the recommendations of the recent draft ICH Q11 guideline, which takes a more "holistic" approach to starting material designation. (See Regulatory Highlights. In *Org. Process. Res. Dev.* **2011**, *15*(5), 970−973.) I am aware that this article is already causing some nervousness in parts of the industry. Hopefully it will serve to promote further discussion of this important matter.

NEW GUIDE FOR ICH Q8/Q9/Q10 IMPLEMENTATION

The Quality Implementation Working Group of the ICH (International Conference on Harmonization) has prepared 'Points to Consider' covering topics relevant to the implementation of ICH Q8(R2), Q9, and Q10 guidelines (on pharmaceutical development, quality risk management, and pharmaceutical quality systems). These supplement the existing Questions and Answers and workshop training materials already produced by this group. The 'Points to Consider' are based on questions raised during training workshop sessions in the three regions (United States, Europe, Japan). They are not intended to be new guidelines, but rather to provide clarity to both industry and regulators, and to facilitate the preparation, assessment, and inspection related to applications filed for marketing authorizations. The following topics are covered: criticality of quality attributes and process parameters; control strategies; level of documentation in enhanced (QbD) regulatory submissions; role of models in quality by design; design space; process validation/continuous process verification.

For most of these topics there is little actually new. The main exception is the discussion of the role of models. Here a model is defined as "a simplified representation of a system using mathematical terms"; models can enhance scientific understanding and possibly predict the behaviour of a system under a set of conditions. For the purpose of implementation, models can be categorized on the basis of their intended outcome, e.g. to support process design, to support analytical procedures, or to monitor or control processes. Within each of these categories and on the basis of their role in assuring product quality, models can be further classified as having low, medium, or high impact. For example, a model for design space determination would generally be considered a medium-impact model, while a model for formulation optimization would be considered a low-impact model. A model could be considered to have high impact if prediction from the model is a significant indicator of quality of the product (e.g., a chemometric model for product assay).

The level of detail for describing a model in a regulatory submission is dependent on the impact of its implementation in assuring the quality of the product. For low-impact models, a discussion of how the models were used to make decisions during process development should suffice. For medium-impact models, the submission should also include model assumptions, a tabular or graphical summary of model inputs and outputs, relevant model equations, statistical analysis where appropriate, and a comparison of model prediction with measured data. Higher-impact models should be further justified by, for example, discussion of the appropriateness of the sample size, number and distribution of samples, data pretreatment, justification for variable selection, model inputs and outputs, model equations, statistical analysis of data showing fit and prediction ability, rationale for setting of model acceptance criteria, model validation, and a general discussion of approaches for model verification during the lifecycle.

The document also makes some interesting points about the relationship between risk and criticality. Risk includes severity of harm, probability of occurrence, and detectability, and therefore the level of risk can change as a result of risk management activities. The criticality of a Quality Attribute is primarily based upon severity of harm and does not change as a result of risk management. However, the criticality of a Process Parameter is linked to the parameter's effect on any critical quality attribute. It is based on the probability of occurrence and detectability and therefore can change as a result of risk management. This ICH-endorsed guide for implementation can be obtained from the Web site http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf.

SUPPLY-CHAIN SECURITY

The previous "Regulatory Highlights" (*Org. Process. Res. Dev.* **2011**, *15*(5), 970−973) reported on the adoption by the EU in July last year of the Falsified Medicines Directive. The implications of this directive for industry are discussed in a series of articles in the November 2011 issue of *Pharmaceutical Technology Europe*. Alison Williams, of authentication consultants Aegate, summarises the current counterfeiting situation in Europe and what action companies are taking and will be required to take by 2013. Data from the EC suggest that counterfeit medicines in the legal supply chain in Europe are growing at a rate of 10−20% per annum, and the counterfeiting business is now thought to be worth €128 billion globally. A recent coordinated effort by Interpol, involving 81 countries, confiscated 2.4 million illegal and counterfeit pills with an estimated value of $6.3 million; 13,500 Web sites were shut down, and 55 individuals are currently under investigation or under arrest.

Legislative requirements for unique bar-coding of medicines are emerging across the globe at present, with several countries moving towards requiring a two-dimensional (2D) datamatrix code. In India, for example, there will be a legal requirement to uniquely code every exported medicine by 1 July 2012. Throughout 2012, there will be a consultation process by the European Commission (EC) to determine which technical method of unique coding is required to create a harmonised approach across Europe. Authentication systems are currently in voluntarily operation in some EU states, and others are planning pilots for 2012. However, many companies are waiting to hear the outcome of the EC's consultation as to which code they should apply before investing in the printing technology. It is likely to be another 3−4 years before the fully protective measures required under the legislation come into force.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has proactively initiated a project aimed at setting up a cost-effective and scalable pan-European product verification system that is to be run by stakeholder organisations on a nonprofit basis. Their proposal is for a European central hub connected to a series of national or regional data repositories that serve as the verification platforms, which pharmacies and other registered parties can use to check a product's authenticity. The system will be interoperable between the various countries and will allow for the reconciliation of parallel traded products through the European central hub. Other articles in the *Pharm. Technol. Eur.* issue consider packaging design, serialisation, bar-coding standards, optical character recognition, and the use of web-based authentication systems.

Susanne Keitel, director of the European Directorate for the Quality of Medicines and Healthcare (EDQM), writes about two initiatives to combat counterfeiting. (*Pharm. Technol.* **2011**, *35*(10), 133−134). The Medicrime Convention will constitute, for the first time, a binding international legal instrument to combat counterfeiting by criminalizing these activities. Also, a new EDQM project called eTACT aims to develop a traceability and mass-serialization system that authorities, manufacturers, suppliers, distributors, healthcare professionals, and even patients can use. Different levels of access will be accorded to each type of stakeholder but will enable all to verify that an item exists, is genuine, and has been dispensed only once by a registered pharmacy. The system hinges around a Unique Medicine Identifier (UMI) to be placed on the secondary packaging of medicinal products. The UMI is formed by combining the product number(s), a nonsequential and unpredictable serial number, the batch number, and the expiry date of the item. The eTACT system will rely on a central EDQM repository, supported by decentralized repositories among the manufacturers or with national bodies in an information-sharing model. UMI scanning will become mandatory for manufacturers supplying, and for pharmacies verifying, pharmaceutical products.

Also on this topic, the FDA's guideline on the use of physical/chemical identifiers in drug products, the draft of which was reviewed in a previous "Regulatory Highlights" (*Org.*

Process. Res. Dev. **2009**, *13*(5), 842−847), was approved in October of last year.

INCREASING GMP REQUIREMENTS FOR ACTIVE INGREDIENTS

In January 2012, the EU Commission published a concept paper to extend the scope of the existing Directive 2003/94/EC on good manufacturing practice for medicinal products to "GMP for APIs" (http://ec.europa.eu/health/files/gmp/2012_01_20_gmp_cp_en.pdf). Under the proposals, European companies which manufacture drug substances would become legally obliged to observe the current good manufacturing practice guidelines (i.e., ICH Q7). At present the onus is on drug product manufacturers, specifically their QPs, to ensure that their drug substances are manufactured in accordance with GMP; this measure would back up that customer oversight with legal authority. API manufacturers will also be obliged to ensure that any starting materials are sourced from the premises claimed by their manufacturers. The directive would not strictly apply to APIs for investigative use. The concept paper is available for comment until 20 April 2012.

WATER FOR INJECTION

In recent years, a common discussion in pharmaceutical water circles has been "can you make WFI quality water using methods other than distillation?". Two recent articles present the current state of these discussions from industry and regulatory perspectives. Greb (*Pharm. Technol.* **2011**, *35*(9), 48−52) summarizes the concerns which European regulators have expressed regarding the adequacy of nondistillation systems such as Reverse Osmosis (RO) as a final purification step. Bevilacqua and Soli (*Pharm. Eng.* **2011**, *31*(6), 50−61) summarise the findings of a joint USP/ISPE survey on industry attitudes and practice, and also provide a short history of water regulations and standards. Distillation is currently estimated to be the final step in over 99% of all WFI systems. The motivation for this almost exclusive dependence on distillation is due to pharmaceutical standards, regulatory expectations (real or perceived), and the industry's history and inertia. However, the growing emphasis on "green engineering", as well as the need to minimize costs, is focusing attention on less energy-intensive methods.

While United States and Japanese pharmacopoeias now allow WFI to be made by any process which is suitably validated to consistently meet the specifications, the European Pharmacopoeia (EP) still requires firms to produce WFI through distillation. The European Medicines Agency (EMA) is reluctant to move from this position, citing concerns about biofilm, endotoxins, microbial fouling, and metabolic by-products, which render RO systems inherently less robust than distillation. With distillation, the reduction of micro-organisms and their cellular components comes from a phase change and subsequent separation in addition to the heat that is supplied to kill organisms, whereas membrane systems retain bacteria upstream by mechanical separation, which can be flawed.

Experts within the industry generally agree that modern RO designs can easily overcome the problems identified and that distillation systems can also be subject to the same problems. The FDA's well-known *Guide to Inspection of High Purity Water Systems* (July 1993) is replete with examples of inadequately designed distillations. The ISPE position is that the issue of "distillation vs RO" is the wrong question to consider; the discussion should not be so focused on the last step in the water purification process but rather on the system as a whole—i.e. the entire water generation hardware (pretreatment, purification, distribution, controls, and instrumentation), the sanitization system, and maintenance practices. The survey results indicate that there is not one single approach to achieve the target of reliably producing WFI; there are multiple purification sequences, multiple sanitization methods, and multiple microbial/endotoxin control strategies which have already demonstrated their adequacy in meeting the required standards. In June 2011, EP decided that advances in membrane systems since the late 1990s now warrant a review of its previous policy, and it is likely that ultimately the EP monograph on WFI will be revised. However, robust long-term data on quality comparability will need to be carefully assessed first.

CLEANING VALIDATION

A pair of thought-provoking articles by Andrew Walsh discusses the origins of currently applied acceptance criteria for API cleaning validation and the numerous problems that these engender for the industry (Cleaning Validation for the 21st Century: Acceptance Limits for APIs. In *Pharm. Eng.* **2011**, *31*(4 and 5)). The author is particularly critical of the formula used to determine allowable daily exposure to particular contaminants, with its dependence on maximum and minimum doses, surface area of equipment, and the application of safety factors. Safety factors (ranging from 10^{-1} to 10^{-6}) are often applied to differentiate between dosage forms intended for topical, oral, or injectable application, or between commercial and clinical drugs. It is here argued that this does nothing to actually improve safety or decrease risk. Also, it distracts attention from the main issue, which should be to reduce contamination as far as practicable (without heroic efforts). The inclusion of surface area in the equation has the counter-intuitive consequence of requiring smaller equipment to be cleaner than larger equipment for processing the same drug, when all equipment should be equally clean. The emphasis on minimum dose fails to take into account the actual safety profile of drugs and can result in, for example, drug residues being considered "acceptable" when they exceed their threshold of teratogenicity. It means high-dosage drugs may have calculated limits which would in reality amount to gross contamination, while low dosage drugs may have such miniscule limits that they could never be verified.

The author proposes an alternative approach where a "maximum safe exposure" is taken as the starting point for calculations, regardless of dosage, but this should not be confused with an "acceptable" level. Companies should strive, within reason, to minimize all contamination. Their risk analysis would then focus on obtaining a high "margin of safety"—defined as the ratio of the "safe" limit to the level of residue actually found throughout the company's experience of cleaning each particular drug. This is argued to be in line with the FDA's draft Process Validation guideline, released last year. The author is currently chairing an international task team to write a cleaning guide for ISPE and ASTM, which is expected to be published later this year.

SAMPLE SIZE FOR OUT-OF-SPECIFICATION (OOS) INVESTIGATIONS

An article by Torbeck (*Pharm. Technol.* **2011**, *35*(12), 38, 54)) discusses the difficulties of conducting OOS investigations from a statistician's viewpoint. Such investigations are required whenever any OOS result is generated in an analytical lab and may involve repetitions of the test to determine whether the OOS result was an aberration. The number of retests required in order to outweigh the original result has been a matter of controversy since the notorious *Barr* case of the early 1990s. Torbeck discusses the pros and cons of various commonly used approaches. Ideally, one would wish to calculate the sample size using a statistical formula, but this may require the input of information which is not readily available, such as the historical variance of the process or product over a large number (>30) of lots, and the size of the difference to be detected (difficult to determine in advance because one does not know how far out of specification any future OOS result may be). "Thus, there seems to be an inherent and unintended conflict within the industry on sample size. One is not allowed to adjust the number of retests depending on the results obtained, but that is the very information we need to statistically and scientifically determine the sample size." Given these practical difficulties the author feels that a default requirement of seven passing results out of eight tests (suggested by the *Barr* judgment) is as good an approach as any. He has extended an open-ended invitation to those interested in this issue to send their comments and solutions, which may be shared in a future column.

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dx.doi.org/10.1021/op300032j | *Org. Process Res. Dev.* 2012, 16, 545−549