Organic Process Research & Development **2007,** *11,* 797–801

Regulatory Highlights

Regulatory Highlights for January to August 2007

Pharmaceutical Impurities

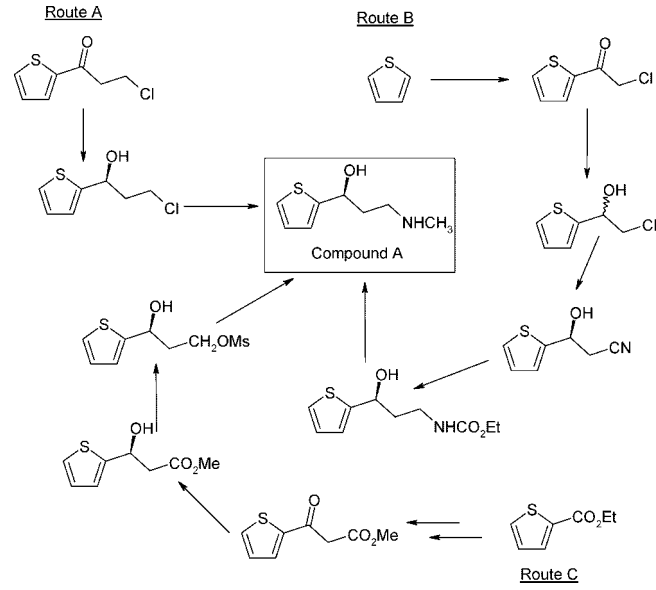
A special themed issue of *Advanced Drug Delivery Reviews* (Vol. 59/1) appeared in January 2007 with the title "Pharmaceutical Impurities: Analytical, Toxicological and Regulatory Perspectives". Edited by A. K. Basak, A. S. Raw, and L. X. Yu of the U.S. FDA Office of Generic Drugs, the issue comprises seven articles that illustrate the concerns and approaches of the FDA and of the industry, in terms of both new drugs and generics. "A pharmaceutical impurity is any component that is not the chemical entity defined as the drug substance or an excipient in the drug product. For this reason the safety of pharmaceuticals is dependent ... in part upon the inpurities that it may contain."

The opening article ("Assuring quality of drugs by monitoring impurities", pp 3–11) by independent consultant S. Ahuja sets the scene by defining commonly used terms, listing the main sources of impurities (synthesis-related, formulation-related, degradation-related), and the main analytical methods employed for detecting, separating, and quantifying them. The author emphasises the importance of kinetic studies to predict stability of a drug susbtance and to evaluate degradation products, while also acknowledging the limitations of such predictions. A case study on developing an impurity profile for terbutaline sulfate, a bronchodilator drug, is outlined in summary, although the reader is referred to the author's book *Impurities Evaluation of Pharmaceuticals* (Dekker, New York, 1998) for the real detail.

M. D. Argentine, P. K. Owens, and B. A. Olsen (Eli Lilly) have contributed an article on "Strategies for the investigation and control of process-related impurities in drug substances" (pp 12–28). This is written mainly from the perspective of the analytical chemist and provides numerous references on how particularly difficult separation and quantification problems have been solved. The article focusses on four specific areas of impurity investigation: the need for orthogonal methods for detecting impurities in order to provide a high degree of confidence that all impurities have been found; stereochemical impurity control considerations; special requirements for toxic impurities; and control of impurities in API starting materials, the latter two aspects being of most relevance to the process chemist.

Control of impurities in API starting materials requires both a knowledge of which impurities are present and an appreciation of the capability of subsequent processing steps to reject those impurities. Impurities may be predicted by a consideration of potential synthetic routes to the starting material; an example of this is provided for the case of a substituted thiophene (see Scheme 1). Three possible routes were identified for the synthesis of "Compound A", presumably the regulatory starting material for Lilly's antidepressant drug Duloxetine, and potential impurities associated with each route were evaluated.

Scheme 1



Evaluation of vendor samples using screening methods, including stress testing, can reveal unknown impurities that may not have been predicted. The impact of downstream processing is illustrated by a case study where a chiral impurity was known to be present in an intermediate, and additionally the process gave rise to a small amount (ca. 1%) of racemization. It was demonstrated that the final crystallization successfully rejected the wrong enantiomer to below the acceptable limit of 0.5% even when levels of 5% were spiked into the process.

Genotoxic impurities were discussed in the previous "Regulatory Highlights" (*Org. Process Res. Dev.* **2007**, *11*, 317); they present a particular analytical challenge in terms of very low allowable limits. Examples cited in this article include a process-related impurity in the analgesic drug pethidine hydrochloride that has been implicated as a cause of Parkinsonian symptoms, where a limit of 0.1 ppm was established. There is also a section on the determination of sulfonate esters, which have the potential to be present in basic drugs that are isolated as sulfonic acid salts. The authors describe a case study in which the potential for formaldehyde remaining as a toxic impurity in an unspecified API was investigated. Formaldehyde was used as a reactant to produce a rather late intermediate (1), which was converted to another isolated intermediate (2) and thence to the final API. A toxicological assessment determined that a specification of NMT 10 ppm formaldehyde in intermediate 2 would ensure acceptable levels in the API. A method was developed and used to analyze several production batches of intermediate 1, giving responses well below 10 ppm. Samples of intermediate 1 were then spiked with formaldehyde at 5000 ppm and converted to intermediate 2, where again the response was well below 10

10.1021/op700190v CCC: $37.00
Published on Web 09/05/2007

ppm. These studies provided a compelling justification for not requiring a routine specification for formaldehyde as a process impurity.

The theme of genotoxic impurities is revisited in the article by U.S. FDA scientists D. Jacobson-Kram and T. McGovern ("Toxicological overview of impurities in pharmaceutical products", pp 38–42). This provides an overview of current official guidelines from the International Conference on Harmonization (ICH) and the European Medicines Agency (EMEA), together with recent recommendations of the Pharmaceutical Research and Manufacturers of America (PhRMA). The ICH guideline Q3A(R) suggests that an impurity is qualified as long as it was present in the API used in preclinical and clinical studies at a level equal to or higher than found in the marketed product. Also, even if the level in the marketed product is higher than what was used during development, the impurity may still be qualified as long as the absolute amount tested in those studies is large compared to the exposure resulting from consumption of the marketed product. The authors are critical of the provision in the ICH guideline that qualification testing of impurities can be performed on the API containing the impurity, instead of on the isolated impurity itself. They find this particularly inappropriate for highly toxic chemicals, citing calculations to show that powerful mutagens such as 9-aminoacridine would not be detected by a typical Ames assay of an API even if they were present around the qualification threshold of 0.15%. The article concludes by noting that ICH guidances do not provide clear recommendations for handling these types of impurities and suggests that this may be rectified by a forthcoming FDA guideline on genotoxic impurities.

Two articles deal specifically with impurities in generic pharmaceuticals, the first from the manufacturer's viewpoint, the second from a regulatory perspective. The article by J. Kovaleski et al. (Teva Pharmaceuticals USA, pp 56–63) is mainly concerned with new impurities that were not part of the impurity profile of the innovator drug product, specifically novel degradation products that arise from subtle differences in the formulation. Some interesting case studies in this area are described. Their main approach to controlling API impurities, however, is to agree appropriate specifications with the API suppliers.

The article by A. K. Basak et al. (FDA Office of Generic Drugs, pp 64–72) discusses the similarities and differences between Abbreviated New Drug Applications (ANDAs) and New Drug Applications (NDAs) and gives an overview of FDA draft guidance documents "ANDAs: Impurities in Drug Substances" and "ANDAs: Impurities in Drug Products". It discusses various approaches to qualifying impurities, the preference being to reduce them below the appropriate qualification thresholds. If this is not possible, an impurity might be qualified by comparative analytical studies, comparing the analytical profiles of the drug substance with those in an already-approved drug (usually but not necessarily the reference listed drug (RLD)), or by reference to appropriate scientific literature. Toxicity tests are the least preferred method and should only be used when impurities cannot be qualified by any of the above procedures. As case studies, the reader is referred to the Model Quality Overall Summaries for various types of drug product available on the agency's website www.fda.gov/cder/ogd.

Other articles in the issue deal with "The role of degradant profiling in active pharmaceutical ingredients and drug products" (K. M. Alsante et al. (Pfizer), pp 29–37) and "Progress in QSAR toxicity screening of pharmaceutical impurities and other FDA regulated products" (J. F. Contrera et al. (FDA), pp 43–55).

More on Genotoxic Impurities

Since the publication of the special *Advanced Drug Delivery Reviews* issue, genotoxic impurities have acquired a significantly higher profile within the industry, with the total recall of Roche's AIDS drug viracept (nelfinavir) and the cancellation of its European marketing authorization by EMEA. (*Chem. Ind*., 9 July 2007; *New York Times*, 23 July 2007) Batches of the drug manufactured at Roche's plant in Switzerland were apparently contaminated with traces of ethyl mesylate arising from reactor cleaning procedures. Supplies of the drug in the USA are not affected, as they are produced by Pfizer in a different facility; however the availability of this important medicine in third world countries has been severely disrupted.

Alkyl mesylates have long been a regulatory concern, as they are reactive, direct-acting, genotoxic and possibly carcinogenic alkylating agents. This means that basic APIs presented as mesylate salts attract increased suspicion from regulators, leading to a reluctance among manufacturers to develop such salt forms. Where they are developed, they are kept well away from lower alcohols. However, an article last year by D. J. Snodin of Parexel Drug Development Consulting (*Regul. Toxicol. Pharmacol.* **2006**, *45*, 79–90) argues that this concern is misplaced, citing mechanistic considerations and experimental data to suggest that alkyl mesylates ought not to be formed and that they would in any case be rapidly decomposed. He argues that the near ubiquitous hydrochloride salts in fact represent a similar or greater potential hazard.

GMP Certificates

Drug and API manufacturers who have been successfully inspected by European regulatory authorities should be issued a GMP certificate no more than 90 days following the inspection. These are for the purpose of confirming to the manufacturer the overall conclusion of an inspection with respect to GMP compliance. In some cases, particularly outside the European Economic Area (EEA), they may be used to support regulatory submissions. However, for European submissions they do not replace the need for an active substance manufacturer to satisfy the applicant's Qualified Person that appropriate GMP standards are maintained. The requirement for the authority to issue a GMP certificate does not extend to manufacturers of Investigational Drug Products, although individual member states may do so at their own discretion. Further details of European Community procedures regarding the issue and update of these certificates can be found in a recent document from EMEA (www.emea.europa.eu/Inspections/docs/CoCP/CoCP_GMP_certificates_procedure.pdf), which comes into effect on 30 September 2007.

Analysis of Regulatory Inspections

The EMEA has published a review and analysis of the findings of regulatory inspections conducted on their behalf in the 10-year period to 2005 (http://www.emea.europa.eu/Inspections/docs/2302207en.pdf). The deficiency database provides

a valuable tool in identifying those practices of manufacturers that are of greatest concern, provides management within EEA inspectorates with a measure of consistency of GMP inspection standards, and can also indicate those areas where further training of inspectors and the provision of technical advice to industry may be of benefit. Observed GMP deficiencies are classified into 40 categories, ranging (in alphabetical order) from "Analytical validation" and "Batch release procedures" to "Warehousing and distribution activities". Data from 435 inspections, comprising 255 preapproval, 132 routine, 29 variations, and 9 "for cause" inspections has been analysed; 119 were inspections of API facilities, mostly conducted in countries outside the EEA. Concerns over documentation (quality systems and procedures) head the list by a significant margin, making up 24% of the 9500 deficiencies recorded. However, for the 2% of deficiencies regarded as "critical", that is, where they may give rise to a product that would be harmful to the patient, this incidence declines to 13%, taking second place to "Design and maintenance of premises" with 16%. In terms of API manufacturing the main critical deficiencies were in the areas of process validation (17.6%) and the potential for microbiological contamination (14.7%). The latter figure may be explained by the fact that, for most of the time period covered, small molecule APIs were not considered to be subject to GMP in the European Union, and so it was mainly biological active substances that were inspected.

Cleaning Limits for API Manufacturing

A novel proposal has recently emerged from an expert group of VFA, the Association of Research-based Pharmaceutical Manufacturers in Germany, and is aired on the European Compliance Academy (ECA) Web site (http://www.gmp-compliance.org/pa4.cgi?ecanews=928&ca=n). The authors observe that, unlike in pharmaceutical production, where residues on the surface of equipment may be 100% carried over into the next product, in API production the carry-over risk is much lower, for technical and chemical manufacturing reasons. Essentially, the major part of any residue is likely to end up in the reaction solvent rather than in the isolated API. They thus propose setting residue limits on API production equipment that would be 10 times higher than the corresponding limit for pharmaceutical production equipment. This, it is argued, would provide equivalent assurance of quality in the final product. API equipment would still be subject to the constraints that it must have no visible residue and that the acceptable residue must never exceed 1000 ppm. Apparatus and equipment used for physical end-treatments such as drying, mixing, or milling would remain subject to the more stringent pharmaceutical requirements. Comments on this proposal to the Web site are invited.

Pharmaceutical Quality Systems

The Draft ICH Consensus Guideline "Q10: Pharmaceutical Quality Systems" was released for consultation in May 2007, complementing the Q8 and Q9 guidelines that have appeared over the previous few years. (www.ich.org/LOB/media/MEDIA3917.pdf) This document is somewhat shorter (15 pages) than the equivalent guideline from FDA (28 pages), which was discussed in the previous "Regulatory Highlights" section (*Org. Process Res. Dev.* **2007**, *11*, 314–315). It also has a subtly different focus. Whereas the FDA guideline closely follows the ISO9001 model, Q10 focusses on two broad aspects, namely, Management Responsibility and Continual Improvement. The largest section is concerned with the continual improvement of process performance and product quality, but continual improvement of the pharmaceutical quality system itself is also emphasised. The guideline recognises that each product will have a lifecycle, of which four distinct lifecycle stages are envisaged: pharmaceutical development, technology transfer, manufacturing, and product discontinuation. A series of tables compares and contrasts the aspects of the quality management system appropriate to the different lifecycle stages. For example, in the area of Change Management, at the development stage "Change is an inherent part of the development process and should be documented; the formality of the change management process should increase as the product moves through development." Even in the Product Discontinuation stage "Any changes should go through an appropriate change management system." Unlike the FDA guideline, it does not highlight those areas where GMP requirements and Quality Management desiderata coincide.

Like the FDA guideline, Q10 is not intended to create any new expectations beyond current regulatory requirements, and content that is additional to current GMP requirements is optional. There is no intention of requiring external certification of any company's system (e.g., along ISO9001 lines) or for quality manuals to be submitted as part of any official applications. Although GMP implicitly requires manufacturers to have a quality management system of some sort, it need not correspond to the Q10 model.

Q10 has now reached Step 2 of the ICH process, which means it is open for public comment (until November 2007) and potential revision. Until this stage, it has mainly had input from the industry side, whereas in the next phase the regulatory authorities will have more input.

The theme of "Quality systems apropriate for pharmaceutical development operations" is picked up by V. Mathews (Eli Lilly) in an article for *American Pharmaceutical Review* (May/June 2007). Whereas the cGMP regulations and guidelines do not strictly apply to the preclinical development phase, he draws attention to the increasing regulatory emphasis on pharmaceutical development and on the product development information generated during this phase. EU authorities in particular have requirements concerning the quality of the data submitted with an application; for example, they may not accept supporting registration information unless it has been generated on instrumentation that has been suitably calibrated or qualified. The author contends that it makes good business sense for companies to develop a robust quality system for pharmaceutical development areas, although a full cGMP system would likely be counterproductive. He discusses what quality system would make sense from business, regulatory and patient safety perspectives, taking FDA's six-system quality structure (Quality Management, Materials, Facilities Utilities and Equipment, Production, Laboratory, Packaging and Labeling) as his framework. Recognizing the importance of the documentation produced in pharmaceutical development areas, he recommends there should be clear requirements (e.g., SOPs) stated for good documentation practices, use of notebooks, logbooks and data

binders, requirements regarding the issuing of reports, and record retention.

Commissioning and Qualification

The May/June 2007 issue of *Pharmaceutical Engineering* (Vol. 27, No 3) contains a number of articles on the theme of Commissioning and Qualification (C&Q), which together provide a useful overview of regulatory expectations in this area together with the technologies available to assist with it.

In their article "Testing, commissioning, qualification and acceptance of biopharmaceutical skids" (pp 8–24), R. F. Greenwald and T. Smit outline details of a suggested Equipment Acceptance Chain (EAC), comprising in chronological order Factory Inspection Testing (FAT), Site Acceptance Testing (SAT), Start-Up and Commissioning, and Installation Qualification, the authors having identified these as steps endemic to all projects. Checklists and matrices are provided for each stage. One useful aspect of SAT is that mechanical deficiencies detected at this stage can be easily rectified without going through the elaborate change control procedures that would be invoked if the problem was uncovered only at the later Validation stage. Although the article focusses on biopharmacetuical skids, defined as "any packaged assembly of equipment, piping, controls, and instrumentation designed to complete one step or unit operation in a process", it contains useful points to consider for any piece of equipment to be used in API processing.

The following article by J. Davey (pp 26–34) addresses the difficult issue of qualifying older equipment, where the existing documentation set would not meet current industry expectations. The specific focus of the article is on packaging machinery, but the concepts will have wider applicability. The author describes a risk-based approach, the key to the method being "to reverse engineer the documentation using the machine as the starting point". The machine is divided into small parts or assemblies, the function of each part is described and subjected to a Failure Mode and Effects Analysis (FMEA). Criticality classifications are assigned according to whether a failure of the part would impact product sterility, product efficacy, product appearance and/or operational efficiency. This then allows an appropriate control method to be chosen. For the really critical parts the control may amount to a full validation, but in some cases the inclusion of an appropriate operational instruction may suffice. The author recommends the completion of a traceability matrix to document the exercise.

In his article "Integration of commissioning and qualification with other phases of the project lifecycle" (pp 36–46) J. Devlin emphasises the importance of involving C&Q personnel from the earliest planning stages of an engineering project and provides a number of examples from his own experience where lack of advance planning led to considerable delays in commissioning and consequent cost overruns. In one case, a decision was taken not to construct a permanent gantry around high-level equipment, as a mobile platform would be slightly cheaper and would suffice for the envisaged routine maintenance. They failed to appreciate that more frequent access would be required during the commissioning phase, for which expensive temporary scaffolding had to be erected.

Two further articles on the same topic appear as "on-line exclusives". "Effective commissioning strategy" (C. Ward, S. Anisko, J. Oberlag, and M. B. Davis) discusses the important functions of commissioning, how to structure a successful commissioning team, how to define a commissioning master plan, the importance of design documentation and good documentation practices, and the integration of commissioning documentation with qualification and validation documentation. An early System Impact Assessment identifies systems that have "direct impact" on product quality and therefore require both commissioning and qualification/validation activities; whereas those systems having only "indirect impact" on product quality require only commissioning. While commissioning is generally regarded as an engineering activity, validation challenges the system from a quality perspective. The authors propose an approach that integrates and thus streamlines both activities, ensuring good communication between the different groups throughout the project, and avoiding unnecessary duplication of tasks.

"Risk-based equipment qualification: A user/supplier cooperative approach" is a contribution from members of the Equipment Validation Workgroup of GAMP Italia. They note that in most cases pharmaceutical users are just buying and installing standard pieces of equipment yet expend significant human efforts and financial resources in C&Q activities that are sometimes excessive and redundant, quite often merely repeating the verifications already performed by the manufacturer. They outline a possible risk-based approach, taking account of the safety aspects (operator and environment) and business aspects of risk as well as product quality aspects (GxP). The approach depends on close user/supplier cooperation, with the user drawing up a generic User Requirements Specification (URS) for the equipment, which can assist in identifying appropriate suppliers and designs. The supplier(s) then use the URS to identify which requirements can be satisfied with a standard basic element of their model, which can be satisfied with an optional element, which involve redesign of an existing element and which require design of an entirely new element; the resulting C&Q effort on the user's part would then increase accordingly. A number of flowcharts and block diagrams are provided to describe the procedure in greater detail. This article has subsequently reappeared in the July/August print edition of the magazine (Vol. 27/4, pp 50–58).

PQRI Recommendations on Particle Size Analysis

Particle size and particle size distribution (PSD) are critical quality attributes of APIs intended for oral administration; thus the use of appropriate analytical methods to quantify these attributes is of paramount importance. A mini-review of this area from the Product Quality Research Institute (PQRI) has recently appeared (Snorek, S. M.; Bauer, J. F.; Chidambaram, N. *J. Pharm. Sci.* **2007**, *96*, 1451–1467). PQRI is a collaborative process involving scientists from FDA, the pharmaceutical industry (e.g., Abbott, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Schering-Plough) and academia; thus, this document may be taken as a "semi-official" guideline. A diverse array of analytical technologies is available in this area, including acoustic spectroscopy, chord-length measurement, disc centrifugation, dynamic image analysis, elliptically polarized light scattering, electrical sensing zone, hydrodynamic chromatography, laser diffraction, light obscuration, photon correlation spectroscopy, polarization intensity

differential scattering, sieve analysis, scanning electron microscopy, optical microscopy and time of flight. The analytical method chosen will depend on the size range and the shape of the particles encountered, and so different methods are appropriate for different products. The recommendation is to make a preliminary examination of a sample by manual optical microscopy, using a series of magnifications, so that an overall qualitative assessment of size and shape may be made. Scanning electron microscopy may also be beneficial in some cases to provide additional information about the third dimension or about the presence of submicrometer particles. Thereafter, a more practical (rapid) technique may be chosen appropriate for the material being analyzed and which provides PSD results that are consistent with the information obtained by microscopic examination. The review offers advice on approaches to analysis during preclinical, clinical and manufacturing phases of a project. It lists the national and international standards (ISO, BS, and ASTM) associated with each method, along with available reference materials. It discusses aspects of method validation and approaches to setting specifications and acceptance criteria. Numerous references to original literature are given, making this a concise yet comprehensive source of information for analytical chemists engaged in this area.

Post-Approval Changes for Veterinary Drugs

Animal drugs tend to have a lower profile in the industry than human drugs, but they nonetheless are subject to a similar level of regulatory oversight. In May, FDA's Center for Veterinary Medicine (CVM) issued new guidance on Chemistry, Manufacturing and Control (CMC) changes to an approved New Animal Drug Application (NADA) or Abbreviated New Animal Drug Application (ANADA) (www.fda.gov/cvm/Guidance/dguide83.pdf). The recommendations are broadly in line with those of BACPAC, FDA's equivalent guideline for human APIs (currently withdrawn from operation). All changes in each condition established in an approved application must be notified to FDA. Applicants must make an assessment of the effect of each proposed change on the safety, quality or purity of the animal drug, and classify it as either *major*, *moderate* or *minor* according to its potential to have an adverse effect. Major changes should be notified to FDA via a Prior Approval Supplement to the application; moderate changes require a Change Being Effected (in 30 Days) Supplement; minor changes only require notification in the next annual report. The guideline offers detailed advice on how to classify various changes in manufacturing site, manufacturing process, specifications, container closure systems and other miscellaneous changes. Unlike BACPAC, however, it does not suggest what supporting documentation should be submitted, or what specific information should be developed to justify the change. Applicants are instead advised to consult "all relevant FDA guidance documents" for appropriate recommendations.

GMP for Dietary Supplements

On June 22, FDA officials announced new standards for manufacturing and testing all dietary supplements applicable to domestic and foreign manufacturers (*Chem. Eng. News* **2007**, July 2, 6). The full text of the new final rule (ca. 500 pages) is published in the Federal Register as 21 CFR part 111 and takes effect for large plants in June 2008 (June 2010 for smaller companies). The standards lay out practices to ensure quality during manufacturing, labeling, and storage of dietary supplements, listing requirements for quality-control procedures, the design of manufacturing plants, and the testing of ingredients and final products of this $21 billion industry. In principle, testing must now be performed on all lots of all ingredients used in the product, but the FDA has also proposed a mechanism whereby manufacturers can apply for relief from the 100% testing requirement by submitting evidence of appropriate vendor qualification. At the moment it appears that the new GMP rules apply only to dietary supplement products and not to the dietary ingredients themselves. However, there is bound to be a knock-on effect, with ingredient manufacturers coming under increasing customer pressure to improve quality and consistency. A fuller discussion of this appears in *Washington Report, Pharm. Technol.*, August 2007.

FDA Final Guidance on Pharmaceutical Solid Polymorphism

This guideline, issued July 2007, is primarily aimed at generic manufacturers, and provides advice on polymorphism issues associated with the CMC section of an ANDA (http://www.fda.gov/cder/guidance/7590fnl.pdf). The guideline has been available as a discussion draft since December 2004, and the finalised version is essentially the same as this. One subtle difference is the suggestion that XRPD could be used "to provide unequivocal proof of polymorphism", whereas in the draft the role of XRPD was only "to support the existence of polymorphs", the main burden of proof coming from single crystal XRD. The final version also refers extensively to measurements of "apparent solubility", where the draft spoke simply of "solubility", recognizing that, for metastable forms, the true thermodynamic solubility may not be easily measurable. The only other difference is to remove a reference to crystalline habit in assessing pharmaceutical processing steps. The main thrust of the guideline remains that a generic API presented as a different polymorph (or solvate/hydrate/amorphous form) from that in the reference listed drug is regarded as *the same* API for ANDA purposes, but that the generic manufacturer should assess the impact of any change in crystalline form on solubility, dissolution, bioavailability and bioequivalence, as well as on manufacturability and stability of the drug product. Only those polymorphic forms that are likely to occur during manufacture or storage of the drug substance or drug product need be considered. If all polymorphs are known to be highly soluble, as defined by the Biopharmaceutics Classification System (BCS) criteria, then a specification for polymorphic content is unlikely to be required in either drug substance or drug product. However, if solubility/dissolution is a limiting factor for bioavailability, then appropriate specifications for the drug substance should be set. Only in rare cases would polymorphic form characterization in the drug product be recommended, as drug product performance testing (e.g., dissolution testing) would generally provide adequate control of polymorph ratio changes for poorly soluble drugs.

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