Organic Process Research & Development

Regulatory Highlights

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Regulatory Highlights for February–July 2012

■ ICH GUIDANCE ON DRUG SUBSTANCES FINALIZED

Last year saw the publication of the draft (step 2) version of Q11, the International Conference on Harmonisation's (ICH's) *Guideline on the Development and Manufacture of Drug Substances*; this was summarised previously (*Org. Process Res. Dev.* **2011**, *15*, 970). Now, almost one year later, this guideline has been finalized (step 4), and only awaits formal adoption by the regional regulatory authorities before becoming fully operational. The finalized text (available from the Web site www.ich.org) is substantially the same as the draft version with only a few subtle changes.

The section on Design Space (3.1.6) has been extended—mainly to emphasise certain points about Design Spaces already established in the Q8 guideline (*Pharmaceutical Development*). There is also an additional paragraph concerning design space for biotechnology/biological drug substances. Here, factors such as process variability and drug substance complexity may increase the level of residual risk remaining after approval of the design space, and thus an applicant may be required to provide proposals on how movements within the design space will be managed post approval.

According to the new version, "for biotechnological/biological drug substances, the reason for each significant change (to the manufacturing process) should be explained" as part of the submission of Manufacturing Process Development Information (section 3.2) "... together with an assessment of its potential to impact the quality of the drug substance". In the draft version this requirement appeared to apply to all drug substances.

In the section on Considerations in Developing a Control Strategy (6.1.2) a distinction is now drawn between the critical control attributes (CQAs) of the drug substance and its specification. Not all CQAs need to be included in the specification; some may be ensured through upstream controls such as in-process testing, material attributes, or process analytical technology (PAT).

For a more detailed discussion of the guideline, see the article by Angie Drakulich (*Pharm. Technol.* **2012**, *36*(2), 34–37).

■ "BIOSIMILAR" DRUG APPLICATIONS

This year has seen the publication on both sides of the Atlantic of new guidelines covering "biosimilar" drug products, which are generic versions of previously approved biological drugs. Unlike small-molecule drugs whose structure can usually be completely defined and entirely reproduced, biological agents such as proteins are typically more complex so that a generic copy is unlikely to be entirely identical to the original product. This has made it difficult for generic versions to gain approval without going through the same costly testing procedures as the originator drug.

The European Medicines Agency (EMA) has operated a system for "biosimilar" approvals since 2005, and has now (May 2012) proposed a revision to their original guideline (EMA/CHMP/BWP/247713/2012). In the United States, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) for the first time created an abbreviated licensure pathway for "biosimilar" products there. The Food and Drug Administration (FDA) has now (February 2012) published a set of three draft guidelines detailing what studies should be undertaken when using this abbreviated process. Unsurprisingly, both agencies require considerably more testing than would be the case for a small-molecule generic, with assessment of comparability in biological activity as well as in physicochemical properties.

The EMA guideline specifically applies to products containing recombinant DNA-derived proteins and derivatives, but the principles could also apply to other biological products on a case-by-case basis. The FDA guidelines cover all protein products. Both agencies have essentially the same approach, but the FDA guidelines provide much greater detail. Both require the applicant to define a reference biological product which has already been approved in the respective countries or regions, as the application will rely in part on the scientific knowledge gained from that reference product. The FDA guidance also provides clear definitions for "proteins", which are distinguished from "chemically synthesized polypeptides", the latter being approved via the usual ANDA process.

"Biosimilarity" is defined by the FDA to mean that the biological product is highly similar to the reference product (although there may be minor differences in clinically inactive components) and that there are no clinically meaningful differences in terms of safety, purity, and potency. To meet the higher standard of "interchangeability," an applicant must also demonstrate that the product produces the same clinical result as the reference product in any given patient and that the risk to a patient in terms of safety or diminished efficacy of switching between the two products is not greater than the risk of using just the reference product.

Both agencies agree that the approval of a "biosimilar" product is fundamentally different from the approval of manufacturing process changes to the original licensed product, although these also normally require a demonstration of product comparability before and after the change. The applicant for a biosimilar product is likely to have no direct knowledge of the original manufacturing process for the reference product and will likely have developed a different process (e.g., different cell line, raw materials, equipment, processes, process controls, acceptance criteria).

FDA's first guideline, "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product", discusses nine factors to be considered in assessing whether the products are highly similar:

(1) expression system
(2) manufacturing process
(3) assessment of physicochemical properties
(4) functional activities
(5) receptor binding and immunochemical properties

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(6) impurities
(7) reference product and reference standards
(8) finished drug product
(9) stability

Product characterization studies should be performed on the most downstream intermediate best suited for the analytical procedures used. The attributes evaluated should then be stable through any further processing steps. For these reasons, characterization studies are often performed on bulk drug substance. However, if this is reformulated and/or exposed to new materials in the finished dosage form, the impact of these changes should also be considered.

The second guideline details the "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product". It recommends that sponsors use a stepwise approach to develop the evidence needed to demonstrate biosimilarity. This approach should comprise the following:

(1) Extensive structural and functional characterization of both the proposed product and the reference product. "The more comprehensive and robust the comparative structural and functional characterization, the more useful this will be in determining what additional studies (animal and/or clinical) may be needed."
(2) Consideration of the role of animal data in assessing toxicity, biosimilarity and immunogenicity.
(3) Conducting comparative human pharmacokinetic (PK) studies and perhaps pharmacodynamic (PD) studies.
(4) Comparison of the clinical immunogenicity of the two products.
(5) If there are residual uncertainties about the biosimilarity of the two products, the sponsor should then consider what comparative clinical safety and effectiveness data may be adequate.

The FDA encourages sponsors to consult extensively with them after completion of comparative structural and functional analysis (before finalizing the clinical program) and throughout development as needed. The agency intends to use a risk-based *totality of the evidence* approach to evaluate all available data and information submitted.

The third guideline provides "Questions and Answers Regarding Implementation of the BPCI Act of 2009". These are grouped in three categories: Biosimilarity or Interchangeability (15 questions), Provisions Related to Requirement to Submit a BLA for a "Biological Product" (2 questions), and Exclusivity (2 questions).

The BPCI Act also includes a 12-year exclusivity period from the date of the first licensure of the reference product, during which no "biosimilar" application referencing that product can be approved, and a 4-year exclusivity period during which no "biosimilar" application referencing that product can be submitted. An exclusivity period is also granted for the first biological product determined to be *interchangeable* with the reference product for any condition of use, although this period is not specified. Similarly, an exclusivity period (also unspecified) can be granted to certain biological products for which pediatric studies are conducted.

A potential difficulty for manufacturers arises from legislative requirements in both Europe and America that the reference product chosen for the comparability studies must previously have been granted a license *in that country/region*. This means that two complete sets of testing may need to be undertaken for the "biosimilar" to gain approval from both agencies. See "Biosimilar developers face a reference product dilemma." (Greer, F. *Pharm. Technol.* **2012**, *35*(4), 81−82).

The guidance documents are available from the respective Web sites (www.ema.org and www.fda.org/cder). For further discussion of their background and content, see the article by Amy Ritter ("Looking for fingerprints: bioanalytical characterization of biosimilars", *Pharm. Technol.* **2012**, *35*(4), 36−41).

DOCUMENTATION REQUIREMENTS FOR CLINICAL BIOLOGICAL DRUGS

The EMA has also released a new "Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials", which is effective since April 2012. This details which data should be submitted with the request for a clinical trial authorization in the Investigational Medicinal Product Dossier (IMPD). The information should be provided in the usual Common Technical Document (CTD) format (Manufacture, Characterization, Control of the Active Substance/IMP, Reference standards or materials, Container closure system, Stability) for both the active substance and the finished product. Reference to an Active Substance Master File or a Certificate of Suitability (CEP) is not acceptable for biological/biotechnological active substances.

Manufacturing processes and their control strategies are continuously being improved and optimized, especially during the development phase and early phases of clinical trials. These improvements and optimizations are considered by the agency as normal development work and should be appropriately described in the submitted dossier. Changes to the manufacturing process and controls during development should be summarized, and the rationale for changes should be presented in order to establish an appropriate link between prechange and postchange batches. Process modifications may require adaptation of in-process and release tests, and thus these tests and corresponding acceptance criteria should be reconsidered when changes are introduced.

Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to ensure that the change would not have an adverse impact on clinical characteristics of the product. This exercise should normally follow a stepwise approach, including comparison of quality attributes of the active substance and relevant intermediates, using suitable analytical methods. Where the manufacturer's accumulated experience and other relevant information are not sufficient to assess the risk introduced by the change, or if a potential risk to the patients is anticipated, a comparability exercise based only on quality considerations may not be sufficient. The guideline contains an appendix providing a "non-exhaustive" list of changes which would generally be regarded as "substantial". During early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product. For the "first in human" clinical trial, it is recommended to use investigational product representative of the material used in the nonclinical studies.

During the clinical trial phases, where process validation data are incomplete, more reliance is placed on quality attributes of the active substance in demonstrating pharmaceutical quality, product consistency, and comparability after process changes. Therefore, these quality attributes should not just be limited to the tests included in the specification for which preliminary acceptance criteria have been set.

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As knowledge and experience increases, the addition or removal of parameters and modification of analytical methods may be necessary. Specifications and acceptance criteria set for previous trials should be reviewed and, where appropriate, adjusted to the current stage of development.

Validation of analytical procedures during clinical development is seen as an evolving process. For phase I clinical trials, the suitability of the analytical methods used should be "confirmed", while for later trials the suitability should be "demonstrated". It is not clear what distinction is intended here, but it is not necessary to provide a full validation report.

The complete guideline is available from the EMA Web site (www.ema.org).

NEW GUIDELINE ON PROCESS VALIDATION

The EMA has also released a new draft guideline on process validation, which is open for consultation until the end of October 2012. (EMA/CHMP/CVMP/QWP/70278/2012-Rev1). This replaces the agency's previous guideline on process validation, and brings it into line with the ICH Q8, -Q9, and -Q10 documents. It is not directly relevant to the manufacture of the active substance or other starting materials, although it may contain information useful for such activities. It is intended to apply to medicinal products for human and veterinary use. The fundamental principles described are applicable to biological products, but these should be considered on a case-by-case basis.

The main innovation in the revised guideline is the possibility to implement continuous process verification (CPV) if an "enhanced" approach to pharmaceutical development has been employed or if substantial knowledge and understanding has been gained through historical data and manufacturing experience. In this sense it follows the path taken by the FDA in their recent validation guideline revision (see *Org. Process. Res. Dev.* **2009**, *13*, 391; *Org. Process. Res. Dev.* **2011**, *15*, 325); however, here CPV is presented as an alternative approach, and it is emphasized that process validation can still be performed in the traditional way if desired. A "hybrid "approach—with some steps validated traditionally and others by CPV—is also acceptable. However, regardless of the validation approach initially employed, companies should continuously monitor product quality to ensure a state of control is maintained throughout the commercial part of the product lifecycle. It is recognized that validation studies may not be complete at the time of the submission of the product application. In this case the process validation scheme should provided; an annex lists the minimum information required here. Following completion of the scheme, a full report should be generated and made available for inspection.

NEW PROGRAMME FOR JOINT INSPECTIONS OF API MANUFACTURING

With the majority of active ingredients for pharmaceutical products now being sourced from low-cost countries such as China, it has become increasingly difficult for western authorities to maintain the degree of vigilance over production quality which their public expect.

The EMA has now released a "Programme to rationalize international GMP inspections of API manufacturers" (EMA/INS/GMP/129953/2012). This arises from a pilot exercise on international collaboration conducted between 2008 and 2010 involving authorities from Australia, Europe, and the United States. The purpose of the programme was to foster cooperation and mutual confidence between participating regulators through better communication and exchange of information on inspection planning. There is now a desire to extend this co-operation to other authorities which fulfill certain requirements, such as maintaining a functioning API inspectorate, a routine API inspection programme, an ability and willingness to participate in joint inspections and to provide inspection reports. However, other organizations, which may not fulfill all the listed criteria may be accepted as partners and be given access to information arising from the programme for the benefit of public health globally. The overall objective is to help to better distribute inspection capacity, allowing more sites to be monitored and reducing unnecessary duplication.

The programme envisages that joint inspection teams will comprise representatives of two or three participating authorities. However, other organizations—not involved in the inspection teams—may also have input into the planning of the inspections, for example by requesting that the scope be expanded to cover areas of their particular interest. The reference GMP standard for the inspections will be ICH Q7. For sterile active substances (not covered by Q7), additional regional guidelines will be followed as appropriate. It is expected that the inspection team's findings/observations and the preliminary conclusions of the inspection will be jointly agreed on site. Unless otherwise agreed, separate final inspection reports will be prepared to close out the inspection process, one by each of the inspecting authorities. In the case of a negative inspection result, the inspecting authorities will liaise with each other to ensure a common understanding and, if possible, an agreed conclusion before closing out the inspection process. Each participating authority is responsible for any follow-up actions within their territory on the basis of the commonly agreed outcome.

GMPS FOR EARLY STAGE DEVELOPMENT

The question of how Good Manufacturing Practice (GMP) guidelines should be applied during early stages of development continues to be discussed across the industry and is now the subject of a new initiative by the International Consortium on Innovation and Quality in Pharmaceutical Development (IQ Consortium)—an association of pharmaceutical and biotechnology companies aiming to advance innovation and quality in the development of pharmaceuticals. They have assembled a multidisciplinary team (GMPs in Early Development Working Group) to explore and define common industry approaches and to come up with suggestions for a harmonized approach. Their initial thoughts and conclusions are summarized in *Pharm. Technol.* **2012**, *36*(6), 54−58.

From an industry perspective, it is common to consider the "early" phase of development as covering phases 1 and 2a clinical studies. During this phase, there is a high rate of product attrition and a high probability for intentionally introducing change into synthetic processes, dosage forms, analytical methods, and specifications. The quality system implemented during this early phase should take into account that these changes and adjustments are intrinsic to the work being performed prior to the determination of the final process and validation of the analytical methods during later stages of development.

FDA guidance is already available on GMP requirements for phase 1 materials. (See *Org. Process. Res. Dev.* **2008**, *12*, 817.)

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Because many aspects of phase 2a clinical studies are similar in their scope and expectations, the working group feels there is an opportunity to extend this guidance across all early phase studies. Because products and processes are less well understood in the early phases of development, activities should focus on accumulating the appropriate knowledge to adequately ensure patient safety. Focusing on this area should ensure that beneficial therapies reach the clinic in an optimum time scale with minimal safety concerns.

A follow-up article (*Pharm. Technol.* **2012**, *36*(7), 76−84) describes the working group's approach to the subject of Analytical Method Validation. Their assessment has uncovered the need to differentiate the terms "validation" and "qualification". Method qualification is based on the type, intended purpose, and scientific understanding of the type of method in use. Although not used for GMP release of clinical materials, qualified methods are reliable experimental methods that may be used for characterization work such as reference standards and the scientific prediction of shelf life. For example, in early development it would be sufficient for methods used for in-process testing to be qualified, whereas those methods used for release testing and for stability determination would be more fully validated.

In early development, a major purpose of analytical methods is to determine the potency of APIs and drug products to ensure that the correct dose is delivered in the clinic. Methods should also indicate stability, identify impurities and degradants, and allow characterization of key attributes. In the later stages, when processes are locked and need to be transferred to worldwide manufacturing facilities, methods need to be cost-effective, operationally viable, and suitably robust such that the methods will perform consistently. irrespective of where they are executed.

The authors advocate that the same amount of rigorous and extensive method-validation experiments, as described in ICH Q2, "Analytical Validation", is not needed for methods used to support early stage drug development. For example, parameters involving interlaboratory studies (i.e., intermediate precision, reproducibility, and robustness) are not typically performed during early phase development, being replaced by appropriate method-transfer assessments and verified by system suitability requirements. Because of changes in synthetic routes and formulations, the impurities and degradation products formed may change during development. Accordingly, related substances are often determined using area percentage by assuming that the relative response factors are similar to that of the API. As a result, extensive studies to demonstrate mass balance are typically not conducted during early development.

Detailed recommendations are provided for each aspect of method validation (specificity, accuracy, precision, limit of detection, limit of quantitation, linearity, range, robustness) according to the nature of the test (identification, assay, impurity, physical tests) for both early- and late phase development. These recommendations are also neatly summarized in a matrix form.

In subsequent months the magazine will publish additional articles from the working group detailing their recommendations for Specifications, Drug Product Manufacturing, and Stability.

■ OTHER ARTICLES OF INTEREST

"Evaluating Impurities in Drugs", Wadkar, K. R.; et al. *Pharm. Technol.* **2012**, *36*(2), 46−51; *Pharm. Technol.* **2012**, *36*(3), 58−72; *Pharm. Technol.* **2012**, *36*(4), 76−86. This three-part series is contributed by a group of analytical scientists at Neuland Laboratories in Hyderabad. Part I discusses the multivarious origins and sources of impurities, mostly concentrating on aspects of the chemical synthesis. Part II concentrates on chiral and polymorphic impurities, whereas Part III discusses genotoxic and stability impurities. The articles are illustrated with numerous examples, and over 150 references are provided.

"Identifying Counterfeit Medicines with Industry-Suitable Technologies", Jordan, F.; Kutter, M. *Pharm. Eng.* **2012**, *32*(3). This article presents the latest pharmaceutical anti-counterfeit technology developments and describes different criteria to help select those that best safeguard patient safety and the integrity of pharmaceutical brands. The same issue of the magazine contains several other articles on the same topic. In "Risk and Reputation: A Science and Risk-Based Approach to Brand Protection", G. E. Ritchie, et al. present a novel approach which involves intentionally varying the product composition from one batch to another (within regulatorily acceptable limits). This generates a unique NIR spectrum for each batch, which can be used as both a quality and a security measure. In "The Case Against Serialization", J. Robinson discusses the growing legislative requirements in various countries for unique package identifiers such as radio frequency ID tags and 2D bar codes and argues such measures are likely to be costly and ineffective.

"Product Quality Lifecycle Implementation", Davis, B.; et al. *Pharm. Technol.* **2012**, *36*(4), 120−127. This article provides an overview of a new Guide Series from the International Society for Pharmaceutical Engineering (ISPE). Parts 1 and 2 are currently available to purchase from the Web site, www.ispe.org. They summarise enhanced QbD approaches to development and discuss the issues of criticality, design space, and control strategy. Part 2 consists of a detailed case study.

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