Organic Process Research & Development

REGULATORY HIGHLIGHTS

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Regulatory Highlights for February–July 2011

NEW GUIDELINE ON DRUG SUBSTANCES

The most significant regulatory development during the past six months is the appearance of the long-awaited draft Q11 guideline from the International Conference on Harmonization (ICH) on the Development and Manufacture of Drug Substances. This complements the earlier Q8 guideline (Pharmaceutical Development) where the main focus was on finished drug products, although many of its concepts have been taken on board by active ingredient (API) manufacturers as well. The new guideline is divided into chapters covering:

- Manufacturing process development,
- Description of manufacturing process and process controls,
- Selection of starting materials and source materials,
- Control strategy,
- Process validation/evaluation,
- Submission of manufacturing process development and related information in Common Technical Document format, and
- Lifecycle management.

The document concludes with five detailed illustrative examples of how the principles outlined might be applied. The guideline applies to biotech-derived APIs as well as small molecules; indeed the majority of examples cited relate to biotech processes. The focus is mainly on the development of commercial manufacturing processes, but the principles presented are "important to consider" during investigational stages also.

In common with the Q8 guideline, Q11 offers a choice of two approaches to process development: the traditional approach and an enhanced "Quality by Design" approach — both of which are equally acceptable, although the latter potentially offers greater flexibility in manufacturing. "In a traditional approach, set points and operating ranges for process parameters are defined and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and more extensive scientific knowledge are used to select process parameters and unit operations that impact critical quality attributes (CQAs) for evaluation in further studies to establish any design space(s) and control strategies applicable over the lifecycle of the drug substance."

At a minimum, manufacturers should identify potential critical quality attributes (CQAs) of the API, define an appropriate manufacturing process, and determine a control strategy to ensure attainment of the CQAs. An enhanced approach would additionally involve identifying the material attributes and process parameters which can impact the CQAs and determining the functional relationships that link these. An example is given of setting process parameters to control the level of a hydrolysis impurity in a drug substance intermediate. Through experimentation, the water content of the precursor and the time of reflux during workup were identified as the critical parameters. A traditional control strategy would simply define limits for these (e.g., NMT 1.0% water in the precursor and NMT 4 h reflux). An enhanced approach could deploy an understanding of the second-order kinetics of the hydrolysis side reaction to elucidate the interaction of these parameters, as illustrated in Figure 1.

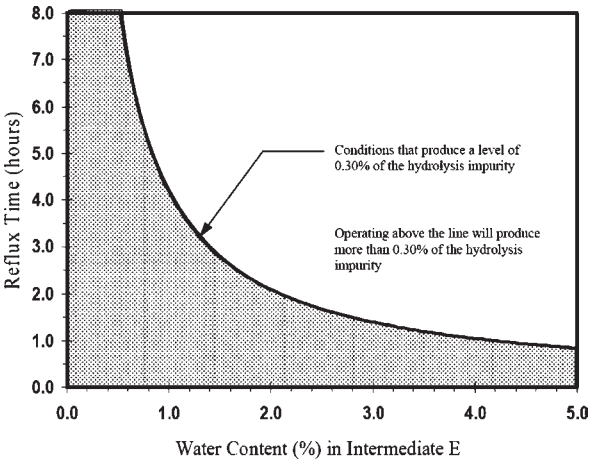

Figure 1. Interdependence of reflux time and water content in the formation of hydrolysis impurity.

Here the shaded region below the line could be defined as a design space; process changes within this region could then be handled entirely within the company's internal change control procedures, with no need to file regulatory supplements.

Elements of a control strategy could include

- controls on raw material attributes,
- controls implicit in the design of the manufacturing process, such as the order of addition of reagents,
- in-process controls, and
- controls on release of the final drug substance.

Particular emphasis is given to the selection of the API starting material(s), which marks the point(s) in the chemical synthesis where the Good Manufacturing Practice (GMP) provisions are expected to be applied. Interestingly, the recommendations here closely resemble those made by the US Food and Drug Administration (FDA) in a draft 2004 guideline which was subsequently withdrawn. Manufacturers should provide a justification for the assignment of any starting material which is not a commercial commodity with a significant nonpharmaceutical market; compounds produced by custom synthesis are not regarded as commercial commodities in this sense. Justifications for a noncommercial starting material could include

- its sequential position in the synthesis, with earlier intermediates being inherently more acceptable,
- its influence on the impurity profile of the final API, where intermediates which contribute significant residues are less likely to be acceptable — even when such residues are below their specification limit,
- the degree of chemical and analytical characterisation of the compound, and

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- a starting material should always be an isolated and purified compound, and should constitute a significant structural fragment of the API.

Commonly available chemicals used to create salts, esters, or other simple derivatives are not considered starting materials, but rather reagents.

However, these recommendations should be considered as a whole, rather than each being applied in isolation. A hypothetical example is given of a six-stage synthesis of a chiral API starting from a commercial nonchiral precursor. The stereogenic centre is introduced in the first step, generating a small amount of the wrong enantiomer impurity, which ultimately generates some of the wrong enantiomer of the final API. But it is accepted that in this case it is unnecessary to designate such an early intermediate as the starting material, since the enantiomeric impurity can be well-controlled by a specification on intermediate 3. Taking the full facts and understanding of the processes into consideration, intermediate 3 is recommended as the regulatory starting material.

This draft guideline has now reached step 2 of the ICH process; i.e. it has been agreed upon by the expert working group and is transmitted to the regulatory authorities in the three regions (USA, Europe, Japan) for internal and external consultation. It is available from the Web site www.ich.org.

IMPLEMENTATION OF QUALITY GUIDELINES

Subsequently, ICH has also published an official "Points to Consider" document with recommendations for the implementation of their earlier guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality Systems) (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtC_16_June_2011.pdf). The new document is based on questions that have been raised during workshop sessions organised by ICH in the three regions. It mainly deals with three issues:

- criticality of quality attributes and process parameters,
- control strategy, and
- level of documentation in enhanced (QbD) submissions.

Further points to consider addressing the role of modelling in QbD and on design space are promised for the future.

NEW LIMITS FOR RESIDUAL CUMENE

ICH are also proposing a minor revision to their Q3C guideline for residual solvents in drug substances. As a result of new carcinogenicity studies in rodents, it is now recommended that cumene be moved from Class 3 (low-toxicity solvent) to Class 2 (toxic solvent) with a permitted daily exposure of 0.7 mg/day. The appropriate concentration limit would be 70 ppm. Details of the calculations are given in the draft guideline, available from the ICH Web site.

NEW GUIDELINE ON β-LACTAM FACILITIES

The FDA has contributed to the ongoing discussion on dedicated facilities with a new draft guideline: "Non-Penicillin Beta-Lactam Risk Assessment: A CGMP Framework". It has long been recognized that penicillin drugs must be manufactured and handled in dedicated facilities — a specific requirement of the cGMP regulations. The requirements for other potentially sensitizing drugs, though, have been more ambiguous. The new guideline divides β-lactam antibiotics into five classes: penicillins, cephalosporins, penems, carbacephems, and monobactams. It recommends that the manufacture of any one class be physically separated from the manufacture of any other class, as well as from the manufacture of non-β-lactam products. Manufacturing that is restricted to one specific class of β-lactam compound would generally not mandate separate facilities and air handling systems for each separate compound, and could permit production campaigning and cleaning as sufficient control. The dedicated β-lactam facility need not be located in a separate building, but must be structurally isolated from areas in which other products are manufactured. The draft guideline is available from www.fda.gov/cder. Click "Guidance, Compliance & Regulatory Information" and then "Newly Added Guidance Documents".

CLARIFICATION ON QUALITY OF INVESTIGATIONAL MEDICINAL PRODUCTS

The European Medicines Agency (EMA) has published a set of new Questions and Answers regarding the quality of Investigational Medicinal Products (IMPs). In answer to the question: "On which basis should specifications for related impurities be set?", the agency recommends: "Safety considerations should be taken into account. The limits should be supported by the impurity profiles of batches of active substance used in non-clinical and clinical studies. Results between batches should be consistent (or the clinical batches should show better purity results than non-clinical and previous clinical batches). Compliance with ICH requirements is not required, if proper justification is provided." Although there is nothing new here, it useful to have the official clarification. Where specifications are set for potential genotoxic impurities, the agency's 2007 guidance (EMEA/CHMP/SWP/431994/2007) should be applied. Other questions deal with notification of amendments to the IMP Dossier and the submission of batch data for all proposed manufacturing sites (www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002c2b0&jsenabled=true).

EU FALSIFIED MEDICINES DIRECTIVE

A new Falsified Medicines Directive has now been formally adopted by the European Parliament and the EU Council (http://register.consilium.europa.eu/pdf/en/10/st17/st17938.en10.pdf). This contains substantial changes in the provisions with respect to GMP/GDP for APIs and Excipients and will have comprehensive consequences for the industry dealing with these materials. The new provisions include:

- A written confirmation of compliance with EU-GMP for APIs imported from non-EU countries will be mandatory, unless the exporting country is already on the list of equivalent countries. This confirmation is to be provided by the competent authority of the API exporting country.
- A registration of all EU-based activities related to APIs will be mandatory; this applies to manufacturers, importers, distributors, and brokers of APIs. Annual notification of any changes is also required, with changes impacting quality or safety requiring to be notified immediately.
- The Qualified Person (QP) of the final dosage form manufacturer will have extended responsibilities. (S)he has to verify the API activity registration as well as the safety, quality, and authenticity of APIs and excipients by audits. (S)he has to

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state dates and outcomes of the audits in the so-called "QP declaration". Moreover (s)he must inform the competent authority where there is any suspicion of falsified medicines or starting materials.
- It will be the responsibility of the final dosage form manufacturer to perform a formal risk assessment to establish which GMP requirements should apply to the excipients used for the medicinal product manufacture. In particular the source of the excipients, the intended use, and previous instances of quality defects have to be taken into account.

EU member states are now required to transpose this Directive into their national laws within an 18 months period.

NEW GUIDANCE ON API DISTRIBUTION

The increasing complexity of API supply chains has prompted the Pharmaceutical Inspection Co-operation Scheme (PIC/S) to issue a new Question and Answer document to help clarify some of the difficult control and traceability issues which arise (www.picscheme.org/publication.php?id=18). The document is intended to provide guidance to inspectors on two topics: (a) Supply Chain & Distribution and (b) Repackaging & Relabeling operations. It deals with 13 questions, including:
- Should records other than GMP records (e.g., financial records) be examined during inspections?
- Who is considered to be the original manufacturer if an API undergoes further processing after its last manufacturing step?
- Could distributors of APIs subcontract production steps (e.g., micronisation, sterilisation)?
- How does the finished product manufacturer ensure its knowledge about and the integrity of the whole API supply chain?
- What kind of information is requested about transport conditions of APIs? Does the shipping process need to be validated?
- Which aspects should be focused on during inspections of brokers/traders and of repackagers/relabellers?
- What could be considered as an authentic Certificate of Analysis and how can its authenticity be guaranteed?
- What level of quality testing is expected from relabellers?
- Is it acceptable to hide the origin of an API after repackaging/relabeling operations?
- What measures should be implemented at a repackaging site where different batches are blended?
- Should stability studies be performed on repackaged APIs?

API MANUFACTURING SITE INSPECTIONS

Information on the compliance status of API manufacturing sites is becoming increasingly available to the public via the Internet. The previous *Regulatory Highlights* (*Org. Process Res. Dev.* **2011**, *15*(2), 325−330) featured the World Health Organization's site prequalification programme for certain APIs. The first results of this have now been summarised in a WHO newsletter (http://www.who.int/medicines/publications/Newsletter_1-2011.pdf). 126 sites were included in the programme, of which 49 were approved on the basis of recent satisfactory inspections by other authorities, and a further 31 were approved by WHO inspectors. Six sites failed the inspection "as a result of missing GMP compliance". The ICH Q7A guideline was used as the basis of these inspections. The principle deficiencies noted related to standard operating procedures (SOPs), materials management, and cleaning.

At the same time, the EMA has launched a new version of its EudraGMP database giving the general public access to information on manufacturing inspections performed by regulatory authorities from all European Economic Area (EEA) countries (http://eudragmp.ema.europa.eu/inspections/displayWelcome.do;jsessionid=ac10292ad31545c965af0114f57a0af80a1a3ad0e33.rlmNb38InljyqA4IpR9BcxaNbNq). Previously, limited information coming from only some European countries was available. The information in the database is continually updated by European regulatory authorities: the Agency expects around 3,000 new certificates to be imported every year. It also expects the database to grow rapidly over the next few years, following the introduction of inspections in countries outside the EU and new GMP requirements for active substances. However, users of the database should note that European legislation does not require routine GMP inspections for all API manufacturers, so the absence of a certificate for a particular manufacturer does not mean that it does not comply with GMP rules. In addition, the database restricts access to information of a commercially or personally confidential nature.

Routine inspection of API sites is required by US legislation, and now the FDA has announced a new web portal on its inspection activities (http://www.accessdata.fda.gov/scripts/inspsearch/). This searchable Inspections Database includes the names and addresses of inspected facilities, inspection dates, type of FDA-regulated products involved, and final inspectional classification. It has long been FDA practice to publish Warning Letters on their Web site. With this new initiative, observations from the so-called Form 483 will also be published. This form is filled out during the inspection and contains observations identified by the investigator.

COLLABORATION OF FDA AND EMA ON QUALITY BY DESIGN

The EMA and the FDA have launched a three-year pilot program, starting April 2011, that will allow parallel evaluation of marketing applications and supplements which incorporate Quality by Design elements (ICH Q8 and Q11) and which are submitted to both agencies at the same time (http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/03/WC500103620.pdf). In a first step, the pilot will include only chemical entities (and not biologicals), encompassing new drug applications and supplements/variations as well as scientific advice. Participation will be voluntary for companies which want to submit a filing in the US and in the EU at the same time. Under this program, both agencies will assess the parts of the applications relevant to QbD, such as development, design space, and real-time release testing. The evaluation will be performed separately by each agency, with regular communication and consultation throughout the review, with the aim of having a common list of questions for the applicants and a harmonised evaluation of their responses. Participation in the pilot is voluntary, and interested applicants/sponsors are asked to notify both agencies three months prior to submission of an application. At the end of the exercise in 2014 both agencies will jointly assess and publish the outcome of the pilot programme.

BATCH REQUIREMENTS FOR PROCESS VALIDATION

An interesting perspective on the number of validation batches to be performed is given in an article by James Agolloco ("Risk Based Thinking in Process Validation", *Pharm. Technol.*,

Feb 2011, *35*(2), 68−76). Since the 1980s, three validation runs has been taken as the norm, and is indeed recommended as standard in the ICH Q7A guideline on GMP for APIs. However, the FDA have never endorsed any specific number of validation runs, and their recently revised guideline on validation (discussed in the previous *Regulatory Highlights*, *Org. Process Res. Dev*. **2011**, *15*(2), 325−330) makes no direct mention of this issue. It does, though, emphasize the achievement of "statistical confidence" in the process, which might imply a need for significantly more than three performance qualification batches. In this article it is argued that the emphasis on statistical considerations, while scientifically justified, in practice leads to an unreasonably large number of "Stage II" performance qualification runs, which would cause interminable delays with little if any quality improvement. A sample size of 30 units is generally considered to be statistically appropriate, but for many medicinal products this would exceed annual production requirements.

A risk-based proposal is offered as an alternative. This focuses on the life-cycle approach adopted by the FDA guideline, where validation runs (Stage II) are no longer seen as an isolated activity, but rather integrated with process design (Stage I) and continuous process verification (Stage III). "When Stage I is performed as described, the scale-up and commercial demonstration exercise that follows in Stage II of the guidance entails an expectation that the exercise is more likely to be successful because of the increased process understanding and product knowledge the firm has gleaned from its developmental efforts. Under those circumstances, an extended Stage II demonstration with numerous lots might be of less benefit than it would when the development effort was weaker." Also, the additional scrutiny of routine production batches during Stage III would in time generate the desired degree of statistical confidence.

Taking these and other considerations into account, the author's overall conclusion is that "essentially no change in historical practices is warranted". He suggests that the number of Stage II batches should be predicated on a risk assessment of each process, and gives some guiding figures − ranging from 1 to 9 − based on his own industrial experience. His recommendations for API processes are perhaps a little naïve (since his experience is mainly with drug products) but nonetheless valuable as a basis for further discussion.

- One batch: low-volume products (e.g., less than 5 batches produced per year) and simple changes to well-defined products
- Three batches: chemical synthesis steps using a named reaction, and simple unit operations relying on physical phenomena
- Five batches: chemical synthesis steps using a reaction or process previously validated by the firm
- Seven batches: biological fermentation or cell-culture processes similar to one previously validated by the firm
- Nine batches: novel chemical or biological synthesis processes.

FDA ASKS HOW TO IMPROVE REGULATIONS

The FDA is providing an opportunity for drug manufacturers, scientists, and other interested parties to influence the future direction of regulation by formally asking for submissions on how to improve the existing regulations (http://fdatransparencyblog.fda.gov/). They particularly seek opinions on:

- Where are regulations ineffective?
- Do regulations address current public health challenges?
- Is there a need to update regulations?
- Can regulations be revised in ways that make them less burdensome without making them less effective?
- Are there regulatory requirements that are redundant, are inconsistent, or needlessly overlap?

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