APV Focus Group Drug Regulatory Affairs

International Association For Pharmaceutical Technology

Newsletter, Issue 1/2010

Editorial

The APV Focus Group Drug Regulatory Affairs considers itself to be a forum for an open scientific discussion of any issues relevant from a regulatory point of view within the field of marketing authorisation and pharmacovigilance of medicinal products. In this context we would like to inform you about current developments and draw your attention to APV events in a newsletter which will be issued on an irregular basis for the time being. Interested readers are welcome to provide proposals as to which topics the Focus Group should address and/or comment on. Please send your suggestions to the e-mail address of the Focus Group. Of course any kind of feedback and proposals concerning the contents of the newsletter and events organised by the Focus Group will also be appreciated.

Your Focus Group Members

International Conference on Harmonization

ICH Q8, Q9 and Q10 – background and work of the ICH Implementation Working Group (IWG)

Jean-Louis Robert

In 1990, 20 years ago, the International Conference on Harmonization (ICH) has started its activities. The objective was to achieve technical and scientific harmonization in registration for marketing authorization between Europe, Japan and the United States.

The experts are coming from the Regulatory Authorities of the European Union (EU), of the Ministry of Health, Labor and Welfare (MHLW) and of the Food and Drug Administration (FDA) and from Industry associations: European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA) and Pharmaceutical Research and Manufacturers of America (PhRMA). In addition, observers are coming from Health Canada, Swissmedic, World Health Organization (WHO) and International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). If initially the scope of ICH was new chemical entities and biotechnology derived products, it became clear with the time that the requirements described in the initial published guidelines were equally important for known/existing active substances. Therefore International Generic Pharmaceutical Alliance (IGPA) and World Self Medication Industry (WSMI) joined the process as interested parties (see also www.ICH.org).
In addition in Europe, the regulators (e.g. stability, impurities) and the European Pharmacopoeia (the general monograph "Substances for pharmaceutical use") have already applied these concepts and principles described in the ICH guidelines for existing/known active substances and corresponding products.

At the beginning of ICH guidelines addressed the following topics: stability, analytical validation, impurities, specifications, common technical document, GMP for active pharmaceutical ingredients.

In 2002/2003, the ICH Steering Committee asked the Quality experts to define the future vision in pharmaceutical quality. After some discussions, this has ended in the following statement in Brussels, in July 2003:

"Develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science".

The guidelines which describe this new paradigm in quality are:
- Q8 (R2): Pharmaceutical Development
- Q9: Quality Risk Management
- Q10: Pharmaceutical Quality System
- Q11: Development and Manufacture of Drug Substances (chemical/biological entities): in progress

Q8R2, emphasizes on the importance of pharmaceutical development in order to ensure that a medicinal product of consistent quality is released on the market. It also provides guidance, which additional opportunities in manufacturing flexibility are possible (e.g. real time release testing, design space) when performing an enhanced development program providing more product and process understanding, especially interaction between and among critical process parameters and critical quality attributes.
Q9 provides general guidance on different risk management tools which can be used in the pharmaceutical area including pharmaceutical development. It does not promote one tool against another; it also indicates that a manufacturer can use its own risk management tool. The more formal use of risk management will help Industry to better identify for instance CPPs and CQAs, to better retrospectively reevaluate their development process and the Regulators to better understand the applicant's approach and/or strategy to development and manufacturing of its product.

Q10 is in principle not new requirements. A Quality System, under GMP, has in all cases to be implemented. However a Q10 type quality System promotes in addition two key enablers, Pharmaceutical Risk management and Knowledge Management, and addresses the lifecycle approach.

This new paradigm can be summarized as follows:
Science is no longer isolated; it is living across the lifecycle of the product/process within an efficient Quality Management System. This allows a better utilization of modern technology. Appropriate implementation of knowledge management will facilitate continual improvement of product and process throughout product lifecycle.

Following the adoption of these three guidelines and to ensure a harmonized implementation, the ICH SC installed an implementation working group with the following main tasks:
- Communication and training
- Technical issues and documentation
- Influence of this new paradigm on existing ICH guidelines

A series of Q&As on different topics (design space, real time release testing, quality system) have been published so far and can be seen under the ICH website.
Stakeholders are encouraged to submit any question they mave have on the implemen-

tation of the three ICH guidelines not yet covered by the published Q&As to the IWG via the ICH website (www.ich.org).
Three training workshops (Tallinn (Estonia) June 2-4, 2010; Washington October 6-8, 2010; Tokyo October 25-27, 2010) have or will take place in order to further pass the message around the implementation of Q8, 9 and 10. They are based around one case study and address development (industry speaker), assessment (regulator: assessor speaker), manufacturing (industry speaker) and inspection (regulator: inspector speaker).
Breakout sessions (BOSs) around different topics design space, control strategy, quality risk management and pharmaceutical quality system will take place and allow discussion between Regulators and Industry. The outcome of the BOSs will be used in order to further facilitate the implementation of these concepts and principles described in these three guidelines.

Conclusion
One of the objectives of the three guidelines (Q8, Q9, Q10) was to facilitate the introduction of new technology in the pharmaceutical field and to show which opportunities (regulatory flexibility) can be reached when applying the principles and concepts therein described. These principles will also be the basis for applying for the "Post approval change management protocol" as foreseen in the EU Variation Regulation EC 1234/2008.
The ICH IWG is organizing training workshops, bringing together industry and regulators from all over the world, and publishes Q&As to facilitate the implementation of the new quality paradigm.

New Regulatory Requirements on Residues of Metal Catalysts or Metal Reagents under Development

Dorothee-Christine Kriha, Rainer Fendt

Background
With the introduction of the current EMA guideline (CHMP/SWP/4446/2000, published in February 2008, effective as from 1st September 2008) and the development of a future harmonized ICH guideline initiated by the ICH Steering Committee in November 2009 (ICHQ3D), recommendation is given on maximum acceptable concentration limits of metal residues that arise from the use of metal catalysts or metal reagents in the synthesis of drug substances and excipients. Such metal residues do not provide any therapeutic benefit to the patient and should therefore be evaluated and restricted based on safety and quality criteria.
Nevertheless, manufacturers of pharmaceutical ingredients are facing some major problems when it comes to implementing the EMA guideline. Therefore, the following comments on the current regulatory requirements are made with the aim of further improving some practical aspects of the guideline. They are also intended to contribute to the further development of ICH Q3D since a harmonized ICH Guideline will help to ensure appropriate control of these impurities, to the benefit of public health.

Introduction and classification

The general set of safety limits defined for all (classes of) metals that are currently included in the CHMP-SWP/QWP guideline is highly appreciated. It is of course especially important to establish appropriate controls for those metals with clearly established toxicological concerns.

However, from metals not classified yet as Class 1, 2 or 3, how much scientific literature and toxicology information will be expected from the authority to justify the proposed acceptance criterion? Will summary information be enough if it clearly states the overall safety of the metal? Clarification on the basis for the metals limit calculation is also recommended: is it taken into account that the toxicology of some metals depends on the state of oxidation?

Analytical procedures

The CHMP guideline states that 'any harmonized procedures for determining levels of metallic residues as described in the pharmacopoeias should be used, if feasible'.

However, the commonly used pharmacopoeial methodology was intended to control metals which form a sulfide precipitate, such as lead or copper, even including metal residues from other sources (e.g., the equipment), the control of which primarily is a task of the GMP/Quality System rather than a problem the pharmacopoeias should deal with.

Most analytical methods used to control these extraneous metals are non-specific and have not been developed to detect low-level residues of metal catalysts and reagents as often used in modern synthetic processes. The three major pharmacopoeias have already initiated a revision of their respective chapters, with the USP being most advanced. The European Pharmacopoeia Commission has decided to align the revision process with the deliberations at the level of the ICH Q3D Expert Working Group in order to ensure consistency. As demonstrated by this decision, it is crucial that pharmacopoeial requirements, which, in contrast to regulatory guidelines, are of a legally binding nature, are consistent with these guidelines. In addition pharmacopoeial harmonization in this area is vital for a globally acting industry.

Batch results, testing frequency and deletion of tests

In the CHMP guideline it is implied that synthetic manufacturing processes are known or suspected to lead to the presence of metal residues only due to the simple use of a metal catalyst or metal reagent.

Companies should be allowed to apply their knowledge of the product and the manufacturing process as the production operation may be conducted in a manner that excludes carry-over and results in a consistent removal of potential metal residues, e.g. when performing distillation or in case heterogeneous gas phase catalysts are used.

In July 2010, the EMA published on its website a new Q&A document ("Impurities - Harmonisation of Policies on Setting Specifications for Potentially Genotoxic Impurities, Heavy metal Catalysts Residues and Class 1 Solvents Residues") that addresses this issue and clarifies that metals not used or suspected to be present do not need to be included in the specification.

However, in conjunction with the given examples it remains unclear which conditions need to be fulfilled to claim that a metal is not suspected to be present. Moreover example 2 goes obviously beyond the generally accepted approach to demonstrate that a substance is not likely to be present as the not exceeding of 30% of the guideline limit is directly connected to the requirement to routinely control the metal by a suitable limit in a synthesis intermediate. A justification for this tightened point of view is not provided.

It is supported that class 1 metals are in the prime focus due to their toxicity, however the given statement that "class 2 and 3 metals could be treated similarly but somewhat less strictly" offers too much room for interpretation and requires a more precise guidance.

Furthermore, it needs to be clarified how the information about the concerned metallic residues should be disclosed to manufacturers of medicinal products. It is mentioned that "[…] the test may be deleted from the relevant specification if the drug product manufacturer sufficiently demonstrates that the adequate removal of the metal residue from the pharmaceutical substance or the drug product is guaranteed."
What is meant by relevant specification? Does it refer to the specification of the pharmaceutical ingredient manufacturer or to the substance specification included in the MA application or does it refer to the finished drug product specification?

In section "REPORTING LEVELS OF METALLIC RESIDUES" it is more clearly stated "[…] that the manufacturers of pharmaceutical substances provide a clear statement on the identity and quantity of all metal residues present in their compounds to the drug product manufacturers."
It is generally understood that manufacturers of medicinal products need information about the content of metallic residues in order to comply with the EMA guideline. Do the requirements in this section allow for issuing a statement on identity and quantity of all metal residues rather than including the information in the supplier's specification? It is preferred that, as long as a certain metal is "not likely to be present", a separate pharmaceutical substance manufacturer's statement is acceptable, and an inclusion in the supplier's CoA can be avoided.

However, compliance with this request by pharmaceutical substance manufacturers may result undoubtedly in confidentiality issues with this information, for instance in case of a patented metal catalyst used in the synthesis. To ensure proper safety evaluation on the one hand and protection of intellectual property of the API or excipient manufacturer on the other it should be possible in these certain cases to disclose the sensitive information ONLY to the competent authority or –preferably– to the EDQM, or to issue generic statements identifying only the relevant class of metal and related limits.