EDQM: 50 YEARS OF LEADERSHIP IN THE QUALITY OF MEDICINES

PAVING THE WAY FOR THE FUTURE

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CLOSING PLENARY SESSION

THE WAY AHEAD
RECOMMENDATIONS FROM THE WORKSHOPS
Impurities

Genotoxic impurities ICH M7
Antibiotic impurities EMA guideline
Elemental impurities ICH Q3D

Erik Wolthers

Impurities - Currently

• Monographs specifications are based on approved specifications and reflect quality of approved products on the European market (batch results at release and end of shelf-life);
• Transparent monographs: specified and unspecified impurities listed, the list of impurities controlled by each method indicated;
• Revisions upon information from CEPs or NPAs or manufacturers;
• Commission has clearly defined the procedures to implement the above guidelines in General texts similar to residual solvents.
Impurities - Future

• Cooperation with manufacturers is crucial to obtain all necessary information regarding impurities (identification) and required samples (API + imp.)

• Monographs on Antibiotics: find a balance between the needs of the assessors and of the industry; balance between regulatory science and practical feasibility

• ICH Q3D guideline will apply to FP, Implementation strategy: Chapter 2.4.8 will be deleted from individual monographs (except if vet use only); Chapter 5.20 will reproduce ICH Q3D guideline (once adopted by CHMP) instead of current EMA guideline and Chapter 2.4.20 will be revised accordingly.

• Needs for support in implementation of ICH Q3D guideline expressed by users.

Herbals
Herbals

1. Mandatory general tests for pesticides in essential oils and for arsenic in herbal drugs are not justified, but they should be considered in individual cases.

2. The improvement of TLC identification of herbal drugs and herbal drug preparations in the EP can be achieved by the introduction of HPTLC, a better description of the methods and the chromatograms, the introduction of a SST, an intensity marker, and pictures of sample chromatograms. The general chapter will be published in Pharmeuropa.

Herbals

3. The semi-quantitative use of HPTLC maybe a future concept for quality control but needs further discussion amongst the different stakeholders.

4. The extensive analysis described for dried herbal drugs is not appropriate for fresh herbal drugs. It is recommended to establish different levels of analytical requirements depending on the provenance of the fresh herbal drug and the methods of processing into the herbal drug preparation. For homoeopathic preparations there are separate texts and individual monographs, which are not concerned by the above mentioned.
Biologicals (1/2)

• Users are supportive of already existing General chapters and general monographs
• Flexibility vs. need for details
• Robust vs. advanced technology
• P4 procedure - two-phase learning approach:
  - evaluate needs, elaborate monograph;
  - when biosimilars come up, evolve and standardise the thinking
• Need to work together: pharmacopoeias, industry, regulators
Biologicals (2/2)

• Monographs need more flexibility than a monograph for a chemically defined substance
• Need to translate flexibility into working reality (already started by P4Bio WP – rFIX)
• Glycan analysis approaches to be harmonised within Ph. Eur.
• A monograph should not be suitable only for one manufacturing material; biosimilars have lots of common aspects (even if not identical molecules)
• Ph. Eur. useful for ATMPs developers and assessors
• Product-specific monographs for ATMPs not a reality today

Role of the OMCL Network
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• Routine annual Post Marketing Surveillance programmes (PMS) are established on basis of Risk-Based criteria in most of the member states.

• Not all OMCLs have influence on their routine PMS test programmes. A questionnaire to get an overview of the bodies responsible for PMS testing in the individual member states is proposed to be launched.

Role of the OMCL Network

• Collaboration between OMCLs, assessors and inspectors could still be improved on national level

• The MSS and CAP programmes also contribute to the development of Ph. Eur. monographs and General chapters

• Comparative testing of biosimilars as potential future field of activity
Combatting Illegal Medicines

- OMCL Network has developed effective programmes and tools to detect counterfeit/illegal medicines
- Rarely inside the legal distribution chain
- Most cases in the illegal market
- The big problem: dietary supplements => education
- Network approach of CoE/EDQM fosters cooperation
- In particular: MEDICRIME convention; SPOCs model
Combatting Illegal Medicines

- Awareness raising; strategies to identify harms:
  - Promising first project on estimation of magnitude of illicit use of drugs concluded (sewage epidemiology)
  - Strengthening of legislation with respect to medicines “disguised” as dietary supplements important
  - Updated monographs with state-of-the-art methods are important but not sufficient
  - New approaches: e.g. link to pharmacovigilance signals to be considered
Experience with Ph. Eur. monographs

Tobias Gosdschan

Strengths of the Ph.Eur.

Very positive feedback from all stakeholders

• One standard throughout Europe, facilitating submission for Marketing Authorisation Applications for manufacturers & facilitating assessment by authorities.

• Close to its users.

• Working in partnership with individual manufacturers and associations.

• Transparent processes, consensus based approach, user friendly.
Expectations

- Balance between flexibility and too rigorous standards (complex substances/compounds vs. well defined molecules)
- Timely reflection of new scientific and regulatory developments (input and support by stakeholders are essential).
- Balance between the introduction of new techniques and users’ ability to apply them.
- Continue to pursue harmonisation/convergence with other Pharmacopoeias for global standards.
- Guidance on cross validation of alternative methods.
- Include impurity profiles of additional synthetic routes.
- Earlier availability of reference material.

Pharmacopoeial Harmonisation
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Challenges

• Globalisation of supply chain and markets vs. local/regional needs
• Different regulatory environments and cultures sometimes hinder harmonisation

Recommendations

• Harmonisation/convergence is crucial and reduces costs globally
• Evaluate resources put into different harmonisation activities vs. benefit

Pharmacopoeial Harmonisation

• Prioritise topics to cope with limited resources and time available to pharmacopoeias
• Make the PDG process more transparent to users: set up a common website?
• Assess the outcome of prospective API harmonisation pilot and provide feedback to stakeholders on how to proceed: continue, different procedure or discontinue?
  - Add further APIs or even excipients to working programme
• Facilitate global harmonisation of pharmacopoeial standards through the development of the GPhP
Finished Product Monographs

• Need for FPM acknowledged: Globalised world, increasing number of generics
• Added value recognised (e.g. support CAs in their duties, facilitate assessment, ease the comparison and testing of medicinal products)
• At the moment: Setting of standard via P4 procedure
• File to be submitted as part of the MA (Module 3); suitability of the monograph to be demonstrated by the MAA
Finished Product Monographs

- Dissolution main critical issue: proposed, however «unless otherwise justified and authorised»; needs to be discriminatory
- Wish for harmonised monographs
- Need for more communication on the future principles related to the elaboration (e.g. different forms of API) or revision of FPM expressed
- Wish for more involvement of industry in pilot phase

Quality by Design
QbD (1/2)

- The Ph. Eur. already provides a framework to apply QbD (General Notices, specific chapters)
- The Ph. Eur. does not represent a barrier/disincentive to the implementation of QbD and the use of innovative technologies (neither today nor in the future)
- There are different means to comply with Ph. Eur. Monographs (traditional and/or QbD approach)
- Use of alternative methods could be facilitated by provision of additional tools for verification of method performance; discriminatory power should be on the same level

QbD (2/2)

Analytical QbD

- Ph. Eur. methods remain the reference methods for regulators
- « Analytical Target Profile » is independent from the technology that is used.
- Better understanding about the performance of analytical procedures (e.g. robustness)
- Gain experience on easier methods before moving to more complex methods
- Better knowledge of product manufacturing process and suppliers is a prerequisite to potentially identify « the unexpected »
- Before Ph. Eur. can capture an agreed common practice on the application of analytical QbD principles, more information/experiences are necessary
Certification

Certification (1/2)

- Well-established system for assessment of pharmaceutical substances and for inspections of API manufacturers.
- Beneficial for Authorities and Industry, saving resources, facilitating harmonisation/convergence in assessment and inspection; good tool for exchange of knowledge.
- Clear and timely procedures
- Transparency of the CEPs is welcome by all users.
- In case an active substance is covered by a CEP, the level of information exchanged between the API manufacturer (CEP holder) and the MAH varies. From assessors’ point of view there is room for improvement regarding information to be shared with the MAH as the MAH should be able to take full responsibility for the quality of the API.
Certification (2/2)

• New challenges: implementation of ICH M7 and ICH Q3D; assessment and probably content of CEPs to be adapted accordingly.

• Procedures are encouraged to continue to evolve with the developments in Council of Europe and international regulations; close cooperation with other institutions.

• Look for international acceptance of CEPs outside Europe and outside the current countries accepting CEPs.

• Contribute further to international collaboration for inspections of API manufacturers to reduce the burden, save resources and increase the oversight of API manufacturers.