ICH Q8, Q9 and Q 10 – Impact and Challenges for the Pharmacopoeias

Dr. Susanne Keitel
European Directorate for the Quality of Medicines & HealthCare (EDQM)
Disclaimer:

- The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
The Council of Europe

- Founded in 1949
- Development of European common and democratic principles
- 47 member countries
- Headquarters in Strasbourg

Core values:
Protection of human rights (European Convention on Human Rights & Fundamental Freedoms), pluralist democracy & the rule of law
The European Union

- ... a political and economic community of 27 Member States
- ... traces its origins to the European Coal and Steel Community formed among 6 countries in 1951 and the Treaty of Rome in 1957
- ... current legal framework based on the Lisbon Treaty (2009)
- ... comprises a single market created by a system of laws which apply in all Member States
The European Union
The EDQM

- A Council of Europe Directorate – a partial agreement
- 1964: Activities based on a Convention of the Council of Europe to promote free movement of medicines in Europe
- Mandatory status reinforced in 1975 in the EU pharmaceutical legislation
- 1994: EU signs the EP Convention
- 2009: 37 signatory parties and 23 observers
EDQM’s Pharmacopoeial Activities

- Elaboration of the European Pharmacopoeia
- Establishment and provision of reference standards (chemical and biological)
- Certification of Suitability to the Monographs of the European Pharmacopoeia
1. The scope of the pharmacopoeias – is there still a need for them in the 21rst century?
2. Challenges of globalisation – how does it impact the pharmacopoeia?
3. Challenges of the new ICH concepts – what will the role of pharmacopoeias be?
4. Conclusion
The role of the Pharmacopoeia is to Guarantee the Quality of Medicines

- Harmonised specifications for substances of different origins (worldwide trade)
- Transparent monographs (impurity profile)
- Specifications and valid analytical working methods
- Common Reference Substances
Why a Monograph?

- A public standard, an independent evaluation
- One single quality for everybody
- Protection of public health via a standard which represents one known quality
- Simplify the compilation of dossiers for industry and as a result of this the evaluation of marketing authorisation
What Type of Monograph?

- All active ingredientes and excipients of general interest

- Priority: therapeutic interest, number of patients treated, number of countries where the product is approved, mandatory quality
Fields Covered

- Active substances (organic, inorganic)
- Excipients
- Substances of biological and biotechnological origin (insulin, somatropin...)
- Vegetable drugs and preparations, essential and fatty oils
- Radiopharmaceuticals
- Vaccines, sera (human, veterinary), blood derivatives
- Homoeopathic preparations
- Dosage forms
- ....
The Users

- Pharmaceutical industry
- Pharmaceutical industry suppliers
- Regulatory authorities (medicines agencies)
- OMCLs
- Others…
Objectives of the Pharmacopoeia

- Provide authoritative quality standards for medicinal substances that are IMPORTANT for PUBLIC HEALTH
- RESPOND RAPIDLY to new risks to public health (new impurities, TSE, counterfeit medicines etc.)
- Facilitate the FREE MOVEMENT and trade of medicines among countries, e.g. EU 1963 decision for harmonised pharmaceuticals in European market; 1964 creation of European pharmacopoeia
- Facilitate ACCESS to high-quality medicines, by allowing free movement

ENSURING THE SAME QUALITY OF MEDICINES FOR ALL CITIZENS
The European Pharmacopoeia is…

- A public health instrument
- A source of standardisation
- A reference and a model for quality in the field of medicines
- Harmonisation of work for 36 European countries \( \mathbb{E} \) free movement
- Competition of industry at « eye level » as they are bound by the same health standards
- Activities based on a Convention under the aegis of the Council of Europe
Impact of Globalisation

- New routes of API synthesis may result in different impurity profiles
- Cost pressure in public health systems may cause frequent changes in suppliers
- A globally acting industry needs harmonised regulatory requirements
- ....
General Principles in Elaborating Monographs

- SAFETY FIRST!
- Products of proven safety
- Products evaluated and approved by competent authorities of Member States
- Impurity profiles for existing, approved synthetic routes
- Robust, validated analytical methods based on collaborative laboratory testing
Directive 2003/63/EC

“The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.
Directive 2003/63/EC

However, where a material in the European Pharmacopoeia ... has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.”

Directive 2003/63/EC, 3.2 Content: basic principles and requirements
The “New Concepts”

- Quality Risk Management (Q9)
- Pharmaceutical Development (Q8)
- Pharmaceutical Quality Systems (Q10)
A Note of Caution

The new concepts described in ICH Q8
- Remain optional
- Require high upfront investments
- Return on investment for all types of products?
- Still to be answered: Will the majority of companies implement them?

Not only a tiered system for industry, but also need for a tiered regulatory framework, including the pharmacopoeias!
Legal Situation in the EU

“(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.”

(Directive 2003/63/EC, Introduction and general principles)
… However

The quality of a medicinal product is essentially influenced by

- The characteristics/properties of the starting materials
- The manufacturing process

« Quality cannot be tested into products, Quality has to be built in by design »
Thus

PAT or advanced technologies can be used to generate data as a basis for batch release and to test the final product (ds/dp) itself, e.g. NIRS for identification or assay.
Regulatory Guidance

“…. Results of in-process tests and controls may constitute sufficient grounds for batch release and provide greater assurance of the finished tablet meeting certain criteria in the specification without the tests being repeated on a sample of the finished product…”

(Note for Guidance on Parametric Release, CPMP/QWP/3015/99)
Opportunities in Batch Release

Examples of finished product tests which have been shown possible to be replaced by real-time release

- Identification of active substance/excipients (including functionality related characteristics)
- Water content
- Uniformity of mass/content
- Dissolution

---

ICH
“Regulatory Flexibility” in the Pharmacopoeia

“This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls.....
“Regulatory Flexibility” in the Pharmacopoeia

“… Parametric release in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.”

(European Pharmacopoeia, 1.1 General Statements)
«Regulatory Flexibility» in the European Pharmacopoeia

- Concept of «Alternative Methods of Analysis»
- Parametric release see “Method of preparation of sterile products” (chapt. 5.1.1.)
- Production section in monographs
«Regulatory Flexibility» in the European Pharmacopoeia

But: pharmacopoeial specifications are legally binding in the EU and EP Member States

API, excipients and finished product need to meet pharmacopoeial specifications throughout their shelf-life, if tested
Excipients: FRC & ICH Q8 (1)

- FRC: a controllable physical characteristic of an excipient that is shown to impact on its functionality
- Non-mandatory FRC section added to excipient monographs to provide information about FRCs that may be critical for the intended function of the excipient
- Information on FRC provided:
  - name
  - name and methodology
  - name, methodology, typical values
Excipients: FRC & ICH Q8 (2)

- FRC concept in line with “quality by design” cf. ICH Q8
- Critical characteristics to be identified during development work
- Depending on the application, an FRC may or may not be relevant, thus …
- FRC section contributes to the desired regulatory flexibility
PAT Working Party

- Established on request of the EMEA PAT team
- Composition:
  - licensing authorities and inspectorates
  - industry
  - academia
  - chair: Prof. G. Ragnarsson, Medical Products Agency, Sweden
Current activities in the context of PAT

1) Review of General Notices and General Chapters
   - Update General Notices to take account of real time release
   - Revision of general chapters, e.g. NIR to accommodate changes from « bench-top » to « in-line » measurements
Current activities in the context of PAT

2) Relationship between sample size and acceptance criteria

Uniformity of dosage units:
To ensure consistency of active substance amount among dosage units, currently a test is performed on the basis of a random sample, where n = 30
PAT tools enable to monitor larger sample sizes e.g. by NIR at-line with \( n \) between 100 and 10000. In this case, traditional acceptance criteria for \( n = 20 \) (based on the acceptable number of outliers 85-115 \% resp. 75-125 \% range) no longer applicable and appropriate, too strict for higher sample size.
Currently discussed:

“Development of a content uniformity test suitable for large sample sizes”

Sandell, Vukovinsky et al.

→ A one-tiered counting test for UDU giving the same assurance as the current harmonised pharmacopoeial test.
Count the number of samples outside 85 -115 %

Proposed Acceptance limits

<table>
<thead>
<tr>
<th>n</th>
<th>100</th>
<th>250</th>
<th>500</th>
<th>1000</th>
<th>10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>4</td>
<td>23</td>
<td>47</td>
<td>239</td>
<td>479</td>
</tr>
</tbody>
</table>
Status in PAT working party

- the « Sandell » proposal is under discussion as an alternative to chapter 2.9.40 (UDU)
- It covers only the first tier of the UDU test
- Other process-capability related tests/criteria might be considered
Current activities in the context of PAT

- Addition of new general chapters on analytical techniques such as
- NIR-imaging
- tera hertz spectroscopy
- acoustics
- effusivity
The Role of the Pharmacopeia

- Provides specifications and test methods for «conventional» applications
- Elaborates further guidance on the «new principles»
- Provides official standards for the «validation» of enhanced control strategies during their development and life-cycle management
- Provides official standards for market surveillance
The Role of the Pharmacopoeia

- Has to consider the needs of a globally acting pharmaceutical industry AND small and medium-sized enterprises
- BUT first priority in all activities is the protection of public health!
Conclusion

- Pharmacopoeias are key-players in ensuring safe standards to protect public health
- Pharmacopoeias can react quickly to newly arising challenges
- Application of the new ICH concepts is already possible in the present framework of pharmacopoeial requirements, further guidance being developed
- Changes to the present paradigm in setting specifications will need to be closely followed by the pharmacopoeias – however: safety first!
Thank You for Your Attention!