The European Approach on Large Sample Sizes in the context of a PAT Environment

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Content

1. Introduce Council of Europe and the European Pharmacopoeia
2. Challenges of the new ICH concepts – are adaptations of Ph.Eur. needed?
3. Activities in the context of PAT and the large sample size issue
4. Conclusion
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
European Regulatory Network

European Authorities

European Union

- European Union
  - Council
  - Parliament
  - Commission
  - DG Health & Consumers
    - Brussels

Council of Europe

- Pharmaceutical/Pharm. care
- Blood Transfusion
- Organ Transplantation

European Medicines Agency
- EMA
  - London

European Directorate for the Quality of Medicines & Healthcare Care

EDQM
- Strasbourg

Ph. Eur.**

Certification***

OMCL*

Network

*OMCL: Official Medicines Control Laboratories
**Ph. Eur: European Pharmacopoeia
***Certification: Certification of Suitability of Monographs of the European Pharmacopoeia

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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
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
The “New Concepts”

- Pharmaceutical Risk Management (Q9)
- Pharmaceutical Development (Q8)
- Pharmaceutical Quality Systems (Q10)

Quality system

- Quality Risk Management
- Existing GMP
- Pharmaceutical development

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.... 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!

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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

API and/or final product can be released on data generated by PAT and/or advanced technologies.

e.g. use of NIR data for assay or uniformity of dosage units.
…reflected in (1) 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)

➡ Guideline on Real Time Release Testing currently under public consultation (EMA)
“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.....
... furthermore

“... 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)

=> needs to be extended to RTRt
Summary « Regulatory flexibility » in the European Pharmacopoeia

- 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
- Parametric release or alternative methods may be used (General Notices)
- Future revisions need to further adapt to PAT environment
PAT Working Party

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

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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 testing
  →will be updated once the EMA Guideline is adopted
Current activities in the context of PAT (2): Revision of chapter 2.2.40
NIR Infrared Spectroscopy

• to accommodate changes from « bench-top » to « in-line » measurements
• Prepared in close consultation with EMA Quality Working Party
• to be aligned with the ongoing revision of the EMA Note for guidance on NIR (e.g. delete validation requirements)

→ under enquiry in Pharmeuropa 23.3, will be adopted in parallel with the revised version of the EMA Note for Guidance on NIR

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Current activities in the context of PAT (3): “Content uniformity for large sample sizes”

Problem statement:

• 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) are no longer applicable and appropriate, too strict for higher sample size.
Discussion started based on scientific papers

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


→ An alternative test for UDU giving the same assurance as the current harmonised pharmacopoeial test was proposed.
Current draft in Pharmeuropa 23.2:

Chapter 2.9.47

„Demonstration of Uniformity of Dosage Units using large sample sizes“

• proposes Option I (parametric test) and Option II (non-parametric test)
• will be introduced in detail by Dr. Holte (EP Expert from the Norwegian Medicines Agency)
Questions from industry have been raised as to which alternative approach regulators would accept.

Assessors have suggested that an alternative pharmacopoeial approach such as 2.9.47:

- would provide clear guidance to applicants
- would be helpful during MAA dossier assessment
- may be used by applicants having access to large sample size information
Draft chapter 2.9.47 in Pharmeuropa 23.2:

- recognises
  - that chapter 2.9.40 *Uniformity of Dosage Units* is harmonised by PDG (EP/JP/USP) and will continue to exist
  - that chapter 2.9.40 is needed when samples are tested in a market surveillance situation or when applicant does not use PAT tools
- intends **not** be a disincentive to make use of PAT-generated data
- should ideally been internationally harmonised
- has been identified as Q/A item by ICH IWG and shared with them upon their request
Further draft (under discussion)

- EP experts wish to consider and promote also concepts already used in other industries
- Draft underway applicable typically for sample sizes >250
- Based on capability indices Cpk
- Compares output of in control process data to the alert or rejection limits
- Linked to a predefined sampling plan

→ Formal public consultation in Pharmeuropa will follow once available
Current activities in the context of PAT (4)

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

→ review process underway
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 (cntd)

• Has to consider the needs of a globally acting pharmaceutical industry AND small and medium-sized enterprises

• In the field of PAT:
  Several activities underway to support PAT implementation in close collaboration with regulatory authorities
Acknowledgement:

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Thank you!