La Pharmacopée Européenne entre harmonisation et innovation

The European Pharmacopoeia: harmonisation and innovation

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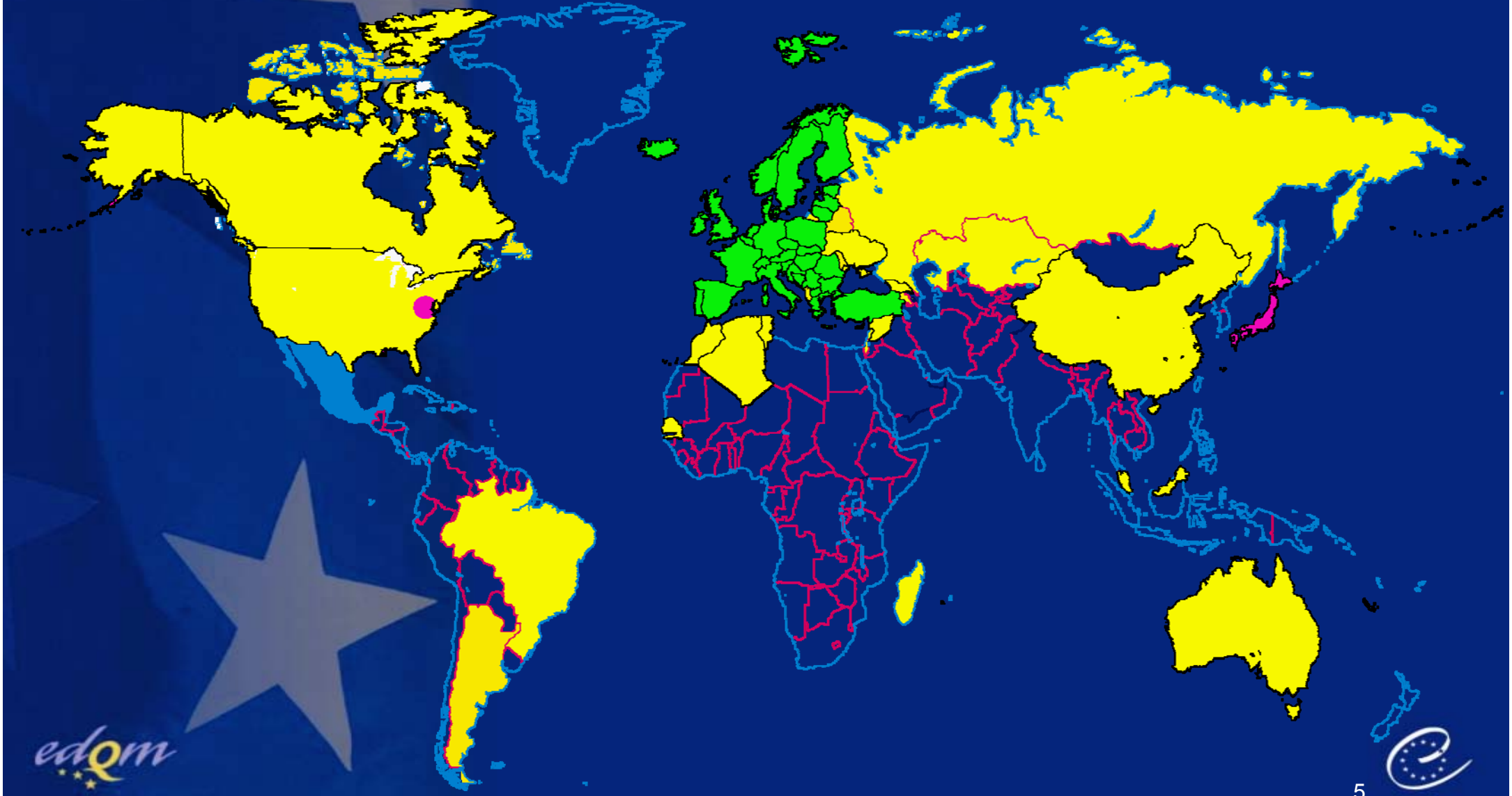
I. EDQM

EDQM

- A Council of Europe Directorate – a partial agreement within DG Democracy
- 1964: Activities based on a Convention of the Council of Europe to promote free movement of medicines in Europe
- 1975: Mandatory status in all EU Member States by reference to the Ph. Eur. in the EU pharmaceutical legislation
- 1994: EU signs the Ph. Eur. Convention
- 2012: 37 signatory parties and 25 observers

Ph. Eur. Members and 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

II. Ph. Eur. and harmonisation

Harmonisation: why?

Notably:

- Pharmaceutical industry is globalised,
- Reduce costs,
- Facilitate access to medicines for patients.

PDG & harmonisation

(Pharmacopoeial Discussion Group)

PDG & Harmonisation (1)

- Pharmacopoeial Discussion Group (PDG) set up in 1990
- Drives international harmonisation of pharmacopoeial requirements among the world's three major pharmacopoeias, the Ph. Eur., JP and USP - a single set of global specifications.
- Scope: general methods of analysis and excipient monograph,
- Aims:
  - Avoid redundant testing by suppliers and pharmaceutical industry to meet different standards
  - Reduce the overall cost of pharmaceutical research world-wide by avoiding duplication of work (preparation of dossiers and studies)
  - Reduce the time required for medicines to be made available to patients

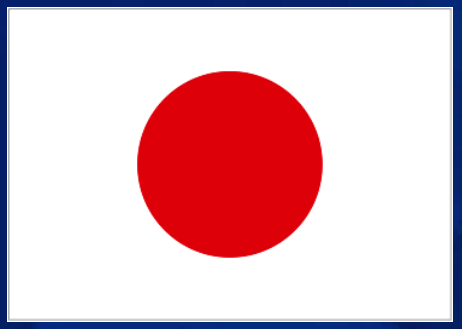
PDG & Harmonisation (2)

- Monographs and general methods of analysis proposed by national associations of manufacturers of pharmaceutical products
- To ensure rapid publication of signed-off texts, the PDG procedure has been woven into the Ph. Eur. procedure
- Texts are published in Pharmeuropa and approved by the Ph. Eur. Commission

- Priority of pharmacopoeias according to EU legislation
  Ph. Eur. > national pharmacopoeia > third country pharmacopoeias, e.g. USP, JP

PDG & Harmonisation (3)

Three major pharmacopoeias



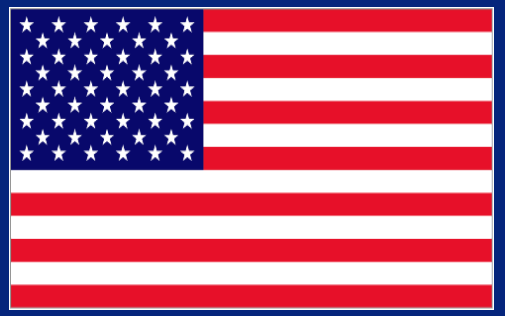
Japanese Pharmacopeia

Governmental

Ph. Eur.

EDQM, Council of Europe

Inter-governmental



US Pharmacopoeia

Independent of Government

PDG & Harmonisation: status update (4)

- 28 of the 35 General Chapters and 41 of the 61 excipient monographs of the current work programme have been harmonised.
- 17 General Chapters published in the chapter 5.8 and considered interchangeable

Other harmonisation initiatives

Other harmonisation initiatives (1)

- Harmonisation of API monographs out of scope of PDG
- Bilateral initiative between Ph. Eur. and USP
- Pilot phase included four monographs*, all adopted by the Ph. Eur. Commission
- Expansion of the pilot phase to cover the first revision request on these monographs before enlarging it to new candidate molecules

* *Rizatriptan benzoate* , *Montelukast sodium*, *Celecoxib*, and *Sildenafil citrate*

Other harmonisation initiatives (2)

- First Global Summit of Pharmacopoeias
  - 17 & 18 November 2011, Beijing, China
  - Hosted by Chinese Pharmacopoeia and co-hosted by USP
  - Main proposal made:
    - Creation of an Index compiling all APIs monographs existing in Pharmacopoeias worldwide which might be extended to FPs

Other harmonisation initiatives (3)

- International Meeting Of World Pharmacopoeias
  - 29 February and 1-2 March 2012, WHO, Geneva
  - Hosted by WHO
  - Main proposal made:
    - Elaboration of « *Good Pharmacopoeia Practices*» to favour prospective harmonization, which procedure WHO could facilitate

Follow-up activity meeting during the FIP Centennial Congress (03-08/10/2012 – Amsterdam)

III. Innovation and Ph. Eur.

“Regulatory Flexibility” in the Pharmacopoeia (1)

“An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. 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 (2)

“… 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)

Alternative Methods

"… The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used…"

«Regulatory Flexibility» in the European Pharmacopoeia

Concept of Alternative methods of analysis see ”General Notices”

✓Parametric release see “Method of preparation of sterile products” (chapter 5.1.1.)

✓Production sections in certain monographs

✓ ....

«Regulatory Flexibility» in the European Pharmacopoeia

But: pharmacopoeial specifications are legally binding in the EU and Ph. Eur. Member States,

API, excipients and finished product need to meet pharmacopoeial specifications throughout their shelf-life, if tested,

The Ph. Eur. needs to remain 'state of the art'

Developments in Regulatory Environment
e.g. Guidelines, ICH Q8/Q9/Q10/Q11, REACH

Increased demand for Generic and Biosimilar products
e.g. New sources

Scientific / technical evolutions
e.g. Fast LC, NIR, PAT, new molecules, new therapies
e.g. CT

New risks to Public Health
e.g. Genotoxic impurities, TSE, contamination/ falsification (heparins)

Developments in Manufacture and Globalisation
e.g. continuous manufacturing, changed routes of synthesis

III. a) Ph. Eur. and the ICH quality paradigm

QbD - Demystification

- A systematic approach will facilitate the process to achieve quality and should automatically generate more knowledge.
- Not necessarily new requirements:
  - Pharmaceutical development has been a requirement in the EU for a long time
  - QbD does **not** require the establishment of e.g., design space or real time release testing: a company might decide based on full scientific understanding not to establish a design space or RTR testing.
  - The level of development will depend on the complexity of the process and product and on the opportunities chosen or wanted by the applicant.

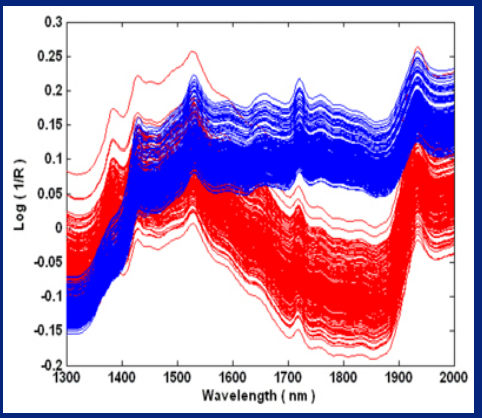
Excipients: FRC & ICH Q8 (1)

- 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 (1)



- Establishment of a PAT Working Party based on a request from EMA

Composition:

- licensing authorities and inspectorates
- industry
- academia
- chair: Prof. G. Ragnarsson, Medical Products Agency, Sweden.

PAT Working Party (2)

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

Revision of Chapter 2.2.40 NIR (Near Infrared Spectroscopy)

- to accommodate changes from “bench-top” to”in-line” measurements
- prepared in close consultation with Joint CHMP/CVMP Quality Working party
- to be aligned with the ongoing revision of the QWP Note for guidance on NIR (e.g. Delete validation requirements)

→ published for consultation in Pharmeuropa 23.3, will be adopted in parallel with the revised version of the QWP Note for guidance on NIR

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.

Hence, 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 large sample sizes.

Discussion Started Based on Scientific Papers

"Development of a content uniformity test suitable for large sample sizes"

- Limberg, Savsek, Pharmeuropa Scientific Notes 2 (2006) 45
- Sandell, Vukovinsky et al., Drug Inf J 40 (2006) 337
- Andersen, Diener et al., Drug Inf J 43 (2009) 287

→ An alternative test for UDU, giving the same assurance as the current harmonised pharmacopoeial test was proposed.

Chapter 2.9.47 « Demonstration of Uniformity of Dosage Units using large sample sizes »

Defines two options

- Option I (parametric test)
- Option II (non-parametric test)

Applicable to n ≥ 100

Adopted at the April 2012 session of the Ph. Eur. Commission

Chapter 2.9.47 « Demonstration of Uniformity of Dosage Units using large sample sizes »

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

Current Activities in the Context of PAT

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

→ review process underway

III. b) new developments in the field of biologicals

Creation of HCP Working Party

Will provide recommendations with regard to the development, validation and use of in-house or commercial kits or test methods for the detection and quantification of host-cell proteins.

Creation of RCG Working Party

Raw materials for the production of cellular and gene transfer products.

- Producers of the raw materials
- Developers of the products
- Assesors of the applications for CT and MA

IV. Conclusions

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!

THANKS A LOT FOR YOUR ATTENTION!

Website: www.edqm.eu