EDQM & European Pharmacopoeia: State-of-the-art Science for Tomorrow's Medicines

International Conference organised by the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe

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Workshop on General Methods

Moderator

Prof. Dr. Michel Ulmschneider, Chair of the General Methods Working Party

Chromatographic Separation Techniques

CHALLENGES RELATED TO HARMONISATION

PROF. JOS HOOGMARTENS

Chapter 2.2.46

- Current version published in Supplement 9.2 (implemented 1st July 2017)
- What are the changes proposed?
- Chromatographic Separations Working Party

Definitions

New definitions are added:

- Plate height *H*
- Reduced plate height *h*
- Relative retardation R_{rel} (TLC)
- S/N – *h* observed in blank over 20 x $w_{1/2}$
- Separation factor α

Planar chromatography (TLC, paper chromatography)

TLC - Adaptations in mobile phase composition proposed

- Definition "minor component**s**" ≤ 100/n
- Other components may be adapted by ± 10 % absolute
- No more reference to "pH ±1.0" for non-ionisable substances

Gas Chromatography

- No major changes
- Temperature program adjustments proposed:
  - Temperature: ± 10%
  - Ramp rates, hold times: ± 20%

Supercritical Fluid Chromatography: deleted

System Suitability in Chromatography

- Mainly rewording
- RR and t_R not mandatory unless otherwise stated in monograph – no acceptance criteria
- Peak symmetry of reference solution used for quantitation:
  - **9.2**: 0.8 -1.5
  - **Proposal**: 0.8 -**1.8**
- More detailed descriptions

Liquid Chromatography Apparatus

- **9.2**: No specifications
- **Proposal** - Isocratic and Gradient

  If changes lead to strong increase of N → avoid extra-column band broadening: connections, sampling rate, detector cell volume

Dwell volume (Gradient): no change proposed

Liquid Chromatography Stationary Phase, Isocratic and Gradient

- **9.2:** No change to identity of substituent = no replacement C18 ↔ C8
- **Proposal**: idem + similar physico-chemical characteristics + similar surface modification and extent

  Allowed: Totally Porous Particles (TPP) → Superficially Porous Particles (SPP)

Liquid Chromatography Column Parameters

Internal diameter (dc) – Isocratic and Gradient

- **9.2** ± 25 %
- **Proposal** ± 25 % when no change in L or dp

Liquid Chromatography Column Parameters

- **9.2**
  - Length ± 70 %
  - Particle size (dp) - Isocratic: 50 % ↓
    - Gradient: no adjustment
- **Proposal** - Isocratic and Gradient
  - L/dp within - 25 % to + 50 % (change from HPLC to UHPLC possible)
  - For SPP: other L and dp provided *N* within – 25 % to + 50 %

always comply : SST + elution order and separation of specified impurities

Liquid Chromatography Flow rate

Using method as described

9.2 and **proposal**: isocratic: ± 50 %

gradient: no change

Using different column dimensions - Isocratic and Gradient

- **9.2** $F_2 = F_1 (L_2 \times dc_2^2)/(L_1 \times dc_1^2)$
- **Proposal** $F_2 = F_1 (dc_2^2 \times dp_1)/(dc_1^2 \times dp_2)$

Liquid Chromatography Flow rate (F) (2)

Additional proposal - Isocratic and Gradient

- dp ≥ 3 µm to < 3µm : additional F↑ provided ↓*N* < 20%
- dp < 3 µm to ≥ 3µm : additional F↓ to ensure ↓*N* < 20%

Liquid Chromatography
Adaptation of gradient timing after change in column dimensions

New proposal

- Adaptation factor

$tG_2 = tG_1 (F_1 / F_2)[(L_2 \times dc_2^2)/(L_1 \times dc_1^2)]$

- Gradient adaptation in 3 steps
  - Adjust L/dp
  - Adjust flow rate F
  - Adjust gradient timing

Liquid Chromatography
Mobile phase composition

- Isocratic (also cf. TLC)
  - **9.2**: the minor component ± 30 % rel or ± 2% abs ; other components max ± 10 % abs
  - **Proposal**: idem but minor component**s** ≤ 100/n
- Gradient
  - **9.2:** minor adjustments in f(SST, t_R principal peak ±15%, final composition not weaker) – not applicable if column dimensions changed
  - **Proposal**: idem + first peaks sufficiently retained

Liquid Chromatography
Mobile phase pH

- Isocratic
  - **9.2**: Aqueous component ± 0.2 pH units, and ± 1.0 pH units for non-ionisable substances
  - **Proposal**: delete ref. to non-ionisable subst. (cf. TLC)
- Gradient
  - **9.2:** No adjustment
  - **Proposal**: ± 0.2 pH units

Liquid Chromatography
Mobile phase buffer component

- **9.2:** Isocratic ± 10 %
  Gradient: no adjustment
- **Proposal:** Isocratic: ± 10 %
  Gradient: ± 10 %

Liquid Chromatography
Injection volume

Isocratic and Gradient

- **9.2:** may be decreased provided detection is OK; no increase permitted
- **Proposal**: may be decreased provided SST, detection, repeatability OK; may be increased provided SST, linearity, resolution OK

If column dimensions change

$$Vinj_2 = Vinj_1 \, (L_2 \, dc_2^2 / \, L_1 \, dc_1^2)$$

Not applicable for TPP → SPP

Liquid Chromatography
Other parameters

9.2 and Proposal: *no changes for*

- Column temperature

  Isocratic ±10 °C Gradient ± 5 °C
- Detector wavelength: no adjustment permitted

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Main hurdles overcome within PDG

- Resolution: calculation based on $w_{1/2}$ (Ph. Eur.) instead of w_{base} (USP)
- Symmetry factor: after negociation with USP, since <621> does not include a requirement: 0.8-1.5 →0.8-1.8
- Potential switch from HPLC to UHPLC with/without validation of modified method?

  Final agreement for L/dp approach for isocratic and gradient

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Harmonisation status

- Comments received after public enquiry from USP and JP examined by Ph. Eur. Experts

Further discussion to take place in July 2019 to examine new comments

- Late comments received from EMA QWP on regulatory aspect of adjustments of chromato-graphic conditions (change from HPLC to UHPLC without variation)

Discussion with QWP members to take place in July 2019

Acknowledgments

- Members of the CST WP for their constant support and valuable expertise, during the past 10 years
- Dr. Ulrich ROSE, for his support since 2014, in promoting the Ph. Eur. perspective at PDG meetings and teleconferences
- Isabelle MERCIER, Secretary to the CST WP, for her support of the working party and the Pharmacopoeial Discussion Group

General Methods of Analysis

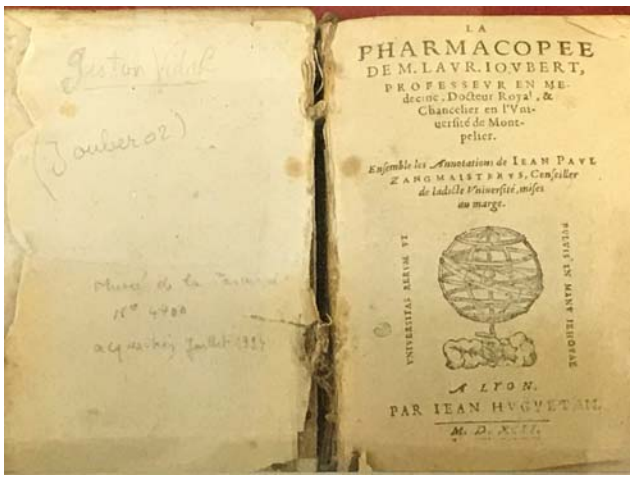
Prof Dr Michel Ulmschneider

Archeology

What is a pharmacopoeia ?

It is a book... a catalogue that contains receipts, describing how to prepare medicines, and the price to pay for it, for example.

In Lyon, France, 1592



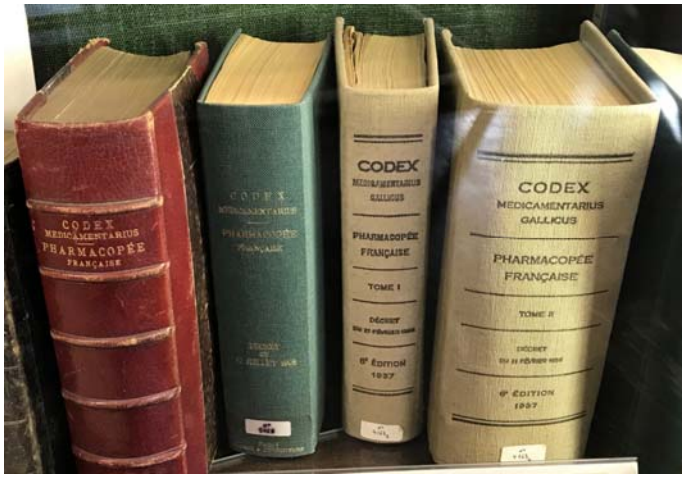
Historical notes

- The first pharmacopoeias date back to the early middle age: always local, valid within a town, in rare cases within a region.
- Official and private pharmacopoeias were published.
- National pharmacopoeias appeared at the edge of the 18th-19th century, e.g. Switzerland 1775, Netherlands 1806, France 1818; and even later : the British Pharmacopoeia was published in 1864.
- During the 19th century national codex gradually replaced local ones.

- **The European Pharmacopoeia dates back to 1964.**
- **A first printed version was issued in 1967.**

Many books, all different !

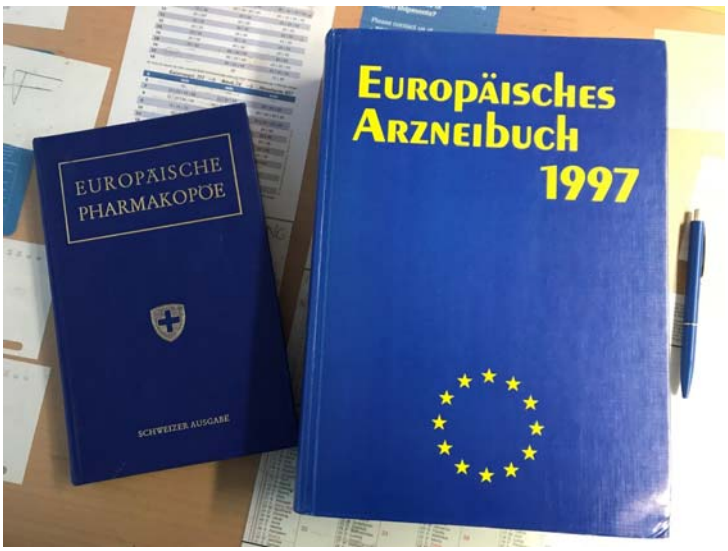
No consistency, no equivalence, no rules, no standards



Nowadays, it still is a book, but harmonised at the European level...

German translations of the Ph. Eur.:

- **The first Swiss copy, 1968**
- **The 1997 issue, in one volume, co-edited by the German, Austrian and Swiss NPAs, a private initiative for the German speaking areas**



Well… still many books…

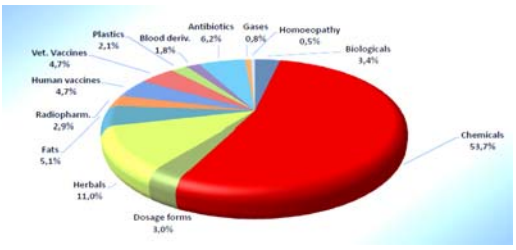
For each edition, a first set of volumes is published followed by eight updates, the supplements…

No longer receipts to prepare medicines

But legally binding documents (quality standards), monographs and general texts to control components of medicine...

- **General Notices**
- **General chapters:** procedures, analytical techniques, guidelines
  Section 2. : Methods of analysis
  Section 5. : General texts

  } General methods (GM)
- **General monographs:** on classes of products, dosage forms
- **Monographs:** finished products and substances from A to Z



Setting the scene

What is the concern with GMs ?

Going ahead with the revision process of GMs :

- More than 300 GMs and texts to maintain up-to-date
- Most texts were not reviewed since first publication (> 15 years)
- Facing the increasing amount of helpdesk queries
- Solving problems with some standard methods (e.g. LOD) : all groups are concerned, but none has the responsibility in up-dating the chapter

And :

- Impact on individual monographs not evaluated
- New methods and texts are usually out-of-scope of regular groups

Ideally, the objective would be…

- To shift from a reactive approach to a pro-active approach
- To include recent techniques and produce a Pharmacopoeia which is scientifically state-of-the-art
- To improve existing methods to take into account recent progress in analytical technology and regulatory practice
- To standardise the content and format of the texts
- To introduce and/or improve elements of equipment performance and qualification
- To introduce and/or improve universal system suitability tests
- To suppress toxic reagents or materials

➢ *To increase user-friendliness*

How to proceed ?

With the creation of a dedicated working party mandated to :

- Develop a flexible approach for the revision of GMs
- Elaborate a template for GM texts
- Identify and fix the prioritisation of revisions
- Apply practice experimented in other working parties that also elaborate general chapters, like VSADM, PAT
- Elaborate a revision strategy and action plan for GMs
- Communicate on revisions and new publications, by press releases, social media, etc.

MG demystified

MG's Terms of Reference

- Drafting and revision of general chapters, particularly in the field of chemical and physico-chemical analysis, allocated to the working party by the Commission
- If needed, requests the nomination of ad hoc specialists to create sub-groups fort specific general chapters on the work program, and management of the activities for the elaboration or revision of these general chapters within the sub-groups
- If needed, cooperation with other groups of experts and working parties which are in charge of elaboration and revision of general chapters
- Maintenance of template for general methods

MG's Profile for Experts

11 members from industry, OMCLs, NPAs, academia

- Members of OMCLs, national pharmacopoeia authorities, licensing authorities, universities or pharmaceutical/chemical industries
- Current expertise and extensive knowledge in pharmacopoeial methods and/or instruments used in the quality control of active substances, excipients and/or medicinal products and in development of control methods
- Several years of experience in one or more of the following fields :
  - Method development and verification in e.g. analytical or pharmaceutical development, a regulatory authority, or other testing laboratory
  - Quality control of active substances, excipients and/or medicinal products
  - Market surveillance of quality of medicinal products in a regulatory authority
  - Assessment of the relevant parts of applications for marketing authorization within a medicines agency

Doing the job

MG in practice

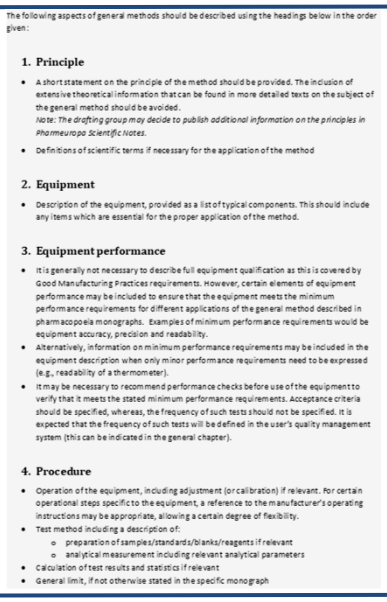
- Because methods can vary widely in complexity, specialised knowledge is required, and this may be the difficult part of the job... i.e. appointing these specialists
- The rule would be that MG decides on a case-by-case basis how to tackle a given topic
- Face-to-face meetings are still beneficial, to start the drafting project, to review public comments after public inquiry, etc.
- There is a clear necessity for optimal communication between secretariat, sub-groups and working party
- MG should also collaborate hand-in-hand with other groups :
  - This means, other groups could re-allocate tasks to MG in order to release pressure, or if expertise is not or no longer available
- Make concrete proposals to the COM on the best approaches to take over revision needs of general methods

MG's first achievements

• Template for general methods	presented at 159th session
• X-ray fluorescence spectrometry, 2.2.37	adopted at 156th session
• Optical rotation, 2.2.7	adopted at 158th session
• Osmolality, 2.2.35	adopted at 161st session
• Loss on drying, 2.2.32	adopted at 161st session
• UV/Visible spectrophotometry, 2.2.25	adopted at 162nd session
• Detection of residual solvents, 2.4.24	adopted at 163rd session

Template for General Methods

- For information : a guidance for creating and revising general methods
- Reflects the content and degree of details to be provided in general methods in view of drafting a guide for the elaboration of general methods at a later stage
- Provides harmonisation in the content of general test methods
- Flexible
- May be subject to revision according to feedback and experience



The following aspects of general methods should be described using the headings below in the order given:

1. Principle

- A short statement on the principle of the method should be provided. The inclusion of extensive theoretical information that can be found in more detailed texts on the subject of the general method should be avoided.
  Note: The drafting group may decide to publish additional information on the principles in Pharmeuropa Scientific Notes.
- Definitions of scientific terms if necessary for the application of the method

2. Equipment

- Description of the equipment, provided as a list of typical components. This should include any items which are essential for the proper application of the method.

3. Equipment performance

- It is generally not necessary to describe full equipment qualification as this is covered by Good Manufacturing Practices requirements. However, certain elements of equipment performance may be included to ensure that the equipment meets the minimum performance requirements for different applications of the general method described in pharmacopoeia monographs. Examples of minimum performance requirements would be equipment accuracy, precision and readability.
- Alternatively, information on minimum performance requirements may be included in the equipment description when only minor performance requirements need to be expressed (e.g., readability of a thermometer).
- It may be necessary to recommend performance checks before use of the equipment to verify that it meets the stated minimum performance requirements. Acceptance criteria should be specified, whereas, the frequency of such tests should not be specified. It is expected that the frequency of such tests will be defined in the user's quality management system (this can be indicated in the general chapter).

4. Procedure

- Operation of the equipment, including adjustment (or calibration) if relevant. For certain operational steps specific to the equipment, a reference to the manufacturer's operating instructions may be appropriate, allowing a certain degree of flexibility.
- Test method including a description of:
  - preparation of samples/standards/blanks/reagents if relevant
  - analytical measurement including relevant analytical parameters
- Calculation of test results and statistics if relevant
- General limit, if not otherwise stated in the specific monograph

Absorption spectrophotometry, ultraviolet and visible, 2.2.25

- Addition of UV-Vis detectors used in liquid chromatography and in PAT applications
- Equipment qualification section improved
- Clarification of requirements
- Replacement of potassium dichromate (REACH regulation) by nicotinic acid for equipment qualification CRS, to test absorbance accuracy and linearity

  ➢ Revision of this chapter was carried out by a sub-group of MG members and appointed ad-hoc specialists

Loss on drying, 2.2.32

- Diphosphorous pentoxide (toxic and obsolete) replaced by molecular sieves as drying agent
- Use of "high vacuum" discouraged
- Other instruments allowed with validation (microwaves, halogen lamps, etc.)
- Since Ph. Eur. 9.4, a new CRS material is proposed : sodium aminosalicylate for equipment qualification
  - ➢ Impact on about 1100 monographs
  - ➢ Revision of this chapter was carried out by a sub-group of MG members

Additions to the work program

- Implementation of pharmacopoeial methods, 5.26
  - ➢ Guidance to assess to which extent a method is suitable and adequately performing for its intended purpose given the actual conditions of use in the laboratory of concern
- Equivalence testing of alternative methods, 5.27
  - ➢ The aim of this chapter is to provide information on the requirements for equivalence testing in the situation where instead of the official method (i.e. the pharmacopoeial method), an alternative method of analysis is used for control purposes
- Balances, 2.1.7
  - ➢ As a response to an official survey
- Detection of nitrosamines in active substances, 2.5.42
  - ➢ Following the sartans medicine crisis

Revisions in the work program

- Identification reactions of ions and functional groups, 2.3.1
  - Replacing the chloride test using potassium dichromate (REACH). A test based on silver sulfate was elaborated by the Group 10A. MG will review at a global level this possibility and amend the general chapter
- Evaporative light scattering detection, 2.2.62
  - Continuation of drafting started by Antibiotics Group (7)
- Arsenic, 2.4.2
  - Widening specifications of the reagent silver diethyldithiocarbamate, and introducing UV spectrophotometry in addition to the visual detection

Climate change

Challenges

- Versatility of instruments and methods
- Obtaining reliable up-to-date information on instruments
- Enrolling method specialists and experts
- Be careful with conflict of interests if manufacturers are involved
- Perform laboratory testing
- Revision of some historical methods (e.g. wet chemistry)
- Finding the right balance to not turn the GM into a textbook
- Always keeping secretariat and chair in the drafting loop
- Information of all stakeholders (internal and external)

Key questions

- Authorities are more and more behind on technology and the expectations of users
- It takes time to come up with a good quality text :
  - Pharmacopoeia : 3 to 5 years until adoption of a new chapter
  - Technology : in less than 2 years, many updates, new fields of applications, possible obsolescence, roll-out of newer or alternative techniques, etc.

Data R-e-Volution

- Big Data
- Data sciences, data mining, machine learning, clouding and networking
- Once associated they multiply possibilities and lead to fast improvements in analytical sciences

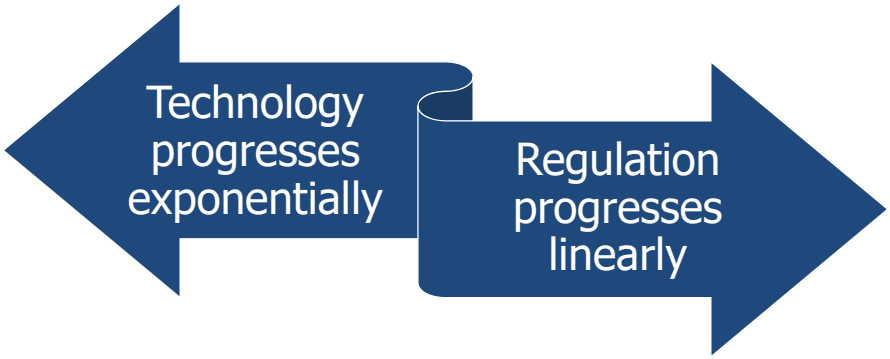
➢ *Disruptive technologies can be a consequence*

Paradigm shifts

- Quality by Design
- Continuous manufacturing
- Real time release testing
- Personalised medicine
- Miniaturisation of instruments

We face opposite trends

Time does not tick the same way



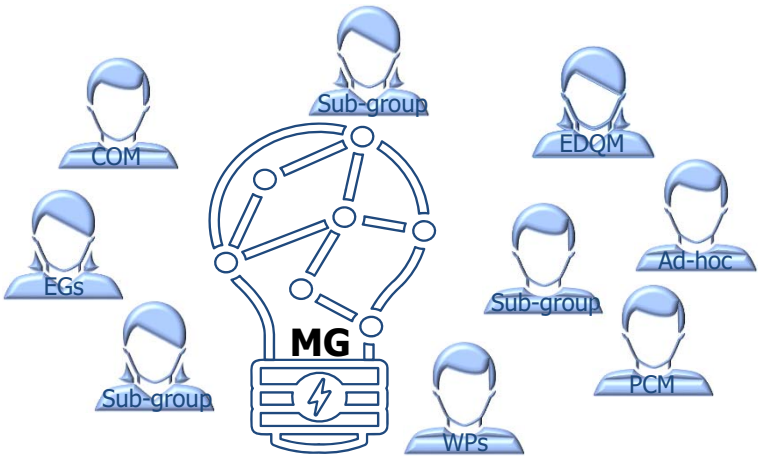
Conclusions

The essence of MG is to make

analytical knowledge available

and productive

MG's network makes it possible



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Reference Standards for Ph.Eur. Chapters

Dr Stefan Almeling
Deputy Head of Laboratory Department,
EDQM, Council of Europe

Background

Traditionally Ph.Eur. reference standards were established in relation to specific monographs rather than for equipment performance control.
In the recent years the situation has slightly changed in that some reference standards used for equipment or method performance control were described:

Recent examples:

- Sodium Aminosalicylate dihydrate for equipment qualification CRS
- Amoxicillin trihydrate for equipment verification CRS
- Paracetamol for equipment qualification CRS
- Nicotinic acid for equipment qualification CRS
- *EI Standards (Cd, As, Pb, Hg)*

WHERE ARE WE TODAY?

Ph.Eur. Chapter 2.2.48. Raman Spectroscopy

Paracetamol for equipment qualification CRS

Material thoroughly characterised for identity, purity, homogeneity

Table 2.2.48.-1. – *Wavenumber shifts (and acceptable tolerances) of polystyrene, paracetamol and cyclohexane*

	Wavenumber shifts[A] [cm^{-1}]	Tolerances	
		Benchtop [cm^{-1}]	Hand-held [cm^{-1}]
Polystyrene[B]	620.9	± 1.5	± 2.5
	1001.4	± 1.5	± 2.0
	1031.8	± 1.5	± 2.0
	1602.3	± 1.5	± 3.0
	3054.3	± 3.0	NA[E]
Paracetamol[C]	797.2	± 1.5	± 2.5
	857.9	± 1.5	± 2.0
	1168.5	± 1.5	± 2.0
	1236.8	± 1.5	± 2.0
	1323.9	± 1.5	± 2.5
	1648.4	± 1.5	± 3.0
	2931.1	± 2.0	NA[E]

NICOTINIC ACID FOR EQUIPMENT QUALIFICATION CRS

Ph.Eur.: 2.2.25. (COM 11/2018)

Control of absorbance accuracy. Control the absorbance accuracy at an appropriate number of wavelengths in the intended spectral range using suitable solid or liquid filters to check that the absorbance measured at the test wavelength matches the certified absorbance of the filter or the absorbance value that is calculated from a certified specific absorbance. *Nicotinic acid for equipment qualification CRS* may be used.

Acceptance criteria

The difference between the measured absorbance and the absorbance of the certified material is ± 0.010 or ± 1 per cent, whichever is greater, for each combination of wavelength and absorbance assessed (applies to absorbance values not greater than 2). Tolerances for higher absorbance values should be defined on the basis of a risk assessment.

NICOTINIC ACID FOR EQUIPMENT QUALIFICATION CRS

CRS leaflet info:

2.2 Analytical information related to the intended use
Specific absorbance:
213 nm: = 430.7
261 nm: = 422.5

2.3 Uncertainty of the assigned property values
Uncertainty of the assigned specific absorbance values, expressed as expanded uncertainty (95% confidence interval, coverage factor of k=2): U_{213nm}: ±3.5, U_{261nm} :±2.8

SODIUM AMINOSALICYLATE DIHYDRATE FOR EQUIPMENT QUALIFICATION CRS

Ph.Eur. 2.5.12. Water: Semi-micro determination

… Instrument qualification is carried out according to established quality system procedures, for example using a suitable certified reference material (**sodium aminosalicylate dihydrate for equipment qualification CRS** may be used).

SODIUM AMINOSALICYLATE DIHYDRATE FOR EQUIPMENT QUALIFICATION CRS

2.2 Analytical information related to intended use, when applicable

2.2.32. – Loss on drying

Certified loss on drying value[1)]: 169.6 mg/g
Uncertainty[2)]: 0.4 mg/g

Test procedure: Determine the loss on drying in triplicate using 1000 mg of substance per determination. Drying conditions: 105 °C until constant mass (Ph. Eur. method 2.2.32. d))

Container dimensions (recommended): diameter about 50 mm; height about 30 mm.

2.5.12. – Semi-micro determination of water

Certified water content[1)]: 171.6 mg/g
Uncertainty[2)]: 1.0 mg/g

Test procedure: Carry out the test in triplicate using 100 mg of substance per determination.

Hydranal composite 5 was found suitable. If other solvents/titrants are used, carry the suitability test described in Ph. Eur. 2.5.12.

SODIUM AMINOSALICYLATE DIHYDRATE FOR EQUIPMENT QUALIFICATION CRS

Additional leaflet info:

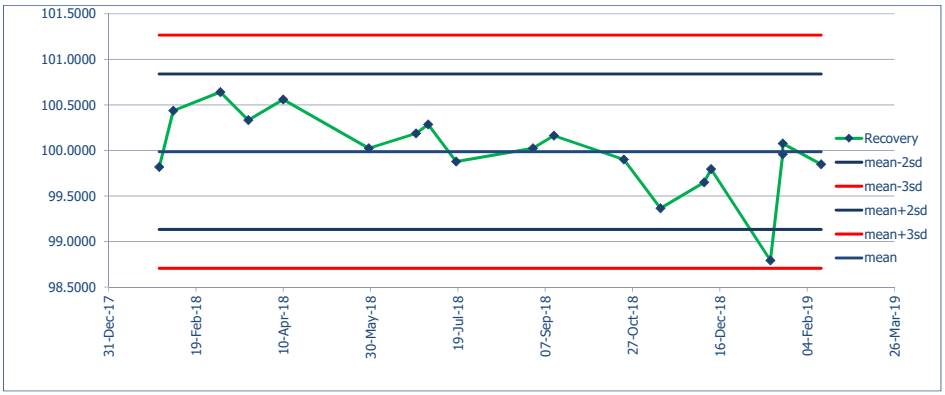
Suggested acceptance criteria:
Taking into account inter-laboratory standard deviation as well as the mean intra-laboratory standard deviation obtained the inter-laboratory study for the value assignment, the result of a measurement performed (following the above experimental conditions) is considered acceptable if the mean of 3 replicate determinations falls within the following limits:

Loss on drying (2.2.32.):	167.2 mg/g to 172.0 mg/g
Semi-micro determination of water (2.5.12.):	165.4 mg/g to 177.8 mg/g
Micro determination of water (2.5.32):	167.3 mg/g to 173.7 mg/g

It is understood that a laboratory may apply a different approach to set acceptance criteria.

SODIUM AMINOSALICYLATE DIHYDRATE FOR EQUIPMENT QUALIFICATION CRS

KF statistical equipment control chart



ELEMENTAL IMPURITIES SOLUTION CRS

Ph.Eur. 2.4.20. DETERMINATION OF ELEMENTAL IMPURITIES

ACCURACY

Verify the accuracy using a certified reference material or by performing a test for recovery. *Elemental impurity solutions CRS* may be used.

INFORMATION LEAFLET Ph. Eur. Reference Standard

Lead solution CRS batch 1

1. **Identification**

Catalogue code: Y0001996 Unit Quantity: ca 10 mL

2. **Scientific Information**

2.1 Intended use

Reference Standard for laboratory tests as prescribed in the European Pharmacopoeia.
Established for use with chapter: 20420.

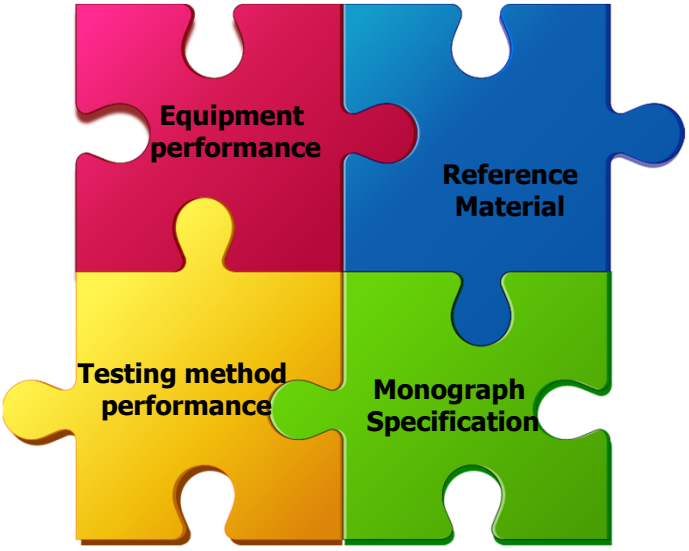
2.2 Analytical information

Mass fraction of lead in the solution:	0.9996 mg/g
Associated expanded uncertainty:	U = 0.0050 mg/g, k = 2
Density of the solution:	1.013 g/mL at 21.6 °C
Solvent composition:	about 2.5 % m/m nitric acid

Traceability to the SI base units kilogram and mole is achieved through an uninterrupted chain of calibration measurements that link lead solution CRS 1 to a primary material characterised by a National Metrology Institute at the highest metrological level (High purity lead BAM-Y004).
The IUPAC standard atomic weight for lead shall be applied.
Dilutions of lead solution CRS 1 should be made with 2.5 % nitric acid.

CRS may also be suitable for other purposes, e.g.:
- standard for quantification
- for spiking/recovery testing

AND TOMORROW ?!

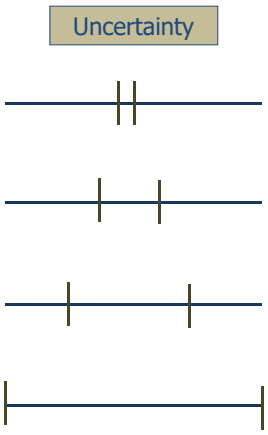


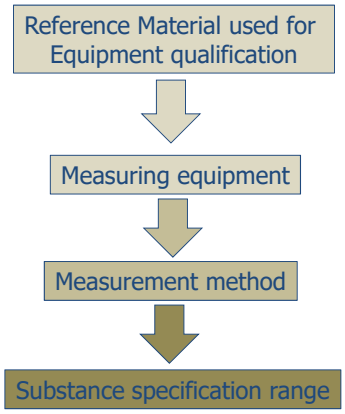
ARE YOU CERTAIN OF YOUR RESULT?

Neither the production nor measurement processes are devoid of error, there will always be some dispersion in the observed product value either for repeated measurements of one item or for measurements of a series of items.

Conformity assessment is focused on determining actual product errors: **apparent dispersion due to limited measurement capability should normally be small.**

ARE YOU CERTAIN?





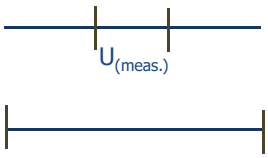
HOW "SMALL" IS SMALL ENOUGH?

ISO GUIDE 98-3 (GUM) – Type B evaluation of uncertainty
Method of evaluation of uncertainty by means other than statistical analysis of a series of observations, e.g.:

- Previous measurement data
- **Manufacturer`s specifications**
- Data provided in calibration and other certificates
- …

Ph.Eur. limit setting
Limits are based on data obtained in normal analytical practice; they take account of **normal analytical errors**, of **acceptable variations in manufacture** and compounding and of **deterioration** to an extent considered acceptable...

PRODUCT SPECIFICATION AND MEASUREMENT UNCERTAINTY



Measurement method

Substance specification range

ISO GUIDE 98-3 (GUM)

Assuming that a two-sided specification limit correspond to the mean ± 3sd (i.e. 99.73%), and a normal (Gaussian) distribution of the measurement results, the related measurement uncertainty can be calculated as follows:

$$u_{(meas.)} = \frac{a}{\sqrt{9}}$$

where *a* is the specification range/2

EXAMPLE OPTICAL ROTATION - SUCROSE

Ph.Eur. 2.2.7. Optical Rotation

EQUIPMENT PERFORMANCE

The accuracy of the scale is checked near the value to be measured or over an appropriate range, usually by means of certified quartz plates. Other certified reference materials may also be suitable (e.g. sucrose solutions).

Optical rotation measurements may be used to quantify the amount of an enantiomer or the ratio of enantiomers present in a sample. For that purpose, the linearity must be checked, for example using sucrose solutions.

Measuring equipment

Measurement method

Substance specification range

Ph.Eur. Monograph: 01/2016:0204 Sucrose

Specific optical rotation: +66.3 to +67.0

EXAMPLE OPTICAL ROTATION - SUCROSE

Ph.Eur. Monograph: 01/2016:0204 Sucrose
Specific optical rotation: +66.3 to +67.0

$$u_{(meas.)} \leq \frac{a}{\sqrt{9}} = \frac{{}^{1}/_{2} * (67.0 - 66.3)}{\sqrt{9}} \leq 0.117$$

k=2

$$U_{(exp.)} \leq 0.233$$

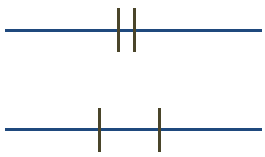
Substance specification range

Measuring equipment

Measurement method

REFERENCE MATERIAL REQUIREMENTS

Uncertainty



Reference Material used for Equipment qualification

Measuring equipment/method

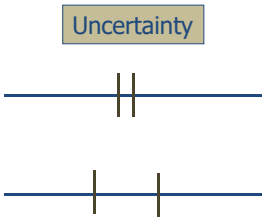
Reference material (RM): A material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be **fit for its intended use** in the measurement process.

WHAT IS NEGLIGIBLE?

Although different rules (1/3-rule to 1/5-rule) are often applied in metrology, no clear rule could be identified as regards to what can be considered "small" or "negligible".
Mathematically, the underestimation of the combined standard uncertainty ($u_{(x)}$) is as below, depending on the rule applied:

Omitting an uncertainty contributor of:	Underestimation of the combined standard uncertainty:
1/3	5%
1/4	3%
1/5	2%

REFERENCE MATERIAL REQUIREMENTS



Reference Material used for Equipment qualification

↓

Measurement equipment/method

$$U_{(exp.RM)} \leq k \times \frac{a}{\sqrt{9}} \div 3 \leq 2 \times \frac{0.35}{9} \leq \pm\ 0.078$$

NIST Sucrose CRM:
Certified value for specific optical rotation: **+ 65.517° ± 0.134**

CONCLUSION

- **Reference standards for equipment qualification and control as described in the Ph.Eur. General methods are a highly relevant tool to ensure reliability off measurement results.**
- **Reference Standards for equipment qualification are highly characterized specimens that may be employed for additional purposes.**
- **Education and guidance of the users on the appropriate use of such standards is paramount.**
- **Suitability of compendial reference standards for equipment qualification is demonstrated, for other standards this must be carefully evaluated.**
- **Equipment / method capability should be taken into account when setting substance specific limits.**

Thank you for your attention

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Feedback on the work of the Ph. Eur. Vibrational Spectroscopy and Analytical Data Modelling (VSADM) Working Party

Prof. Dr. MANEL ALCALÀ BERNÀRDEZ
Universitat Autònoma de Barcelona (Spain)

Universitat Autònoma de Barcelona

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

VSADM scope

- Former Near Infrared (NIR) WP (-2013)
- Vibrational Spectroscopy and Analytical Data Modelling (VSADM) WP (2014-)
- Drafting and revision of general chapters
  - Chemometrics and multivariate data analysis
  - Measurement techniques or other vibrational spectroscopies
  - Provide support to the Process Analytical Technology (PAT) WP

VSADM members

- **Profile**
  - Current **expertise vibrational spectroscopy** related to quality control of active substances and excipients and in development of control methods
  - **Several years of experience** in one or more of the following fields:
    - NIR and other vibrational spectroscopic techniques for quality control in a pharmaceutical manufacturing setting
    - Development of pharmaceutical control methods using chemometrics
    - Assessment of applications for marketing authorization
    - Market surveillance of quality in of texts
    - Pharmaceutical quality control in an independent testing laboratory

VSADM members

- **Current**
  - Prof. Dr M. Ulmschneider (Chair)
  - Prof. Dr M. Alcalà Bernàrdez
  - Prof. Dr K. Baumann
  - Dr M. Josefson
  - Mrs K. Kreft
  - Mr W. Oziminski
  - Dr H. Rebière
  - Prof. Dr C. Saal
  - Dr W. Schuh
  - Prof. Dr H. W. Siesler
- **Former**
  - Dr Neville Broad
  - Prof Pierre Chaminade
  - Dr Silvano Lonardi
  - Ian Linch

VSADM meetings

- **Number of meetings (n=22...24)**
  - 2014 (Apr, Set, Dec)
  - 2015 (Feb, Apr, Aug, Set, Nov, Dec)
  - 2016 (Apr, Oct, Dec)
  - 2017 (Feb, Apr, Oct, Dec)
  - 2018 (Jan, Apr, Oct, Dec)
  - 2019 (Mar, May, Oct, Dec)

VSADM chapters

- **Measurement techniques**
  - 2.2.24 Absorption Spectrophotometry, Infrared
  - 5.24 Chemical Imaging
  - 2.9.52 Scanning Electron Microscopy
- **Analytical Data Modelling**
  - 5.21 Chemometric Methods Applied to Analytical Data
  - 5.28 Multivariate Statistical Process Control (MSPC)

2.2.24 ABSORPTION SPECTROPHOTOMETRY, INFRARED

- ***Revision of chapter*** 04/2019:20224
- **European Pharmacopoeia 9.7**
- ATR measurements
- Simplification of accuracy test of band positions

5.24 CHEMICAL IMAGING

- ***New chapter*** 01/2018:52400
- **European Pharmacopoeia 9.3**
- Combination of spectroscopic techniques with spatially resolved sensing technologies to obtain chemical and physical information of a surface
- IR, NIR, Raman

2.9.52 Scanning Electron Microscopy

- ***New chapter*** XXXX:20952
- **Pharmeuropa 30.2**
- Extremely powerful imaging technique that is far superior, in terms of resolution, magnification and depth of field, to light microscopy
- Provides topographical and compositional information
- Combination with X-ray microanalysis enables elemental analysis to be performed
- Well-established technique to examine and characterize a wide range of pharmaceutical materials, in solid, semi-solid and liquid form

5.21 CHEMOMETRIC METHODS APPLIED TO ANALYTICAL DATA

- ***New chapter*** 04/2016:52100
- **European Pharmacopoeia 8.7**
- Introduction to the use of chemometric techniques for processing analytical data sets
- The objective is to provide indications on good chemometric practice
- It is not an exhaustive review of these techniques, as refinements and innovations are constantly being introduced

5.28 Multivariate Statistical Process Control

- ***New chapter*** XXXX:528000
- **Pharmeuropa 31.3 (July 2019)**
- It is an introduction to the use of Multivariate Statistical Process Control for monitoring and controlling manufacturing processes
- The objective is to provide guidance on good practice and requirements
- This chapter complements general chapter **5.21.** Chemometric Methods applied to Analytical Data

Future

- **New name**
  - **S**pectroscopy and **D**ata **A**nalysis
  - SDA WP
- **New revisions and drafts**

Feedback on the work of the Ph. Eur. Vibrational Spectroscopy and Analytical Data Modelling (VSADM) Working Party

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GLOBAL SUPPLY

Analytical QbD – An Industry Perspective

Graham Cook Ph.D
Global Quality Operations

General Methods Workshop
EDQM and Ph.Eur.: State-of-the-art Science for Tomorrow's Medicines
Strasbourg, France
19-20 June 2019

Breakthroughs that change patients' lives

Overview

- What is Analytical Quality by Design (AQbD)?
  - Principles and Tools
  - How are the principles and tools applied to method development?
  - What are the benefits of applying AQbD?
- Will AQbD affect the pharmacopoeias?
  - How is the regulatory framework evolving?
  - MHRA/BP/Industry AQbD project

Disclaimer: This presentation features terminology and definitions, such as ATP and MODR, that has been used in the literature but are not necessarily endorsed by Pfizer

How do we apply Quality By Design (ICH Q8) to analytical methods?

ICH Q8 Pharmaceutical Development defines Quality by Design as…

We will adopt a consistent development process rather than an empirical simplex type approach

We know what the method has to be able to do

"a systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management"

We know how the method works and more importantly what makes it fail

We understand how method parameters influence performance

We leverage our expertise and experience to build in ruggedness and minimise method failures

Enhanced Development: Pharmaceutical and Analytical Method

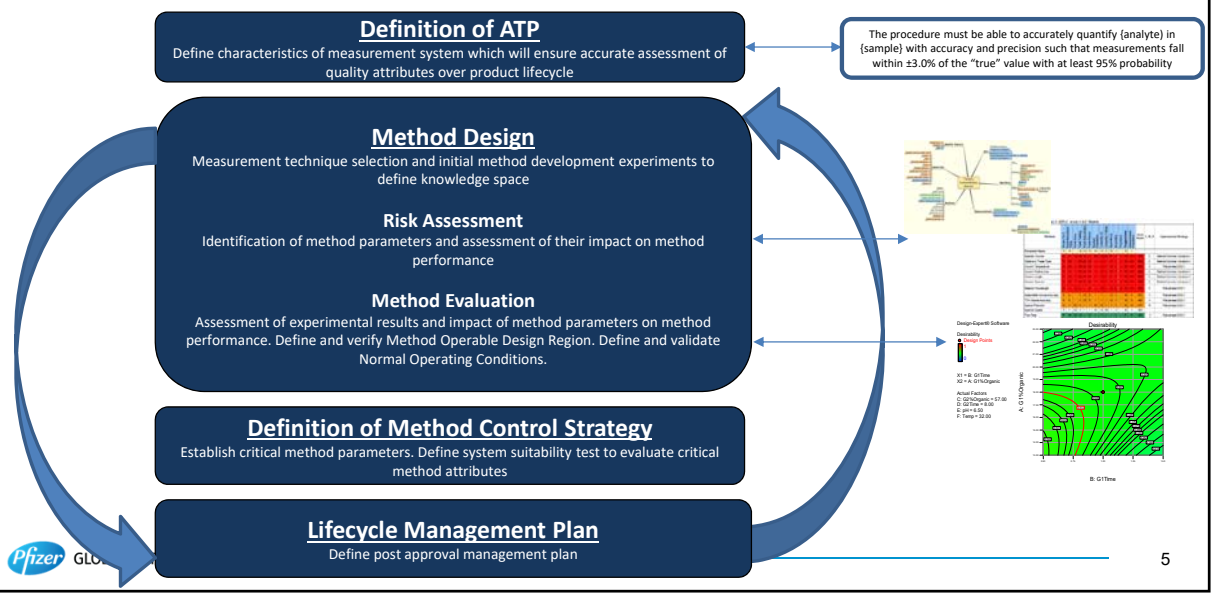
Outcomes of Analytical Development:

- A rugged method designed for a specific purpose within an overall product control strategy, operating within defined ranges which is capable of providing accurate results with a known variance
- Understanding and control of method parameters that impact method performance within a defined operating space

Other considerations:

- More efficient deployment of resources e.g. resources for method development vs fixing method issues, living with problematic methods, or regulatory efforts to change to a better method
- Potential to communicate method understanding and method capability in regulatory submissions to help inform the product control strategy

Analytical QbD - the individual elements for enhanced development



What are the benefits?

- Method understanding and robustness
  - Reliable analytical procedures with performance criteria based on the requirements of the reportable result
  - Less likelihood of 'failure' (which can better ensure product supply),
  - More efficient investigations if OOS/OOT results are observed
  - Knowledge and understanding about how procedure performance is impacted when both individual and combined critical inputs are changed
  - Performance qualification and verification provide assurance through the method lifecycle (with associated parameter or operating environment changes) that it remains fit-for-purpose.
- Confidence in the results – better decision making
- Enhanced assurance of quality for patients

Overview

- What is Analytical Quality by Design (AQbD)?
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  - What are the benefits of applying AQbD?
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Quality by Design and the Pharmacopoeias

- Pharmacopoeial requirements are typically embodied in the legislative framework
  - Pharmacopoeias usually allow flexibility to demonstrate compliance through alternative methods and/or a variety of science- and risk-based approaches (Quality by Design)
  - For example, Ph.Eur. General Notices include:
    - 'The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its **design**, together with its **control strategy** and data derived, for example, from **validation studies** of the manufacturing process.'
    - 'An enhanced approach to quality control could utilise process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone. Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.'
- Functionality - Related Characteristics
  - Non-mandatory content of excipient monographs that may facilitate application of PAT/QbD
- Alternatives to 'Zero tolerance' tests
  - For example, instead of using Ph.Eur. 2.9.40, Ph.Eur. 2.9.47 provides an alternative 'large n' approach for evaluating Uniformity of Dosage Units

Interest in Analytical QbD among Industry and Regulators

Various initiatives exploring development and application of AQbD principles and tools

ICH Q2 revision and Q14 Analytical Procedure Development

- Q14 Analytical Procedure Development
  - Aims to harmonise Analytical Procedure Development and description of Analytical Procedure Development process
  - Improve regulatory communication between industry and regulators
  - Facilitate more efficient, sound scientific and risk-based approval and post-approval change management of analytical procedures.
- Q2(R1) Revision of 'Validation of Analytical Procedures: Text and Methodology'
  - Scope to include validation principles for spectroscopy (e.g., NIR, Raman, NMR or MS), which often require multivariate statistical analyses
- Intended to complement with ICH Q8 to Q12 Guidelines, and ICH Q13 for Continuous Manufacturing
- Dialogue between ICH Q12 Product Lifecycle Management and ICH Q2/Q14 Expert Working Groups relating to Post-Approval Changes for Analytical Procedures

Some Pfizer Experiences with AQbD in Regulatory Filings

- Three submissions around 2011:
  - QbD concepts applied to analytical methods including: ATP, critical method attributes and critical method parameters, MODR
  - Requests for 'regulatory flexibility':
    - Two submissions: Changes to the method within the (ATP and) MODR would not require notification to the BoH
    - Third submission: No specific mention of post-approval changes to methods
  - Many questions received!
- Another submission in 2015:
  - Robustness demonstrated through multifactor statistical studies (without mentioning AQbD)
  - We didn't really ask for anything beyond approval of our specs, methods and validation packages – No questions received related to AQbD
- Conclusions from Pfizer AQbD Workshop in 2015:
  - AQbD concepts add value internally, but from a regulatory perspective, timing is not right
  - QbD concepts in general and AQbD, specifically, seem not to be able to add regulatory flexibility
  - AQbD jargon (e.g. ATP and MODR) should be confined to internal use only

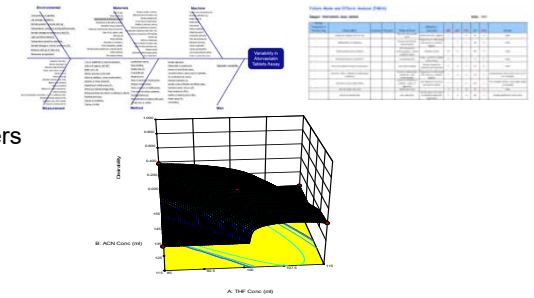
Collaborative AQbD Project – An Industry Perspective (1)

- MHRA/BP AQbD project with industry support, including Pfizer
  - Project aligned to two of the key priorities in the Agency corporate plan
    - Ensure the safe production and supply of medicines and healthcare products through enhanced systems
    - Support and enhance innovation and accelerate routes to market to benefit public health
- QbD concepts applied to the development of an assay for Atorvastatin in Atorvastatin Tablets
  - Multi-source finished product Monograph in development by BP
  - Practical focus: 'Learn by doing'
  - Tested applicability of AQbD concepts in a pharmacopoeial context

Collaborative AQbD Project – An Industry Perspective (2)

- Practical AQbD concepts investigated for Atorvastatin Tablets Assay
  - Explored definition of Analytical Target Profile
  - Effect of formulation studied – 5 products selected as representative
  - Applied risk assessment tools (Ishikawa Fishbone, FMEA) to identify the method parameters to study
  - Design of Experiments (DoE) applied to generate understanding of the impact of the method parameters on 'Method Desirability' function
- MHRA/BP consultation on presentation of information for users of the British Pharmacopoeia e.g. in a Monograph

Empirical ATP 2: Combined Measurement Uncertainty
The analytical method must be capable of quantifying Atorvastatin in Atorvastatin Tablets from 70% to 130% of the true value, with an accuracy and precision (CV) such that results reside within not more than 3.0% of the true value, with 95% probability.



Collaborative AQbD Project – An Industry Perspective (3)

- Different perspectives
  - Drivers for ATP for pharmacopoeial monograph assay vs. new innovator medicinal product
  - Application to finished product formulations
- Some similar challenges and similar benefits to industry application of AQbD
  - Where to best focus resources to maximise scientific learning
  - Dealing with unanticipated problems
  - Enhanced method understanding and robustness
    - Method conditions
    - Establishing control and monitoring performance
    - Understanding variability
  - Making the correct decisions with the data

Conclusions

- Analytical Quality by Design
  - Systematic science- and risk-based approach to analytical method development
  - Benefits include enhanced method understanding and method robustness
- Regulatory system is evolving
  - No clear mechanism to incorporate AQbD concepts in regulatory filings at present
  - ICH Q2/Q14 EWG initiated
  - Pharmacopoeias are not barriers to QbD and embody some content that is consistent with QbD
  - Complementary initiatives can advance understanding and application of AQbD concepts

Conclusions

Will Analytical Quality by Design affect the pharmacopoeias?

…You decide!

Acknowledgements

Pfizer colleagues including:
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Brent Harrington

MHRA/BP AQbD project team members

Efpia ICH Q2/A14 EWG reps:
Oliver Grosche
Christof Finkler

European Pharmacopoeia - General Methods Workshop

Continuous Manufacturing: What Impact on the Pharmacopoeia

Moheb Nasr, Ph.D.
Nasr Pharma Regulatory Consulting (NPRC)

Strasbourg, France
June 19, 2019

Outline

- Introduction – Manufacturing Innovation and CM
- Current Regulatory Environment
- Regulatory and Quality Consideration
- Remaining Regulatory Gaps
- Recent Developments
- Compendial Considerations
- Conclusions

Why do we need innovation?

- Develop and deliver critical medicines to patients
  - Address unmet medical needs and improve quality of human life
  - Increase global availability
  - Improve quality assurance, especially for "old" drugs
- Enhance manufacturing efficiency and reduce cost
- Develop and produce medicines with environmental friendly processes
- Modernize regulations to become more aligned with 21st century quality vision (science and risk-based)

Manufacturing Innovation: Business Concerns and Challenges

- High cost of drug development
- Time constrain and need to speed up delivery of critical medicines
- Uncertain commercial forecast
- Building modern facilities while maintaining old and under utilized sites
- Conservative pharma culture and fear of the unknown
- Unpredictable return on investment of new and unproven technologies
- Complexity of supply chain
- Continual improvement is not built into corporate business models

Manufacturing Innovation: Regulatory Concerns and Challenges

- Lack of global harmonization
  - Unpredictable acceptability and support of "new" manufacturing approaches by global regulators
- Conservative culture (industry and regulators)
- Post-approval regulations
  - Lack of regulatory incentives for innovation and continual improvement
- Lack of trust
  - Need to boost confidence and build trust

Benefits of Continuous Manufacturing

- Considerable benefits to industry, regulators, and the Patient
  - Integrated processes with fewer separate unit operations (safer, faster response times, more efficient, shorter times, integrated control)
  - Smaller equipment footprint (more flexibility, lower costs, environmental friendly)
  - Better utilization to maximize the benefits of QbD and PAT
  - Real time product quality information leading to RTRT
  - Easier to scale up/down to accommodate changing supply needs

Current Regulatory Environment (1)

- The current regulatory environment supports advancing regulatory science and innovation
  - ***Regulators encourage industry meetings***
- Recent ICH Guidelines (Q8, 9,10 &11) emphasize science- and risk based approaches to assure product quality
- **Important to note that regulatory expectation for assurance of reliable and predictive quality is very much the same for batch and continuous processing**
- CM can be effectively executed within the existing regulatory framework, and there are no major regulatory hurdles for manufacturers to implement continuous manufacturing

Current Regulatory Environment (2)

- Several ICH and regional guidelines describing regulatory expectations, GMP, and post approval changes
- Recent and relevant ICH guidelines in place, including ICH Q8-11, ICH Q IWG training materials and point to consider papers
  - ICH Q12 - Step 3
  - ICH Q13 & 14 under development
- Large number of global and regional conferences on continuous manufacturing in the last 5 years
  - **International Symposia on Continuous Manufacturing of Pharmaceuticals (ISCMP, 2014, 2016, and 2018) enabled significant collaboration between regulators, industry and academia**

Relevant Regulations, Guidelines, and Standards Supporting CM

- ICH Guidelines (Q8, 9, 10,11 and IWG PTC documents)
- FDA Guidances (e.g. PAT and PV)
- EU Guidelines (e.g. PV/CPV, NIR, RTRT)
- ASTM Standards (e.g. ASTM E2537)

Regulatory Considerations (1)

- The definition of a batch (based on quantity manufactured or duration of the process) should be stated and discussed with regulators prior to manufacture
  - In this context, a batch can be defined based on the production time period, quantity of material processed, equipment capability, or production variation (e.g., different batches of in-coming materials), and also can be flexible to meet variable market demands by leveraging the advantage of operating continuously over different periods of time
- **From a regulatory perspective, it is expected that the size of batch is established prior to initiation of each production run**

Regulatory Considerations (2)

- In-process controls (IPCs) and sampling considerations are different than batch process and should be established accordingly
- Acceptable procedures for handling deviations must be defined
- Stability Considerations are similar to batch process
- In addition to typical regulatory and quality/GMP requirements, regulators expect further explanation on:
  - Process development and manufacturing process description
  - Control Strategy
  - Quality and GMP considerations

Manufacturing Process Description

- In general, the expectations are similar to traditional batch processes
- Need to provide sufficient information to explain engineering and technology principles to regulators to facilitate science and risk based assessment
- Many elements of process design and development should be treated as " Supporting Information" per ICH Q12 – Step 2
- Important to discuss and agree on broad filing strategy with regulators prior to filing
  - ICH Q13 need to confirm and elaborate on established conditions approach outlined in Q12
  - Performance based approach to define and justify established conditions is potential regulatory enabler

Control Strategy (CS)

- Control strategy should assure that the manufacturing process consistently produces product of the desired/intended quality
- Special Considerations for CS in CM:
  - State of control and process dynamics
  - Raw materials and intermediates
  - Equipment
  - Product collection or rejection
  - Traceability
  - Process monitoring and sampling
  - Specifications

KEY QUALITY/GMP CONSIDERATIONS (1)

- cGMP supports the implementation of continuous manufacturing
- Pharmaceutical Quality System (PQS)
  - Need to assess the need to revise/update existing PQS
- Batch Release aspects
- Start-Up and Shutdown Procedures
- State of Control: Product Collection and In-Process Sampling
- Process Validation (PV) and Continued Process Verification (CPV)
- Material Traceability in Continuous Manufacturing
- Handling of Raw Material and In-Process Materials

KEY QUALITY/GMP CONSIDERATIONS (2)

- Detection and Treatment for Non-Conformity
- Personnel Procedures and Training
- Material Carry-Over
- Material Diversion
- Production Floor Product Monitoring
- Raw Material Variability
- Equipment Failure

Bridging Existing Batch Manufacturing To CM

- Continuous processes can be introduced as a post-approval manufacturing change
  - Risk-based approach is useful to determine the type of bridging information needed to support continued product quality
  - ICH Q12 can be a great enabler
- Physicochemical Equivalence Considerations
  - Need to establish physicochemical equivalency
- Bioequivalence considerations depend on level of risk of manufacturing changes

Remaining Regulatory Gaps

- Lack of global harmonization
  - ICH Q13 should facilitate harmonization, reduce divergence and accelerate implementation
- Level of details in regulatory filing
  - Q12 established conditions and performance based approach
  - Q13 a potential enabler
- Modeling and predictive process control
- Unique aspects of bioprocessing to promote continuous, intensification and integration approaches
- Alignment on performance based approach

Recent Developments (1)

- Significant implementation progress in the last 5 years
  - Five continuous manufactured drug products approved in US (Vertex's Orkambi and Symdeko, Johnson &Johnson's Prezista, Eli Lilly's Verzenio and Pfizer's Daurismo
  - Four in EU (Vertex's Orkambi and Symkevi, Johnson &Johnson's Prezista, and Eli Lilly's Verzenios)
  - One in Japan (Johnson &Johnson's Tramacet)
  - Many more under development and regulatory review

Recent Developments (2)

- Detailed and transparent discussions and detailed case studies at conference, e.g. ISCMP III (October 3&4, 2018), IFPAC Cortona (October 8-11, 2018) and USP Roundtables
- ICH Q13 under development and is expected to provide:
  - Key definitions and high-level scientific principles of CM
  - Regulatory expectations (e.g., control strategy and process validation) related to continuous manufacturing
  - More alignment on some key areas, e.g., regulatory consideration for model maintenance and update

Compendial Considerations (1)

- Current QA standards, including compendial requirements, will remain
- Fully integrated end-to-end CM is not fully aligned with today's regulatory schemes
- Role of compendial requirements in CM to be discussed and clarified in Q13 (and Q14)
- More reliance on RTRT for batch release and confirmatory end product testing
- Additional general chapters needed, e.g. terms and definitions, material characterization, advanced analytics, predictive models (development and validation), new formulations, new excipients, etc.

Compendial Considerations (2)

- Compendial monographs and general chapters need to be updated
- Material properties aspects
  - Greater understanding of physical characteristics is required (impact of material variability on process to ensure state of control)
  - Role of models to relate input material variability to CM process
  - Additional QC on materials (APIs and excipients) is needed
    - Are current standards for batch process adequate for CM?
    - What are the internal controls needed beyond CoA information?
- Finished DP must meet product quality and product performance tests specified in Pharmacopeia
  - CM process must ensure DP continue to meet DP CQAs

Conclusions

- Regulators are supportive of pharmaceutical manufacturing innovation
- Regulatory expectations are similar, for most part, to batch processing
  - Opportunities to challenges old practices, e.g. process validation
- Risk-based assessments and more utilization of QbD tools, including PAT, are critical to development and implementation of continuous manufacturing
- Need to evaluate PQS and relevant SOPs to ensure successful implementation and compliance with GMP
- ICH Q13 should provide regulatory clarity and propose/revise regulatory tools to accelerate adoption
- Current QA standards, including compendial requirements, need to be updated
  - Additional general chapters and monographs need to be revised to address unique aspects of CM

Questions???