

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

19-20 June 2019, Strasbourg, France

Workshop on Finished Product Monographs

Moderator

Dr Tobias Godschan, Outgoing Chair of the European Pharmacopoeia Commission

Experience of the U.S Pharmacopeial Convention

Bruk Alemayehu
Senior vice president, Chemical Medicines



Topics

- ▶ Trusted resources
- ▶ Development and scope of Standards
- ▶ Ongoing commitment
- ▶ Partner with us



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To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.



USP and FDA



USP & FDA Work Together to Protect Public Health

► USP: Private Not-For-Profit Organization

- Engaged in the development and revision of compendial standards for drugs (and other products)
- Public standards related to identity, strength, purity, quality, packaging, labeling

► US FDA: Government Agency

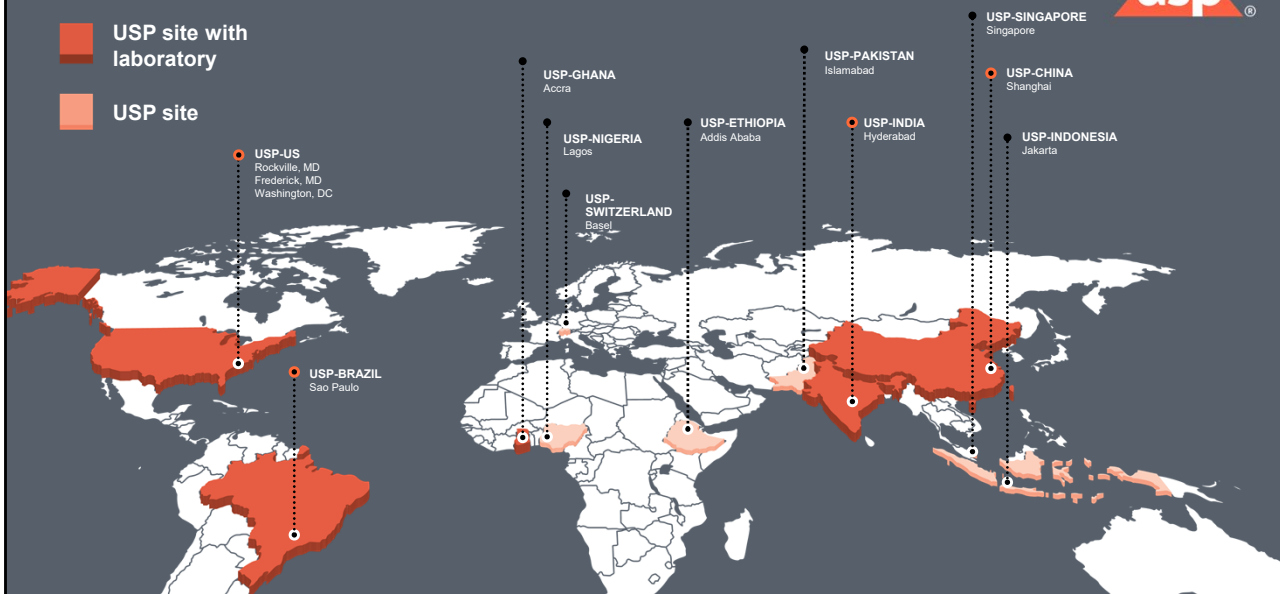
- Engaged in the promulgation and enforcement of drug (and other product) regulatory requirements
- Safety, Efficacy, NDA/ANDA (private license) approvals for marketing, manufacturing processes, etc.

We work globally



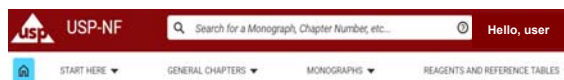
■ USP site with laboratory

■ USP site



USP – public standards

USP standards used in over 140 countries



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USP-NF Documentary and Reference Standards



USP 42 - NF 37

General Chapters	364
Total Monographs	4990
Substance Monographs	2227
Product Monographs	2763

PF 44 (1-6)

New General Chapter	22
Revised General Chapter	40
New Monographs	100
Revised Monographs	511

USP Reference Standards

Current Catalog	3815
New to Catalog in 2018	91



Documentary Standards

Reference Standards



For quality standards to be impactful, consider...

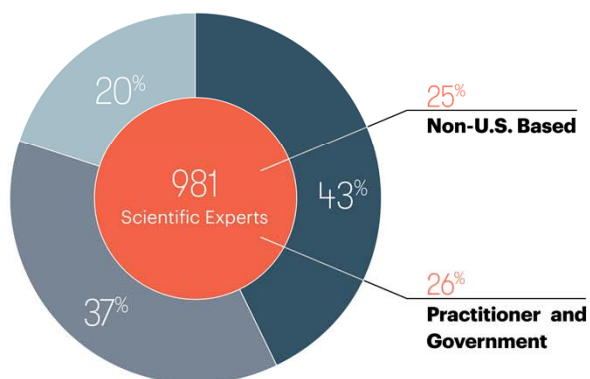


Scientific experts and volunteers develop our standards



981 Scientific Experts- Volunteers and Government Liaisons

- 428 Expert Committee Members
- 362 Expert Panels-Only Members
- 191 Government Liaisons



Developing standards



Anatomy of drug product monograph



Title

DEFINITION

States the required APIs and required percentages of the labeled amounts

IDENTIFICATION

- A. (Are the actives present?)
- B. (Are the actives present?)

ASSAY

- (Are the required percentages of the labeled amounts present?)
- o Solvents and Mobile phase
 - o Stock, System suitability, Standard, and Sample solution preparations
 - o Chromatographic system description
 - o System suitability requirements
 - o Calculation
 - o Acceptance criteria

PERFORMANCE TESTS

Dissolution <711>

- (Are the release requirements met?)
- o Dissolution conditions
 - o Analytical procedure (see Assay for an example)
 - o Tolerances

Uniformity of Dosage Units <905>

(Are the requirements met?)

IMPURITIES

Organic Impurities

- (Are impurities sufficiently controlled?)
- o Analytical procedure (see Assay for an example)
 - o Acceptance criteria

ADDITIONAL REQUIREMENTS

Packaging and Storage

Labeling

USP Reference Standards <11>

How do we build a monograph?



Atorvastatin Calcium Tablets

DEFINITION

Atorvastatin Calcium Tablets contain an amount of atorvastatin calcium $[(C_{33}H_{34}FN_2O_5)_2Ca]$, equivalent to NLT 94.5% and NMT 105.0% of the labeled amount of atorvastatin.

IDENTIFICATION

- **A.** The UV absorption spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Buffer: 0.05 M ammonium citrate buffer pH 4.0 prepared as follows. Dissolve 9.62 g of anhydrous citric acid in 950 mL of water, adjust with ammonium hydroxide to a pH of 4.0, and dilute with water to 1000 mL.

Mobile phase: Acetonitrile, stabilizer-free tetrahydrofuran, and *Buffer* (27:20:53)

Supported by:

- ▶ Validation package(s)
- ▶ Specifications and SOPs
- ▶ Letter of approval
- ▶ Additional supporting data (such as CoAs, stability data)



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Required supporting information



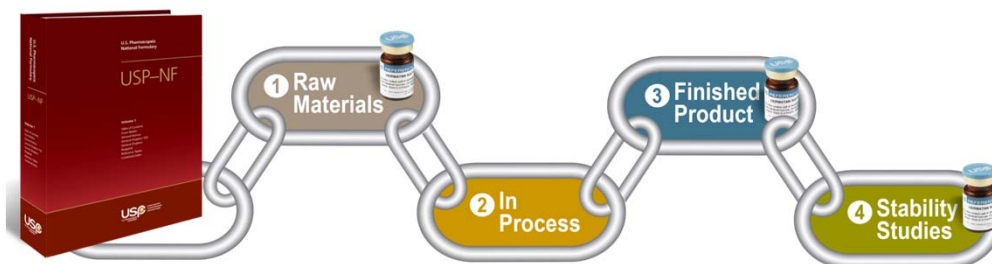
- ▶ **Shelf life specifications** along with current US FDA approval status (NDA, ANDA, etc.)
- ▶ **Analytical procedures**
 - Modern system suitability requirements
 - Representative chromatographic and/or spectral data
 - All tests as described in general chapters <1> to <5> including Performance tests such as <711> and <905>
- ▶ **Validation data** for all analytical procedures
 - Requirements per <1225> and current FDA/ICH guidelines
 - Brands of chromatographic columns used in validation
 - Forced degradation / stability data
- ▶ **Specific tests** such as Microbial tests <61> & <62>; Bacterial endotoxin <85>; pH <791>
- ▶ **Batch records / Certificates of Analysis** for at least 3 batches
- ▶ **Chemical information:** names, structures, molecular formula, molecular weight
- ▶ **Packaging and storage** requirements
- ▶ **Labeling** requirements
- ▶ **Reference material candidate materials** needed to support the testing: supply and/or source of supply
- ▶ **Rationale and data** are required to support requests for revision to an official monograph
- ▶ Description and Solubility information for drug substance monographs

Integrated control strategy



Official drug products are prepared “from ingredients that meet **USP or NF standards.**” [General Notices 3.10.]

- ▶ Drug product monographs rely on drug substance monograph controls for:
 - Identification and tests for counterions [prevents formulation (excipient) related false positives]
 - Process impurities [non-degradants, including non-degradant stereo isomers]



Flexible monograph approach



- ▶ **Address differences** in drug substance, ingredient, or product attributes
 - Polymorphic forms
 - Impurity profiles
 - Product-specific dissolution tests
- ▶ Labeling
- ▶ Different tests or acceptance criteria as approved by the **US FDA**
- ▶ Flexible approach is not used for **Assay**

Formulation-specific critical quality attributes



USP uses the flexible monograph approach

- ▶ Multiple tests for the same quality attribute are individually numbered; additional text may aid the user in determining whether the test is applicable.

Dissolution, Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*

Organic Impurities, Procedure 2 [Use Organic Impurities, Procedure 2 if Assay, Procedure 2 is used.]

- ▶ Drug product labeling must identify the test number used, generally when a test other than Test 1 applies

Labeling: The labeling states the *Dissolution* test used only if *Test 1* is not used. The labeling indicates which test for *Organic Impurities* is used only if *Procedure 1* is not used.

Flexible monographs - examples



Example monographs with multiple dissolution tests

- ▶ Diltiazem HCl ER Capsules – 20 tests
- ▶ Metformin ER Tablets – 16 tests
- ▶ Nifedipine ER Tablets – 12 tests
- ▶ Theophylline ER Capsules – 10 tests
- ▶ Tamsulosin HCl Capsules – 10 tests
- ▶ Olmesartan Medoxomil Tablets – 4 tests

Challenges to establishing standards



Lack of access to critical information for monograph development

Prior to Public Comment Period

- ▶ Partnering with stakeholders to help develop new standards and bring existing standards Up-to-Date
- ▶ Identifying relevant impurities and appropriate limits, especially if USP laboratories are developing and/or validating Up-to-Date analytical procedures
- ▶ Coordinating multiple performance tests

During/Post Public Comment Period

- ▶ Working with stakeholders to get more clarity / specificity in PF comments
- ▶ How to resolve statements indicating the proposed specifications are not appropriate for the public standard
- ▶ Identifying contacts with FDA-approved applications to ensure they are engaged and the proposals are suitable

call for candidates

2020—2025

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Important dates:

Jul 2018: USP launched the 2020-2025 Call for Candidates

Jan 2020: Deadline for Expert Committee chair applications

May 2020: Deadline for Expert Committee member applications







Jul 2020: 2020-2025 Council of Experts and Expert Committees begin their work



For additional information visit callforcandidates.usp.org or contact USPVolunteers@usp.org.

2020-2025 Expert Committees

2020-2025 Council of Experts – Expert Committees

Chemical Medicines	Biologics	Excipients	Dietary Supplements & Herbal Medicines, Food Ingredients	Healthcare Quality & Safety	General Chapters
					
1 Antibiotic, antiviral, & antimicrobial 2 Cardiovascular, cough, cold & analgesics 3 Gastrointestinal, renal, endocrine, ophthalmic, oncology, dermatology & animal health 4 Nonradioactive imaging agents, aerosols, radiopharmaceuticals, psychiatric, & psychoactive 5 Pulmonary & steroids 6 Over-the-counter (OTC) methods & approaches	1 Peptides & insulins 2 Therapeutic proteins 3 Advanced therapies (cell, gene, tissues, & genome-editing)* 4 Antibiotics using microbial assays 5 Complex products & vaccines	1 Simple: Carbohydrates, minerals & salts 2 Complex: Polymers, oils, fats, waxes, plants & clays 3 Excipient test methods*	1 Food ingredients 2 Non-botanical dietary supplements 3 Botanical dietary supplements & herbal medicines 4 Admission, evaluation & labeling*	1 Nomenclature & labeling 2 Healthcare quality 3 Compounding 4 Healthcare information & technology*	1 Packaging & distribution 2 Microbiology 3 Dosage forms 4 Chemical analysis 5 Physical analysis 6 Statistics 7 Measurement and Data Quality*
* Represents a new Expert Committee					

Thank You



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Finished Product Monographs Perspective of a Regulatory Authority

Andrea Cseh-Pálos

National Institute of Pharmacy and Nutrition, Hungary
EDQM and European Pharmacopoeia, 19-20 June 2019, Strasbourg

Overview

- Introduction
- Assessment issues, challenges
- Examples
- Proposals
- Potential advantages

INTRODUCTION

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Finished Product (FP) monographs

Goal: provide harmonized standards in Ph.Eur.
also for **finished products (FP)**

- that contain an API for which a Ph.Eur. monograph exists (or on the work program)
- that have been authorized in at least one of its member states
- that have a high public health interest

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How to read and apply FP monographs...

General principles for Monographs on Finished Products (FPs) containing chemically defined active substances

- https://www.edqm.eu/sites/default/files/general_principles_for_monographs_on_finished_products_june_2017_e.pdf

...shall be read in conjunction with the

- Ph. Eur. General Notices,
- relevant dosage form monograph and
- general monograph on Pharmaceutical Preparations.

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ASSESSMENT ISSUES CHALLENGES

6

Suitability of the FP monograph specifications (methods and acceptance criteria) to adequately control the quality of the product

- needs to be demonstrated in the marketing authorisation application (MAA)
- assessment of these data is part of the marketing authorisation procedure.

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FPMs are legally binding...

- The same set of parameters and limits are not necessarily appropriate for different products (different excipients, packaging materials, FP manufacturing method, clinical batches)
- All products on the market should be covered
 - ⇒ Potential for unnecessary wide limits – lowest common denominator/lowering of standards

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FPMs are legally binding...

- EU (CHMP, QWP) guidelines will be less efficient tool for assessment
- (these guidelines are the basis for a common assessment approach)
- **Will it be possible to ask for tightening?**

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Dissolution testing procedure (test conditions, acceptance criteria)

If specified in the FP monograph:

- *shall be mandatory unless otherwise stated in the monograph (“unless otherwise justified and authorised”).*

BUT: should be sufficiently discriminatory to assure batch-to-batch consistency and where appropriate, consistency with those batches for which satisfactory evidence of efficacy has been demonstrated.

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Dissolution limit & method

- based on results of *in vivo* studies
- different for each individual product



establishing a common FPM dissolution method and specifications for generic products is challenging.

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If the product is **not** adequately controlled by the respective monograph...

- To be evaluated whether the proposed specifications and analytical methods are adequate for the specific product
 - ⇒ Feedback from authorities to the Ph.Eur. COM
 - ⇒ valuable information for review and potential revision of the monograph

Questions:

- When? During assessment or after approval?
- What will be the **legal position** for the product in the interim period?

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Impact on existing products

- Need for variations – to demonstrate the compliance even if in-house method is more appropriate
- Need for demonstrating that the in-house method is „at least equivalent” – validation, cross validation...
- Associated workload for applicants and NCAs
- If „not comply” – what to do? – withdraw? suspend ?– it was already authorized!

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Questions

- How to handle if the applicant does not submit a variation application to implement the FP monograph *in time*?
- Which type of variation?
- Until now no Category for that in the “Classification Guideline”.
- The following two categories were agreed by EMA via CAPs.
- Type IB: **B.II.d.1.z.** – Control of finished product (*Conformance to Ph.Eur. new drug product monograph*)
- Type IB **B.III.2.z.** (*Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State, (Drug Product)*)

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EXAMPLES

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Case 1

The product was approved just after the implementation date of FPM with:

- wider limit for total impurities (0.5% instead of 0.2%)
- in-house HPLC method for related substances

No variation since the approval

- The analytical method is different as described in the monograph
- No demonstration that the in-house method is at least equivalent to the FP monograph

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Justification of the applicant

- The limit for total impurities does not take into account any specified impurities
- The drug product specification includes two specified impurities both with a limit of nmt 0.2% (in line with ICH Q3B (R2) and maximum daily dose of 100mg/day.)
- Total impurity limit for the corresponding API is nmt 0.5%, → higher than the total impurity limit for finished product.
- **The product is other salt (or base) of the API**
⇒ the monograph does not apply

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Case 2

Change to align with the Ph.Eur. monograph

Present:

- *Include only individual degradants > 0.1% in the calculation of total degradants.*
- *The sum of all individual degradants = Total degradants*

Proposed

- Include only individual degradants **and process impurities** > 0.1% in the calculation of the total impurities.
- The sum of all individual degradants **and process impurities** = Total Impurities

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Related substances test

FP monographs

- limit degradation products arising during manufacture and shelf-life of the finished product, (including those impurities of synthesis that are also degradation products).

FP monographs are not

- designed to control impurities of synthesis that are not degradation products.
- necessarily take account of all possible impurities in future products.

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Case 2

the proposed calculation for total impurities includes individual degradation products and process impurities which exceed the reporting threshold of $> 0.1\%$.

The variation was accepted without any questions/comment!

Questions:

- Unspecified impurities – only degradation products or any?
- Total – should include also process impurities??

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Case 3

Change to align with the Ph.Eur. monograph

Only one (shelf-life, wider) specification is implemented

⇒ removal of separate, (tighter, accepted release) specification for impurities

Was it really necessary??

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PROPOSALS

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Proposals

A binding general text specifically for FPs would be useful

- The existing „*General principles ...*”* document should be amended/completed (see next slide) and moved into the General Notices
- https://www.edqm.eu/sites/default/files/general_principles_for_monographs_on_finished_products_june_2017_e.pdf

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Proposals for General Notices

Flexibility should be kept – the product should be assessed on its own merit

Clear procedure is needed:

- in case wider limit or a better analytical method is authorized based on sound justification
- on notification procedure of the COM and proposal for revision of FPM...

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Proposals for General Notices

Limits for impurities: to be introduced

„unless otherwise justified and authorized”

For alternative methods: the statement

*„In the event of doubt or dispute, the methods of analysis of the Ph.Eur. are alone authoritative” –
for FP should not be valid!*

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Introduction of a General Chapter

- Similarly to General Chapter 5.10.
- As a guidance/help for proper interpretation of the requirements
- The status of the dissolution methods and requirements should be clarified (mandatory or example)
- Limits for impurities:
 - Clarification is needed – (any individual and total vs. only any or total degradation products, reporting threshold....)
- General monograph of „Pharmaceutical Preparations” (2619) should refer to this general chapter.

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POTENTIAL ADVANTAGES

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Potential Advantages

At present:

- **ICH Q3B and ICH Q6A:** strictly applicable only for „new drug products”
 - legally more binding requirements (mandatory), for existing products as well
- **ICH Q3B:** no limit only thresholds for degradation products
 - possibility to ask for tighter limit as proposed by the applicant (in case it is unnecessarily wide and not properly justified by stability data at the time of authorization)

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Long term advantages

- Early development of the product (generics): the already existing monograph can be a good starting point – target requirements – easier assessment
- Analytical method validation - in case (only) the monograph method(s) are used, assessment of the validation document is easier – as only verification is needed

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Thank you for your
kind attention!

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Finished product monographs

Perspective of an OMCL

BRENIER Charlotte

Head of Chemical Medicines and other Health Products Physicochemical department
Laboratory Controls Division

19-20 June 2019

EDQM International conference, Strasbourg

Presentation of the French OMCL FR_ANSM

- ◆ The French OMCL FR_ANSM is the Laboratory Controls Division of the French Competent Authority ANSM (French National Agency for Medicines and Health Products Safety)
- ◆ This Laboratory Controls Division (CTROL) is located on three sites in France:
 - Saint-Denis: control of biological products
 - Lyon: control of vaccines in collaboration with the 2 other sites
 - Montpellier-Vendargues: control of chemical medicines, API, medical devices and gene therapy products.
- ◆ The laboratory Controls Division is involved in:
 - Market Surveillance
 - Batch release
 - Elaboration of standards (participation in EDQM working and expert groups)

French OMCL FR_ANSM

Quality management – ISO 9001

ANSM was audited according to ISO 9001:2015 at the end of 2018 and received the attestation in January 2019 in the scope of:

- Surveillance of health products,
- Handling of high risk situations
- **Control of health products**
- Inspection

French OMCL FR_ANSM

Quality management – ISO 17025

The laboratory control division, as part of the OMCL network, is regularly audited through MJA (Mutual Joint Audits) coordinated by EDQM.

- Ongoing attestations (*EN ISO/IEC 17025 version 2005*) :

Last audits carried out respectively in December 2015, May 2017 and in June 2017 for Saint-Denis, Montpellier-Vendargues and Lyon sites.

Audited activities: batch release for vaccines and **technics for market surveillance on all health products**.

The **attestations of compliance** obtained are valid until June 2020 for Saint-Denis site and **October 2021** for Montpellier-Vendargues and Lyon sites.

- Ongoing process

The laboratory control division is engaged in the implementation of the new version of the standard (ISO/ IEC 17025:2017).

French OMCL FR_ANSM

Control of chemical medicines (market surveillance)

- ◆ Context of controls
 - Annual market surveillance program
 - ❖ Includes reference and generic products
 - ❖ Based on a risk based approach for the selection of products
 - ❖ Concerns national products, MRP/ DCP, CAP
 - Emergency requests (*about 20% of the batches controlled*)
 - ❖ Suspicion of quality defect, emerging subjects of concern, new impurities
 - ❖ Pharmacovigilance, inspection feedbacks
 - ❖ Suspicion of falsification
 - ❖ Judicial requisitions

French OMCL FR_ANSM

Control of chemical medicines (market surveillance)

- ◆ Methods used for controls
 - Methods from MA files
 - ANSM methods (*market surveillance methods applied to generic series*)
 - EDQM/ OMCL network methods (*market surveillance methods for MSS studies*)
 - Ph. Eur. monographs
 - Other methods from USP, BP, scientific publications
- ◆ Typical results obtained (*2018, 526 batches including API*)
 - 6% of non compliance within the market surveillance program
 - 30% of non compliance for batches controlled on emergency requests

French OMCL FR_ANSM

Control of generic medicines

Current methodology for the control of generic series (national products, MRP, DCP):

- Choice of the critical parameters to be controlled depending on the product (example: assay, related substances, dissolution test, pH, ...)
- Choice of the methods involved:
 - ❖ For some tests, such as assay or related substances:
 - A **common method** (typically HPLC) is retained.
 - The compliance is checked against each manufacturer set of specifications
 - In case of non compliance: the reference method (MA file) is applied
 - ❖ For some tests, such as dissolution,
 - most often the specific methods described in MA files are applied
 - In some cases, additional tests using a common dissolution method are carried out to compare dissolution profiles.
- Conclusion: the compliance of each batch depends on the specifications described for shelf-life in each MA file. The set of **specifications can be different from a manufacturer to another one.**

The same methodology is applied for European MSS studies.

ANSM

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French OMCL FR_ANSM

Involvement in the elaboration of Ph. Eur. standards

- ◆ The French OMCL is involved in the elaboration of API and FP Ph. Eur. monographs:
 - Expert/ chair in EDQM groups 10C and 10D
 - ❖ Elaboration of API Ph. Eur. monographs
 - Expert in P4 group
 - ❖ Elaboration of API monographs
 - ❖ Elaboration of FP monographs:
 - Deferiprone tablets (2986) and deferiprone solution (2987) in 2017
 - Rivaroxaban tablets 3021 in 2017

ANSM

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Example 1 of Market surveillance study: Anticancer drug (solution for injection)

- ◆ 5 finished products (solutions for injection) commercially available in France were controlled using common methods and applying the specifications of each manufacturer.
- ◆ The products were controlled just before expiry date.
- ◆ A monograph for the active substance is described in the Ph. Eur., not for the finished products.

Example 1 of Market surveillance study: Anticancer drug (solution for injection)

- ◆ Composition of the finished products:
 - Active substance: 2 mg/ mL
 - Sodium chloride, hydrochloric acid (to adjust the pH), water for injection
- ◆ Aspect of the solution
 - Clear solution
- ◆ Example of physico-chemical tests retained for the controls:
 - Extractable volume
 - pH
 - Assay

Example 1 of Market surveillance study: Anticancer drug (solution for injection)

	Appearance	Extractable volume	pH	Assay
Specifications from manufacturers/ <i>results</i>				
Finished product 2 mg/ml, manufacturer A	Clear solution <i>Complies</i>	≥ nominal volume <i>Complies</i>	2.5 – 4.0 <i>3.02</i>	92.5 -105.0 % <i>100.4 %</i>
Finished product 2 mg/ml manufacturer B	Clear solution <i>Complies</i>	≥ nominal volume <i>Complies</i>	2.7 – 3.3 <i>3.12</i>	92 – 105 % <i>100.5 %</i>
Finished product 2 mg/ml manufacturer C	Clear solution <i>Complies</i>	≥ nominal volume <i>Complies</i>	2.5 – 3.8 <i>3.28</i>	95.0 – 105.0 % <i>100.4 %</i>
Finished product 2 mg/ml manufacturer D	Clear solution <i>Complies</i>	≥ nominal volume <i>Complies</i>	2.5 – 3.5 <i>3.03</i>	95 – 105 % <i>98.7 %</i>
Finished product 2 mg/ml manufacturer E	Clear solution <i>Complies</i>	≥ nominal volume <i>Complies</i>	2.5 – 3.5 <i>3.10</i>	1.85 – 2.10 mg/ml (92.5 – 105 %) <i>1.99 mg/ml</i> (99.5 %)
<i>Specifications that could be proposed in a FP monograph</i>	<i>Clear solution</i>	<i>≥ nominal volume</i>	<i>2.5 – 3.5</i>	<i>95.0 – 105.0 %</i>

Anticancer drug, solution for injection Conclusion

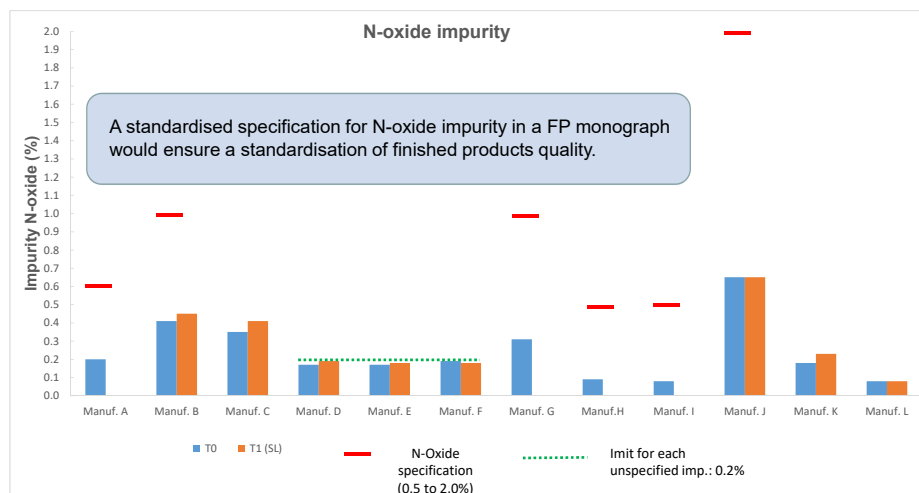
- ◆ The **composition** of the controlled anticancer drugs (2 mg/ mL) **is the same** (active substance dissolved in the same medium).
- ◆ The elaboration of the Ph. Eur. **FP monograph** would have permitted to ensure a standardisation of the limits (see example of pH and content ranges)

⇒ Standardised quality of medicines for the patient

Example 2 of Market surveillance study: Analgesic tablets

- ◆ 26 finished products (tablets) have been controlled within the French OMCL including film-coated and orodispersible tablets (4 FP were obtained from other OMCLs).
 - ◆ The following tests were carried out:
 - Identification of the active substance by HPLC
 - Uniformity of dosage units (Ph. Eur. 2.9.40)
 - Disintegration test for orodispersible tablets
 - N-oxide impurity determination at T0 (reception of the sample) and T1 (about shelf-life).
- ⇒ some manufacturers have a specification for that degradation impurity and some manufacturers don't specify it.

Focus on the results obtained for impurity N-oxide in orodispersible tablets



Example 3 of Market surveillance study: MSS Repaglinide

- ◆ Repaglinide is used for the treatment of type 2 diabetes.
- ◆ A European market surveillance study (MSS) was organised by EDQM in 2016. The OMCLs were in charge of the control of finished products available on their market and a common testing sample (named CTS) was analysed by each OMCL.
- ◆ 15 finished products were controlled within the French OMCL:
 - Repaglinide CTS (0.5 mg tablets)
 - Repaglinide 0.5 mg tablets and repaglinide 2 mg tablets from 7 other manufacturers
- ◆ The following tests were carried out:
 - Identification of the active substance by HPLC
 - Assay for CTS only
 - Uniformity of dosage units (Ph. Eur. 2.9.40)
 - Dissolution test

Example 3 of Market surveillance study: MSS Repaglinide

- ◆ The Testing Common Protocol provided by EDQM was followed:
 - Use of "generic methods" (common methods) as a screening study.
 - Each product had to comply with its actual specifications approved in the relevant dossier.
 - In case of out of specification results, the OMCLs had to come back to the method described in the product dossier in order to conclude on the quality of the product.

⇒ This approach is the same as that used for national market survey.

Example 3 of Market surveillance study: MSS Repaglinide - Dissolution test

- ◆ Repaglinide is considered to be slightly soluble (BCS Class II active substance) but many products contain excipients as meglumine in order to improve the solubility. This survey dissolution method was proposed in order to **verify the immediate release form**. In case of not compliance of results at stage S1, OMCLs had to perform the test according to the method described in the MA file of the product.
- ◆ Principle: the test was performed as a **survey method**. Quantification was performed by a unique isocratic HPLC method with UV detection at 210 nm.
- ◆ Dissolution Parameters
 - Apparatus:
Paddle Temperature: $37 \pm 0.5^\circ \text{C}$, Speed: 75 rpm, Medium: 900 mL of 0.1 N HCl, Sampling time: 45 minutes.
 - Chromatographic parameters:
Column: Zorbax SB-C8, $5\mu\text{m}$, $150 \times 4.6 \text{ mm}$. Flow rate: 1.0 mL/min.
Wavelength: 210 nm. Injection volume: 100 μL . Column temperature: 40°C .
Run time: 6 minutes. Retention time: About 4 minutes for Repaglinide peak.
- ◆ **Survey method specification:** Q = 75% at 45 minutes.

ANSM 16

Example 3 of Market surveillance study: MSS Repaglinide - Results

Description of the sample	Identification (HPLC)	Assay 95%-105% RSD %	CU 2.9.40 AV ≤ 15	Dissolution $\geq 80\%$ t =45 min	Conclusion
REPAGLINIDE 0.5 mg, tablet (CTS, Manuf. A)	Positive	101.4% RSD= 0.7%	VA = 2.2	100.7%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf B)	Positive		VA = 5.9	102.5%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf C)	Positive		VA = 4.6	100.6%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf D)	Positive		VA = 3.9	101.0%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf E)	Positive		VA = 5.6	100.6%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf F)	Positive		VA = 6.9	97.8%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf G)	Positive		VA = 3.4	100.3%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf H)	Positive		VA = 3.4	101.6%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf I)	Positive		VA = 3.9	100.3%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf J)	Positive		VA = 4.2	97.8%	Compliant
REPAGLINIDE 2 mg, tablet (Manuf F)	Positive	-	VA = 3.5	97.7%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf G)	Positive	-	VA = 4.8	100.9%	Compliant
REPAGLINIDE 2 mg, tablet (Manuf G)	Positive	-	VA = 3.7	97.9%	Compliant
REPAGLINIDE 0.5 mg, tablet (Manuf H)	Positive	-	VA = 4.5	99.5%	Compliant
REPAGLINIDE 2 mg, tablet (Manuf H)	Positive	-	VA = 4.1	100.4%	Compliant

Generic methods were found suitable to control the quality of finished products and to compare them using standardised methods and specifications.

ANSM 17

Feedback of the French OMCL (FR_ANSM) on the control medicines using standardised methods

- ◆ Generic methods are used for national market surveillance and for European market studies (example of Repaglinide tablets) providing a quality comparison of products commercially available on the market.
- ◆ Some specifications could be standardised (see examples of the anticancer drug and N-oxide impurity in analgesic tablets).

⇒ The perspective of Finished products monographs would help OMCLs to control finished products using common methods and specifications and could guarantee to standardise the quality of medicines.

⇒ **Standardised quality of medicines for the patient**

Finished product monographs

Perspective of an OMCL

I thank you for your attention!

Avertissement

- Lien d'intérêt : personnel salarié de l'ANSM (opérateur de l'Etat).
- La présente intervention s'inscrit dans un strict respect d'indépendance et d'impartialité de l'ANSM vis-à-vis des autres intervenants.
- Toute utilisation du matériel présenté, doit être soumise à l'approbation préalable de l'ANSM.

Warning

- Link of interest: employee of ANSM (State operator).
- This speech is made under strict compliance with the independence and impartiality of ANSM as regards other speakers.
- Any further use of this material must be submitted to ANSM prior approval.

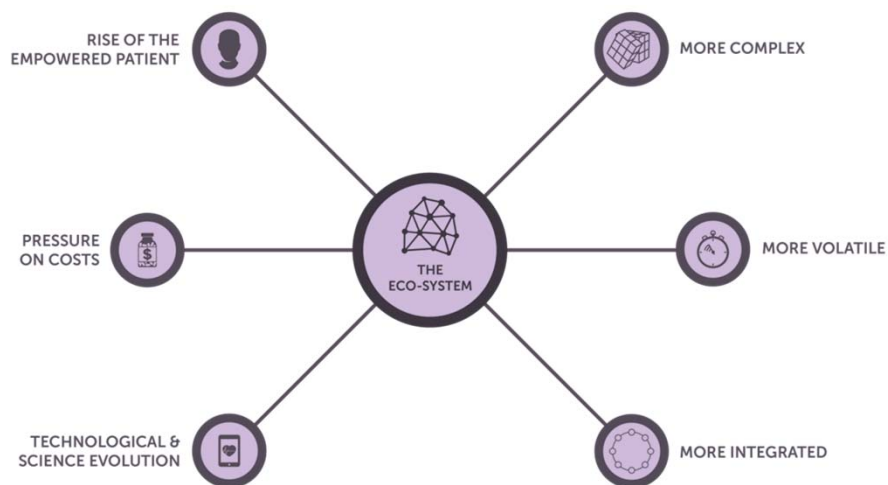
Finished product monographs From an innovator's perspective

Veronique Pinilla
UCB Biopharma



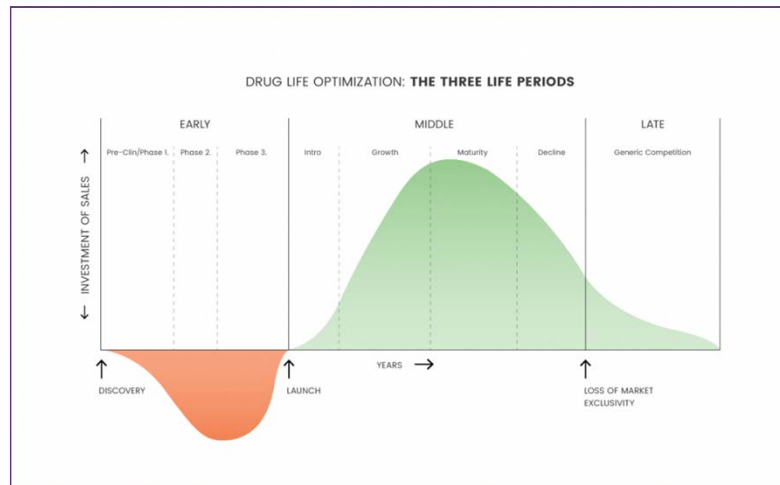
DeOnna, living with rheumatoid arthritis

Important drivers influencing the healthcare eco-system



Drug life cycle from Innovator perspective

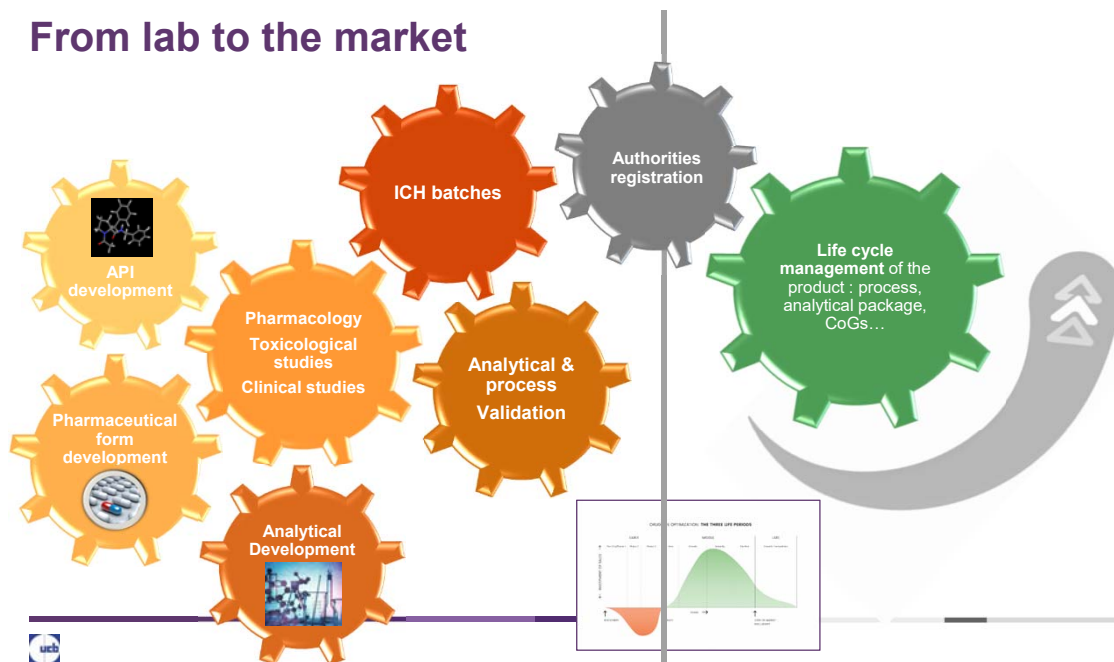
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Source: Stan Bernard, Bernard Associates, LLC, 2013

From lab to the market

4



Challenges & Opportunities

5



Challenges?

- Long development time from 10 to 15 years¹
- The cost of researching and developing a new chemical or biological entity was estimated at € 1,926 million (\$ 2,558 million in year 2013 dollars) in 2016²
- High attrition rate (1 compound approved out of 5 to 10K³ research compounds)
- Aim is to fit patient needs with high quality medicines



Opportunities?

- Optimize LCM to ensure maximum value is derived from the assets in development
- Optimize the CMO/CLO network
- Harmonize & simplify analytical methods/specifications worldwide
- Ensure harmonized quality for pharmaceutical product



1) 13.7 Years as a mean. Source: KMR's pharmaceutical Benchmarking Forum, analysed by Sanford Bernstein, published in SCRIP January 2013

2) DiMasi et al, Journal of Health Economics, January 2016

3) Fabio Pammolli et al., "The productivity crisis in pharmaceutical R&D"; Steven M. Paul et al., "How to improve R&D productivity"; and John Arrowsmith, "Trial watch: Phase II failures: 2008-2010"; "Trial Watch: Phase III and submission failures: 2007-2010"; and "A decade of change"

Monograph as driver for product quality

6



Monographs from Innovator perspective

7

- Drive quality for medicinal products
- Product under patent protection
- Find the best timing considering the network and the maturity of the process
- DS & DP or DS or DP?
- Geographies to be considered : EP? USP? JP? RU? CN? ...Interactions between EDQM & USP, PMDA... are key
- Global unique analytical package
- Impact on reference standard
- Business implication (workload required)



Internal assessment for the elaboration of a pharmacopoeia monograph

8

→ Evaluation of pro/con/risks, considering :

- the analytical package: technical information availability, evaluation of inconsistency with the "technical guidance for the elaboration of a monograph"
- the resources & financial implication: internal workload and cost variations associated
- the timing: having the loss of patent exclusivity in mind to define when to start the monograph
- the competitive advantages if any depending on the market competitors
- the management of the reference standards
- The impact of the testing network, internal and external CMO/CLO



Elaboration of a pharmacopoeia monograph applied to substance under patent protection

9

→ Procedure P4:

- Collaborative work between EDQM and innovator from possibly an innovator monograph proposition
- Evaluation of the existing data and supporting information to justify the analytical methods and specifications: stability data, batch release data, validation reports, justification reports...
- Provide samples, reference materials
- Experimental verification in EDQM laboratory and an official control lab, followed by technical questions/answers with innovator before having finalizing the draft for publication in Pharmeuropa for public enquiry



Elaboration of a pharmacopoeia monograph applied to substance under patent protection

10

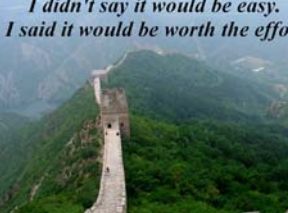
→ Procedure P4:

- As innovator, comments should be sent through the pharmacopoeia section liaison of the local authority of the EU state member
- Once draft monograph adopted by the European Pharmacopeia commission, the publication will follow and then implementation
- As innovator, variations to EMA file should be planned between publication in Eur. Ph. On-line web site and implementation date



- Analytical equivalence ?
- Regulatory impact ? Variation?
- Impact on testing network? Transfer or site verification?
- Equipment purchase?
- Reference standard impact?
- Harmonization with other monographs (USP, JP, ...)



- 
- I didn't say it would be easy.
I said it would be worth the effort*
- Marguerite Guiraud, 2008*

Monograph as driver for product quality

13



A harmonized monograph is a necessity



14

Questions?



Thanks!





GENERIC INDUSTRY PERSPECTIVE ON MONOGRAPHS FOR FINISHED PRODUCTS

Dr.Manish Gangrade
Vice President,
Analytical R&D and Regulatory Affairs (API)
Cipla Ltd., Mumbai, India

European Pharmacopoeia Edge Over



1

European Pharmacopoeia (Ph.Eur.) has a worldwide reputation for its monographs on APIs and excipients.

2

Well aligned with regulatory needs due to close collaboration with European regulators.

3

Up-to-date with scientific and latest technical developments

- E.g. Fostering implementation of relevant modern analytical technologies

4

Referenced by other regulatory agencies for its clarity in spite of availability of specific/ national pharmacopoeias.

Presentation Name

Confidential

Presenter

3

European Pharmacopoeia (Ph. Eur.)

- Provides elaborative representation of chromatograms, information on column make/brand and impurities
- Includes texts for a wide range of general dosage-form monographs, specialized published established monographs (e.g., for vaccines, blood products, insulin, and radiopharmaceuticals)
- *Ph. Eur.* monographs are experimentally verified and validated

EUROPEAN PHARMACOPOEIA 9.3

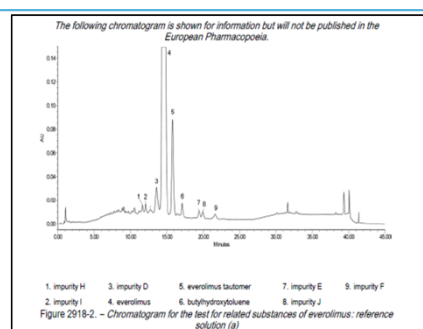
Chromatograms for identification

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.

1. Impurity H 2. Impurity I 3. Impurity D 4. everolimus 5. everolimus dimer 6. butylhydroxytoluene 7. Impurity E 8. Impurity J 9. Impurity F

Figure 2918-2. Chromatogram for the test for related substances of everolimus: reference solution (a)

Impurities Nomenclature



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4

Detailed view of Citaloprami hydrobromidum.

Status	In use							
Monograph Number	02288							
English Name	Citalopram hydrobromide							
French Name	Citalopram (bromhydrate de)							
Latin Name	Citaloprami hydrobromidum							
Pinyin Name								
Chinese Name								
Pharmeuropa	19.1							
Published in English Supplement	9.3							
Published in French Supplement	9.3							
Chromatogram	Available							
Additional information	Not available							
History	View history							
Interchangeable (ICH_Q4B)	NO							
Chapter 5.8 Pharmacopoeial harmonisation	NO							
Reference standards	Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price	SDS Product Code	
		Y0000853	Citalopram for system suitability	4	0.065 mg	79 EUR	201600207	
		Y0001008	Citalopram hydrobromide	1	5 mg	79 EUR	201600207	
Practical Information	Test(s) Brand Name/Information							
	Related substances Columns: Phenomenex Synergi Hydro-RP 80A, l = 0.25 m, diam. = 4.6 mm, 4 µm							
	Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
	2288	Citalopram hydrobromide	SHODHANA LABORATORIES LIMITED IN 500 055 Hyderabad	R1-CEP 2010-228-Rev 01	19/06/2017	VALID		Chemistry
	2288	Citalopram hydrobromide	IPCA Laboratories Limited IN 400 067 Mumbai	R1-CEP 2010-296-Rev 00	08/12/2016	VALID		Chemistry
	2288	Citalopram hydrobromide	ZHEJIANG HUAHAI PHARMACEUTICAL CO.,	R1-CEP 2010-037-	11/05/2016	VALID		Chemistry

Presentation Name

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Presenter

5

Necessity-Finished Products Monographs in Ph.Eur.

Presentation Name

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Presenter

6

Promote the Development of Generic Drugs for Uniform Quality Standard

Cipla

Ph. Eur. monographs play a major role in ensuring that medicinal products throughout Europe meet the same quality standards, thereby contributing to patient safety.

From a quality and standardization perspective, finished product should not be viewed any differently from any other substance (drug substance, excipient) for which a monograph exists.

Each harmonized finished product monograph will provide a reliable basis for making an independent judgement of product quality irrespective of its preparation.

Harmonized tests and limits across Europe with agreement on the content of product monographs with generic manufacturers.

Presentation Name

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Presenter



Current Generic Industry Practice for Specification Development of Finished Product

Cipla

Case Study: Salmeterol Xinafoate and Fluticasone Propionate Inhaler

Methods and Limits drafting

- The method and limits were drafted **based on the API monographs** of Salmeterol Xinafoate and Fluticasone Propionate in Ph.Eur., EU Directive 75/318/EEC, 3AQ11a and General Ph.Eur. chapters

Limit finalization

- The limits were finalized **based on comparison with reference product** (Name: Seretide Evohaler) and trend of batches manufactured during development trials. However, availability of finished product monograph for Salmeterol Xinafoate and Fluticasone Propionate Inhaler in Ph.Eur. would give better clarity in terms of tests, limits and methodology.

Need for justification

- If monograph of Salmeterol Xinafoate and Fluticasone propionate inhaler is available in Ph.Eur., it will **eliminate the need of justification** for any limit outside of $\pm 5\%$ at release for Assay test. (For e.g. BP monograph for same finished product has limit of $\pm 15\%$ for assay test)



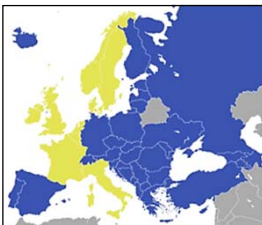
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Different specifications for finished product across Europe



- The European Union (EU) has 28 Member States
- Generic manufacturer apply for marketing authorization through different procedures (NP, MRP, DCP etc.) with their own specifications
- May lead to different drug product specifications across Europe for multiple MA holders

Ease in regulatory assessment



- Assistance for common approved pharmacopoeial grade specifications for finished product across Europe
- Result: Medicines of uniform quality can be available across Europe

Ph. Eur. grants observer status



- The Ph. Eur. Commission, as a consequence of globalization, allows non-Ph. Eur. member state nominations
- Observers for membership of the Groups of Experts and Working Parties
- Ease regulatory access to global market i.e. observers member states

- National pharmacopoeia are in local national language, hence, difficult to access by foreign manufacturer
- A possible difference in each national pharmacopoeial requirement makes it difficult to adopt
- Different implementation timelines

Challenges of National Pharmacopoeias



- Ph. Eur. is published and regularly updated in English and French, the two official languages of the Council of Europe
- Common standard of Ph. Eur. monographs on finished product will allow foreign manufacturers easy access to the monograph and help define the requirements to obtain a Marketing Authorization.
- Fixed timeline for updated product monograph
- Ease in the development of methods by referencing from available monographs.
- Only verification study to be performed.

Advantages of Ph. Eur.



Challenges and Proposals

Challenge

Generic Monographs Development: Multiple Customers and handling of commercial products

Proposals

Ph. Eur. to adopt multi-source approach, taking into account the specifications of more than one marketed product to produce a single monograph.

Encourage incorporation of new product monographs (e.g. complex drug products like liposomal injections, Inhalers etc.)

Methods and impurity limits aligned with corresponding API Monograph. Finished Product Monograph to cover only degradation products.

Performance based attributes can be specified for information only (without mandatory requirement to comply). E.g. Dissolution test, aerodynamic assessment for MDIs.

Acknowledgements

- **Dr. Shrinivas Purandare,**
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- **Ms Sheetal Pise,**
Associate Director-Analytical R&D, CIPLA Ltd.
- **Mr. Darshan Aigal,**
Associate Director-Regulatory Affairs API, CIPLA Ltd.

Thank You

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

Dr. Ulrich Rose
Head of Division
European Pharmacopoeia Department



Finished product monographs **Experiences of the European Pharmacopoeia**

**EDQM and European Pharmacopoeia:
State-of-the-art Science for Tomorrow's Medicines
19-20 June 2019, Strasbourg, France**

Monographs on "finished products"

- development for chemically defined active principles

2012: Ph. Eur. Commission reconsidered its strategy

pilot phase initiated with examples of single-source and multi-source products

2014: strategy decided to widen the scope of Ph. Eur.
start with focus on single-source products
first monograph published in Pharmeuropa

2015: adopted and published in Ph. Eur. 8.7

2016: first monograph has come into force on April, 1st:

Sitagliptin tablets

Content of FP monograph

TITLE

DEFINITION

Tests mandatory unless otherwise specified

IDENTIFICATION

TESTS

RELATED
SUBSTANCES

DISSOLUTION

ASSAY

IMPURITIES



Current focus

Follows critical assessment and discussions:

Takes into account the impact on registered products

- **Single-source monographs** on products that are potential future generics (Procedure 4)
- **Multi-source monographs** also possible: new expert group as from November 2019 (group 17, Procedure 1)
- **Immediate-release** dosage forms
- **solid and liquid** formulations
- Will be expanded subsequently

Work program

Adopted monographs

Product	Monograph number	Ph. Eur. supplement
Sitagliptin tablets	2927	8.7
Raltegravir tablets	2938	9.5
Raltegravir chewable tablets	2939	9.5
Lacosamide tablets	2989	9.8
Lacosamide oral solution	2990	9.7
Lacosamide infusion	2991	9.7
Deferiprone tablets	2986	9.8
Deferiprone oral solution	2990	9.7
Rosuvastatin tablets	3008	10.1

Work program

- In total **27** further monographs are on the work programme
- Single-source and multi-source monographs
- First multi-source monograph adopted at the 163rd session of the Commission in March 2019: **Rosuvastatin tablets**

General documents

- General policy described in:
« General principles for Monographs on Finished Products (FPs) containing chemically defined active substances »
- From this guide is derived the:
Draft « Technical Guide for the elaboration of Monographs on Finished Products containing chemically defined active substances » (still under discussion, not yet approved)

General principles document

“Since the choice of analytical procedures may be affected by the formulation and/or the manufacturing process, it must be demonstrated that the testing procedures described in an FP monograph are suitable for the specific FP. This demonstration has to be documented in the marketing authorisation application. The assessment of these data shall be part of the marketing authorisation procedure.”

Principles and challenges of monograph elaboration

- Title and Definition
- Identification tests
- Impurity policy
- Assay
- Dissolution tests
- Harmonisation

Title and Definition

LACOSAMIDE INFUSION

Lacosamidi praeparatio ad infusionem

DEFINITION

Sterile solution for infusion of Lacosamide (2992).

It complies with the monograph Parenteral preparations (0520) and the following additional requirements.

Content: 95.0 per cent to 105.0 per cent of the content of lacosamide ($C_{13}H_{18}N_2O_3$) stated on the label.

Title: active moiety name

- INNs used
- Degree of hydration and salt are omitted

- **Definition:** includes statement on the scope:
 - The exact pharmaceutical form
 - The **API covered:** specific salt and/or hydrate
- If appropriate states that the preparation is sterile
- Cross-reference to dosage form monograph
- **Content** as percentage of active moiety declared on the label (e.g. 95.0% - 105.0%)

Identification tests

Draft technical guide for finished products

Examples for possible identification tests:

- Spectrophotometric analysis, such as recording of infrared spectra (IR)
- Chromatographic examination by means of liquid chromatography (LC)
- Ultraviolet and visible absorption spectrophotometry (UV-Vis)

Typically a combination of UV and LC (size and retention time of principal peak, compared to CRS) is used, but

... IR direct (Sitagliptin tablets) or after extraction is also possible

Impurity Policy

In accordance with ICH guidelines:

- « Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical Substances », ICH Q6A
- « Impurities in new drug products », ICH Q3B R2



The monograph limits **degradation products** arising during manufacture and shelf-life of the finished product, including those impurities of synthesis that are also degradation products.

Synthetic impurities not taken into account -> they are identified using a CRS and then excluded

Impurity Policy: Rosuvastatin tablets (1)

How impurities are identified and limited:

Reference solution (b). Dissolve **7 mg of rosuvastatin for system suitability CRS** (containing impurities A, B and C) in 2.5 mL of acetonitrile R and dilute to 10 mL with water R.

Reference solution (c). Dissolve the contents of a vial of **rosuvastatin impurity mixture CRS** (containing impurity D) in 1 mL of the solvent mixture.

Reference solution (d). Dissolve 2 mg of **rosuvastatin ethyl ester R** (impurity FP-A) in 20 mL of solvent mixture. Dilute 1 mL of this solution to 100 mL with the solvent mixture.

Identification of impurities: use the chromatogram supplied with **rosuvastatin for system suitability CRS** and the chromatogram obtained with reference solution (b) to identify the peaks due to **impurities A, B and C**; use the chromatogram supplied with **rosuvastatin impurity mixture CRS** and the chromatogram obtained with reference solution (c) to identify the peak due to **impurity D**; use the chromatogram obtained with **reference solution (d) to identify impurity FP-A**.

Relative retention with reference to rosuvastatin (retention time = about 11 min):

impurity A = about 0.9; impurity B = about 1.1; impurity C = about 1.7;

impurity D = about 2.2; impurity FP-A = about 3.1.

Impurity Policy: Rosuvastatin tablets (2)

System suitability: reference solution (b):

– **peak-to-valley ratio**: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rosuvastatin.

Calculation of percentage contents:

- **correction factor**: multiply the peak area of impurity C by 1.4;
- for each impurity, use the concentration of rosuvastatin calcium in reference solution (a).

Limits:

- **impurity C**: maximum 1.5 per cent;
- **impurity D**: maximum 1.5 per cent;
- **impurity FP-A**: maximum 0.5 per cent;
- **unspecified impurities**: for each impurity, maximum 0.2 per cent;
- **total**: maximum 2.5 per cent;
- **reporting threshold**: 0.1 per cent; **disregard the peaks due to impurities A and B.**

Synthetic impurities A and B not taken into account



Assay

- Specific, stability indicating assay for content (usually HPLC)
- Standard specification: 95.0 to 105.0 % of the content stated on the label
- At least 5 tablets used to prepare the test solution
- Repeatability requirements of chapter 2.2.46 not valid. Standard RSD is still under discussion
- When the CRS of the API monograph is used, a conversion factor may be required

e. g. *Rosuvastatin calcium CRS* used for determination of rosuvastatin in rosuvastatin tablets -> conversion factor 0.96

Dissolution test - Disintegration test

- **Current policy:** testing procedures (test conditions, limits and acceptance criteria), if specified in the monograph, are mandatory

- *Flexibility: The tablets comply with the method and acceptance criterion as described below, **unless otherwise justified and authorised***

Under discussion

- Dissolution tests and limits should be sufficiently discriminatory to assure batch-to-batch consistency (purpose is not to demonstrate bioequivalence)
- Provided for quality control only
- According to ICH Q6A: for solid oral drug products for immediate-release containing highly soluble APIs, **disintegration** may be used instead of dissolution (Sitagliptin tablets, monograph 2927) => in line with General Principles
- Quantification: by LC or UV-Vis using either a CRS with assigned content (rosuvastatin tablets) or validated value for specific absorbance (Dronedarone tablets, not yet adopted)

Dissolution test - ongoing discussions

Discussion on dissolution tests is still ongoing



EDQM launched a survey to get the opinion of all possible stakeholders

Dissolution test - ongoing discussions

Two options proposed:

1. Monograph text: *"The tablets/capsules comply with the following dissolution test (method and acceptance criterion). If, for a given medicinal product, this method and the acceptance criterion prove not to be sufficiently discriminatory to assure batch-to-batch consistency, a different method and/or acceptance criterion must be provided in the marketing authorisation application and is subject to approval by the competent authority."*
2. No dissolution test would be provided in individual FPMs; nonetheless, the performance of dissolution testing would remain mandatory through the requirements of the dosage form monograph (e.g. Tablets (0478), Capsules (0016), etc.). A dissolution test (method and acceptance criterion) would need to be developed by each marketing authorisation applicant and submitted in the marketing authorisation application for assessment and approval by the competent authority.

Harmonisation

Informal prospective harmonisation (Ph. Eur. and USP)

- In total 19 monographs harmonised
- 13 API monographs and 6 finished product monographs



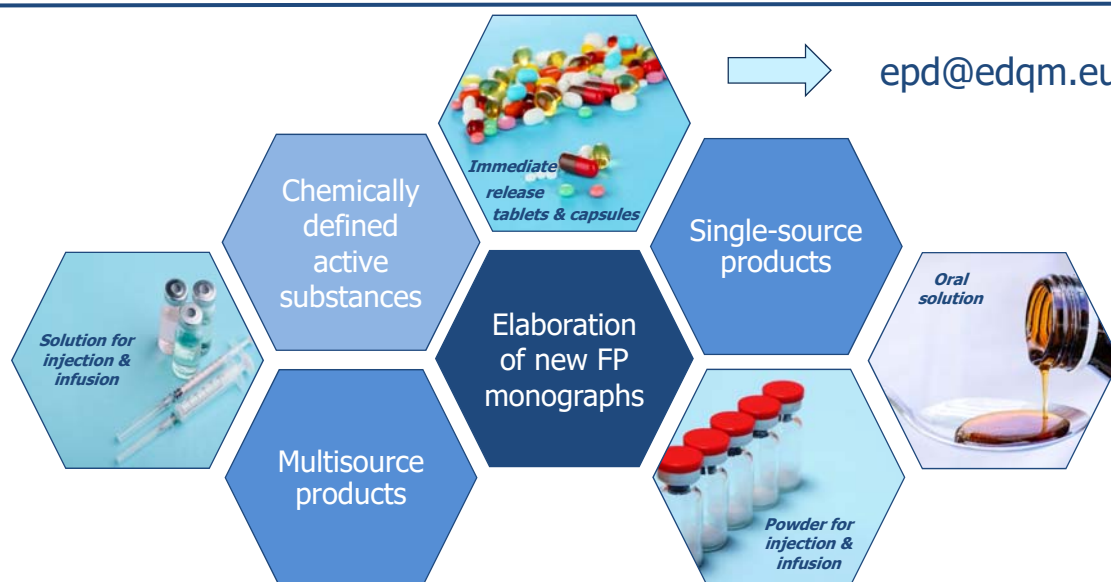
- Further 15 monographs on the work programme

Conclusion

- A number of FP monographs have been elaborated under the P4 procedure (single-source products)
- Several monographs are under elaboration under the P1 procedure (multi-source products)
- A first monograph under P1 has been adopted: Rosuvastatin tablets
- Policies for identification, impurities, assay are clear and agreed
- Revision of the current policy of dissolution tests still under discussion
- Once finalised, the « general policies » document will be integrated in the Technical Guide and in General Notices



Call for candidate FP monographs (\pm API)



Thank you for your attention



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