International Conference, 19-21 September 2022

Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition

Session 1A: Flexibility in the Ph. Eur.: a paradigm shift? (Part I)

Moderator: Prof. Torbjörn Arvidsson,
Former Chair of the European Pharmacopoeia Commission

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

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Flexibility in general texts of the Ph. Eur.

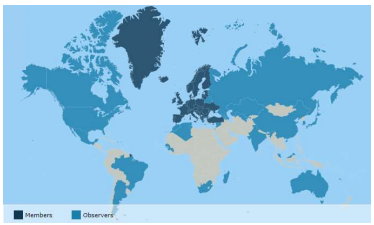
Mr Bruno Spieldenner

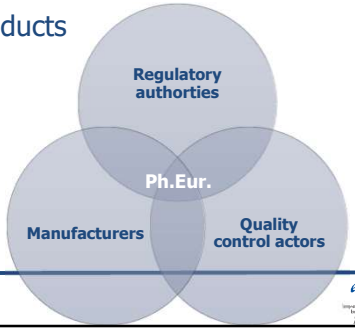
Head of Division on Chemical substances and products, herbals and general methods

European Pharmacopoeia Department, EDQM

The European Pharmacopoeia roadmap

- Promoting public health - one common, compulsory standard for the quality of medicinal products and their components
- Based on the safety for use by patients and in support of the free movement of medicinal products in Europe and beyond
- Legally binding and mandatory on the same date in 39 states and the EU. 28 Observers (26 countries, TFDA and WHO)
- European Union Directive 2001/83/EC as amended, on medicines for human use and and Regulation (EU) 2019/6 on veterinary medicinal products
- Ph. Eur. monographs and other texts are designed to meet the needs of:





"State of the Art" Ph. Eur. – a constant challenge

Needs in regulatory environment and development thereof

Developments in Manufacture and Globalisation

Increased demand for generic and biosimilar products

Scientific / technical evolutions

Taking in account industrial constraints

New risks to Public Health

TO TACKLE THESE CHALLENGES ➔ NEEDS FLEXIBILITY

At the crossroads…

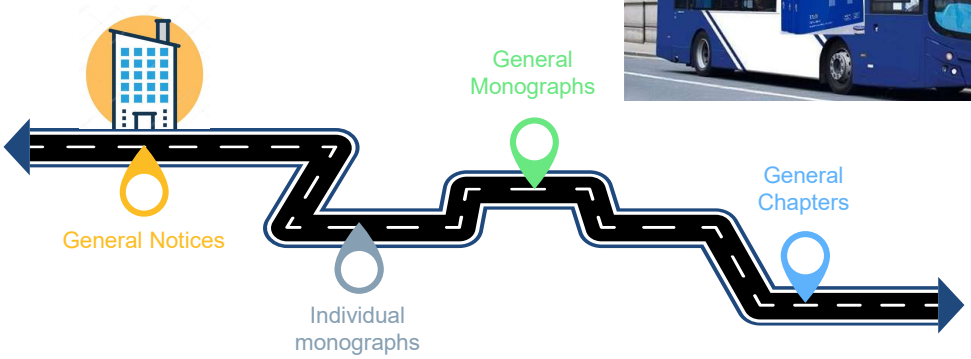
Constraints & legal status

Flexibility

Flexibility in the Ph. Eur.
Really?! a paradigm shift ?

Not a paradigm shift…

Buckle up and join me on the 'Flexibility in the Ph. Eur.' tour



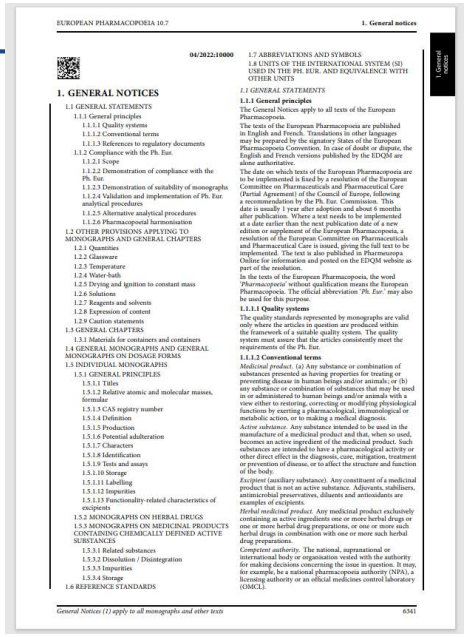
Flexibility HQ: General Notices

At the very beginning of the Ph. Eur.

- address general topics
- aim at providing basic information to the user
- apply to **all** texts incl. general chapters and other texts
- include rules to understand texts, conventional expressions …
- major revision in Supp. 10.7

Essential reading before starting to use monographs and other texts

OF NOTE: SECTIONS ARE NOW NUMBERED FOR BETTER REFERENCING



EUROPEAN PHARMACOPOEIA 10.7 — 1. General notices

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1. GENERAL NOTICES

1.1 GENERAL STATEMENTS
1.1.1 General principles
1.1.1.1 Quality systems
1.1.1.2 Conventional terms
1.1.1.3 References to regulatory documents
1.1.2 Compliance with the Ph. Eur.
1.1.2.1 Scope
1.1.2.2 Demonstration of compliance with the Ph. Eur.
1.1.2.3 Demonstration of suitability of monographs
1.1.2.4 Validation and implementation of Ph. Eur. analytical procedures
1.1.2.5 Alternative analytical procedures
1.1.2.6 Pharmacopoeial harmonisation
1.2 OTHER PROVISIONS APPLYING TO MONOGRAPHS AND GENERAL CHAPTERS
1.2.1 Quantities
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1.5.1 GENERAL PRINCIPLES
1.5.1.1 Titles
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1.5.1.4 Definition
1.5.1.5 Production
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1.5.1.7 Characters
1.5.1.8 Identification
1.5.1.9 Tests and assays
1.5.1.10 Storage
1.5.1.11 Labelling
1.5.1.12 Impurities
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1.5.2 MONOGRAPHS ON HERBAL DRUGS
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1.5.3.1 Related substances
1.5.3.2 Dissolution / Disintegration
1.5.3.3 Impurities
1.5.3.4 Storage
1.6 REFERENCE STANDARDS
1.7 ABBREVIATIONS AND SYMBOLS
1.8 UNITS OF THE INTERNATIONAL SYSTEM (SI) USED IN THE PH. EUR. AND EQUIVALENCE WITH OTHER UNITS

1.1 GENERAL STATEMENTS

1.1.1 General principles

The General Notices apply to all texts of the European Pharmacopoeia.

The texts of the European Pharmacopoeia are published in English and French. Translations in other languages may be prepared by the signatory States of the European Pharmacopoeia Convention. In case of doubt or dispute, the English and French versions published by the EDQM are alone authoritative.

The date on which texts of the European Pharmacopoeia are to be implemented is fixed by a resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care (Partial Agreement) of the Council of Europe, following a recommendation by the Ph. Eur. Commission. This date is usually 1 year after adoption and about 6 months after publication. Where a text needs to be implemented at a date earlier than the next publication date of a new edition or supplement of the European Pharmacopoeia, a resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care is issued, giving the full text to be implemented. The text is also published in Pharmeuropa Online for information and posted on the EDQM website as part of the resolution.

In the texts of the European Pharmacopoeia, the word '*Pharmacopoeia*' without qualification means the European Pharmacopoeia. The official abbreviation '*Ph. Eur.*' may also be used for this purpose.

1.1.1.1 Quality systems

The quality standards represented by monographs are valid only where the articles in question are produced within the framework of a suitable quality system. The quality system must assure that the articles consistently meet the requirements of the Ph. Eur.

1.1.1.2 Conventional terms

Medicinal product. (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings and/or animals; or (b) any substance or combination of substances that may be used in or administered to human beings and/or animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Active substance. Any substance intended to be used in the manufacture of a medicinal product and that, when so used, becomes an active ingredient of the medicinal product. Such substances are intended to have a pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

Excipient (auxiliary substance). Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilisers, antimicrobial preservatives, diluents and antioxidants are examples of excipients.

Herbal medicinal product. Any medicinal product exclusively containing as active ingredients one or more herbal drugs or one or more herbal drug preparations, or one or more such herbal drugs in combination with one or more such herbal drug preparations.

Competent authority. The national, supranational or international body or organisation vested with the authority for making decisions concerning the issue in question. It may, for example, be a national pharmacopoeia authority (NPA), a licensing authority or an official medicines control laboratory (OMCL).

General Notices (1) apply to all monographs and other texts — 6341

Demonstration of compliance with the Ph. Eur.

"*Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements.*"

Compliance

= satisfaction to all **mandatory** parts of a **monograph**

MANDATORY	INFORMATIVE
Definition Production Identification Tests Assay	Characters Storage *Functionality-related characteristics*

The way(s) to compliance - Flexibility

1.1.2.2

(1) An article is of Ph. Eur. quality if it complies with all of the requirements stated in the monograph. This does not im... cribed in a monograph when assessing compl... may obtain assurance that an article is of Ph. Eu... ol strategy and data derived, for example, from validation studies of the manufacturing process.

In certain monogra... hat the analytical procedu... e replaced by a suitable, validated pro... ' procedure), subject to approval by the competent authority.

(2) An en... releas... time r... ded by the need to comply with the Ph. Eur.

(3) *Reduction of animal testing*: the Ph. Eur. is committed to phasing out the use of animals for test purposes, in accordance with the 3Rs (Replacement, Reduction, Refinement) set out in the European Convention for the Pr... Scientific Purposes. In demonstrating compl... ay consider establishing additional system... the competent authority, the choice of tests performed to assess compliance with the Ph. Eur. when animal tests are prescribed is established in such a way that animal usage is kept to a minimum.

(1) WAIVING OF TESTS

NEW EXAMPLE PROCEDURE

(2) PROCESS ANALYTICAL TECHNOLOGY

(3) SUPPORTING THE 3Rs

Flexibility #1: Waiving of tests

1.1.2.2

Compliance ≠ Performance of test

prerequisite | not a prerequisite

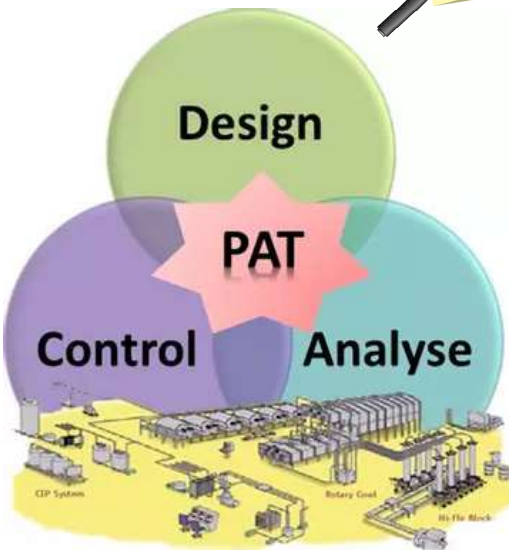
Tests may be omitted based on:

- **Design and control strategy**
- **Process knowledge** : validation studies of the manufacturing process or other suitable justification

Flexibility #2: PAT

1.1.2.2

"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**."



Flexibility #3: supporting the 3Rs

1.1.2.2

- **Consistency of production** to aid the demonstration of compliance (in General Notices since Supplement 8.2 – implemented 1st January 2014)
- Under strict application of a manufacturing **quality system** (e.g. GMP rules and guidelines).
- Constitution of a **product profile** that can replace current release tests based on *in vivo* methods.
- Promotes **minimal use of animals**.
- Reference to the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes of the Council of Europe (1986)

Demonstration of suitability of monographs

1.1.2.3

Manufacturer to evaluate the suitability of the monograph for QC of their article. Their choice of analytical procedures may be influenced by:

- the manufacturing process and/or
- the composition of the medicinal product.

When a competent authority considers a specification described in a monograph insufficient to ensure quality of the article, it may request more-appropriate specifications from the **manufacturer** in line with national or regional regulations.

In such cases, the competent authority informs the Ph. Eur. Commission through either

- the national pharmacopoeia authority or
- the Secretariat of the Ph. Eur. Commission

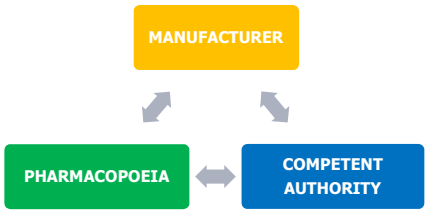
Details of the alleged insufficiency and the additional specifications : provided by the **manufacturer** to the national pharmacopoeia authority or the EDQM (Helpdesk)

➔ the decision to revise the monograph will be taken by the Ph. Eur. Commission.

Demonstration of suitability of monographs (cont.)

- Newly introduced in General Notices as of Supplement 10.7
- But already existing … see EU directive 2001/83/EC, as amended
- The Ph. Eur. is legally binding but the legislation also includes a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market and on the suitability of monographs.

➔ an excellent tool to ensure that monographs are not cast in stone but routinely updated to reflect the state-of-the-art.



Alternative analytical procedures

1.1.2.5

"The tests and assays described are the official analytical procedures upon which the standards of the Ph. Eur. are based. With the agreement of the competent authority, alternative analytical procedures may be used for control purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used. In the event of doubt or dispute, the analytical procedures of the Ph. Eur. are alone authoritative."

- ✓ Users' responsibility to demonstrate comparability to the satisfaction of the *competent authority*
  - ➔ Assessors during assessment of marketing authorisation applications
    - *NB: during assessment of a CEP, the EDQM evaluates a proposed alternative procedure*
- ✓ Compliance required, but alternative procedures may be used: same pass/fail decision
- ✓ The pharmacopoeial procedure remains the reference procedure

X In case of question or issue with pharmacopoeial procedure ➔ CONTACT EDQM (Helpdesk)

NEW CHAPTER 5.27 "COMPARABILITY OF ALTERNATIVE ANALYTICAL PROCEDURES" UNDER ELABORATION (RECENT PUBLIC CONSULTATION: PHARMEUROPA 34.2)

Flexibility in individual monographs

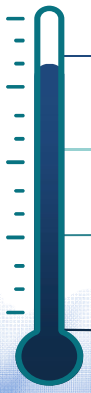
- Specific to an article but not stand alone
- Analytical procedures and acceptance criteria represent required quality standards
- Based on approved specifications backed up by batch data
- Reliance on users' feedback (public consultation)

EXAMPLES

Active substances or excipients
Paracetamol (0049)
Rosuvastatin calcium (2631)
Calcium carbonate (0014)
Etanercept (2895)

Medicinal products
Deferiprone tablets (2986)
Lacosamide infusion (2991)
Cyanocobalamin (58Co) capsules (1505)

ELEMENTS OF FLEXIBILITY



In Production section
when based on risk assessment

Limit as approved by CA
when one limit cannot fit all cases

Example procedure
Validated procedure without the need of comparability

FRC section
Functionnality related characteristics

Flexibility: Example procedure

In certain monographs, identified by the statement

'*The following procedure is given as an example*'

✓ the analytical procedure has been validated for the intended purpose;

A OR B

Implementation*
& use the example procedure

Replacement by another suitable **validated** procedure

No need to demonstrate equivalence to the procedure in the monograph

subject to approval by the competent authority.

* As defined in general notices and further explained in general chapter 5.26

FRC section: flexibility and facilitation

- Activities started at EDQM in 1995 for excipient monographs
- Summarised in general text 5.15
- FRCs are not exhaustive, but constitute typical quality attributes for the excipient:
  e.g. particle size distribution, powder flow, bulk and tapped density, viscosity, melting point
- Non mandatory section: depending on the application, an FRC may or may not be relevant
- FRC concept in line with "quality by design" cf. ICH Q8
- Knowledge of FRCs may facilitate the application of PAT

➔ contributes to the regulatory flexibility

Flexibility in General & Dosage form monographs

General monographs

- Classes of substances/medicinal products
- Mandatory for all substances/products within scope of their definition
- Not cross-referenced in individual monographs (exceptions)

Ex.: Vegetable fatty oils (2098), Allergen products (1063), Vaccines for vet. use (0062)

Dosage form monographs

- Mandatory for all medicinal products within scope of their definition
- Referred to in monographs on medicinal products containing chemical APIs

Ex.: Capsules (0016), Tablets (0478), Parenteral preparations (0520), Eye preparations (1163) …

Provide a frame that is universally valid to articles in scope

Provide "what" to achieve in terms of quality not necessarily the "how"

Contains open statements: "Unless otherwise justified and authorised", "use suitable method", "either method A or B", etc… *(terms defined in General Notices)*

Flexibility in General Chapters/Texts

General chapters

- become mandatory when referred to in a monograph or other general chapter
- general requirements for equipment, equipment qualification or calibration
- Elements of validation of analytical procedures

EXAMPLES

2.2.46 Chromatographic separation techniques
2.4.20 Determination of elemental impurities
2.5.42 *N*-Nitrosamines in active substances
2.8.26. Contaminant pyrrolizidine alkaloids

General texts

- specific to certain topics (e.g. Microbiology, Chemometrics, regulatory guidelines)
- Aim at establishing best practices
- often published for information and guidance
- A potential approach not the only approach

EXAMPLES

5.1.6. Alternative methods for control of microbiological quality
5.21 Chemometric methods applied to analytical data
5.25 Process analytical technology
5.26 Implementation of pharmacopoeial procedures

More to come in the following presentations !!

Thank you for your attention

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Demonstration of compliance with the Ph. Eur.

… and flexibility

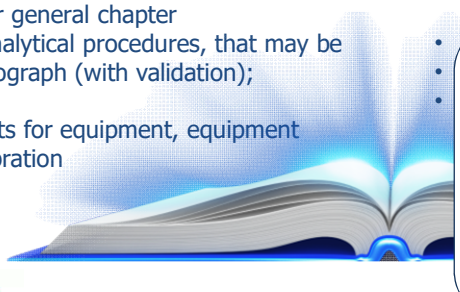
Flexibility in General Chapters

General chapters

- avoid repeating standard procedures or requirements in each monograph
- become mandatory when referred to in a monograph or other general chapter
- provide standard analytical procedures, that may be used when no monograph (with validation); guidance
- general requirements for equipment, equipment qualification or calibration

General texts

- aspects that cannot be treated in each individual monograph
- specific to certain topics (e.g. Microbiology, Chemometrics)



General chapters

2.2.46 Chromatographic separation techniques
2.5.42 *N*-Nitrosamines in active substances
Calcium carbonate (0014)
Etanercept (2895)

General texts

5.26 Implementation of pharmacopoeial procedures
Lacosamide infusion (2991)
Cyanocobalamin (58Co) capsules (1505)

No spoiler: more to come in the following presentations

Continuous manufacturing and Ph. Eur.: PAT chapter and related topics

Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition

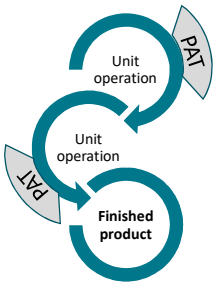
Strasbourg, 19-21 September 2022

Øyvind Holte, PhD

Norwegian Medicines Agency

Traditional batch manufacturing vs. Continuous manufacturing

Batch manufacturing



Continuous manufacturing

- No isolation of intermediates. Towards the end of each unit operation, material is increasingly mature/ completed
- New un-processed material is continuously fed into each unit operation, while at the same time, processed material is transfered to the next unit operation
- Critical process parameters and/ or critical material attributes are continuously monitored
- Little or no end testing
- Different options for batch definition
  - Quantity of output material
  - Quantity of input material
  - Run time at a defined mass flow rate

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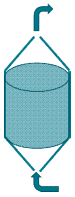
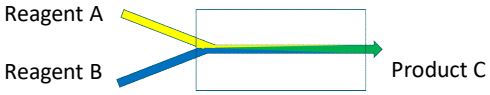
Types of continuous manufacturing

- **Biotech** (perfusion reactor)



- **Chemical synthesis** (flow chemistry)



- **Finished product**
  - Example tablets:
    Blending (twin-screw) – granulation – compression – film coating

- **End-to-end manufacturing** (no isolation of drug substance)

PAT analytics vs. traditional analytical methods

Traditional analytical methods

- Benchtop instrumentation
  Sample is removed from the process and transferred to the instrument
- Each analytical run: Calibration based on established standard materials
- Significant time delay from sampling to analytical result

PAT analytics

- Hand-held or integrated with the manufacturing process equipment, e.g. by measurement probe
- Calibration based on library of samples, characterised by a traditional reference method
- Analytical result immediately available

PAT analytics are not restricted to continuous manufacturing

PAT analytics vs. traditional analytical methods

Illustration: Prof. Jukka Rantanen
University of Copenhagen

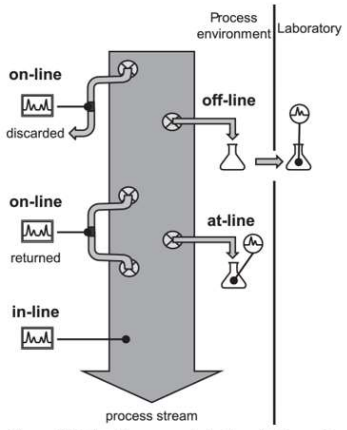


Figure 5.25.-1. – *Process analytical interfacing modes*

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Different control strategies – same quality

Traditional control strategy

- **Fixed process conditions**, verified by process valiadtion
- **Fixed material quality**, incl. functionality-related characteristics
- At-line/off-line **in-process controls** of intermediate products
- Full off-line **end-testing** of finished product according to specification

Typical PAT approach

- **Enhanced pharmaceutical development**
  - Risk-based identification of potentially critical quality attributes (CQA) and critical process paramters (CPP)
  - Formal experimental designs (DoE), multivariate data analysis (MVDA)
- **Enhanced process monitoring**
  - Process Analytical Technology (**PAT**), typically in-line or on-line
- **Adaptive manufacturing process**, feed-back/ feed-forward controls
- **Real Time Release (RTR) testing**
  - Predictions based on e.g, PAT, process monitoring, raw material attributes

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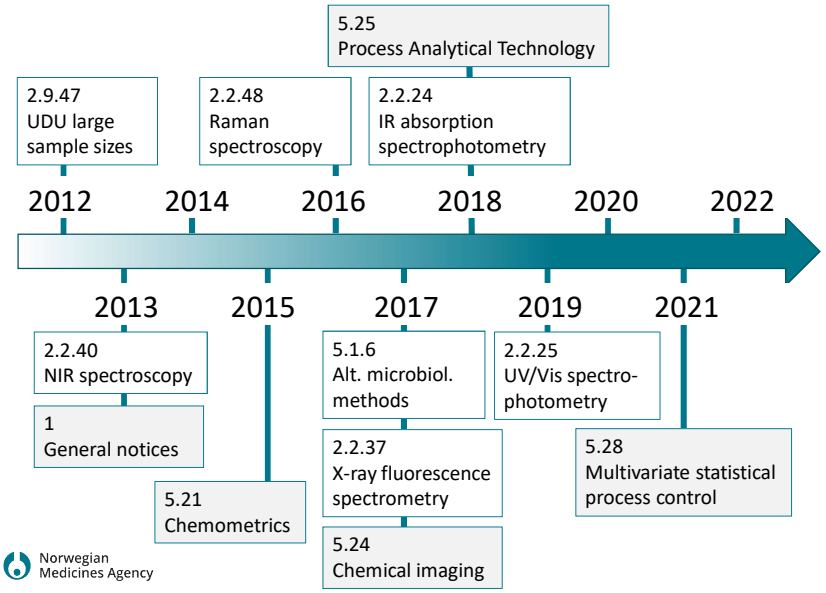
Ph.Eur. chapters that support PAT



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Flexibility in the Ph.Eur. – a paradigm shift?

Flexibility and agility vs.
control and established standards?

- No disagreement between standards and modern control strategies
- Demonstration of quality is critical, but the "how" is up to the manufacturer
- PAT WG celebrated 'mission complete' in 2019
  There should be no disincentive in the pharmacopeia to the application of well-developed PAT analytics

The needs of the regulatory authorities and the manufacturers are the same:
High quality medicinal products

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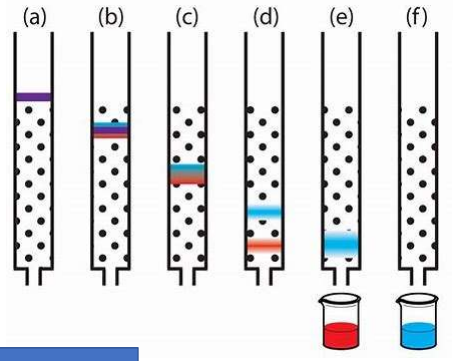
2.2.46: Adjustments of chromatographic conditions

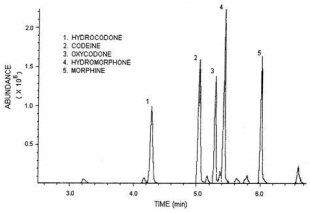
Anders Karlsson, Ph.D, Ass. Prof, Senior Principal Scientist, AstraZeneca, Gothenburg
Member of the CST WP - EDQM - Strasbourg

Outline

- Chromatography
- Introduction
- Content, definitions and theoretical aspects
- System Suitability Test (SST)
- Adjustments accepted – GC and LC isocratic and gradient elution
- Other guidance included
- Actual changes – Chapter 2.2.46

Chromatography





Mobile phase → Pump → Injector → Column with stationary phase → Detector → Integrator

Introduction

- Within the pharmaceutical industry, chromatography is the most important and used technique – Quality Control (QC) and during new drug development
- A high number of important active pharmaceutical ingredients have individual monographs in the Ph. Eur.
- Liquid and gas chromatography are useful techniques for accurate QC testing using the monograph procedures
- Assay, identity, dissolution, amount of impurities and excipient quality
- Chapters 2.2.28, 2.2.29 and 2.2.46 (Revised in 11th Edition) are part of Ph. Eur. describing gas and liquid chromatography in general, including adequate adjustments permitted

Content, definitions and theoretical aspects

- Describing the chromatographic peak – ”gaussian” (normal distributed)
- Equations and calculations for
  - Retention – ”adsorption to the stationary phase”
  - Selectivity – ”how well separated two chromatographic peaks are”
  - Resolution – ”how pure two closely peaks are”
  - Noise – ”baseline noise”
  - Symmetry factor – ”skew peaks”
  - Efficiency – ”narrow peaks”
  - System repeatability – ”precision”

System Suitability Test (SST)

SST (in-house procedure) may include	SST (as requested in chapter 2.2.46, System suitability)	SST (as requested in individual monograph)
Identity of peaks	-	-
Column efficiency	-	-
Critical resolution between two closely eluted compounds	-	Resolution or P/V requirement
Precision	System repeatability in **assays** (API & excipients ≈ 100%)	If different from default requirement
System sensitivity	S/N ≥ 10 @reporting threshold LOQ ≤ reporting threshold	If different from default requirement
Peak symmetry	0.8-1.8 for peak used for quantitation	If different from default requirement

Compliance with the system suitability criteria is required **throughout** the chromatographic procedure. No sample analysis is acceptable unless the suitability of the system has been demonstrated.

Adjustments accepted (2.2.46) – LC isocratic and gradient elution

- The adjustments described in 2.2.46 can be made without additional revalidation work and regulatory interaction
- However, important to perform a risk assessment when adjusting monograph methods
  - Define problem and the scientific mitigation (experimental work and implementation
- All SST requirements stated in 2.2.46 and individual monograph must be fulfilled for the adjusted QC procedure

What could trigger adjustments of the pharmacopoeial procedure?

SST not compliant although using prescribed column	Need to adjust e.g. flow rate, mobile phase composition
Prescribed column not available Use of similar column (stationary phase)	May need to adjust dimensions and hence flow rate, mobile phase composition
Using LC equipment with different dwell volumes – change in retention order and resolution	Adjust gradient and flow rate
Want to reduce time and solvent consumption	Use of UHPLC column

Adjustments accepted (2.2.46) - LC column

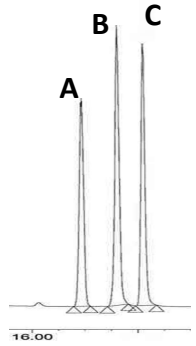
- Change to similar chromatographic support, surface modification and extent of chemical modification; but no change of identity of substituent allowed (e.g. no replacement of C18 ➔ C8)
- Change of stationary phase under the same column reagent description (see also Knowledge Database for the column used during development)
- Column dimensions – adjustments making switch from HPLC to UHPLC possible (sustainability)
- Length and/or dp (particle size) may be modified provided L/dp within - 25% to + 50% of the prescribed L/dp ratio

Condition: SST must be fulfilled

+ equivalent selectivity and elution order of specified impurities

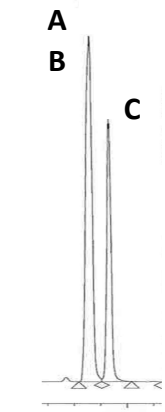
Example, HPLC QC-method – switch of LC-column (mobile phase buffer pH = 7.6)

Microsphere C 18 (pH stable)



Pass the SST criteria

Atlantis C 18 (pH stable)



Fail the SST criteria

Another 5 – 10 ”high pH stable LC-supports” were tested with same results!

Adjustments accepted (2.2.46) – particle size

When particle size changed, adjust flow rate *F*:

$$F_2 = F_1 \times \frac{dc_2^2 \times dp_1}{dc_1^2 \times dp_2}$$

dc = internal diameter
dp = particle size

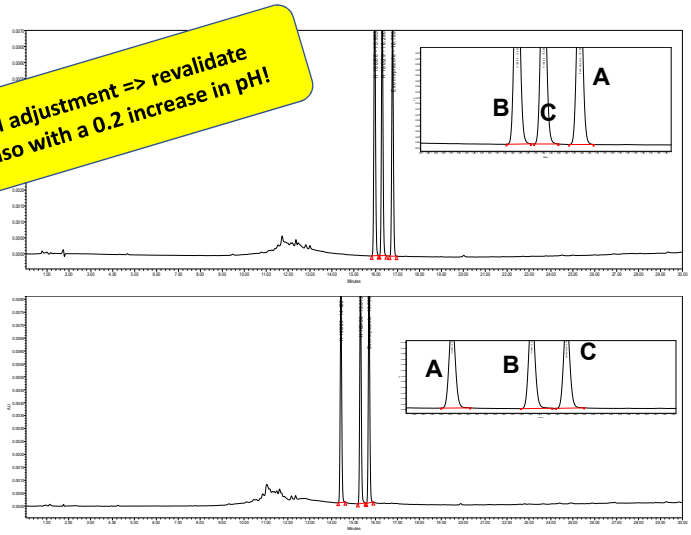
Additional change ± 50% allowed when column dimensions changed

Adjustments accepted (2.2.46) – mobile phase

- Aqueous component pH: ± 0.2 units, unless otherwise prescribed
- Salt concentration in buffer component: ± 10%
- Concentration of the solvents used
  - ➢ minor component (defined as < 100/n): ± 30% relative
  - ➢ no component more than ± 10% absolute
- Flow rate of the mobile phase ± 50% (only isocratic) when no change in column dimensions (*L* or *dp*)

Modified QC HPLC method (Atlantis C 18) - mobile phase buffer pH change from 7. 6 to 7.1 or 8.1)

Outside 2.2.46 pH adjustment => revalidate
SST criteria pass also with a 0.2 increase in pH!



Adjustments accepted (2.2.46) – other

Injection volume:

- if change in column dimensions : $V_{inj2} = V_{inj1} \times \frac{L_2 \times dc_2^2}{L_1 \times dc_1^2}$

- If no change in column dimensions, adjustment allowed if SST fulfilled

+ special attention to

- ➢ detection limit & repeatability of peak response if decreased,
- ➢ linearity & resolution if increased (overloading – deformed peak(s))

- **Detector wavelength** – not allowed to change

Adjustments accepted (2.2.46) – LC gradient elution

- Similar to isocratic elution – but less adjustments are allowed and are conditioned to:
  - satisfaction of SST
  - demonstration of equivalent selectivity and elution order of peaks due to specified impurities

- Supplier of equipment used for gradient elution differ
  ⇒ Different dwell volumes: equation is available how to handle

  ⇒ Different gradient times : equation and example available

Adjustments accepted (2.2.46) – GC

Stationary phase:

– *particle size*: maximum reduction of 50 per cent; no increase permitted (packed columns);

– *film thickness*: − 50 per cent to + 100 per cent (capillary columns).

Column dimensions:

– *length*: − 70 per cent to + 100 per cent;

– *internal diameter*: ± 50 per cent.

Column temperature: ± 10 per cent.

Temperature programme: adjustment of temperature is permitted as stated above; adjustment of ramp rates and hold times of up to ± 20 per cent is permitted

Flow rate : ± 50 per cent.

Other guidance included (2.2.46)

- Brief description of how to integrate chromatographic peaks
  - Straight forward for assay, dissolution and identity
  - Complex chromatogram e.g. peaks partly resolved
    - ➢ This should be part of the ”GMP driving license for chromatography”
- Reporting threshold
  - LOQ often 10 times the baseline noise
  - Generally all peaks at or above the 0.05% level should be included in the total

Actual changes – Chapter 2.2.46

Signal-to-noise ratio (**20** or 5 times pw at half height)

Symmetry factor (0.8-**1.8** instead for 0.8-1.5)

Allowable adjustments in GC e.g. column dimensions and injection volumes have been harmonised

Adjustment of column dimensions now based on the L/dp ratio as was already stated in USP (**isocratic**)

Retention times and relative retentions only for information in monographs (not mandatory)

- https://www.edqm.eu/en/-/general-chapter-2.2.46.-chromatographic-separation-techniques-now-published-in-ph.-eur.-11th-edition
- **NEW FAQs** **https://faq.edqm.eu/pages/viewpage.action?pageId=48201789**

Does general chapter 2.2.46 apply to chromatographic procedures not described in relevant Ph. Eur. monographs?

- **NO unless** addressed in applications and agreed between applicant and regulatory agencies
- Good position as applicant has developed and validated original chromatographic procedures in line with pharmacopeia's and ICH guidelines
- Science and risk based approach in line with ICHQ12
- Number of variations will decrease – save internal/external resources

Acknowledgements

Prof. Henk de Jong & Prof. Jos Hoogmartens, Chairs of the CST WP

All experts of the CST WP

Dr Michael Wierer and Dr Ulrich Rose, EDQM Secretariat

Thank you for your attention!

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Agence nationale de sécurité du médicament et des produits de santé

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

WANTED

The challenge of the N-nitrosamines detection in APIs – Input of chapter 2.5.42.

Collaboration, Innovation and Scientific Excellence:
the European Pharmacopoeia 11th Edition

International Conference – 20 September 2022 – Strasbourg, France

Hervé REBIERE, *PhD*
General Methods Working Party (Nitrosamines sub group)
French National Agency for the Medicines and Health Products Safety
Laboratory Controls Division (OMCL), France

Overview

- Context
- Nitrosamine substances
- Analytical methods, chapter 2.5.42.

Context

On June 26, 2018, EMA informed EDQM and OMCLs of a quality defect concerning certain valsartan and valsartan/hydrochlorothiazide-based products

Presence of an impurity :

- N-nitrosodimethylamine (NDMA)
- found in the active substance valsartan, manufactured by Zhejiang Huahai Pharmaceutical and marketed worldwide
- would be linked to the change in the manufacturing process of valsartan introduced in 2012 by the manufacturer
- not expected and therefore not looked for during routine controls

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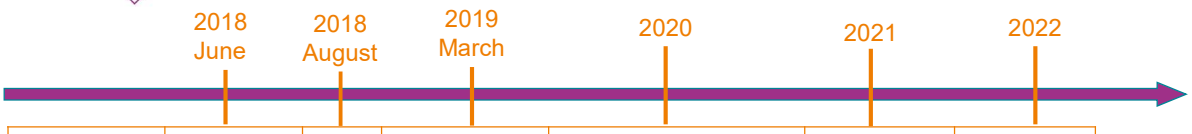
Chronology



Nitrosamines	NDMA 3-180 ppm	NDEA	NMBA, NDBA, NEiPA, NDiPA	MeNP, NMEA, NMPA, MPYR, NPIP, NMOR, NDPhA, CPNP, NDELA	N-nitroso-API	**>> 18**
API - Finished Product	Valsartan - Batch withdrawal - CEP suspended - Drug testing		Irbesartan Losartan, Candesartan, Olmesartan, Ranitidine Pioglitazone Nizatidine	Metformine* Rifampicine Rifapentin Nizatidine Pregabalin Bicalutamide Telmisartan, Ticagrelor Esomeprazole Donepezil Montelukast Deferasirox Minoxidil Oseltamivir Molsidomin	Varenicline Quinapril Fluoxetine …	**>> 25**	**2023 ?**

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* Keire et al. *International regulatory collaboration on the analysis of nitrosamines in metformin-containing medicines*, AAPS journal (2022) 24:56.

Ph. Eur. timeline

2018 Nov	2019 Feb	2019 March	2020 Nov	2021 March	2022
162th EPC	MG nitrosamines sub group	163th EPC	168th EPC	169th EPC	
Request for minor revision: 5 sartan monographs Need of analytical methods capable of detecting nitrosamines at trace level	1st VC meeting: 3 methods available	Adoption 5 sartan revised monographs Implementation Jan 2020 (10.0) Request for revision: - 2034 *Substances for pharmaceutical use* - 2619 *Pharmaceutical preparations*	Adoption Chapter 2.5.42. Implementation Jan 2022 (10.6)	Revision 5 sartans monographs Rapid implementation April 2021	**ALIGNMENT WITH REGULATORY DECISIONS**
	OMCLs : Swissmedic, CVUA Karlsruhe, ANSM	Test section: temporary limit NDMA = 0.300 ppm NDEA = 0.082 ppm		Production section: Extension to N-nitrosamines Reference to 2.5.42	

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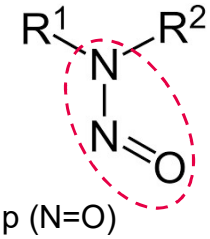
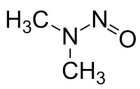
5

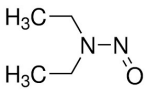
N-Nitrosamines



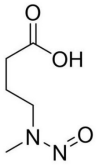
Chemical compounds containing nitroso group (N=O) linked to a nitrogenous fraction



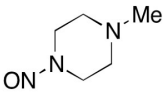
NDMA
N-nitrosodimetylamine
$C_2H_6N_2O$, M=74.08
CAS: 62-75-9



NDEA
N-nitrosodiethylamine
$C_4H_{10}N_2O$, M=102.14
CAS: 55-18-5



NMBA
N-nitroso-N-methyl-4-aminobutyric acid
$C_5H_{10}N_2O_3$, M=146.15
CAS: 61445-55-4



MeNP
1-methyl-4-nitrosopiperazine
$C_5H_{11}N_3O$, M=129.16
CAS: 16339-07-4

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6

Toxicity and acceptable intake

Category 1 : NDMA, NDEA

Category 2 : NMBA, NEiPA, NDiPA, NDBA

SECTION 2: Hazards identification

· 2.1 Classification of the substance or mixture
· Classification according to Regulation (EC) No 1272/2008

GHS06 skull and crossbones

Acute Tox. 3 H301 Toxic if swallowed.
Acute Tox. 1 H330 Fatal if inhaled.

GHS08 health hazard

Carc. 1B H350 May cause cancer.
STOT RE 1 H372 Causes damage to organs through prolonged or repeated exposure.

GHS09 environment

Aquatic Chronic 2 H411 Toxic to aquatic life with long lasting effects.

(Contd. on page 2)

GB

N-Nitrosamine (CAS number)	ng/day*
N-Nitrosodimethylamine, NDMA[1] (62-75-9)	96.0
N-Nitrosodiethylamine, NDEA[1] (55-18-5)	26.5
N-Nitrosoethylisopropylamine, EIPNA[2] (16339-04-1)	26.5
N-Nitrosodiisopropylamine, DIPNA[2] (601-77-4)	26.5
N-Nitroso-N-methyl-4-aminobutyric acid, NMBA[3] (61445-55-4)	96.0
1-Methyl-4-nitrosopiperazine, MeNP[2] (16339-07-4)	26.5
N-Nitroso-di-n-butylamine, NDBA[2] (924-16-3)	26.5
N-Nitroso-N-methylaniline, NMPA[1] (614-00-6)	34.3
N-nitroso-morpholine, NMOR[4] (59-89-2)	127
N-nitroso-varenicline, NNV [5]	37.0
N-nitrosodipropylamine, NDPA (621-64-7)[2]	26.5
N-nitrosomethylphenidate[6]	1300
N-nitrosopiperidine (100-75-4)	1300
N-nitrosorasagilene[7]	18

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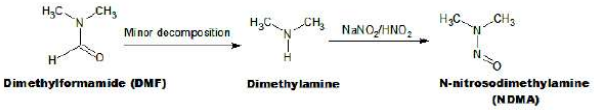
Nitrosamines formation

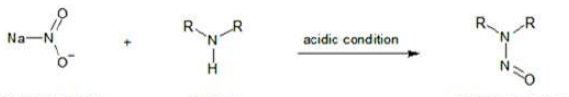
Formation of N-nitrosamine is the result of a reaction between a “nitrosable” precursor (e.g. amine) and a nitrosating agent (e.g. nitrite) in acid conditions. Several causes may originate the formation of N-nitrosamines :

- <u>During API synthesis</u>

In presence of water, solvents, reagents, catalysts

e.g. with tetrazol ring from molecule (e.g. valsartan and losartan)





- <u>During formulation process</u>

Reaction of secondary amines (impurities from API or excipients) with nitrite in acid conditions

e.g. dimethylamine (in API) + nitrite (excipients) form NDMA (heat influence)

- <u>Packaging and storage</u>

e.g. nitrosating agent (nitrocellulose of lidding foil) + dimethylamine (in API)

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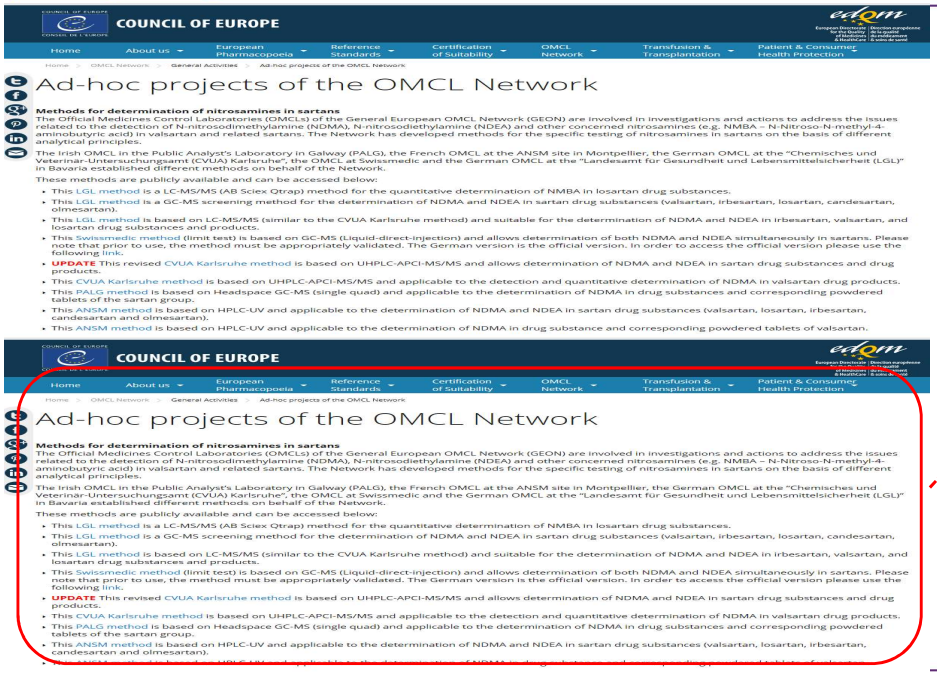
Analytical methods

Detection of contaminant at trace level = analytical challenge

OMCLs developed methods for their national market surveillance = optimisation, validation, collaborative studies, ring tests



HPLC/UV

GC-MS
- Liquid injection
- Headspace

HPLC-MS/MS
- Triple-Quad
- Q-Trap

Ph. Eur. chapter 2.5.42.

Section 2.5. = General chapter
Methods of analysis, assays

Adoption 168th COM (nov-2020)
Into force 01/2022 (Ph. Eur. 10.6)

01/2022:20542

2.5.42. *N*-NITROSAMINES IN ACTIVE SUBSTANCES

This chapter describes analytical procedures for the detection of various *N*-nitrosamines in particular active substances. Procedures A and B have been validated as limit tests (30 ppb) and procedure C has been validated as a quantitative test. The scope of each procedure is defined in Table 2.5.42.-1. With these three procedures, it is possible to analyse the following *N*-nitrosamines: *N*-nitroso-dimethylamine (NDMA); *N*-nitroso-diethylamine (NDEA); *N*-nitroso-dibutylamine (NDBA); *N*-nitroso-*N*-methyl-4-aminobutyric acid (NMBA); *N*-nitroso-diisopropylamine (NDiPA); *N*-nitroso-ethyl-isopropylamine (NEiPA) and *N*-nitroso-dipropylamine (NDPA).

Ph. Eur. chapter 2.5.42.

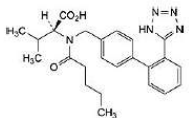
Chapter for information

« … *available to assist manufacturers*. »

04/2021:2423

VALSARTAN

Valsartanum



$C_{24}H_{29}N_5O_3$ [137862-53-4] M_r 435.5

DEFINITION

(2*S*)-3-Methyl-2-[pentanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in valsartan should be avoided or limited as much as possible. For this reason, manufacturers of valsartan for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in valsartan. The general chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

Ph. Eur. chapter 2.5.42.

Analytical toolbox: 3 methods – 7 N-nitrosamines – 5 sartans

Table 2.5.42.-1. – *Scope of the validation*

Active substance (monograph number)	NDMA	NDEA	NDBA	NMBA	NDiPA	NEiPA	NDPA
Candesartan cilexetil (2573)	A*BC	ABC	C	A	AC	AC	C
Irbesartan (2465)	A*BC	ABC	C	A	AC	AC	C
Losartan potassium (2232)	A*BC	ABC	C	A	AC	AC	C
Olmesartan medoxomil (2600)	A*BC	ABC	C	A	AC	AC	C
Valsartan (2423)	A*BC	ABC	C	A	AC	AC	C

* In procedure A, the presence of dimethylformamide (DMF) in the substance to be examined may interfere with the detection of NDMA.

PROCEDURE A (LC-MS/MS)

Liquid chromatography (*2.2.29*) coupled with mass spectrometry (*2.2.43*).

PROCEDURE B (GC-MS)

Gas chromatography (*2.2.28*) coupled with mass spectrometry (*2.2.43*).

PROCEDURE C (GC-MS/MS)

Gas chromatography (*2.2.28*) coupled with mass spectrometry (*2.2.43*).

Highlights: MS detection, use of internal standard, system suitability

Ph. Eur. chapter 2.5.42.

PROCEDURE A (LC-MS/MS) **Limit test (30 ppb)**

Liquid chromatography (*2.2.29*) coupled with mass spectrometry (*2.2.43*).

PROCEDURE B (GC-MS) **Limit test (30 ppb)**

Gas chromatography (*2.2.28*) coupled with mass spectrometry (*2.2.43*).

PROCEDURE C (GC-MS/MS) **Limit test (30 ppb)** **Quantitative test**

Gas chromatography (*2.2.28*) coupled with mass spectrometry (*2.2.43*).

Procedures may also be used to detect/quantify nitrosamines in other drug substances/drug products

➔ require appropriate validation

Chemical Reference Standards

Safety Data Sheet

7 CRS at 500 µg/mL in methanol

Reference standards

Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price	SDS Product Code	
	Y0002258	N-Nitroso-diethylamine CRS	1	1 mL	79 EUR	202000237	NDEA
	Y0002259	N-nitroso-dimethylamine CRS	1	1 mL	79 EUR	202000236	NDMA
	Y0002260	N-nitroso-N-methyl-4-aminobutyric acid CRS	1	1 mL	79 EUR	202000239	NMBA
	Y0002261	N-Nitroso-dibutylamine CRS	1	1 mL	79 EUR	202000238	NDBA
	Y0002262	N-nitroso-ethyl-isopropylamine CRS	1	1 mL	79 EUR	202000241	NEiPA
	Y0002263	N-nitroso-diisopropylamine CRS	1	1 mL	79 EUR	202000242	NDiPA
	Y0002264	N-Nitroso-dipropylamine CRS	1	1 mL	79 EUR	202000240	NDPA

No powder manipulation =
low risk for the analyst during the preparation of standard solutions

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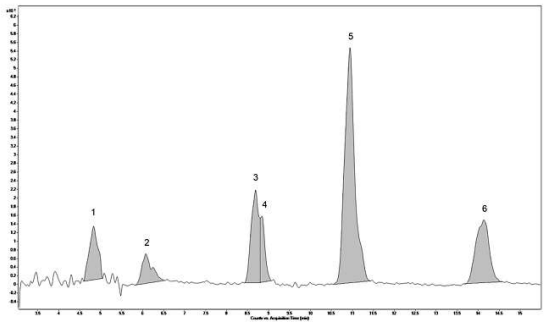
Procedure A by LC-MS/MS



1. NDMA
2. NMBA
3. NDEA-d_{10}
4. NDEA
5. NEiPA
6. NDiPA

Figure 2.5.42.-1. – *Chromatogram of N-nitrosamine analysis in active substances by procedure A: spiked solution*

Separation on C18 column with a 35 min elution gradient

Triple quadrupole MS detection: settings can be adjusted and time segment can be defined

MRM mode with 2 transitions (principal/qualifier)

Specificity: 2 transitions and ratio princ/qual

Sensitivity: S/N calculated at 30 ppb

Caution: DMF may interfere with the detection of NDMA

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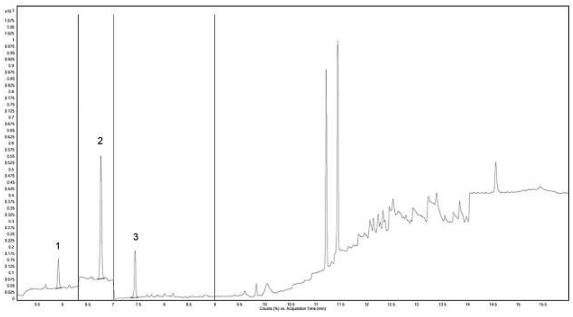
Procedure B by GC-MS



1. NDMA 2. NEMA 3. NDEA

Figure 2.5.42.-2. – *Chromatogram for N-nitrosamine analysis in active substances by procedure B: spiked solution*

Separation on VF-624 column with a 17 min temperature gradient

Liquid injection

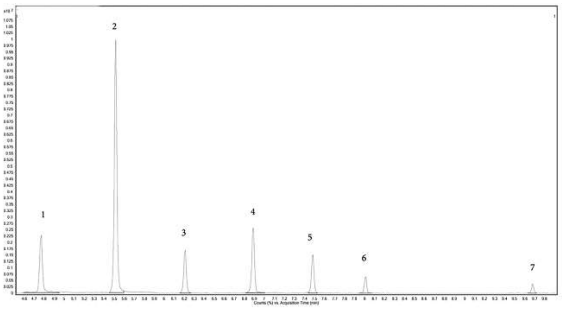
Single quadrupole : settings may be adjusted and time segment can be defined

SIM mode

2 sample preparations depending on sartan

Sensitivity: S/N calculated at 30 ppb

Procedure C by GC-MS/MS



1. NDMA 3. NDEA 5. NDiPA 7. NDBA
2. NEMA 4. NEiPA 6. NDPA

Figure 2.5.42.-3. – *Chromatogram for N-nitrosamine analysis in active substances by procedure C: spiked solution*

Separation on VF-624 column with a 17 min temperature gradient

Liquid injection

Triple quadrupole MS detection: settings can be adjusted and time segment can be defined

MRM mode with 2 transitions (principal/qualifier)

Specificity: 2 transitions and ratio princ/qual

Sensitivity: S/N calculated at 30 ppb

Advantage: validated as quantitative test

Protocol

- 3 solutions are prepared:
  - Test: only API
  - Spiked: API + N-nitrosamine at 30 ppb
  - Reference: only N-nitrosamine at 30 ppb

- System suitability :
  - Repeatability (n=6) RSD ≤ 20%
  - Sensitivity S/N ≥ 10 (principal transition), except NDMA with method A (≥ 10), S/N ≥ 3 (qualifier transition)

Protocol

- Limit test: $\frac{R_S}{R_r} < 0.50$

R_S: Ratio in the test solution

R_r: Ratio in the spiked solution

Examples:

- If 20 ppb found in test solution : $\frac{R_S}{R_r} = \frac{20}{20+30} = 0.40$
- If 30 ppb found in test solution : $\frac{R_S}{R_r} = \frac{30}{30+30} = 0.50$
- If 100 ppb found in test solution : $\frac{R_S}{R_r} = \frac{100}{100+} = 0.77$

- Validity of the test: $\frac{Response\_Principal}{Response\_Qualifier}$ in test solution and spiked solution are equals (±20%)

CONCLUSION

N-nitrosamines are carcinogen substances that must be investigated

Chapter 2.5.42 for information "*available to assist manufacturers*"

Analytical toolbox with 3 methods = 7 N-nitrosamines are covered

MS methods are specific and sensitive (30 ppb)

Other drug substances/products ➔ appropriate validation

Quantitation (methods A/B) ➔ appropriate validation

Other N-nitrosamines/N-nitroso-APIs ➔ not covered

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CONCLUSION

Chapter 2.5.42. ensures
the quality of drug substance
(mitigation of N-nitrosamines)

Safety of patients

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Thank you for your attention

MG nitrosamine sub group: Massimiliano Conti, Oliver El-Atma, Hervé Rebiere, Bruno Spieldenner & Michel Ulmschneider

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Agence nationale de sécurité du médicament et des produits de santé

Avertissement
- Lien d'interêt : personnel salarié de l'ANSM (opérateur de l'État).
- La présente intervention s'inscrit dans un strict respect d'indépendance et d'impartialité de l'ANSM vis à vis des autres intervenants.
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Warning
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