International Conference, 19-21 September 2022

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

Session 2: Challenges related to the control of impurities in complex APIs and excipients

Moderator: Eva Nadal,
Chair of Ph. Eur. Group of Experts 7

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

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

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

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

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

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Challenges in establishment of reference standards for antibiotics

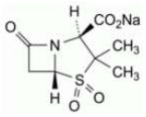
Heiko Dueckert,
Laboratory Department, EDQM, Council of Europe

Outline

- Overview of antibiotics in Ph. Eur.
  - Classes
  - Structural complexity
  - Heterogeneous nature
- Techniques for assay and related substances
  - Variety of techniques
  - Complexity of mixture CRS
- Challenges – CRS Examples
  - Fosfomycin trometamol
  - Clindamycin Phosphate for system suitability
  - Cefoxitin for peak identification A
  - Piperacillin for peak identification
  - Teicoplanin for identification
- Summary

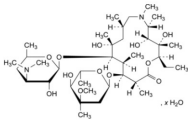
Ph. Eur. antibiotics by class

Beta-lactam



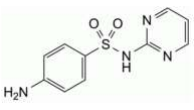
Sulbactam sodium

Macrolide

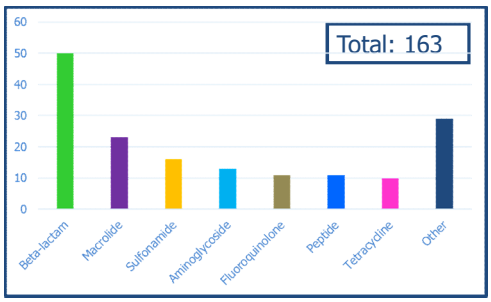


Azithromycin

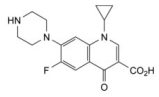
Sulfonamide



Sulfadiazine

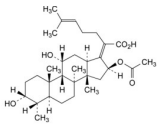


Fluoroquinolone

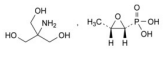


Ciprofloxacin

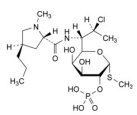
Other



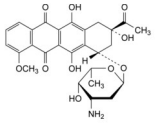
Fusidic acid



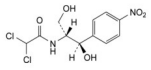
Fosfomycin trometamol



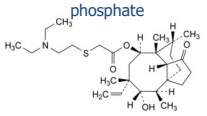
Clindamycin phosphate



Daunorubicin

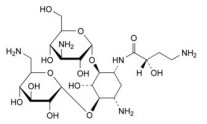


Chloramphenicol



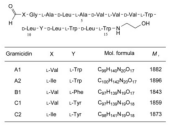
Tiamulin

Aminoglycoside



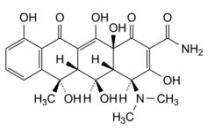
Amikacin

Peptide



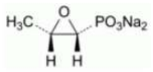
Gramicidin

Tetracycline

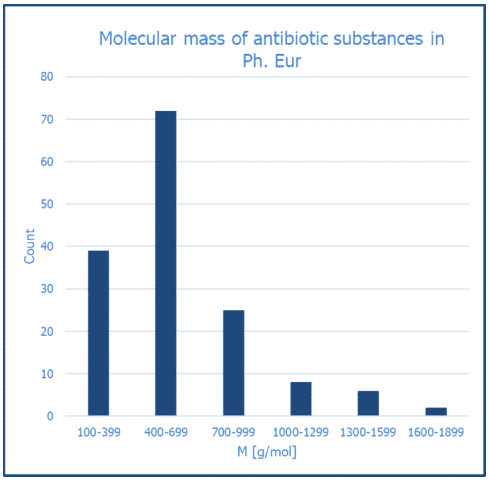


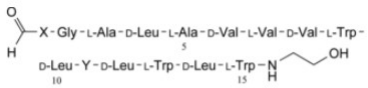
Oxytetracycline

From fosfomycin to gramicidin – molecular mass distribution



Fosfomycin sodium
M = 138 g/mol
(Phosphonic acid form)

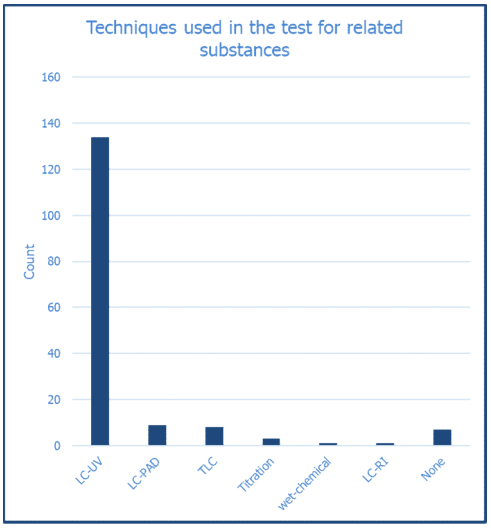


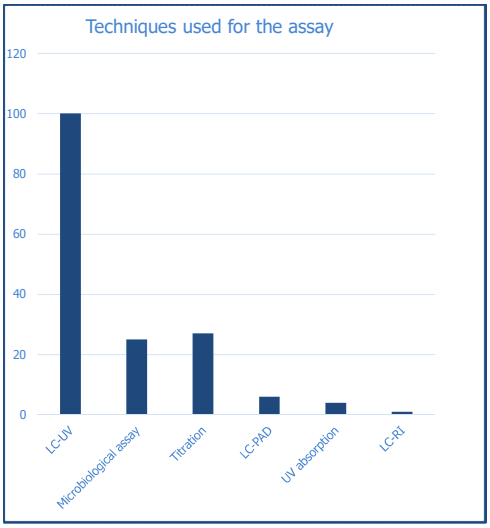


Gramicidin	X	Y	Mol. formula	M_r
A1	L-Val	L-Trp	$C_{99}H_{140}N_{20}O_{17}$	1882
A2	L-Ile	L-Trp	$C_{100}H_{142}N_{20}O_{17}$	1896
B1	L-Val	L-Phe	$C_{97}H_{139}N_{19}O_{17}$	1843
C1	L-Val	L-Tyr	$C_{97}H_{139}N_{19}O_{18}$	1859
C2	L-Ile	L-Tyr	$C_{98}H_{141}N_{19}O_{18}$	1873

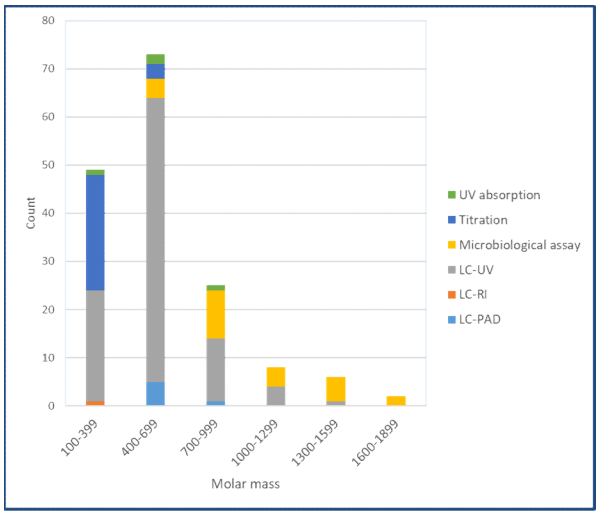
Gramicidin
M = 1882 g/mol
(Gramicidin A1)

Analytical techniques in related substances and assay



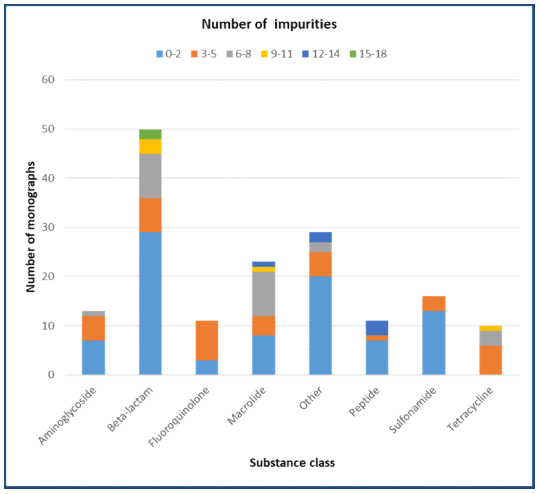


Assay methods

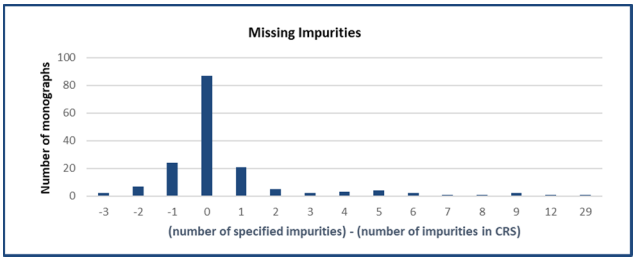


- Low molecular mass: LC-UV and titration
  - Titration based on functional group
- Middle molecular mass: Predominantly LC-UV
  - Single substances or well-defined mixtures
- High molecular mass: Predominantly microbiological assay
  - Heterogeneous mixtures of active substances

Complexity of CRSs - Number of impurities per monograph



Number of impurities:
Impurities in mixture CRS
+ single substance (CRS and R)
+ *in situ* formation



Number of impurities in monograph - Top 5

Monograph name	Number of impurities
Piperacillin	18
Azithromycin	14
Vancomycin	13
Bacitracin	13
Fusidic acid	12

Monograph name: without counter ion/hydration

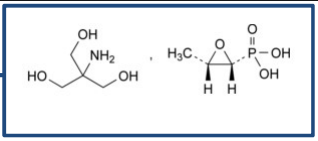
General challenges in establishment of antibiotics CRS

- Analytical / technical challenges
  - Stability of solutions
    - Beta lactams
  - Hygroscopic substances
    - Aminoglycosides
  - Physical form (e.g. sticky solids)
  - Monograph methods are developed for quality control, not for CRS establishment
- Stock management
  - Stability of CRS during storage and transport
    - Example: degradation of impurity F in procaine benzylpenicillin for peak identification
  - Availability of candidate material
    - Azithromycin for peak identification (containing impurities A, B, C, E, F, G, I, J, L, M, N, O and P)

Examples

- Fosfomycin trometamol CRS
- Clindamycin phosphate for system suitability CRS
- Cefoxitin for peak identification A CRS
- Piperacillin for peak identification CRS
- Teicoplanin for identification CRS

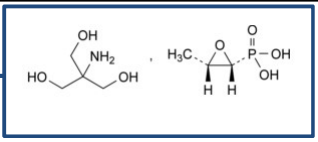
Fosfomycin trometamol CRS



- Fosfomycin trometamol CRS used for LC assay
- Small molecule
  - Fosfomycin is the smallest molecule in Ph. Eur. antibiotics portfolio
- LC-RI method for assay and related substances
  - Low performance of detection technique (lack of sensitivity)

Challenge:
Assignment of content

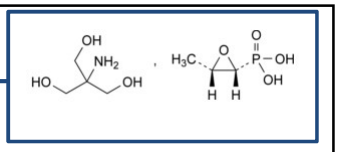
Fosfomycin trometamol CRS – mass balance



- Calculation of content, based on monograph methods
- Mass balance approach:
  (100% - water%) x (100% - related substances%) / 100% = **99.8 %**

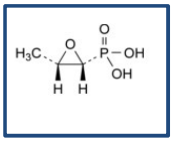
Monograph methods	Relevant for content assignment
Identification A, B, C	No
pH	No
Specific optical rotation	No
Related substances	**Yes (0.14 %)**
Water	**Yes (0.08 %)**
Assay	Yes (verification only)

Fosfomycin trometamol CRS - qNMR

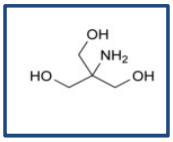


- qNMR results (% m/m):
  - Fosfomycin: 52.4 %
  - Trometamol: 47.3 %
  - Fosfomycin + Trometamol: 99.7 %
- Molar fractions:
  - Fosfomycin: 3.80 mmol/g
  - Trometamol: 3.90 mmol/g
- Excess trometamol: 1.3 % m/m
- Mass balance approach (amended):
  (100% - water% - excess trometamol%) x
  (100% - related substances%) / 100% = **98.5 %**

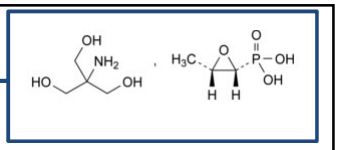
$C_3H_7O_4P$
M = 138.06 g/mol



$C_4H_{11}NO_3$
M = 151.12 g/mol

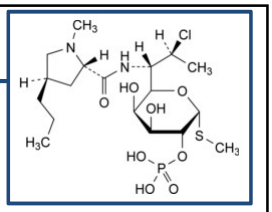


Fosfomycin trometamol CRS - conclusion



- The monograph is suitable to control the API's quality
  - Monograph methods alone (without the assay) are not sufficient for content assignment
- Complementary methods were required for content assignment
- Controlling the quality of a batch according to the Ph. Eur. and characterising a CRS candidate for content assignment are two different activities

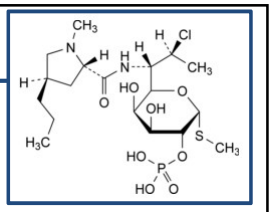
Clindamycin Phosphate for System Suitability

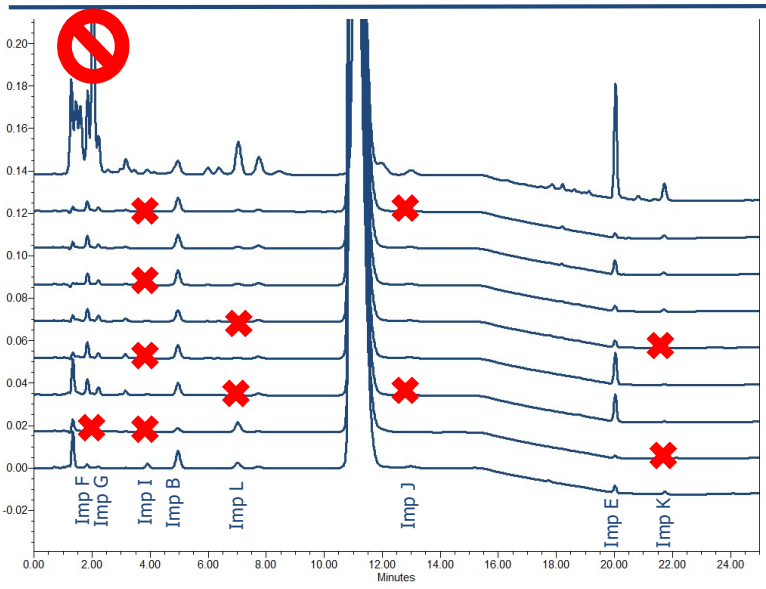


Reference solution (c). Dissolve 3.0 mg of clindamycin phosphate for system suitability CRS (containing impurities **B, E, F, G, I, J, K and L**) in mobile phase A and dilute to 1.0 mL with mobile phase A.

Challenge:
Suitability of material

Clindamycin Phosphate for System Suitability – screening for candidate material



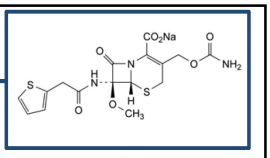


System suitability:
reference solution (c):
- resolution: minimum 2.0 between the peaks due to impurities F and G

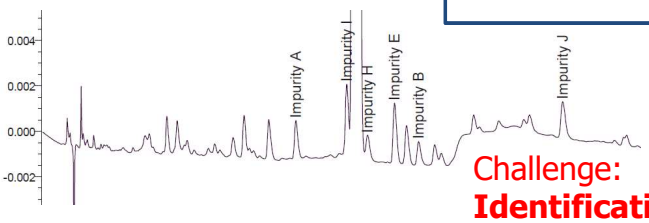
Candidate materials

Currently valid CRS

Cefoxitin for peak identification A CRS

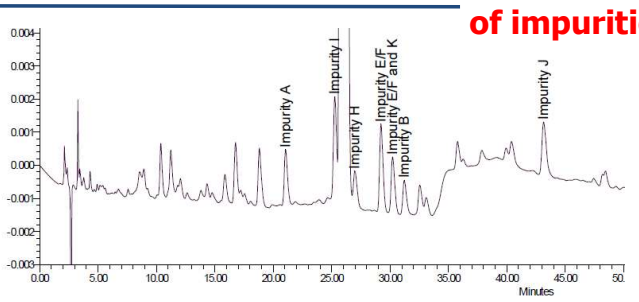


- Currently valid monograph (Ph. Eur. 10.0)
  - Cefoxitin for peak identification CRS (containing impurities A, B, E, H, I and J)
  - Impurities A, B and E: identification by MS
  - Impurities H, I and J: **unknown structure**

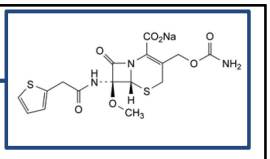


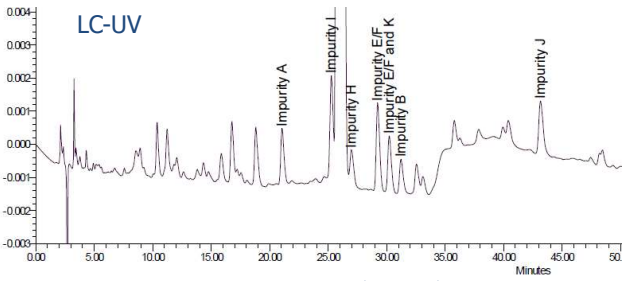
Challenge: **Identification of impurities**

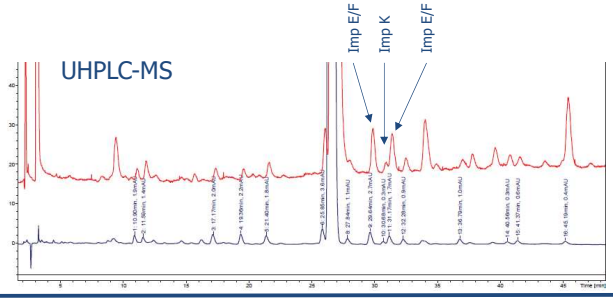
- Revised monograph (Ph. Eur. 11.0)
  - Cefoxitin for peak identification **A** CRS (containing impurities A, B, E, **F**, H, I, J and **K**)
  - Impurities H and I: Identification by NMR
    → **structure added to monograph**
  - Impurity J: Identified by LC-MS
    → **structure added to monograph**
  - Impurities E, F and K: next slide



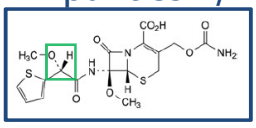
Cefoxitin for peak identification A CRS



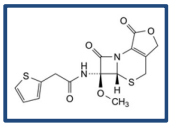




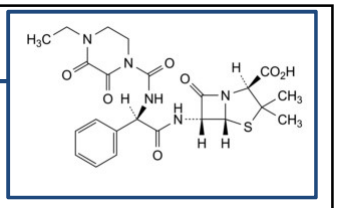
- Impurities E/F: Diasteroisomers



- Only UHPLC separates impurity K from impurity E/F
- Degradation of impurity J forms impurity K (unknown structure)



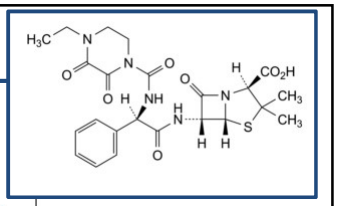
Piperacillin for peak identification CRS

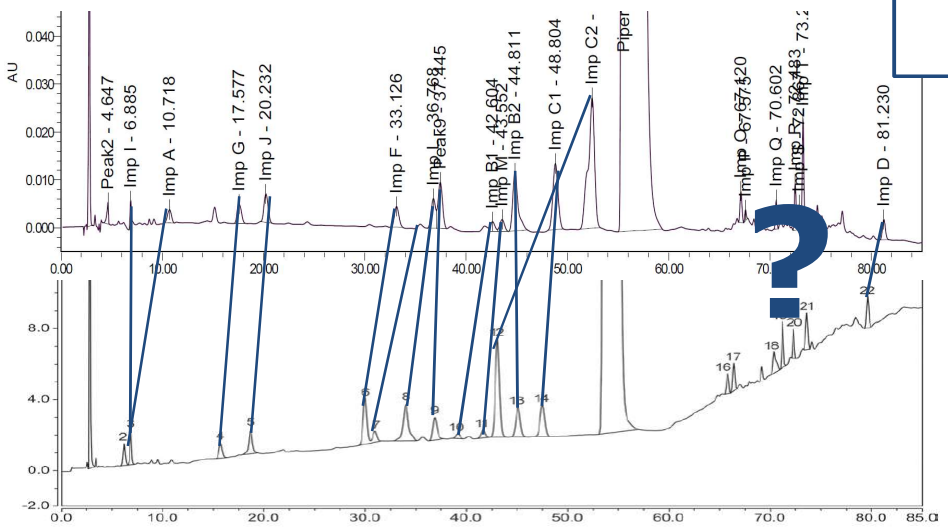


- Draft monograph (Pharmeuropa 29.3)
  - *Reference solution (e)*. Dissolve 6 mg of piperacillin for peak identification CRS (**containing impurities A, B, C, D, E, F, G, I, J, K, L, M, O, P, Q, R, S and T**) in mobile phase B and dilute to 1 mL with mobile phase B.
  - *mobile phase A*: mix 3 mL of a 320 g/L solution of *tetrabutylammonium hydroxide R*, 100 mL of a 27.6 g/L solution of *sodium dihydrogen phosphate R*, 275 mL of *methanol R1* and 622 mL of *water for chromatography R*; adjust to pH 5.5 with *phosphoric acid R*

Challenge:
Identification of impurities

Piperacillin for peak identification CRS – LC profile

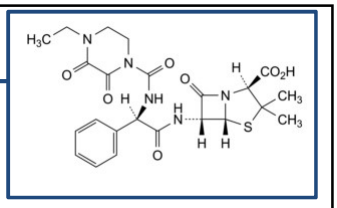




Chromatogram obtained during establishment of the CRS

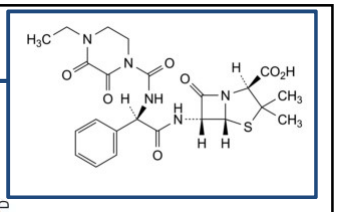
Chromatogram published in the draft monograph

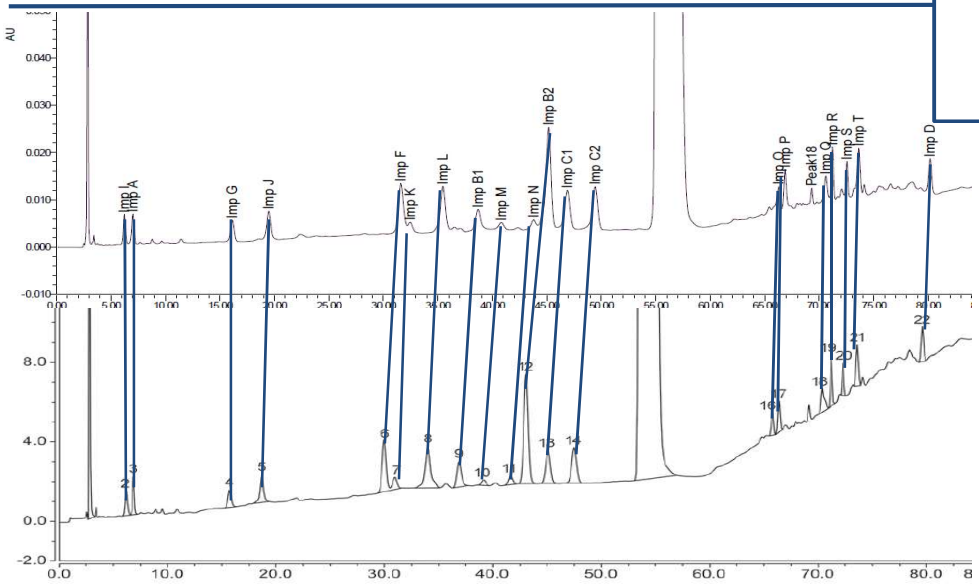
Piperacillin for peak identification CRS – amendment of monograph



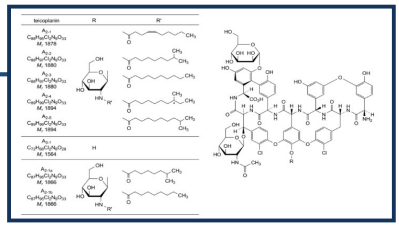
- Monograph published (Ph. Eur. 10.4)
  - *mobile phase A*: mix 3 mL of a 320 g/L solution of tetrabutylammonium hydroxide R, 100 mL of a 27.6 g/L solution of sodium dihydrogen phosphate R, 275 mL of methanol R1 and 622 mL of water for chromatography R; **adjust the apparent pH to 5.5 with phosphoric acid R**

Piperacillin for peak identification CRS – LC profile

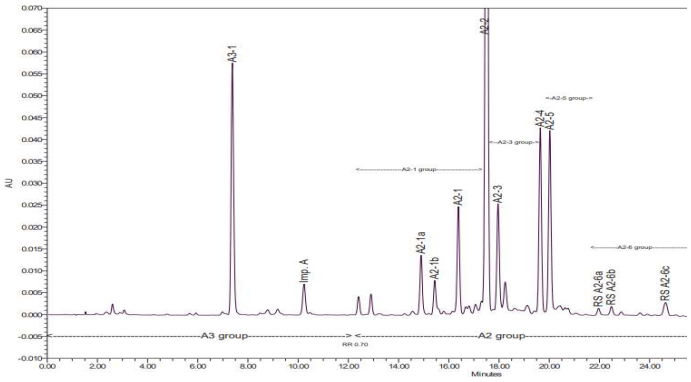




Teicoplanin for identification CRS



- Teicoplanin components A_{3-1} , A_{2-1a} , A_{2-1b} , A_{2-1} , A_{2-2} , A_{2-3} , A_{2-4} and A_{2-5}
- Teicoplanin-like related substances A_{2-6a} , A_{2-6b} and A_{2-6c}



Challenge:
Identification of impurities

- Method transfer: LC-UV towards MS-compatible
- Identification of components by MS-MS

CRS challenges - Summary

- Selection of methods beyond the monograph
  - Non-mass balance indicating monographs
  - Need for orthogonal methods
- Availability of suitable candidate materials (incl. mixtures)
  - Possible solution: Compounding
  - Custom synthesis
- Identification of impurities
  - Structural complexity and heterogeneity of analytes
  - Availability of authentic impurity samples
- Highly specific methods
  - Necessary to fulfil regulatory demands
  - Often come at the price of robustness

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**

2022-09-20

Obstacles faced during development of monographs for antibiotics with complex impurity profiles

Martin Lavén, Ph.D.

Swedish Medical Products Agency
Member of Ph. Eur. Expert group 7

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Ph. Eur. group of experts No 7: Antibiotics

- Aim of the work: development and revision of monographs for the control of quality of medicines
- Scope: Antibiotics, antifungals, antiparasitics, immunosuppressants, chemotherapeutic substances
- 19 members from industry, academia and authorities (regulators and OMCLs*)

*Official medicines control laboratories

Antibiotics: a broad range of substances

- Substances active against bacteria, used to treat bacterial infections
- Classes of antibiotics
  - β-lactams, tetracyclines, aminoglycosides, polypeptides, macrolides etc.
- Complexity
  - Single compound (*eg* phenoxymethylpenicillin)
  - Family of compounds, mixture of closely related compounds (*eg* colistimethate sodium, tyrothricin)
- Production
  - Chemical synthesis (*eg* chloramphenicol)
  - Semi-synthetic: fermentation products modified by synthetic steps (*eg* amoxicillin)
  - Fermentation (*eg* bacitracin)

Guidelines for organic impurities in antibiotics

- ICH Q3A and General monograph Substances for pharmaceutical use (2034)
  - Requirements for Related substances do not apply to products of fermentation and semi-synthetic products derived therefrom
- Active substances for veterinary use: VICH Guideline 10
  - Not applicable to fermentation products and semi-synthetic products derived therefrom
- Guideline on setting specifications for related impurities in antibiotics (EMA)
  - Applies to Related impurities in antibiotics that are fermentation products or semi-synthetic substances derived from fermentation products
- Additional guidelines for impurities (not covered here)
  (*eg* elemental impurities, residual solvents, mutagenic impurities, residues from fermentation)

Guideline on setting specifications for related impurities in antibiotics

EMA/CHMP/CVMP/QWP/199250/2009 corr

- Applies to fermentation products or semi-synthetic substances
- New active substances and new sources of existing substances
- Should not be applied retrospectively, but “it is intended that this guideline will act as a stimulus to establish best practice and to initiate the revision of relevant Ph.Eur. monographs”.
- Implemented 30 June 2013

Guideline on setting specifications for related impurities in antibiotics

- Limits for:
  - Each specified identified impurity
  - Each specified unidentified impurity
  - Any unspecified impurity, with an acceptance criterion of not more than the identification threshold
  - Total impurities

As described in ICH Q3A

Guideline on setting specifications for related impurities in antibiotics: *classification*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Semi-synthetic:
  - single compound
  - family of compounds
- Fermentation:
  - single compound
  - family of compounds
- Peptides
- Veterinary only
- Special cases for very complex impurity profiles

Thresholds

Class	Thresholds		
	Reporting	Identification	Qualification
Semi-synthetic: *single*	0.05/0.03%	0.10/0.05%	0.15/0.05%
Semi-synthetic: *family*	0.10%	0.15%	0.50/0.2%
Fermentation: *single*	0.10%	0.15%	0.15%
Fermentation: *family*	0.10%	0.15%	0.50/0.2%
Peptides	0.1%	0.5%	1.0%
Veterinary only	0.10%	0.20%	0.50%

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICH Q3A thresholds

0.50%: for structurally closely related impurities

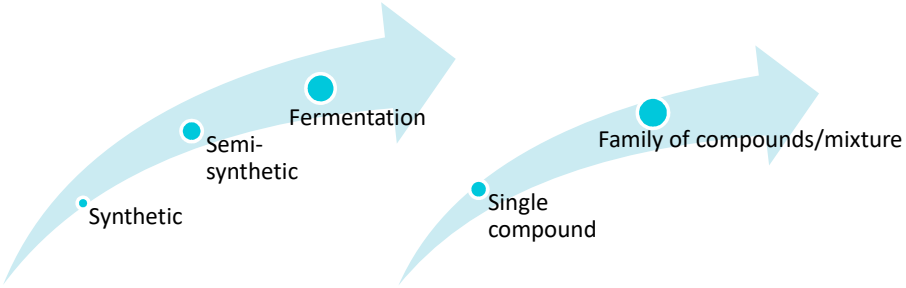
0.50%: for structurally closely related impurities

Not for modified peptides (eg glycopeptides)

VICH GL 10

Development of monographs: *challenges*

- Antibiotics can display very complex impurity profiles



- One related substances method for all sources
  - Different production processes lead to different impurity profiles
  - Monographs for multi-source antibiotics may need to cover very complex impurity profiles

Challenges: *the analytical method*

- High demands on the analytical method
- Needs to separate a high number of impurities
- Sufficient sensitivity needed for detection and quantification
- Robustness may be difficult to achieve when the impurity profile is very complex

Challenges: *identification of impurities*

- Some impurities cannot be isolated (*eg* isomers, unstable)
- Difficulties to obtain batches and impurity standards from manufacturers
- A low limit for unspecified impurities may lead to a great number of specified impurities
- Consequences
  - Method development and validation can be very complicated
  - CRS establishment can be very challenging
  - Correction factors cannot be used
  - Identification of impurities using RRT by the user of the monograph may lead to wrong peak assignment

How obstacles can be tackled: *id of impurities*

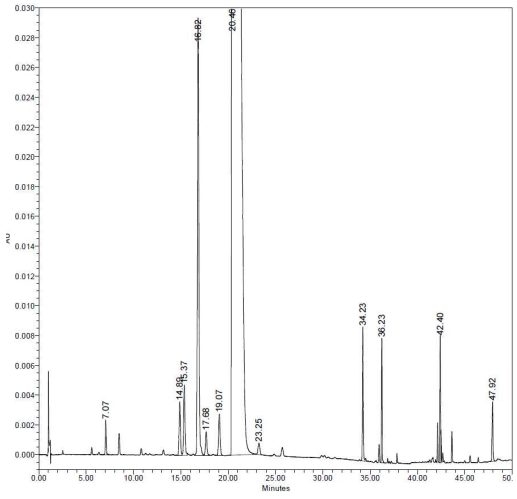
- Make use of the fact that antibiotic batches often contain a number of impurities that can be used for peak identification or use ”dirty batches”
- Using LC-MS and NMR for peak identification and quantification in method development and validation
- The intended limit for unspecified impurities, in line with the EMA guideline, may need to be raised in order to decrease the number of specified impurities
- *In situ* degradation to generate impurities

How obstacles can be tackled: *the method*

- Use of modern techniques such as UHPLC and new column chemistries to improve separation and sensitivity
- Use of other detection techniques than UV, such as MS, for antibiotics with weak chromophores
- Robustness
  - The method should be tested by at least two different labs before publication in Pharmeuropa
  - Read Pharmeuropa and test the method in time!

How obstacles can be tackled

- Ongoing project:
  - Fermentation product
  - UHPLC
  - Batches containing impurities
  - LC-MS (QTOF)
  - NMR



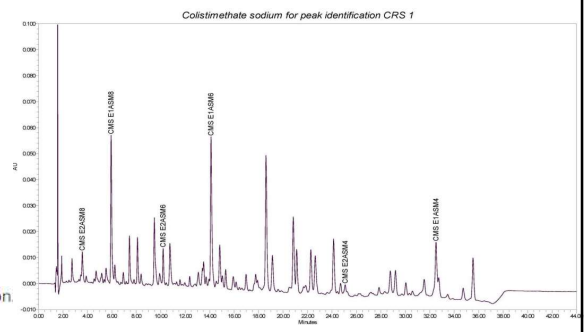
Other strategies to handle complex profiles

- Composition test in combination with related substances test
  - Colistimethate sodium (0319):

Composition. Liquid chromatography (2.2.29): use the normalisation procedure.

Limits:

- *CMS E1ASM8*: 5.0 per cent to 9.5 per cent;
- *CMS E1ASM6*: 6.5 per cent to 9.5 per cent;
- *CMS E1ASM4*: 2.0 per cent to 5.0 per cent;
- *CMS E2ASM8*: 0.5 per cent to 2.0 per cent;
- *CMS E2ASM6*: 0.5 per cent to 2.5 per cent;
- *CMS E2ASM4*: maximum 1.5 per cent;
- *sum of the peaks related to CMS E1 and CMS E2*: minimum 77.0 per cent;
- *disregard limit*: 0.50 per cent.



Related substances. Liquid chromatography (2.2.29) as described in the test for composition.

Limits:

- *any other impurity* (any peak not related to CMS E1 or CMS E2): for each impurity, maximum 1.5 per cent;
- *sum of impurities* (sum of all peaks not related to CMS E1 or CMS E2): maximum 5.5 per cent;
- *disregard limit*: 0.50 per cent.

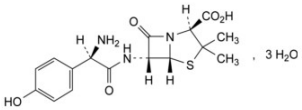
Other strategies to handle complex profiles

- Limit as a sum of impurities
  - Oxytetracycline hydrochloride (0198):
    - "sum of impurities D, E and F: maximum 1.0 per cent"
- A retention time window controlling certain impurities
  - Vancomycin hydrochloride (1058):
    - "any other impurity eluting before vancomycin B: for each impurity, maximum 0.8 per cent, and not more than 5 such impurities exceed 0.30 per cent"
  - Tylosin for veterinary use (1273):
    - "sum of impurities eluting between impurity A and tylosin C: maximum 2.0 per cent"

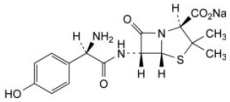
Other strategies to handle complex profiles

- Sometimes unknown impurities as specified
  - Caspofungin acetate, impurity D (Pharmeuropa 34.1):
    - ”unknown structure (dimer)”
- Separate test for ”difficult” impurity
  - Caspofungin acetate, impurity F (Pharmeuropa 34.1)
- Related substances tests not covering all impurities?
  - For complex multi-source antibiotics. Some potential future options:
    - One test for degradation impurities (same for all processes)
    - One test for degradation impurities and common process related impurities
    - Multiple related substances methods covering different sets of impurities

The amoxicillin case



trihydrate



sodium

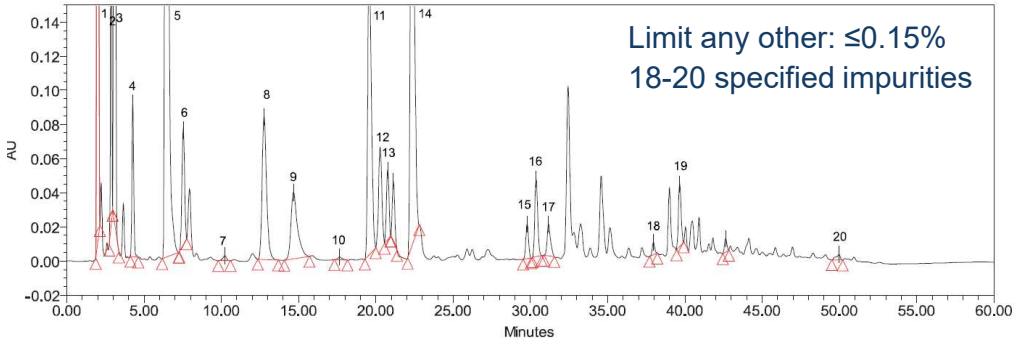
- Multi-source semi-synthetic antibiotic
- Each production process generates an impurity profile which is manageable
- Combining all impurities leads to a very complex impurity profile
- Current monographs, limits:

Trihydrate:
- Any impurity ≤1%
- No specified impurities
- No limit for Total impurities
- No reporting threshold

Sodium:
- Any other impurity: ≤2%
- Impurity J: ≤3%
- Total impurities: ≤9%
- Disregard limit: 0.1%

The amoxicillin case

- Publication in Pharmeuropa 26.2 (2014) of new related substances method



- Not possible to prepare CRSs to cover all specified impurities

The amoxicillin case

- Increased limit for any other impurities: ≤0.30%:
- 8 – 10 specified impurities

Sodium:

Limits:

- *impurity J*: maximum 2.0 per cent;
- *impurity D (sum of isomers D1, D2)*: maximum 1.5 per cent;
- *impurities C (sum of isomers C1, C2), E (sum of isomers E1, E2), G*: for each impurity, maximum 1.0 per cent;
- *sum of impurities F and P*: maximum 0.6 per cent;
- *impurities K, L*: for each impurity, maximum 0.5 per cent;
- *impurity N*: maximum 0.4 per cent;
- *any other impurity*: maximum 0.30 per cent;
- *total*: maximum 4.0 per cent;
- *reporting threshold*: 0.05 per cent.

Trihydrate:

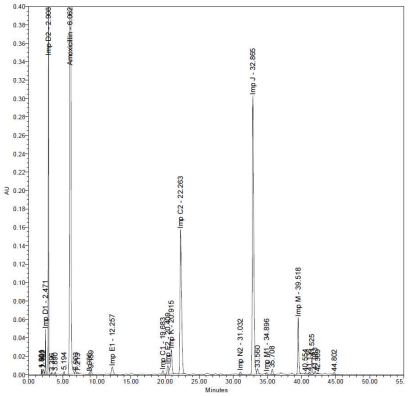
Limits:

- *impurity E (sum of isomers E1, E2)*: maximum 1.5 per cent;
- *impurities C (sum of isomers C1, C2), D (sum of isomers D1, D2), G, I, J*: for each impurity, maximum 1.0 per cent;
- *impurity L*: maximum 0.5 per cent;
- *impurity N*: maximum 0.4 per cent;
- *any other impurity*: maximum 0.30 per cent;
- *total*: maximum 3.5 per cent;
- *reporting threshold*: 0.05 per cent.

- Monographs adopted by Commission in 2015
- Establishment of CRSs still in progress

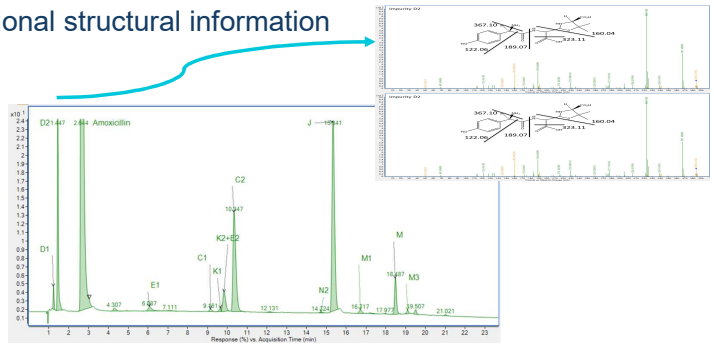
The amoxicillin case

- *In situ* degradation can generate a number of impurities
- Additional CRSs to cover other impurities
- Combination of these approaches promising



The amoxicillin case

- Using LC-MS/MS in development for identification of impurities
  - Transfer to MS compatible conditions
  - Accurate mass instrument (mass deviations typically within 2 ppm)
  - MS/MS for additional structural information



Final remarks

- Can the perfect monograph for control of related impurites be reached?
- New impurities to be added to the monograph via the CEP process
- Stepwise approach
- Obstacles can be succesfully tackled for antibiotics with very complex impurity profiles
  - Colistimethate sodium (0319)
  - Piperacillin sodium and monohydrate (1168 & 1169)
  - Vancomycin hydrochloride (1058)

Summary

- Aim: new and improved monographs for the control of quality of antibiotics
- Antibiotics can display very complex impurity profiles
- One related substances test for all sources increases complexity
- Challenges analytical, practical and limit related
- Overcoming obstacles: Use of modern techniques, inherent complexity of batches, and different approaches to handle limits
- Improvement of monographs is a continous process

Thank you for your attention

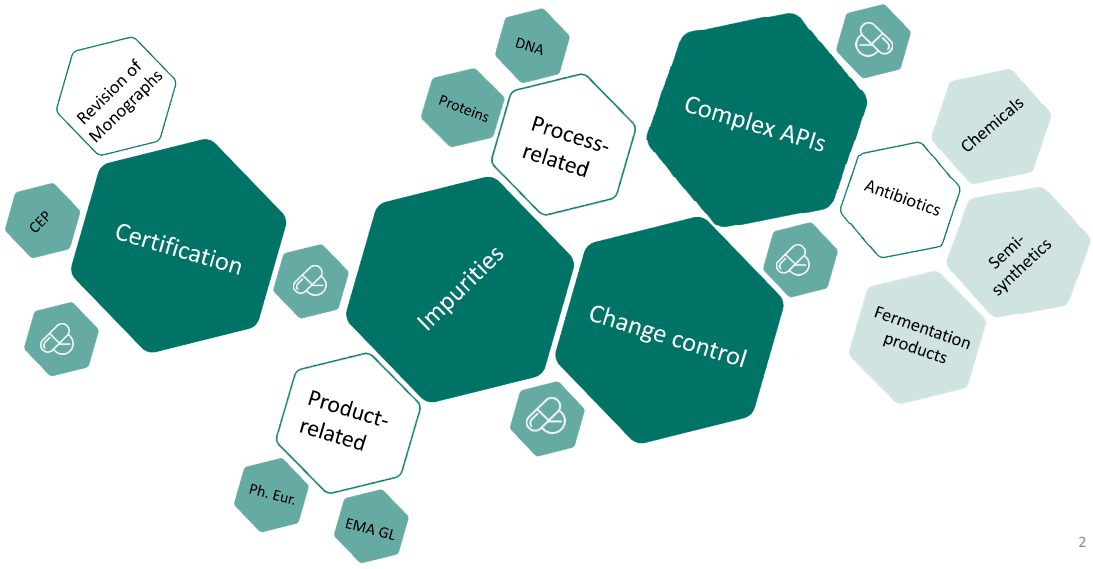
Federal Institute
for Drugs
and Medical Devices

CEPs for complex APIs- Assessor's constraints and considerations

EDQM International Conference, Strasbourg, France
20 September 2022
ute.fischer@bfarm.de

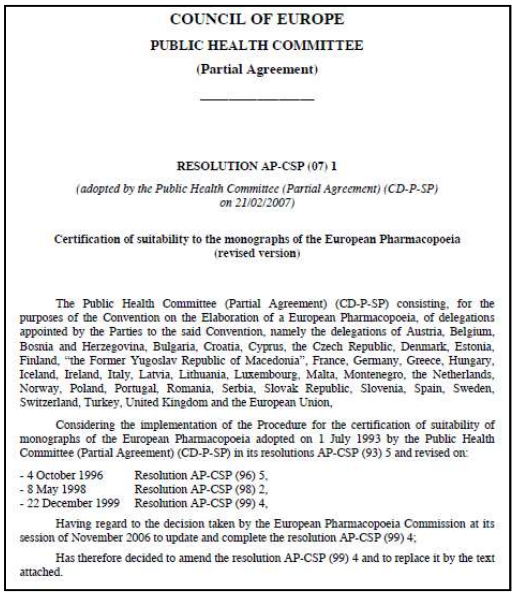
Disclaimer:
Views expressed in this presentation are the author's personal views and not necessarily the views of BfArM

Challenges related to the control of impurities in complex APIs- What We Are Talking About…



Certification

- Certification of suitability to Monographs of the European Pharmacopoeia
- Acc to Public Health Committee 2 Resolution AP-CSP (07) 1)
- To obtain a CEP
- Relates to API/DS only, not to the FP (route of administration is normally not an issue for certification)
- Majority of APIs are obtained from chemical synthesis



COUNCIL OF EUROPE

PUBLIC HEALTH COMMITTEE

(Partial Agreement)

RESOLUTION AP-CSP (07) 1

(adopted by the Public Health Committee (Partial Agreement) (CD-P-SP) on 21/02/2007)

Certification of suitability to the monographs of the European Pharmacopoeia (revised version)

The Public Health Committee (Partial Agreement) (CD-P-SP) consisting, for the purposes of the Convention on the Elaboration of a European Pharmacopoeia, of delegations appointed by the Parties to the said Convention, namely the delegations of Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, "the Former Yugoslav Republic of Macedonia", France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom and the European Union,

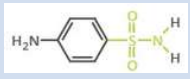
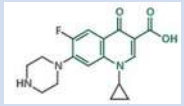
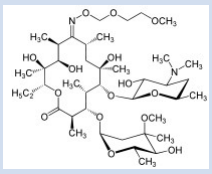
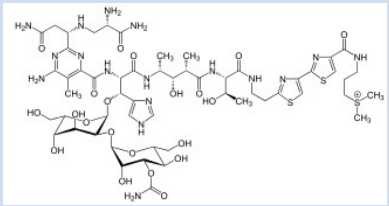
Considering the implementation of the Procedure for the certification of suitability of monographs of the European Pharmacopoeia adopted on 1 July 1993 by the Public Health Committee (Partial Agreement) (CD-P-SP) in its resolutions AP-CSP (93) 5 and revised on:

- 4 October 1996 Resolution AP-CSP (96) 5,
- 8 May 1998 Resolution AP-CSP (98) 2,
- 22 December 1999 Resolution AP-CSP (99) 4,

Having regard to the decision taken by the European Pharmacopoeia Commission at its session of November 2006 to update and complete the resolution AP-CSP (99) 4;

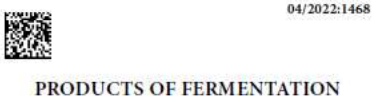
Has therefore decided to amend the resolution AP-CSP (99) 4 and to replace it by the text attached.

Antibiotics

Chemical	Semi-synthetic	Fermentation
◦ Sulfonamides (Sulfanilamide)  ◦ Ciprofloxazin 	◦ Amoxicillin and its salts (from 6-APA) ◦ Clindamycin hydrochloride and clindamycin phosphate (from lincomycin) ◦ Netilmicin (from sisomycin which has no Ph. Eur. Monograph) ◦ Roxithromycin (from erythromycin)  ◦ Amikacin and amikacin sulphate (both from kanamycin)	◦ Erythromycin ◦ Nystatin ◦ Amphotericin ◦ Spiramycin ◦ Neomycin ◦ Polymyxin B ◦ Chlortetracycline ◦ Gramicidin ◦ Bleomycin  ◦ Salt formation: *benzylpenicillin sodium, benzylpenicillin benzathine, demeclocycline hydrochloride, erythromycin stearate, framycetin sulphate, gentamicin sulphate, lincomycin hydrochloride, kanamycin monosulphate, oxytetracycline hydrochloride, phenoxymethylpenicillin K…*

Fermentation products and semi-synthetic products

- **Fermentation products** are “Indirect gene products”
- Primary or secondary metabolites of micro-organisms, irrespective of whether or not the micro-organism have been modified by traditional procedures or by recombinant DNA technology
- GM 1468 “Products of Fermentation” applies
- **Semi-synthetic products** are obtained from a fermentation product + cleavage and formation of covalent bonds followed by extraction/purification steps
- Compliance with GM 1468 is not an issue



Product-related impurities and its control

- GM 2034 (reflecting ICH Q3A) and Ph. Eur. general chapter 5.10 (incl **decision tree**) requirements are to be applied
- Products of fermentation and semi-synthetic products are OUT of the scope of ICH Q3A and of GM 2034 „Related substances“ section
- Fermentation processes involve biological processes, which are more variable and less controllable than synthetic processes and the impurity profile is more complex and less predictable
- Apply the GL on “Setting specifications for related impurities in antibiotics” (EMA/CHMP/CVMP/QWP/199250/2009 corr.) for product-related impurities control in antibiotics

Antibiotics GL and GM2034

Active substances	Semi-synthetic*/ GM 2034/ ≤ 2g / > 2g MDD	Fermentation, single***	Fermentation, family****	Peptides/ Peptides per GM2034
Reporting	0.05% / 0.03%	0.10%	0.10%	0.1%
Identification	0.10% / 0.05%	0.15%	0.15%	0.5%
Qualification	0.15% / 0.05%	0.15%	0.50%**/0.2%	1.0%

*) If the substance consists of a family of compounds, then thresholds for fermentation, family may be necessary

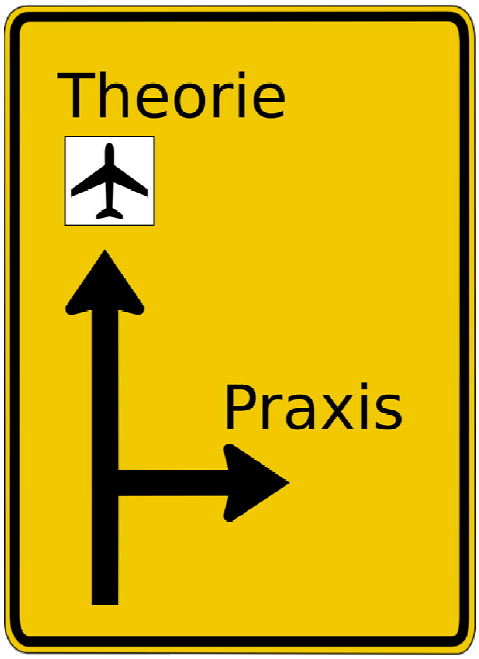
**) Structurally closely related impurity according to definition

***) single substance

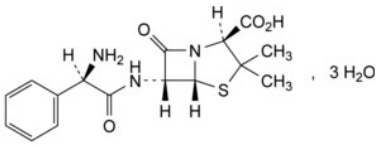
****) mixture of closely related compounds

Fermentation "Family" of Compounds

- Higher qualification threshold of 0.50%, if an impurity is structurally closely related to an active substance containing more than one active compound
- **All related compounds not included in the definition of the active substance are regarded as impurities**
- Control of very complex impurity profiles requires extended efforts (e.g., in resolution of unresolved peaks, identification and qualification of new peaks, fingerprint chromatogram approach)



Setting of Specifications: Ampicillin trihydrate



Semi-synthetic, single component

Ph. Eur.*: Related substances by LC, „Any impurity“ limit **1.0 %**, transparency list with impurities A-N

GL: Report limit 0.05%/ 0.03%, Identification limit **0.10%/ 0.05%**

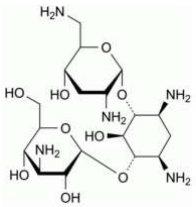
Guideline is stricter than the Monograph

CEP1: *Any unspecified impurity detected by the test for related substances of the monograph is limited to NMT 0.10%, total impurities are limited to NMT 2.0%*
CEP2: *Any unspecified impurity detected by the test for related substances of the monograph is limited to NMT 0.20%, total impurities are limited to NMT 2.5%*

Note: Analytical LoQ should be NMT reporting threshold.

**** Monograph under revision***

Tobramycin



Fermentation, single
Ph. Eur.*: Related Substances by LC: „Any impurity“ limit **1.0% and 0.5 %**
Total limit: 1.5%
Disregard Limit 0.25%
Transparency list with impurities A-C
GL: Report limit 0.10%, Identification limit **0.15%**

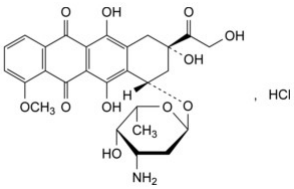
Guideline is stricter than the Monograph

CEP: – Test for related substances by liquid chromatography

Impurity RRT [redacted]	not more than 0.7%
Impurity RRT [redacted]	not more than 0.15%
[redacted]	not more than 0.1%
Any unspecified impurity	not more than 0.1%
Total unspecified impurities	not more than 0.2%
Total impurities	not more than 1.5%

**** Monograph under revision***

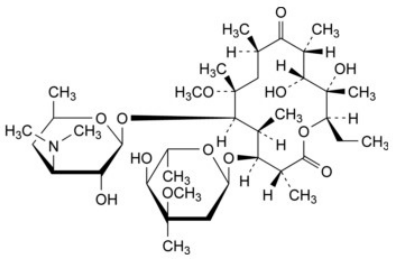
Doxorubicin HCl



Fermentation, single
Ph. Eur.: Related Substances by LC: „Any impurity“ limit **0.5 %**
Disregard Limit 0.05%
Transparency list with impurities A-D
GL: Report limit 0.10%, Identification limit **0.15%**
CEP: “Any unspecified impurity” NMT **0.10%**

- „Any unspecified impurity“ limit: 0.15% (GL), NMT 0.10% on the CEP

Clarithromycin



Semi-synthetic, family of closely rel compounds

Ph. Eur.: Related Substances by LC with disregard limit 0.1%

"Any impurity" ≤**1.0%**, not more than 4 impurities can be ≥ **0.4%**

"Total impurities" ≤3.5%

Specified impurities A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P

GL: Report limit 0.10%, Identification limit **0.15%**

CEP: "Any unspecified impurity" NMT **0.10%**

„Any unspecified impurity" limit: 0.15% (GL), 0.10% on the CEP

Limits in the EMA GL may be different to the Ph Eur Monograph/CEP

Process-related Impurities

- Residual solvents, Elemental impurities, Nitrosamines…
- For antibiotics made by fermentation:
  - Foreign microorganisms!
  - Endotoxins, toxins
  - Host cell residues (residual NA and proteins)
  - Residuals of culture media, substrates and precursors

Limits for Residual Proteins and NA

- Threshold assay to demonstrate absence of residual proteins (e.g., SDS-PAGE) and NA (e.g., PCR)
- Present batch data together with analytical method (description, LoD/LoQ)
- No specific toxicological concerns for residual proteins
- For commercialised API, HCP and NA levels are considered „qualified by use“
- If new API, apply GM 2034 limits (identification threshold 0.10%/0.05%), if limit is exceeded, a justified limit and valid analytical test is requested for the CEP

GM 1468: Change Control

- Change in the manufacturing procedure (upstream/downstream)
- Replacement of the MCB, envisaged “Rejuvenation of MCB”, “re-isolation of MCB”…

→ Subsequent change in the impurity profile of the fermentation product?

- Acceptability of the increase of impurities already present?
- Any new impurities? Adequately controlled using additional/alternative tests?
- Risk mitigation strategy?
- For cell banks: Testing of genetic stability and impurity profile investigation,
  MCB shall be sufficently large…

Histamin

- Adverse events after iv injection of gentamicin since 2015 in horses and in humans
- Main ADRs in humans: decreased blood pressure, allergic reactions, one fatality (in Italy);
  In horses: anaphylactic reactions, colic
- Gentamicin of one manufacturer was affected
- High contents of histamine/histamine like substances were found in suspicious batches, clear correlation between histamine concentration and ADRs
- Histamine levels were linked to fish peptone raw material of a certain supplier used for fermentation

→ API manufacturer changed back to the original supplier for fish peptone

→ Development of HPLC/LC-MS anal method to identify and quantify histamine

→ EP GM 1468 (Products for fermentation) amended by EDQM in 2018

→ Histamine limit of 8 ppm implemented in CEP for gentamicin sulphate

EMEA/H/A-5(3)/1468: EMA/805330/2018; EMEA/V/A/128: EMA/CVMP/766265/2018
https://doi.org/10.1002/ardp.202100260

Tryptophan

- Multisystemic desease Eosinophilie-Myalgie Syndrome (EMS) affecting approx. 1600 persons incl 38 deaths
- Traced back to Tryptophan (≥98.5% purity) manufactured by fermentation
- **Contaminants? Impurity profile?-** RP-HPLC/UV/Fluorescence study reveal > 60 impurities
- Prior modifications in the producer strain (5 mutations) and in the downstream processing (reduced amount of charcoal) and specific **NEW** impurities were found being linked to EMS
- → **New requirements in Ph Eur Tryptophan Monograph**

J.Chromatogr. B 685 (1996) 41-51

Revision of Ph Eur Monograph

- Information becomes available about the profile of API, new peaks detected
- Share information with the Ph Eur experts
- Request for a revision of Monograph to include limits for new identified/qualified impurities

Summary

- Certification relates to API/DS only
- Antibiotics are manufactured either chemically, fermentative or by semi-synthetic processes
- GM2034 and EMA antibiotics GL wrap up the current requirements wrt to report/identify/qualify of impurities in antibiotics
- Control of product-rel impurites is more challenging the more complex the API is
- Control of very complex impurity profiles requires extended efforts
- Limits in the EMA antibiotics GL may be different to the Ph Eur Monograph
- Control of process-related impurities in fermentation products
- „Change control“, „Rejuvenation“ of MCB - Stay alert and watch out the consequences!
- In case of new impurites, request for revision of Ph Eur Monograph

Thank you very much for your attention!

Contact

- Federal Institute for Drugs and Medical Devices
- Kurt-Georg-Kiesinger-Allee 3
- D-53175 Bonn

- Contact person
- Dr. Ute Fischer
- ute.fischer@bfarm.de
- www.bfarm.de
- Phone +49 (0)228 99 307-5537

Zertifikat seit 2010
audit berufundfamilie

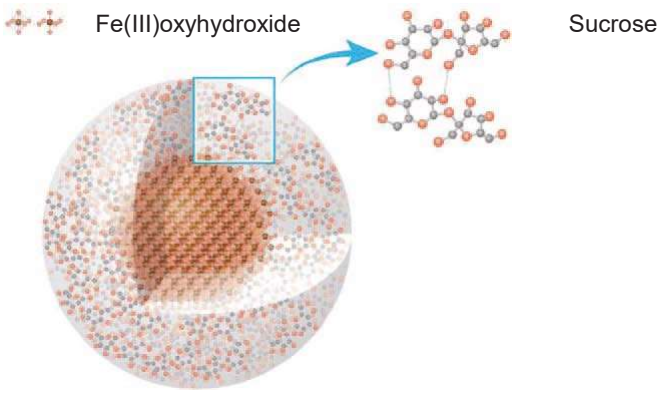
Challenges in setting standards for non-biological complexes

Iron sucrose story

Dr. Erik Philipp
Scientific Director Iron & Head of Chemical Development
CSL Vifor Ltd.
Member of the NBC working group

Iron sucrose

Setting standards for iron sucrose by establishing a monograph for ‘iron sucrose concentrated solution’



Starting point: USP Monograph Iron Sucrose Injection

3406 Iron / Official Monographs

.

Iron Sucrose Injection

Iron Sucrose Injection is a sterile, colloidal solution of ferric hydroxide in complex with Sucrose in Water for Injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of iron. Sodium Hydroxide may be added to adjust the pH. It contains no antimicrobial agent, chelating agent, dextran, gluconate, or other added substances.

Parameters and Limits from USP DP Monograph

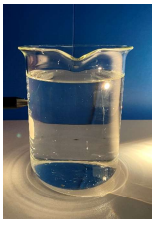
Parameter	Method		Specified Limits	Comment
Molecular weight determination	Size Exclusion Chromatography		Mw = 34'000 Da – 60'000 Da Mn ≥ 24'000 Da P = Mw/Mn ≤ 1.7	Chromatography columns and conditions had to be evaluated
Alkalinity	Titration		0.5 – 0.8 ml 0.1 N HCl/ ml Injection	
Turbidity point	Titration		pH = 4.4 – 5.3	
Reduction potentials		Fe(III) / Fe (II) Fe(II) / Fe (0)	- 750 ± 50 mV - 1400 ± 50 mV	Different values, depending on equipment
Iron(II)	Polarography		≤ 0.4 % m/V	Quantification insufficient
Iron (Assay)	Complexometric titration or atomic absorption spectroscopy		1.9 – 2.1 % m/V	
Sucrose (Assay)	HPLC		260 mg – 340 mg per ml	

Iron sucrose concentrated solution is a drug substance !

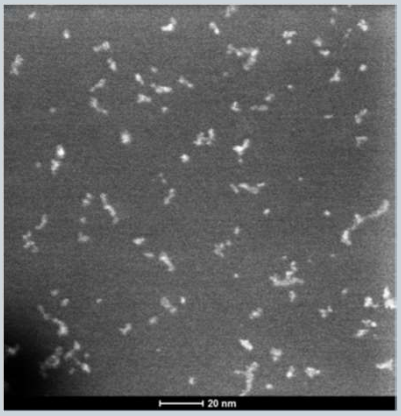
▶ Products of different drug substance suppliers differ in parameters such as

- Concentration (2 – 5 % m/V Fe)
- pH (10.0 – 11.1)
- Chloride content
- Molecular weight
- Viscosity, Density

Iron sucrose: From Tyndall effect to nanoparticles



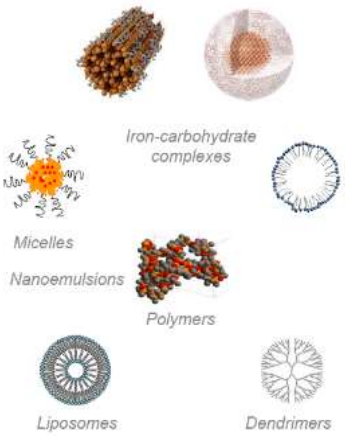
TYNDALL EFFECT



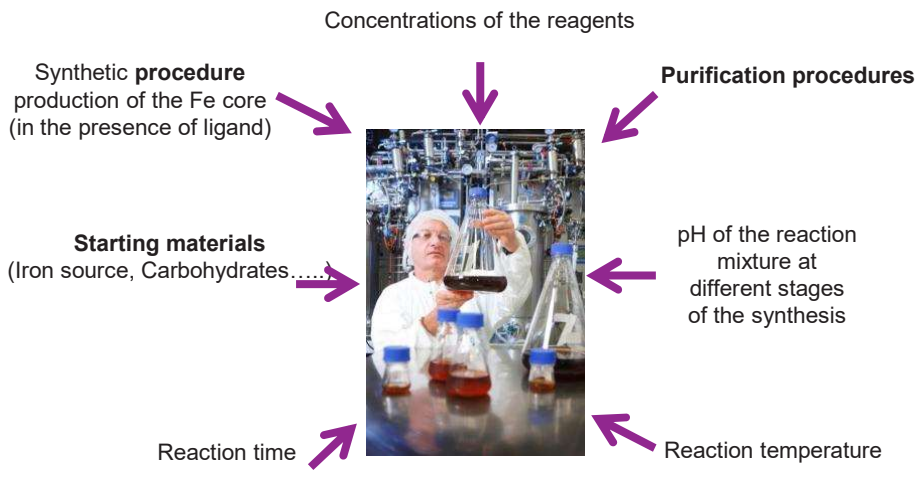
Cryo-TEM

NBCD
A non-biological complex drug product…

- … is a synthetic medicinal product that is not a biological Medicine
- … with an active substance that is not homo-molecular but contains different (closely related, often (nanoparticulate) structures
- … that cannot be fully characterized by physicochemical analytical means.



Parameters that Influence the Manufacturing Process of Iron(III)-oxyhydroxide Carbohydrate Complexes



Schellekens et al. *Reg Tox Pharmacol.*2011;59:176–183

FDA's factors for assessment of nanomaterials

Drug Products, Including Biological Products, that Contain Nanomaterials
Guidance for Industry

1. Adequacy of characterization of the material structure and its function
2. Complexity of the material structure
3. Understanding of the mechanism by which the physicochemical properties of the material impact its biological effects (eg effect of particle size on PK parameters)
4. Understanding the in vivo release mechanism based on the material physicochemical properties
5. Predictability of in vivo release based upon established in vitro release methods
6. Physical and chemical stability
7. Maturity of the nanotechnology (including manufacturing and analytical methods)
8. Potential impact of manufacturing changes, including in-process controls and the robustness of the control strategy on critical quality attributes of the drug product
9. Physical state of the material upon administration
10. Route of administration
11. Dissolution, bioavailability, distribution, biodegradation, accumulation and their predictability based on physicochemical parameters and animal studies

FDA Nanomaterials Guidance 2022

FDA Nanomaterials Guidance 2022

EMA Reflection Paper

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2015
EMA/CHMP/SWP/620008/2012
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product

PV1

Challenges to overcome

Simple use the procedures described in USP was not possible

- USP describes medicinal product Iron sucrose injection with the fixed concentration (20 mg/mL) whereas Ph. Eur. would describe Iron sucrose concentrated solution
- Several manufacturers in the European market with the solutions containing different concentrations
- The monograph should be applicable for a range of concentrations
- Additional requirements by EMA reflection paper (particle size, labile iron, amount of divalent and trivalent iron)
- Products on the market were registered without quality requirements for additional tests listed in EMA reflection paper, the group has no information on the acceptable specification limits

CSL Vifor

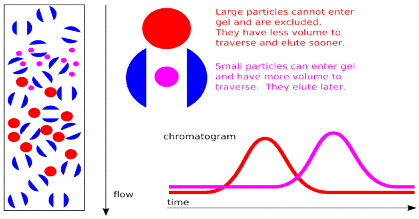
Particle size distribution by SEC

Diapositive 11

PV1 if you would think of anything else please add
PETRUSEVSKA Valentina; 14/09/2022

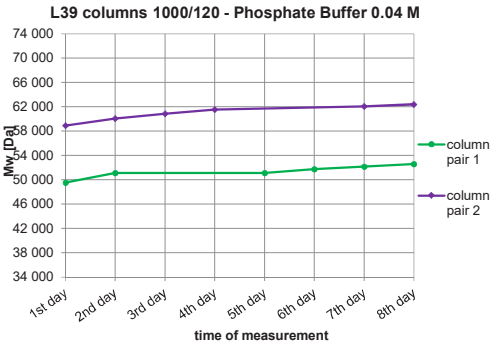
SEC (Size Exclusion Chromatography)

Separation of molecules on the base of their size (and shape)



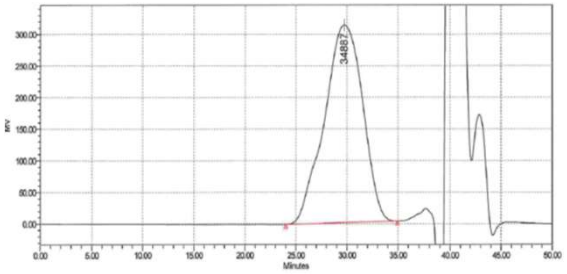
Chromatographic parameter	USP requirement
Mobile Phase	Dissolve 7.12 g of dibasic sodium phosphate dihydrate, 5.52 g of monobasic sodium phosphate and 0.40 g of sodium azide in 2L of water
Flow rate	0.5 mL/min
Column	Packing: L39 (Hydrophylic polyhydroxymethacrylate gel of totally porous spherical resin Type: 7.8 x 300 mm Pore size: 1000 Å and 120 Å

Molecular mass distribution: Reproduciblity issues



Mw values for iron sucrose on 2 different GPC columns from the same supplier

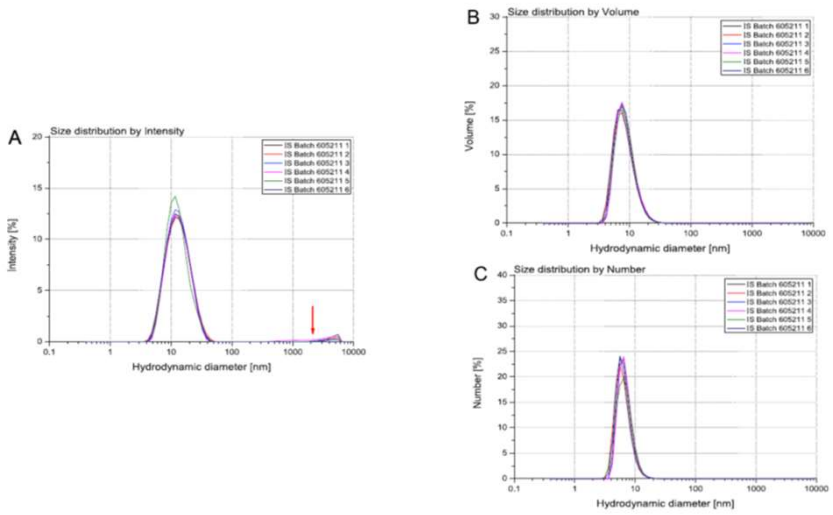
Different column supplier



CSL Vifor

Particle size distribution by Dynamic Light Scattering (DLS)

Particle size determination by DLS



Di Francesco, T., Borchard, G., 2018. A robust and easily reproducible protocol for the determination of size and size distribution of iron sucrose using dynamic light scattering. J. Pharm. Biomed. Anal. 152, 89–93.

Particle size determination by DLS

Z-Average ± SD [nm]	RSD [%]	PDI ± SD	RSD [%]	Size distribution by Volume ± SD [nm]	RSD [%]	Size distribution by Number ± SD [nm]	RSD [%]
12.2 ± 0.5	4.1	0.188 ± 0.022	11.7	11.7 ± 1.8	15.4	6.7 ± 0.2	3.0
11.6 ± 0.1	0.9	0.128 ± 0.006	4.7	9.2 ± 0.1	1.1	7.1 ± 0.2	2.8
12.4 ± 0.1	0.8	0.157 ± 0.017	10.8	9.3 ± 0.8	8.6	6.8 ± 0.2	2.9

- Challenge: Quantification mode and limits have to be defined by the working group

Di Francesco, T., Borchard, G., 2018. A robust and easily reproducible protocol for the determination of size and size distribution of iron sucrose using dynamic light scattering. J. Pharm. Biomed. Anal. 152, 89–93.

CSL Vifor

Labile Iron

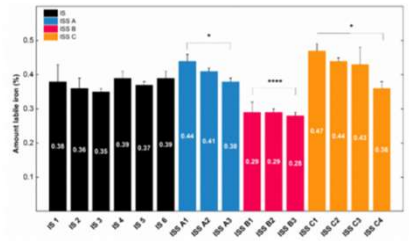
Labile iron in view of EMA

The quality attributes of nano-sized iron-based products that may have a major impact on efficacy and safety include:

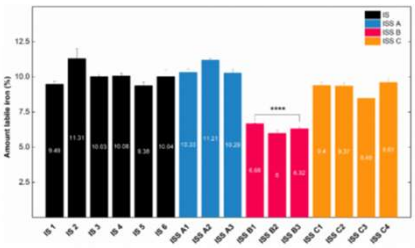
• the stability of the iron-carbohydrate complex, this means: the fraction of labile iron released at the time of administration and the short term stability in plasma, as labile iron has well known direct toxic effects and may influence pharmacokinetics and body distribution

Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product EMA/CHMP/SWP/620008/2012

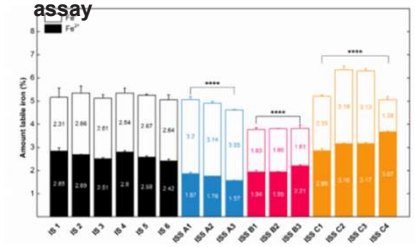
Labile iron : Different results with different tests



Fraction of labile iron determined for IS using the chromazurol B assay



Fraction of labile iron determined for IS using the ferrozine assay



Fraction of labile iron determined for IS using the MAK025 iron assay

Di Francesco, T., Philipp, E., Borchard, G., 2017. Iron sucrose: assessing the similarity between the originator drug and its intended copies. Ann. N. Y. Acad. Sci. 1407, 63–74

Labile iron: further challenges

- Test kits only available from one supplier
- Supplier does not give information about composition of the test kit

▶ Mitigation: Development of a HPLC Method with Deferoxamine as chelator (in progress)

CSL Vifor

Iron(II)

Comparison of analytical methods for the determination of iron(II) in iron sucrose solutions

Evaluation of	CE method	Cerimetry (CER)	Differential Pulse Polarography (DPP)	Cyclic Voltammetry on rotating disk electrode (CV)
Accuracy	98 - 109%	95.8 - 102.4% comparable to CV (10 lots)	quantification insufficient	Fe(II): 102.9 – 104.9 % Fe(III): 99.2 – 101.2 %
Precision	Fe(II): RSD 5.1% Fe(III): RSD 4.0%	Fe(II): RSD 1.9%	0.3% m/V < 10% 0.15% m/V at 30%	Fe(II): RSD 3.6% Fe(III): RSD 1.7% Fe (total): RSD 1.8%
Investment costs	high	low	low	low
Miscellaneous			fingerprint half wave potential	Specific electrode needed

Iron (II) determination, comparison of results from different methods

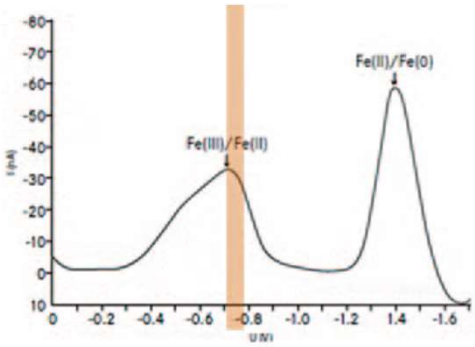
	Cerimetry		Permanganometry	Cyclovoltammentry
iron sucrose 2% m/V Fe n = 10	Fe(II) % [m/V]		Fe(II) % [m/V]	Fe(II) % [m/V]
	1st inflection point	2nd inflection point		
minimum	0.13	0.16	0.20	0.20
maximum	0.19	0.22	0.24	0.28
mean	0.16	0.20	0.22	0.22

▶ Challenge: Suitable method and limits have to be defined by the working group

CSL Vifor

Reduction potential by polarography

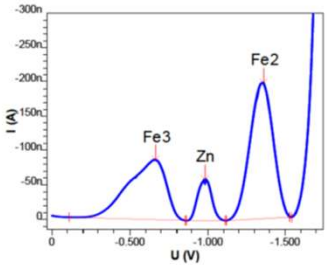
Reduction potential by Polarography



red bar mark the peak voltage ranges for the reduction potential Fe(III) → Fe(II) by USP (iron sucrose injection solution − 0.750 ± 0.050 V)

Polarography against Zn standard

Example determination with 797 VA Computrace



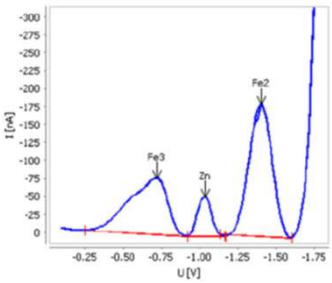
797 VA Computrace

	Potential vs. Ag/AgCl reference	Potential vs. Zn peak
Zn	-0.98 V	--
Fe(III) → Fe(II)	-0.66 V	+0.33 V
Fe(II) → Fe^0	-1.35 V	-0.37 V

884 Professional VA Professional VA

	Potential vs. Ag/AgCl reference	Potential vs. Zn peak
Zn	-1.03 V	--
Fe(III) → Fe(II)	-0.71 V	+0.32 V
Fe(II) → Fe^0	-1.40 V	-0.37 V

Example determination with 884 Professional VA



▶ Problem solved by introduction of Zn standard

CSL Vifor

Conclusion

(''There is light ....'')

Conclusion

What has been achieved ?

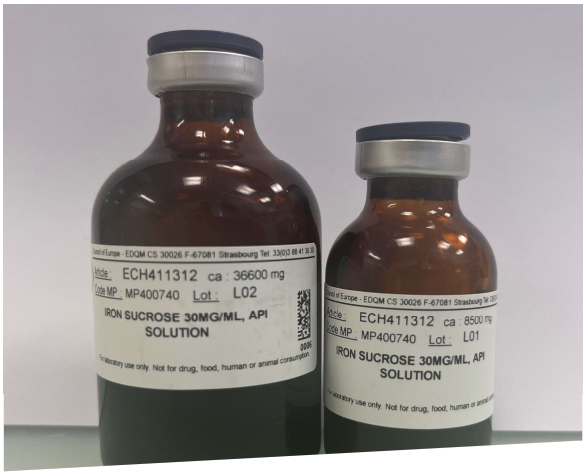
Methods and limits could be implemented for the parameters:

pH, alkalinity, chloride, turbidity point (pH), reduction potential (polarography), assay

Where do we still face challenges ?

Methods for some parameters need to be further developped and limits to be set:

Labile iron (HPLC), iron(II), particle size (DLS), Molecular mass distribution (SEC)



CSL Vifor

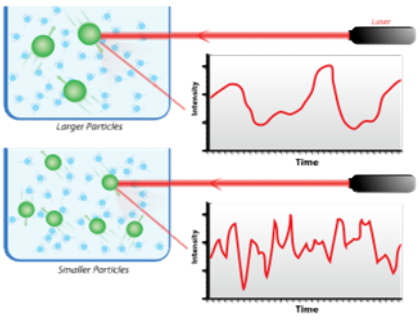
Route scouting and process optimization

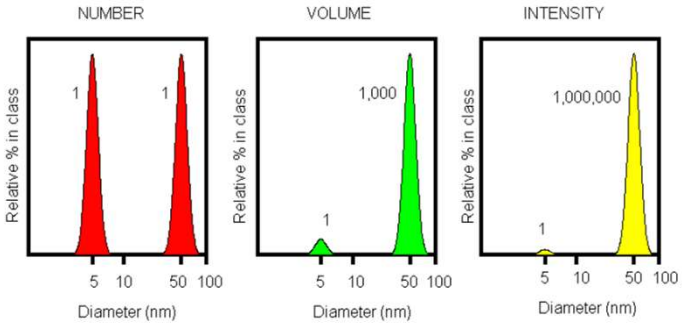
CSL Vifor

Back up slides

DLS (Dynamic light scattering)

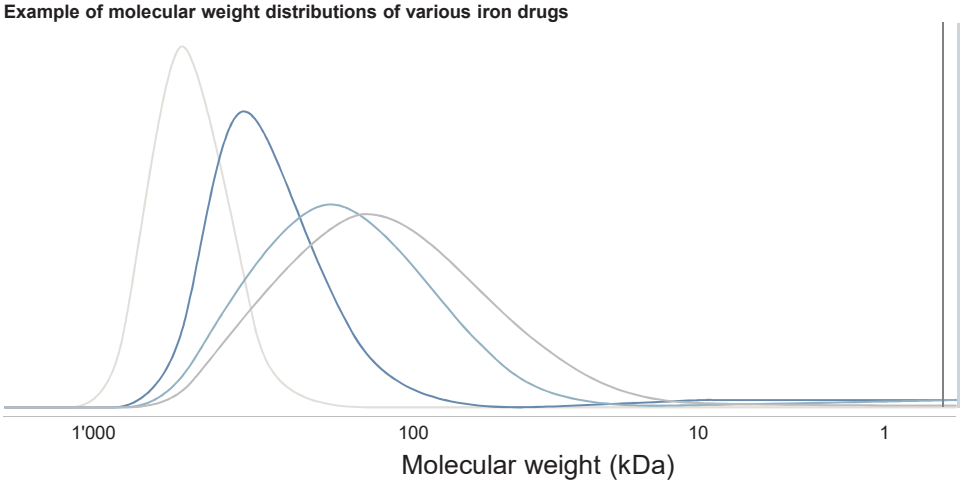
Interference of light scattered by individual particles under the influence of Brownian motion.
Intensity of light is proportional to d^6
(d = particle diameter)

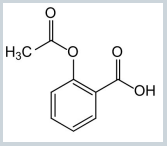




NBCD
A non-biological complex drug product…

Example of molecular weight distributions of various iron drugs

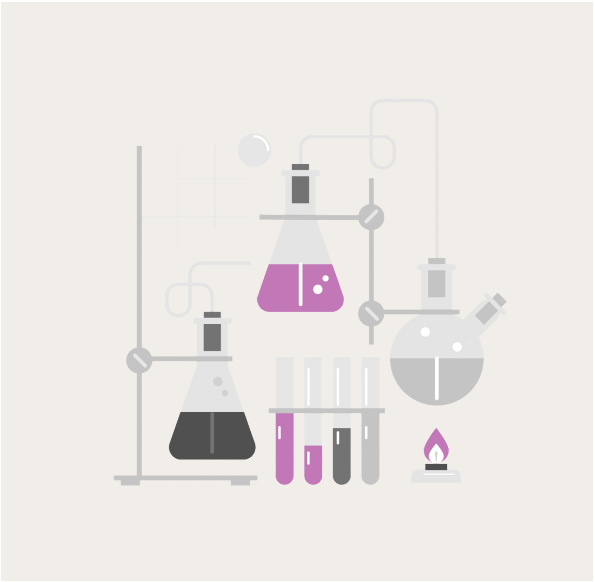




ASPIRIN

Expectations and complexity in setting standards for polymeric excipients

Consideration of solvents and monomers



September 20, 2022, Johanna Eisele

EVONIK
Leading Beyond Chemistry

Disclaimer

This is my personal knowledge and experience. It is not necessarily the opinion of my employer.

This presentation can only provide a small impression on the complexity of polymeric excipients, and no in-depth information is shared.

EVONIK
Leading Beyond Chemistry

Setting specifications on solvents and monomers in polymeric excipients

1. **Polymeric excipients are complex and diverse**
2. **Analytics of polymers**
3. **Setting specifications for residual solvents in polymeric excipients**
4. **Case study 1: solvents in copolymer from emulsion polymerization process**
5. **Case study 2: solvents in copolymer from solution polymerization process**
6. **Case study 3: monomers in Poly(D,L-lactide-co-glycolide)**
7. **Conclusion and summary**

EVONIK Leading Beyond Chemistry

Types of polymeric excipients described in Ph. Eur.

- **Approximately one hundred (100) Ph. Eur. monographs** include a section "FUNCTIONALITY-RELATED CHARACTERISTICS", many of them (co)polymers
  - Synthetic polymers, semisynthetic polymers, sugars, natural proteins, …
- **Homopolymers:** Poly(vinyl) Alcohol, Povidone, Poly(vinyl acetate), Dextrose, PEGs, …
- **Copolymers:** Acrylate Copolymers, PEGylated fatty acids, Polysorbates, Copovidone
- **Round about 15-20 monographs for cellulose varieties:** semisynthetic polymers
- **Not yet listed in Ph. Eur.:** Poly(lactide-co-glycolide)

EVONIK Leading Beyond Chemistry

Polymeric excipients are complex and diverse

- **Chemically very different materials**
- **High or low molecular weight**
- **Different polydispersity** (=different chain length distribution)
- **Linear, branched or cross-linked**
- **Available as powders, granules, clear solutions, polymer latices, …**
- **Different polymerization processes:** emulsion polymerization, solution polymerization, ring-opening polymerization…for synthetic polymers
- **Different preparation processes…** for plant derived natural polymers
- **Different manufacturing scales:** kilograms to tons

EVONIK Leading Beyond Chemistry

Chromatography of polymers is complex

- **Challenges in chromatographic techniques:**
  - Polymers may interact with column materials
  - Polymers may interact with eluent
  - Interaction may vary with molar mass of the polymer in question
- **It takes considerable resources – time and knowledge – to develop robust methods.**
- **Controls and standards must be chosen carefully.**

Even with a good description in a monograph, analytical experts must carefully implement and verify the respective methods on their equipment.

EVONIK Leading Beyond Chemistry

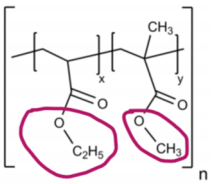
ICH Q3C - Setting residual solvents specifications for polymers

- **ICH Q3C / Residual solvents are limited according to the principles defined in chapter 5.4, using general method 2.4.24 or another suitable method. This is the basis and starting point:**
- **Likely to be present (LTBP): Those solvents that are**
  - 1) used or produced in the final manufacturing step;
  - 2) used or produced in earlier manufacturing steps but they are not consistently removed by a validated process;
- **Supplier of excipients must provide statements / information on residual solvents.**
- **Sources of residual solvents in polymeric excipients:**
  - Solvents are used in the manufacturing process (i.e., in solution polymerization processes, purification)
  - Solvents may be introduced via raw materials containing such solvents
  - Solvents result from degradation during storage (i.e., side chains of polymer may hydrolyze and split of alcohols)

EVONIK Leading Beyond Chemistry

Case study 1: solvents in copolymer from emulsion polymerization process

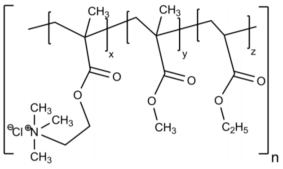
- **Today eight monographs of methacrylic acid / methacrylate copolymers in Ph.Eur.**
- **Case Study 1: METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) DISPERSION 30 PER CENT.**
  - Tablet coating
  - Also described in monographs in USP-NF, JPE and ChP
  - Manufactured by emulsion polymerization. Solvent: water
  - Side chains may hydrolyze after longer storage or at elevated temperatures
  - Ethanol and methanol may form
- **During risk assessment all raw materials were evaluated, and the process analyzed.**
- **Possible sources of residual solvents were analyzed.**



- **A representative lot was tested for Class 1 and 2 Solvents.**
  - Only source identified was degradation: limits for ethanol and methanol were set a < 0.5% and < 0.1%, respectively
  - Screening of residual solvents was performed according to USP <467> (water-insoluble articles)
  - Quantification of methanol and ethanol was performed using an in-house GC-method

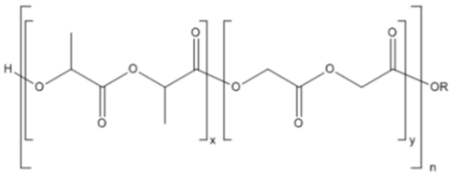
EVONIK Leading Beyond Chemistry

Case study 2: solvents in copolymer from solution polymerization process



- **Case Study 2: AMMONIO METHACRYLATE COPOLYMER.**
  - Tablet coating
  - Also described in monographs in USP-NF and JPE
  - Manufactured by solution polymerization and subsequent extrusion (purification step)
  - Main solvent ethanol, small amounts of methanol
- **During risk assessment all raw materials were evaluated, and the process analyzed.**
- **Possible sources of residual solvents were analyzed: solvents, degradation.**
- **A representative lot was tested for Class 1 and 2 solvents.**
- **Sources of solvents:**
  - Solvents from manufacturing process: limits for ethanol and methanol were set according to Table 2 and Table 3 of 5.4. RESIDUAL SOLVENTS.
  - Screening of residual solvents was performed according to USP <467> (water-insoluble articles)
  - Quantification of methanol and ethanol was performed using an in-house GC-method

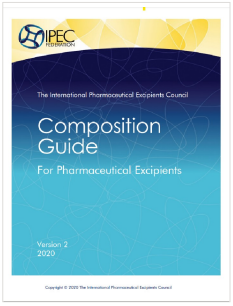
Case study 3: monomers in Poly(D,L-lactide-co-glycolide)



- **Case study 3: Poly(D,L-lactide-co-glycolide)**
  - Parenteral use, depot formulations
  - ChP monograph available, NF draft monograph published
  - Wide range of polymer composition / ratio of D,L-lactide to glycolide: 100:0 to 50:50 molar ratio
- **Manufactured by ring-opening polymerization.**
- **Monomers are not toxic.**
- **Presence of monomers impacts degradation both during storage and in vivo. This can be a desired property.**
- **≤ 0.5 % D,L-lactide ≤ 0.5 % glycolide were set as specifications.**
- **The residual monomer content is determined by gas chromatography (GC, FI-detector) using an internal standard. The sample is dissolved in methylene chloride. The residual monomer content is calculated as mean value of the 3 injections.**

GM 2034: Paragraph on related substances does not apply to excipients

- This is explicitly mentioned in 5.10. **CONTROL OF IMPURITIES IN SUBSTANCES FOR PHARMACEUTICAL USE**
- IPEC recommends to excipient manufacturers to **establish a composition profile**
- The ***IPEC Federation Composition Guide For Pharmaceutical Excipients*** provides an approach
- For excipients where purity can be measured directly, **any undesirable organic and inorganic components** present at or above 0.1% **should be identified and assessed** to determine the need (if any) for quantitative limits
- **Composition profiles may be considered** proprietary information



Communication of excipient composition is a case-to-case decision. Often a CDA needs to be concluded.

EVONIK Leading Beyond Chemistry

By-products and components to be expected in synthetic polymers

- **Many synthetic polymers are manufactured by exothermal polymerization processes.** The raw materials may include monomers, chain modifying agents and initiators, solvents.
- **Residual monomers and residuals solvents are the key impurities** to control in synthetic polymers and are usually identified and specified.
- **Monomers and initiators may also contain minute amounts of stabilizers** to prevent uncontrolled polymerization / degradation. These stabilizers are necessary for both quality purposes (better control of the process) and work safety (to prevent uncontrolled exothermal reactions).
- **By-products may be present** as a result of raw materials and exothermal manufacturing processes. These traces would not require further action unless exceptionally toxic

Suppliers of polymeric excipients will usually evaluate such by-products and document them in a composition profile.

EVONIK Leading Beyond Chemistry

Polymeric excipients are complex and diverse

- **Many different types of polymers are available** that can be used as excipients in drug products.
- **Analytics are complex** as polymers are challenging matrices.
- **Get a thorough knowledge** on the behavior of a polymer in each analysis system.
- **It takes considerable time and effort** to develop a robust and reliable method.
- **Setting the specification** must consider both safety and production capability.
- **Lowest limits are not necessarily the best ones.**
- **Monographs should only limit key impurities** such as monomers and residual solvents, and those by-products / components > 0.1%

Drug product manufacturers must get familiar with the polymers they want to use in their drug product.
Polymeric excipient suppliers will help in most cases!

EVONIK Leading Beyond Chemistry

Thank you!

Dr Johanna Eisele
Global Head of Regulatory Affairs | Health Care

johanna.eisele@evonik.com

Evonik Operations GmbH | Nutrition & Care
Kirschenallee | 64293 Darmstadt | Germany
www.evonik.com

EVONIK Leading Beyond Chemistry


EVONIK
Leading Beyond Chemistry