CO-PROCESSED EXCIPIENTS

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EXCIPIENTS :

Any constituent of a medicinal product other than the active substance and the packaging material.

Falsified medicine Directive
Directive 2011/62/EU

DEFINITION OF EXCIPIENTS

Pharmaceutical excipients are any substance other than the active drug or prodrug which has been appropriately evaluated for safety and is included in a drug delivery system to either :

1. **aid processing of the system during manufacture, or**
2. **protect, support or enhance stability, bioavailability or patient acceptability, or**
3. **assist in product identification, or**
4. **enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use**

IPEC

EVOLUTION OF THE SOURCES OF EXCIPIENTS

- **Food – borne**
- **New chemical entities**
- **New grades of existing materials**
- **New combinations of existing materials**

Particle engineering

FUNCTIONALITY :

A desirable property of on excipient that aids and / or improves the manufacture, quality or performance of the drug product.

IPEC QUALIFICATION / GUIDE

The functionality of excipients depends not only on the intrinsic properties but also on the formulation and manufacturing process.

FUNCTIONALITY – RELATED CHARACTERISTIC

A controllable physical or chemical characteristic of an excipient that is shown to impact on its functionality

EUROPEAN PHARMACOPOEIA

5.15. FUNCTIONALITY-RELATED CHARACTERISTICS OF EXCIPIENTS

This chapter and the Functionality-related characteristics (FRCs) sections in individual monographs are not mandatory and are published for information and guidance.

PREAMBLE

Excipients that have previously been evaluated for safety are used in the formulation of pharmaceutical preparations to bring functionality to the formulation. The intended function of an excipient is to guarantee the required physicochemical and biopharmaceutical properties of the pharmaceutical preparation.

The functionality of an excipient is determined by its physical and chemical ~~properties~~ attributes and, in some cases, also by its content of by-products or of additives used to improve the intended functionality. In addition, the functionality may depend on complex interactions between the constituents of the formulation and stresses related to the process. Excipient functionality can therefore be evaluated only in the context of a particular formulation and manufacturing process, frequently by the use of a number of analytical methods.

WHAT ARE THE INTERESTS OF NEW EXCIPIENTS ?

- To modify the bioavailability
  - Solubility
  - Rate of dissolution
  - Permeability
- To administer drugs by parenteral route or inhaled route
- To avoid to use the excipients known to have au recognised action or effect for specific patients (diabetes – hypertension)
- To improve the functionality

PARTICLE ENGINERRING

- Particle size changes by physical methods
- Granulation : transformation of a cohesive powder into compressible agglomerates
- Crystallisation control
  - Increased crystallinity
  - Change in polymorphic form or the ratios of different polymorph form
  - Spray drying or co spray drying
- Co-crystallisation
- Co-precipitation

Moreton DDIP 96,22, n°1

APPLICATIONS OF PARTICLE ENGINEERING : SOME EXCIPIENTS FOR DIRECT COMPRESSION

- Microcrystalline cellulose
- Lactose
- Sucrose
- Dextrose
- Sorbitol
- Mannitol
- Calcium phosphate

APPLICATIONS OF PARTICLE ENGINEERING : CO-PROCESSED EXCIPIENTS

- **Definition**

" A co-processed excipient is any combination of 2 or more excipients obtained by physical co-processing that does not lead to the formation of covalent bonds. Co-processed excipients have functionalities that are not achievable through sample blending".

Pharmeuropa 27.4 October 2015

WHAT ARE THE INTERESTS OF CO-PROCESSED EXCIPIENTS ?

- **Functional synergy**
- **Complementary of the functions**

HISTORIC OF CO-PROCESSED EXCIPIENTS

- Co-processed microcrystalline cellulose and calcium carbonate (1988)
- Co-processed cellulose and lactose (1990)
- Co-processed glucomannan and galactomannan (1996)

CO-PROCESSED EXCIPIENTS

The combination of excipients is used to maximize the performance of the functionality

METHODS FOR MANUFACTURING CO-PROCESSED EXCIPIENTS

- Dispersion with high shear mixer
- Co-milling
- Homogenization
- Co-precipitation
- Co-crystallisation
- Wet granulation
- Extrusion
- Hot melt extrusion
- Spray-drying

HYDROUS DEXTRATE NF EMDEX

93 % dextrose

maltodextrine

- Co-crystallisation

COMPRESSIBLE SUGAR NF DIPAC

95 % - 98 % sucrose

Starch, maltodextrines or invert sugar

- Co-crystallisation

Both of them are co-processed excipients

They are considered as “classical” direct compression excipients

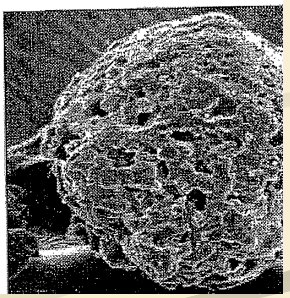
The fronteer is sometimes difficult

Name	Supplier	Ingredients	%	Process
Di-Pac	Domino	Sucrose Maltodextrin	97 3	
Emdex	JRS	Dextrose Maltose Maltodextrin	92 4 4	Spray Crystallised
Pharmatose DCL 40	DMV	B-Lactose Lactitol	95 5	
Sugar Tab	JRS	Sucrose Invert Sugar	93 7	Co-crystallised
Pharmaburst	SPI	Mannitol Sorbitol	70-97 3-30	Melt Extrusion
TIMERx	Endo	Xanthan Gum Locust Bean Gum Calcium Sulphate Filler		Granulate
Ludipress	BASF	Lactose PVP	96.5 3.5	
Starlac 100F	Roquette	α-Lactose hydrate Maize Starch	85 15	Spray Dried
Xylitab 100	Danisco	Xylitol Polydextrose	96.5 3.5	Granulate
Xylitab 200	Danisco	Xylitol Na CMC	98 2	Granulate
StarCap 1500	Colorcon	Corn Starch Pregel Starch	90 10	Co-Spray dried
Advantose FS	SPI	Fructose Starch	95 5	Co- Dried
Ludiflash	BASF	Mannitol PVA Latex solids Crospovidone	90 5 5	Granulate
PanExcea MHC 3330	Covidien	MCC : Hypromellose Crospovidone		Granulate
Cellactose 80	Meggle	α-Lactose hydrate Cellulose	75 25	Co-Spray Dried
Formaxx	Merck	Ca Carbonate Sorbitol	70 30	
Microcelac 100	Meggle	α-Lactose hydrate MCC	75 25	Co-Spray Dried
Avicel HFE	FMC	MCC Mannitol	90 10	Co-Spray Dried
ProSolve	JRS	MCC Silicon Dioxide	98 2	Co-Spray Dried
Avicel CE15	FMC	MCC Guar Gum	85 15	Co-Spray Dried
Avicel DG	FMC	MCC DI Ca Phosphate	75 25	Co-Spray Dried

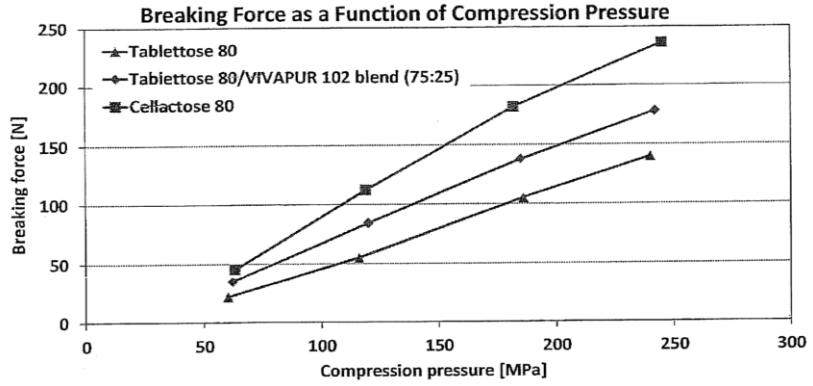
Some commercialy available co-processed excipients

Cellactose 80 (MEGGLE)

- Composition
  - 75% α-lactose monohydrate, Ph.Eur., NF, JP
  - 25% powdered cellulose, Ph.Eur., NF, JP
- Manufacturing process
  - Co-spray-drying
- Physical characteristics
  - Binary composition
  - Mono-particulate

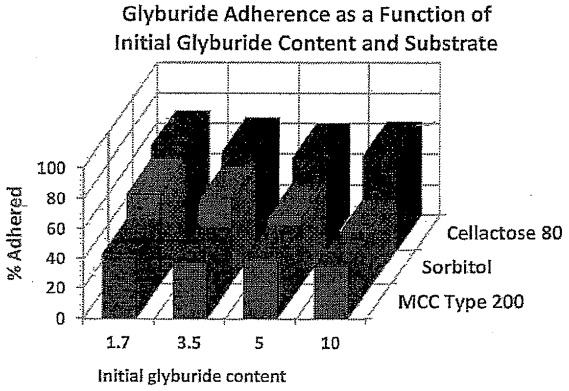


Cellactose® 80 Compactibility



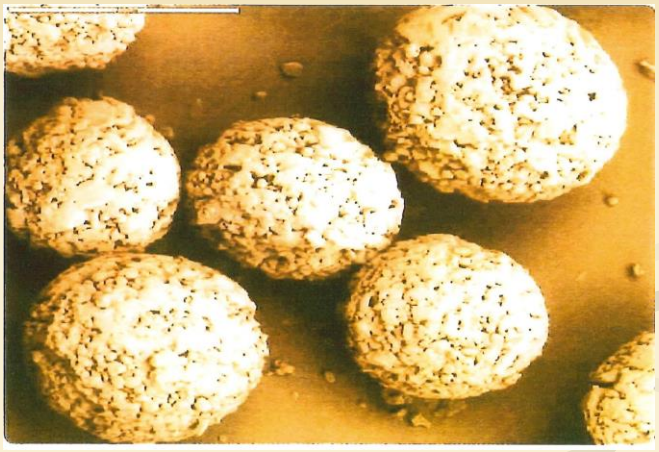
- Synergy is established through co-processing
  - Cellactose® 80 compacts better than the admixture comprising the individual ingredients

Cellactose® 80 Blend Enhancement



- Synergy is established through co-processing
  - Cellactose® 80 improves blending and CU over traditional excipients

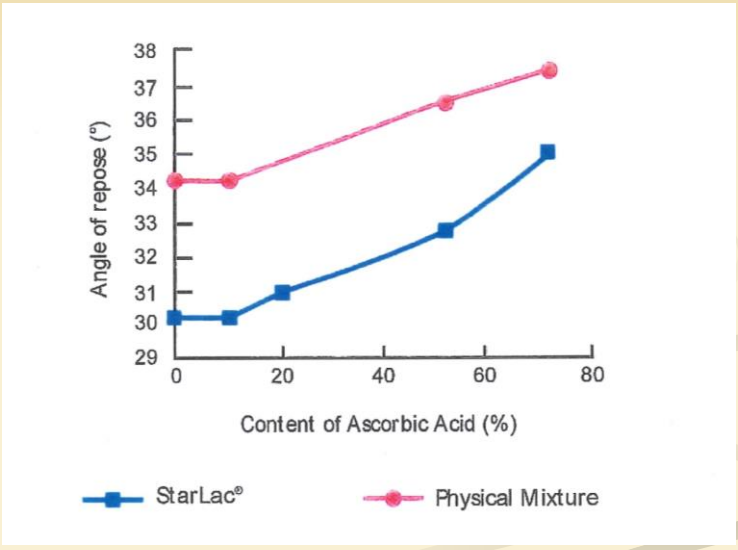
SEM PICTURE OF STARLAC® MAGNIFICATION 100X



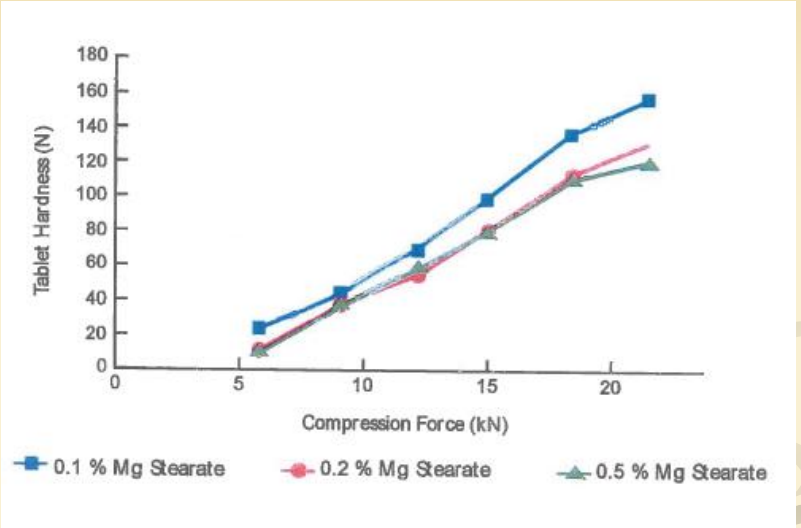
85 % x Lactose monohydrate
15 % white corn starch

- Spray drying

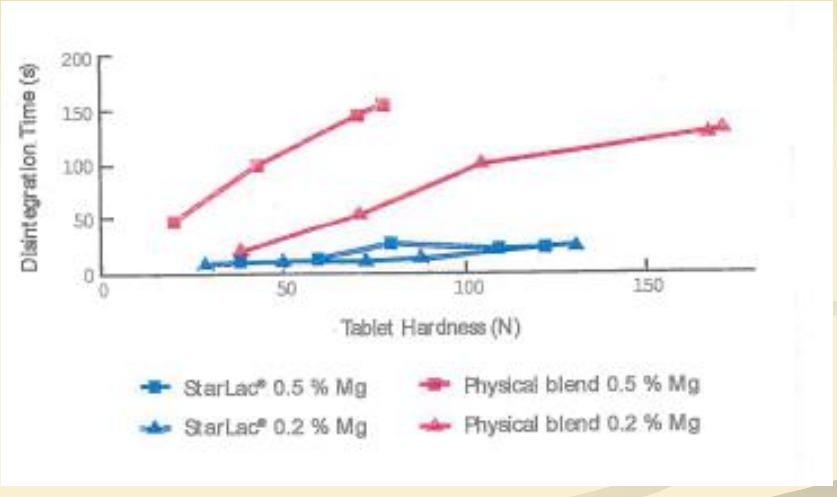
Roquette – Starlac Brochure 21



Roquette – Starlac Brochure 22

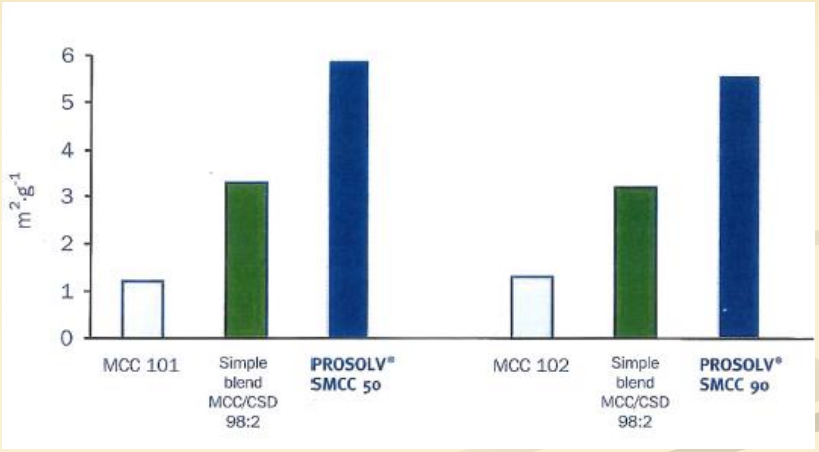


Roquette – Starlac Brochure



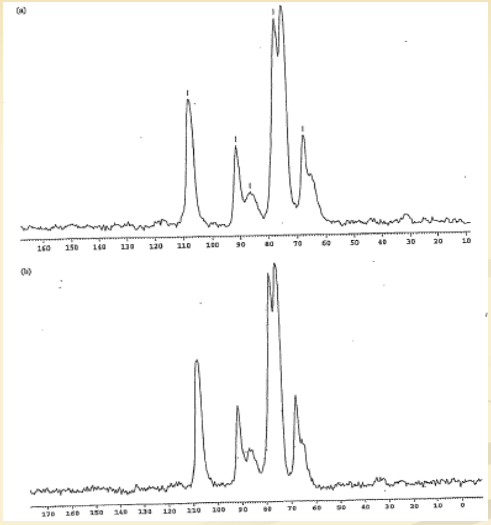
Roquette – Starlac Brochure

SPECIFIC SURFACE AREA OF MICROCRYSTALLINE CELLULOSE, SILICIFIED MICROCRYSTALLINE CELLULOSE (PROSOLV SMCC) AND OF THE BLEND



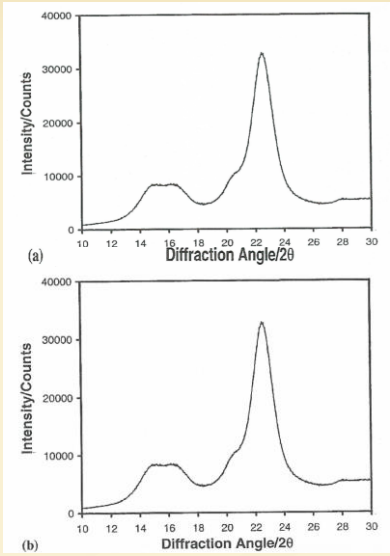
Prosolv SMSCC Brochure

SOLID-STATE NMR SPECTRA OF MICROCRYSTALLINE CELLULOSE (A) AND SILICIFIED MICROCRYSTALLINE CELLULOSE (B)

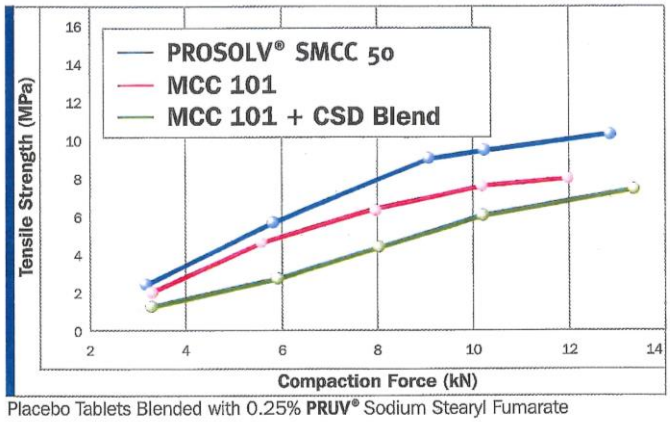


M.J. Tobyn et al, International Journal of pharmaceutics 169 (1998) 183 - 194

X-RAY DIFFRACTOGRAMS OF MICROCRYSTALLINE CELLULOSE (A) AND SILICIFIED MICROCRYSTALLINE CELLULOSE (B)



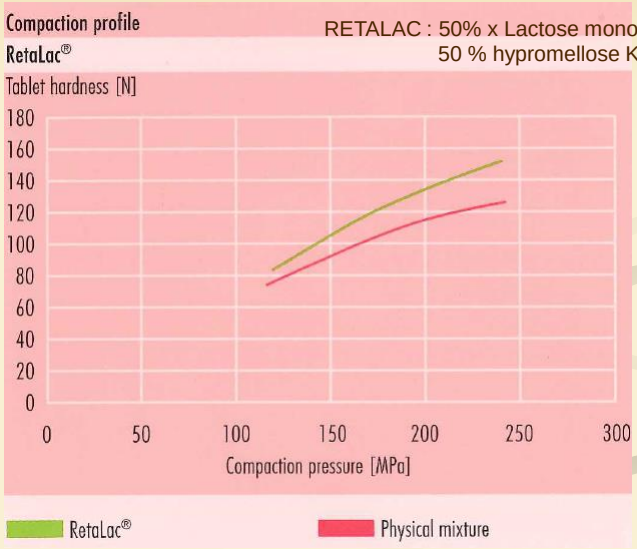
Compaction



Placebo Tablets Blended with 0.25% **PRUV®** Sodium Stearyl Fumarate

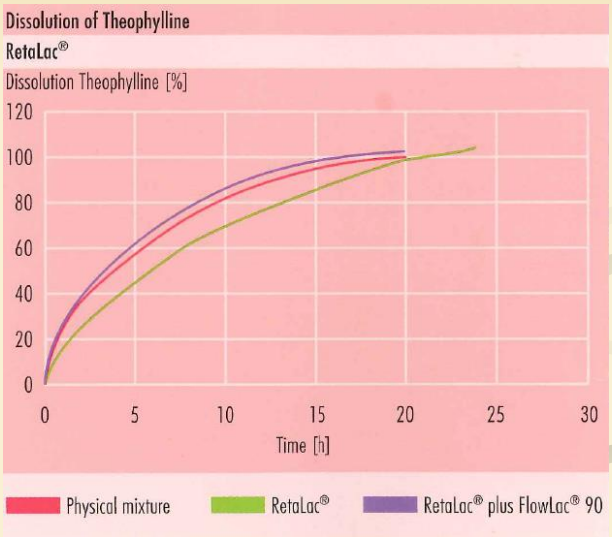
Prosolv SMSCC Brochure

COMPACTION PROFILE OF RETALAC® AND THE CORRESPONDING PHYSICAL MIXTURE (0,5% MG-STEARATE, 8 MM PUNCHES)



RETALAC : 50% x Lactose monohydrate
50 % hypromellose K4M

DISSOLUTION OF THEOPHYLINE FROM TABLETS CONTAINING OF 24.5 % THEOPHYLINE AND 75% EXCIPIENTS (0,5% MG-STEARATE, 11 MM TABLETS)



The co-processed excipients are widely used in marketed products.

DISCUSSION

- The Pharmacopeia draft general monograph on co-processed excipients monograph (2969) has been published for comments in Pharmeuropa 27.4 october 2015
- Despite the rather "high level content" a wide spectrum of comments has been received from users, excipient manufacturers and interested parties.

INTERESTS OF A GENERAL MONOGRAPH ON CO-PROCESSED EXCIPIENT

- To provide a definition and common language
- To point at "particularities" of co-processed excipients and therefore
- To enable to define which quality controls are necessary

The general monograph on co-processed excipients will help users, manufacturers and quality assessors.

THE PROJECT OF A MONOGRAPH ON CO-PROCESSED EXCIPIENTS INTRODUCES SOME QUESTIONS :

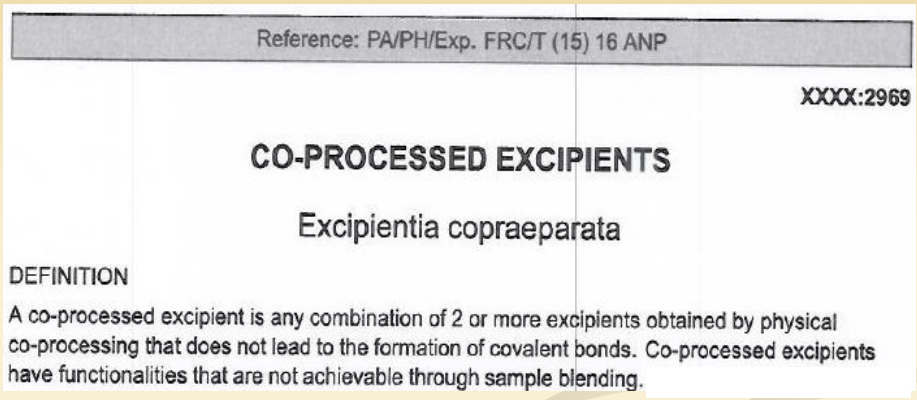
- Does co-processed excipient belong to finish product manufacturing ?
- Does a quality system guarantee the quality of the co-processed excipients ?
- Which information are necessary in a MAA file ?

DISCUSSION

- The answers will be adressed by assesors and inspectors.
- There is an European regulation for pharmaceutical excipients.

REGULATION OF EXCIPIENTS

- EU-GMP requirements for the excipient manufacturer
  Directive 2001/83/EU as amended
- Risk assessment to identify the appropriate level of GMP for excipients
  EU Guideline 2015/C95/02
- Qualification of excipient suppliers (Section 5-27 GMP)
- Quality assurance Agreement (Section 5-28 GMP)
- Formalised quality risk assessment to approve and maintain suppliers of active substances and excipient (Section 5-29 GMP)
- Audit of suppliers (5-36 GMP)



Reference: PA/PH/Exp. FRC/T (15) 16 ANP

XXXX:2969

CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

DEFINITION

A co-processed excipient is any combination of 2 or more excipients obtained by physical co-processing that does not lead to the formation of covalent bonds. Co-processed excipients have functionalities that are not achievable through sample blending.

- **Comments**
  - **What means does not lead to the formation of covalent bonds ?**
  - **The co-processed excipient may require additional stabilizing agents such as antioxidant – emulsifiers**

- **Discussion**
  - **Co-processing does not chemically alter parent ingredients. They do not loose their chemical structure and stability.**
  - **During co-processing, minor necessary components may be formed such as "in situ" salt formation which can disappear**
  - **If covalent bond formation takes place e.g. in situ polymerisation, is-it a co-processed excipient ?**
  - **Without significant chemical changes ?**
  - **Is the emulsifier a component of the co-processed excipient ?**

Reference: PA/PH/Exp. FRC/T (15) 16 ANP

XXXX:2969

CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

The individual components may be pharmacopoeial excipients or non-pharmacopoeial excipients that have previously been evaluated for safety.

- **Comment**

  Is the "safety" concept necessary in this draft monograph
- **Discussion**
  - **General monograph to help manufacturers, users and quality assessors**
  - **To be coherent with the functionality - Related characteristics monograph of the European Pharmacopoeia**

  "Excipients that have previously been evaluated for safety are used in the formulation of pharmaceutical preparations to bring functionality to the formulation"

Reference: PA/PH/Exp. FRC/T (15) 16 ANP

XXXX:2969

CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

The composition of a co-processed excipient is defined and appropriate limits around the nominal percentage content of each component are determined based on the capability of the manufacturing process.

- **Comment**

  Does this mean that every different ratio of one identical combination corresponds to one monograph ?

- **Discussion**
  - **Is it interesting for excipient manufacturers to manufacture "tailored excipients" ?**
  - **Does is need a development of a new analytical method for each ratio ?**

Reference: PA/PH/Exp. FRC/T (15) 16 ANP

XXXX:2969

CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

The individual components of a co-processed excipient comply with the requirements of any corresponding individual monographs and of the general monograph *Substances for pharmaceutical use (2034)*. Any component not isolated during the production process would meet the same requirements if isolated.

Co-processed excipients comply with the requirements of the general monograph *Substances for pharmaceutical use (2034)*.

- **Comment**

  Will the certificate of analysis of each component be present in the MAA file of the product using a co-processed excipient ?

- **Discussion**
  - **To be addressed by the Quality Working Party**

EUROPEAN PHARMACOPOEIA

I- General Notices

1-4- Monographs

« ...

PRODUCTION

Statements under the heading Production draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute mandatory requirements for manufacturers, unless otherwise stated.

Reference: PA/PH/Exp. FRC/T (15) 16 ANP

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CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

PRODUCTION

It must be confirmed that the processing of co-processed excipients produces only a physical interaction between the components, such as hydrogen bonding or ionic association, and that no new covalent bonds are formed. Different techniques can be used to demonstrate that the chemical structure of each component is preserved: chromatographic techniques (liquid or thin-layer chromatography), spectroscopic techniques (Fourier transform infrared (FTIR), infrared (IR) or Raman spectroscopy), differential scanning calorimetry (DSC), solvent separation, or any other suitable technique.

- **Comment**

How to demonstrate only a physical interaction and no new covalent bonds are formed ?

Reference: PA/PH/Exp. FRC/T (15) 16 ANP

XXXX:2969

CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

IDENTIFICATION

Any identification test confirms the presence of each component. The following techniques may be used: FTIR or IR spectroscopy, liquid or thin-layer chromatography, or any other appropriate technique.

5.35 Manufacturers of finished products are responsible for any testing of starting materials2 as described in the marketing authorisation dossier. They can utilise partial or full test results from the approved starting material manufacturer but must, as a minimum, perform identification testing3 of each batch according to Annex 8.

G.M.P.

Reference: PA/PH/Exp. FRC/T (15) 16 ANP

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CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

IDENTIFICATION

In addition, a series of tests are described that differentiate the material from a simple blend of the same components. Such tests may be physical tests, for example particle-size distribution or powder flow. Any test described for functionality-related characteristics may be used.

- **Comments**
  - **Who will do this test ?**
  - **Is-it a mandatory test.**

- **Discussion**
  - **The excipient manufacturer ?**
  - **The finished product manufacturer ?**

Reference: PA/PH/Exp. FRC/T (15) 16 ANP

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CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

TESTS

Generally, when combined, it is not practical to apply the pharmacopoeial tests that are dedicated to the individual components. Specifications are defined for the final co-processed material as a whole; tests may include physical and chemical tests, such as tests for loss on drying, impurities and viscosity, and any other test relevant to the individual components. If the co-processed excipient includes impurities not controlled by the monographs of the individual components, these must be specified and suitably controlled.

- **Comments**
  - **As the production of co-processed excipients does not involue synthetic steps, the formation of new impurities is unlikely.**
  - **In individual monographs of polymeric substances, there is most of the time no control of impurities.**
  - **Information on related substances are considered by some excipient manufacturers as confidential.**

- **Discussion**
  - **General monograph, case by case**
  - **No more stringent that for the new monographs of excipients**
  - **Difficulties to set general thresholds ?**
  - **Responsibilities of the finished product manufacturer and of the marketing authorisation holder.**

Reference: PA/PH/Exp. FRC/T (15) 16 ANP

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CO-PROCESSED EXCIPIENTS

Excipientia copraeparata

ASSAY

Suitable analytical methods are developed to determine the content of each component. It is acceptable to calculate the content of 1 component by difference.

The precision of the proportions of the components in the co-processed excipient is established based on production capability and the ability to achieve consistency of functionality.

- **Comments and discussion**
  - **Instead of assay refer to the GMP documentation ?**
  - **Is it acceptable to calculate the content of a component by difference ?**

CONCLUSIONS

- Always an exciting project
- Work in close collaboration with QWP and GMP IWP

Revision of Ph. Eur. Monograph for Water for Injections

Use of Reverse Osmosis

Dr. Ged Lee
Chairman
WAT Working Party

Outline

- Ph. Eur. Standards for Water
- History of Water for Injections (WFI) monograph
- Situation analysis: status of reverse osmosis
  - **Questionaire**
  - **Data gathering**: use of non-distillation technologies for production of water for pharmaceutical use
  - **Reflection Paper**: Reverse Osmosis and WFI
- Revision of WFI monograph
  - **Stakeholder consultation**
  - **Public consultation** - Pharmeuropa 27.2
  - **Submission for adoption** - 154th Session of the Ph. Eur. Commission

Ph. Eur. WAT Monographs

Water, purified (Ph. Eur. 0008) PW	*Water for Injections* (Ph. Eur. 0169) WFI	*Water, highly purified* (Ph. Eur. 1927) HPW

Other:

Water for diluting concentrated haemodialysis solutions (Ph. Eur. 1167)

Water (^{15}O) injection (Ph. Eur. 1582)

Tritiated (^{3}H) water for injection (Ph. Eur. 0112)

Ph. Eur. WAT Monographs

Water, purified (Ph. Eur. 0008) PW	Water for Injections (Ph. Eur. 0169) WFI	Water, highly purified (Ph. Eur. 1927) HPW
DEFINITION		
➢ for preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised	➢ for preparation of medicines for parenteral administration (bulk WFI) and for dissolving or diluting substances / preparations for parenteral administration (SWFI)	➢ intended for use where water of high biological quality is needed, except where WFI is required

Ph. Eur. WAT Monographs

Water, purified (Ph. Eur. 0008) PW	Water for Injections (Ph. Eur. 0169) WFI	Water, highly purified (Ph. Eur. 1927) HPW
PRODUCTION		
• distillation • ion exchange • reverse osmosis • any other suitable method	• distillation only	• double-pass reverse osmosis coupled with other suitable techniques such as ultrafiltration and deionisation

History Water for Injections (WFI)

1st Publication WFI
Distillation only

1973

1969

Ph. Eur. 1st Edition
Purified Water
physico-chemical tests

Ph. Eur. 3rd Edition – WFI
Revision: replacement of *in vivo* Pyrogens test by LAL (sterile WFI)

1997

1983

Ph. Eur. 2nd Edition, 5th Add. – **WFI**
Revision: editorial changes (bulk WFI/sterilised WFI)
Distillation only

First discussions on RO (double pass):
- limited experience
- membranes robustness, microbiological control
- potential impurities – not detectable by standard methods
- no data available from systems using membrane technique for producing WFI

History Water for Injections (WFI)

Revision initiated:
further guidance to allow closer monitoring of the production

1999

2000

Ph. Eur. 3rd Edition (Suppl.)
Revision: Production section
(Bioburden, TOC, Conductivity)

Renewed discussions on RO
EDQM International Symposium: need for data & guidance
No evidence to support RO as production method for WFI

Highly Purified Water (HPW)

2002

Ph. Eur. 4th Edition
HPW – **new** monograph
WFI – no modification

Adoption by CHMP/CVMP of
Note for Guidance on Quality of Water for Pharmaceutical Use

History Water for Injections (WFI)

2008

Reflection paper on WFI produced by reverse osmosis
EMEA/CHMP/CVMP/QWP/28271/2008
Concerns from regulators –
Biofilm & microbiological safety

Referral to CVMP
Mutual recognition application with WFI prepared by Reverse Osmosis
Scientific basis not open for discussion
Obligation to meet legal requirements

2009
Further discussions in IWG and QWP on use of RO.
135th Session of the Ph. Eur. Commission:
Ph. Eur. requested to take the lead

Industry Survey 2010

Is there any interest in investigating use of alternative systems to distillation for the production of WFI

Do companies have experience of RO for the production of HPW

- System design
- Validation/Qualification
- Membrane efficiency
- Monitoring
- Biofilm formation
- Additional tests

Industry Survey Results 1 : Responses

- 17 Responses
  - 15 pharmaceutical companies
  - 2 companies supplying water systems
- 12 companies expressed an interest in investigating alternatives to distillation
- 5 companies provided supporting data for systems generating HPW using membrane systems

Industry Survey Results 2 : System Design

- RO alone not sufficient – just one of the purification steps
- Additional modules needed:
  - Water pre-treatment
  - Electro-deionisation
  - UV light
  - Ozone
  - Ultrafiltration
  - Membrane degassing
  - Double/triple pass RO
- Purified water as feed water
- Measures included to prevent biofilm formation
  - System design
  - System operation
  - Sanitisation programme

Industry Survey Results 3 : monitoring data

Parameter	Estimated performance of water system	Ph. Eur. monograph limits
Bioburden	10 CFU / 100 mL	10 CFU / 100 mL (action level)
TOC	25 to 350 ppb	0.5 mg/L (= 500 ppb)
Conductivity	0.3 to 2.5 µS.cm^{-1}	0.6 to 4.7 µS.cm-1
Endotoxins	0.025 to < 0.25 EU/mL	0.25 EU/mL

All systems described and reported produce water complying with the existing Ph. Eur. specification for WFI

EDQM Workshop 2012

Objectives

- To assess whether there is sufficient evidence to re-open the debate on the use of non-distillation systems to produce WFI
- To assess the technological developments that may justify a revision of the WFI monograph
- To provide a discussion platform for regulators and the industry

Format

- Regulatory position; inspection views
- International experience; Japan, USP
- Industry experience; distillation, membrane systems
- Case studies; RO
- Cost analyses

EDQM Workshop: Conclusions

Conclusion

There was sufficient evidence for the European Pharmacopoeia Commission to initiate discussions regarding the potential use of membrane systems for the production of WFI and ultimately a revision of the monograph

Issues

- Biofilm
- Control of micro-organisms
- Control of contaminants
- System design
- Monitoring
- WFI specification

Ph Eur: Next Steps

141st Session European Pharmacopoeia Commission; Nov 2011

- Conclusions from the workshop were considered. Technical progress in the use of membrane systems was acknowledged and had to be considered
- *Mandate to the **Ph. Eur. Water Working Party to review the production section** of the Water for Injections monograph (0169) to consider the inclusion of currently available technologies and evaluate whether additional online monitoring is needed*
- Stakeholders to be involved in the discussions
- Water WP reconstituted; membership refreshed

Ph Eur: Meeting of Wat WP

Issues

- Safety of non-distillation techniques
- Are existing specification limits suitable
- Are additional tests needed
- Should the monograph include additional control measures
- Failure mode analysis
- GMP of water production systems
- Impact on other water monographs

↓

Reflection Paper on WFI

Water WP: Reflection Paper

Evidence to support revision of monograph

- Consistent performance of non-distillation systems
- RO no longer used as a final stage of production
- Recognition that all water production systems are a series of interdependent unit processes which rely on the optimum function of each stage to assure the production of water of an acceptable quality. There is a need to have successive treatments to step wise build the water quality
- Advances in the technology and materials used for membrane production
- 20 years of experience in non-distillation technologies.
- System design improvements to avoid deadlegs and allow drainage and sanitisation. (*Applies also to distillation systems*)
- Advances in process controls and in line monitoring of specification parameters. (*Applies also to distillation systems*)
- Improvements in rapid microbial methods reducing time to results
- Evidence supplied that systems are constantly meeting WFI specifications

Water WP: Reflection paper

Issues addressed

- Micro-organisms should be suitably controlled and the final quality of the water appropriate
- Membranes are able to cope with elevated temperatures and harsh environments
- Continuous measurement of physico-chemical parameters – TOC, conductivity, pressure, allow alert limits to be set
- No change to existing specification limits; quality of WFI is appropriate
- System design, operation, and maintenance, including validation and monitoring, is a GMP issue and as such is outside the remit of the Pharmacopoeia
- Revision of annex 1 of the EU GMP Guidelines by IWG was proceeding
- If WFI monograph revised, HPW monograph can be deleted

WFI Monograph: Request for revision

- **146th Session of the European Pharmacopoeia Commission, June 2013**
  - **Endorsement** of *Reflection Paper on WFI*
  - Agreement to **work on the revision of the monograph on *Water for injections* (0169) (WFI) to allow non-distillation technologies for the production of WFI** to be included in addition to distillation
  - Acknowledgement that **design, failure mode and maintenance** of water production systems play an important role in ensuring that **appropriate water quality is established and maintained → *necessary to discuss roles and responsibilities with GMP/GDP Inspectors Working Group and Joint CHMP/CVMP Quality Working Party***

Revision WFI Monograph

- Publication of revised draft monograph ***Water for Injections*** (0169) in **Pharmeuropa 27.2** (April 2015)
- Publication of background document **Reverse osmosis in Ph. Eur. monograph *Water for Injections (0169)*** in **Pharmeuropa (Useful information)**
  - Change to production section only to allow use of reverse osmosis
  - No change to monograph specification
  - No requirement for additional in-line monitoring
  - No change to microbiological methods

Revision WFI Monograph: Pharmeuropa text

PRODUCTION

Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water.

It is produced either:

-by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets. ~~The correct maintenance of the apparatus is essential~~. The first portion of the distillate obtained when the apparatus begins to function is discarded and the distillate is collected; or

-by reverse osmosis which may be single pass or double pass, coupled with other suitable techniques such as deionisation and/or ultrafiltration.

Correct operation, monitoring, and maintenance of the apparatus is essential.

In order to ensure the appropriate quality of the water, validated procedures, ~~and~~ in-process monitoring of the electrical conductivity, and regular total organic carbon and microbial monitoring are applied.

Water for injections in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

Revision WFI Monograph: Pharmeuropa comments

- Support from USP, TGA, Pharmaceutical Industry
- Background document identified as an important reference for the future

Major concerns

- "… by a purification process ***that is equivalent or superior to distillation…"***
- "….Reverse osmosis……***may be suitable***."

Distillation should be the benchmark for quality

- Statement that non-distillation systems should be authorised by the competent authority following a GMP inspection **(GMP issue)**
- … the competent authority may require additional tests.**(GMP issue)**

Revision WFI Monograph: Pharmeuropa comments

Other comments

- The adoption/publication of the monograph should be in parallel with the Q & A document on water production systems being prepared by IWG. **(outside the control of the Ph. Eur.)**
- Extend the list of additional techniques that can be used with RO
- Statement about "first portion" applies to all techniques

Comments outside the scope of the current revision

- **Microbial monitoring** (incubation conditions)
- **TOC limit**
- Test for **nitrates** (conductivity)
- Use of rapid microbiological methods

Revision of WFI Monograph: Proposal of Water WP Response to Pharmeuropa comments

PRODUCTION

Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water.

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-by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets. ~~The correct maintenance of the apparatus is essential~~. ~~The first portion of the distillate obtained when the apparatus begins to function is discarded and the distillate is collected~~; or

-by **a purification process that is equivalent to distillation.** Reverse osmosis which may be single pass or double pass, coupled with other ~~suitable~~ **appropriate** techniques such as **electro-**deionisation, ~~and/or~~ ultrafiltration, **nanofiltration is suitable.**

For all methods of production correct operation, monitoring, and maintenance of the ~~apparatus~~ **system are** ~~is~~ essential. In order to ensure the appropriate quality of the water, validated procedures, ~~and~~ in- process monitoring of the electrical conductivity, and regular **monitoring of** total organic carbon and microbial ~~monitoring~~ **contamination** are applied.

The first portion of water obtained when the apparatus begins to function is discarded.

Water for injections in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

Ph. Eur. Commission – 154th Session

Proposal to adopt revised monograph for WFI

Comment received

- by a purification process that is equivalent to distillation, ***authorised by the Competent Authority*** Reverse osmosis which may be single pass or double pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration, nanofiltration is suitable.

This amendment is necessary because the currently worded monograph permits the introduction of a non-distillation WFI process based on evidence of compliance with the monograph only, without prior regulatory oversight."

Final wording

Notification to the competent authority (i.e. supervisory authority of the manufacturer) is required before implementation. (PA/PH/Exp. WAT/T (14) 7 COM 1R)

Ph. Eur. Commission – 154th Session

Revision of WFI monograph: adopted text

PRODUCTION

Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water.

It is produced either:

-by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets; or

-by a purification process that is equivalent to distillation**.** Reverse osmosis which may be single pass or double pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration, nanofiltration is suitable. Notification to the Competent Authority (i.e. the Supervisory Authority of the manufacturer) is required before implementation

For all methods of production **c**orrect operation, monitoring, and maintenance of the system are essential. In order to ensure the appropriate quality of the water, validated procedures, in- process monitoring of the electrical conductivity, and regular monitoring of total organic carbon and microbial contamination are applied.

The first portion of water obtained when the apparatus begins to function is discarded.

Water for injections in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

Acknowledgements

All Specialists of the Ph. Eur. WAT Working Party

***EDQM Staff**:*
Ph.Eur Secretariat
Emmanuelle Charton
Mihaela Buda
Stephen Wicks
Catherine Lang
John Quinn
EDQM Inspectorate
Thomas Hecker

Packaging materials: current developments

At a glance

1. Place in the Ph. Eur.

2. Glass containers for pharmaceutical use

- History of the chapter
- Ongoing revision

3. Plastic material, plastic containers

- Ongoing revisions
- Further points to consider

Packaging materials in the European Pharmacopoeia

Ph. Eur. – General organisation

- Introduction
- **1. General notices**
  - Hint to General Chapters
    Materials used for containers and Containers
- General chapters
- General monographs
- .....
- Individual monographs

General Notices

- Clarify that texts are applicable only to formulations of materials covered by the preambule of the texts
- Different formulations are allowed, in that case: test methods and limits are subject to Authoritiy agreement
- Similar approach for Containers
- Specific containers may be required by monographs, especially dosage form monographs

Ph. Eur. – General organisation

Introduction

General notices

General chapters

General monographs

.....

Individual monographs

2 - Methods of analysis
3 - Materials for containers and containers
4 - Reagents
5 - General texts

General Chapters

3.1. Materials used for the manufacture of containers

3.1. … subsections

3.2. Containers

3.2.1. Glass containers for pharmaceutical use

3.2.2. Plastic containers and closures for pharmaceutical use

3.2.3.- 3.2.8. Blood bags and syringes (medical devices)

3.2.9. Rubber closures

Ph. Eur. – General organisation

Introduction

General notices

General chapters

General monographs

.....

Individual monographs

More than 2500 monographs
- *Chemicals*
- *Herbals*
- *Antibiotics*
- *Biologicals*
- *Vaccines*
- *Fats*
- *Materials used in the manufacture of containers*
- ....

Individual monographs

e.g.

Dimethicone (138)

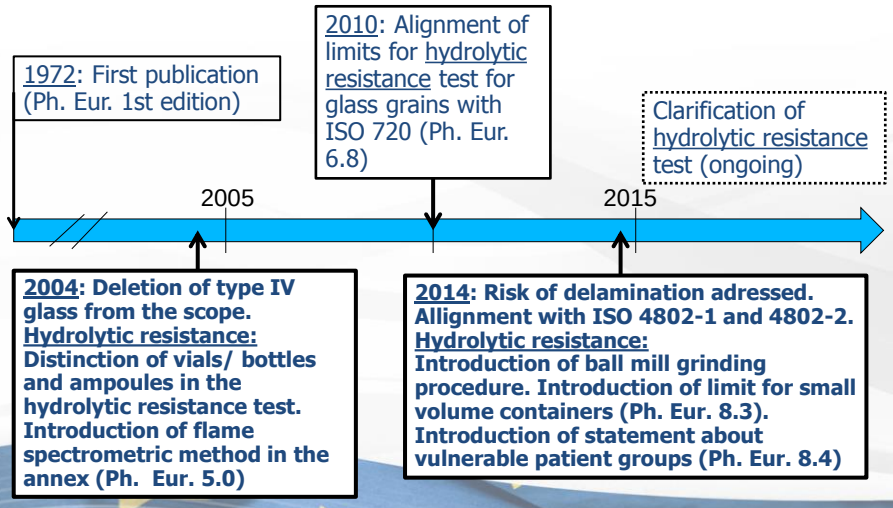
Simeticone (1470)

Poly(vinyl alcohol) (1961)

Poly(vinyl acetate) (1962)

3.2.1. Glass containers for pharmaceutical use

History of the general chapter on glass containers for pharmaceutical use



Hydrolytic resistance test

- Evaluation of helpdesk questions received.
- Webinar organised on 10 December 2015, with a focus on the hydrolytic resistance test using an autoclave. Presentations available on EDQM website. Many questions answered.
- Revision of the chapter proposed in Pharmeuropa 28.4 (October 2016)

Hydrolytic resistance test – revision of the autoclaving procedure description

- Better focus on the reference thermal curve
- Separation of autoclave calibration stage from routine analysis
- Distinction between classic old model and steam autoclaves where freesteaming is not always possible
- Notes to clarify reasons for more accurate measurements and highlight potential sources of errors
- Calibration frequence to be set by the user on the basis of sound QC criteria
- Files record to give evidence of compliance

General Chapters

3.1. Materials used for the manufacture of containers

3.1. … subsections

3.2. Containers

3.2.1. Glass containers for pharmaceutical use

3.2.2. Plastic containers and closures for pharmaceutical use

3.2.3.- 3.2.8. Blood bags and syringes (medical devices)

3.2.9. Rubber closures

Plastic material and plastic containers

Material used for the manufacture of containers

Plastic containers and closures for pharmaceutical use

Recently adopted – to be published in Ph. Eur. 9.2

- **3.1.3**. Polyolefins
- **3.1.4**. Polyolefins without additives for parenteral preprations and for ophthalmic preparations
- **3.1.5**. Polyolefins with additives for parenteral preparations and for ophthalmic preparations
- **3.1.7**. Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations

Identification: IR absorption maxima deleted to cover for a wider range of polyolefins, preparation of spectra using granules or hot pressed films included.

Test for substances soluble in hexane: deleted to take account of wider range of polyolefins

- **3.1.6**. Polypropylene containers and closures for parenteral prearations and ophthalmic preparations

Test for substances soluble in hexane: deleted to take account of wider range of polypropylenes

Ongoing revisions – currently in Pharmeuropa

3.2.3. STERILE PLASTIC CONTAINERS FOR HUMAN BLOOD AND BLOOD COMPONENTS

No longer request use of water for injections in the tests

Replacement of pyrogen test by BET

3.2.9. RUBBER CLOSURES FOR CONTAINERS FOR AQUEOUS PARENTERAL PREPARATIONS, FOR POWDERS AND FOR FREEZE-DRIED POWDERS

Expansion of the scope to include coated, bilayered, lubricated closures

Clarification of autoclaving procedure for preparation of solution S

Inclusion of nephelometric procedure for appearance of solution S

Ongoing revisions – under discussion

3.1.1.1. Materials based on plasticised poly(vinyl chloride) for containers for human blood and blood components

3.1.1.2. Materials based on plasticised poly(vinyl chloride) for tubing used in sets for transfusion of blood and blood components

- *Cover additional plasticisers (e.g. DEHT, TOTM, BTHC, DINCH)?*
- *Publication in Pharmeuropa expected Jan 2017, for comment*

New texts – under elaboration

- 3.1.16. Cycloolefinpolymer with additives for containers for parenteral and opthalmic preparations
- Ethylene-methacrylic acid zinc copolymer (inner lacquer of Al-foil blisters) and heat-sealing coatings (1957)
- 3.2.10. Plastic syringes for aqueous solutions for injection
- Polyamides (1963)

→ Your input is highly appreciated!

Further texts – under revision

- 3.2.4. Empty sterile containers of plasticised poly(vinyl chloride) for human blood and blood components
- …

- Further information can be found on our knowledge database

Challenges

→ Compatibility of container and content

Limit release of material into the content of the container (stability toxicity)

Limit the interaction (adsorption, chemical reaction) of the content of the container with the material of the container

→ Texts for leachables are conceived to mainly aqueous contents

→ Texts can not cover all scenarios, but they can be taken as examples and completed to specific needs.

Challenges (ctd)

→ Heavy metals testing methodology (2.4.8) – ICH Q3D

→ Containers used in/as medical devices

(Ph. Eur. Texts, CEN, ISO, Medical Devices Directive …)

Thank you very much

UPDATE ON HARMONISATION INITIATIVES

Latest news on harmonisation of excipients

Isabelle Mercier

Scientific Officer

European Pharmacopoeia Department - EDQM

Aims of Pharmacopoeial Harmonisation

- Simplification and rationalisation of quality control methods and licensing procedures,
- IH enhances the benefits of the work of ICH and VICH, since some of the guidelines developed depend on pharmacopoeial general chapters for their application

Contents

- Overview of PDG procedure
- Carbohydrates
- Cellulosics
- Other polymers, surfactants, povidones
- Inorganics, saccharins

PDG procedure (1)

Stage 1: identification of subject to be harmonised attribution to a coordinating pharmacopoeia (CP)

Stage 2: investigation – CP collects info on existing spec/methods and grades of marketed products → draft

Stage 3: proposal for expert committee review – preliminary survey with regional ECs

Stage 4: official enquiry in Pharmeuropa, JP forum, USP-PF

PDG procedure (2)

Stage 5A: provisional consensus presented by CP

Stage 5B: sign-off during one of bi-annual PDG meetings or by correspondence

Stage 6: regional adoption and implementation
- 6A: adoption, publication
- 6B: implementation
- 6C: indication of harmonisation → chapter 5.8

CARBOHYDRATES (1)

Wheat starch (0359)
Revision (JP)

- **Total protein** (Kjeldahl) - replace catalyst Sn by TiO_2 and correct volume of sulfuric acid in the blank test
- revised draft to be agreed by JP and USP before publication in fora

Starch, pregelatinised (1267)
New (JP)

- **Issues**:
  one (Ph. Eur., USP) or *two* distinct monographs (JP) to cover grades fully pregelatinised starch and partially pregelatinised starch - how to distinguish them?
- **Proposal**: through collaborative study with IPEC, establish whether viscosity test could differentiate between two grades – ongoing – results for PDG meeting end Oct. 16

CARBOHYDRATES (2)

Lactose (1061) Lactose monohydrate (0187)
Revision (USP)

- Development of validated method for LC-RI method for **related substances** (incl. galactose, glucose, lactulose) and **assay** – in progress
- 5-HMF: control considered unnecessary owing to very low amounts in lactose available on market

Lactose for inhalation
New (USP)

- No individual monograph created but specific tests and/or limits may be included in existing monographs, e.g. BET, microbial contamination, protein determination …
- Tests relating to functionality to be considered as non-mandatory and without limits
  → FRC section in Ph. Eur. monographs and in USP <1059>. JP to reflect on way to implement such tests

CELLULOSICS (1)

Ethylcellulose (0822)
Revision (Ph. Eur.)

- signed-off by PDG in May 2016, implem. **1st July 2017**
- Revision items: name and concentration of any added antioxidant provided on labelling (Ph. Eur. & USP only); assay: packed column → capillary column
- Revision FRC in phpa 28.4 (≠ PDG)

HPC, low substituted (2083)
New (USP)

- **Prospective** harmonisation for Ph. Eur. and USP, implem. on **1st April 2016** - largely based on tests included in harmonised monograph on HPC
- revision FRC in phpa 28.3 (≠ PDG)

Hydroxyethyl-cellulose (0336)
New (Ph. Eur.)

- signed-off by PDG by correspondence in **July 2016** after 3 publications in the fora – main issues: nitrates, sulfated ash [viscosity], assay
- Submit to Commission for adoption Nov. 2016

HPC, low subst.	Ethylcellulose	Hydroxyethylcellulose
• *GC determination of hydroxypropoxy groups % content + Zeisel cleavage*	• *GC determination of ethoxy groups % content + Zeisel cleavage*	• *GC determination of hydroxyethoxy groups % content + Zeisel cleavage*
• Sample digestion @ **130** ± 2°C for **60 min** • Column 30 m x 0.53 mm 3 µm, e.g. DB-1 • *Helium for chrom. R* • Gradient • FID (or TCD)	• Sample digestion @ **115** ± 2°C for **70 min** • Column 30 m x 0.53 mm 3 µm, e.g. DB-1 • *Helium for chrom. R* • Gradient • FID	• Sample digestion @ **165** ± 2°C for **2.5 h** • Column 30 m x 0.53 mm 3 µm, e.g. DB-1 • *Helium for chrom. R* • Gradient • FID

CELLULOSICS (2)

Hypromellose (0348) Methylcellulose (0345)	• **Assay revision** (JP) to include same capillary column as for HPC, HPC low, EC, HEC – digestion conditions maintained – Pharmeuropa 28.4 (Oct. 2016)
Microcrystalline cellulose (0316)	• **Identification revision** (USP) (phpa 28.3, July 2016) to add identification by IR – end of enquiry 30.09.2016
Cellulose acetate (0887)	• **IR identification revision** (USP) signed-off May 2016 – implementation on 1st July 2017

CELLULOSICS (3)

Carmellose sodium (0472)

New (USP)
Stage 3

- **IR** - preparation of sample: KBr or film?
- Identification of **Na**: requested by Ph. Eur., contested by JP
- **Sodium chloride**: solubility problem for highly viscous grades (JP)
- **Sodium sulfate**: limit test – drop it (JP)
- **Assay**: Ph. Eur. proposed assay method from harmonised Croscarmellose sodium – no real agreement within PDG – alternative investigated
- **Viscosity**: flexibility for apparatus, testing conditions, limits; producers to indicate on labelling → no standard method.

OTHER POLYMERS and SURFACTANTS

Polysorbate 80 (0428)

- **Dioxan – CORR** (EP)
  X 1000 added in formula for calculation of content
  Ph. Eur. 9.2 (not later than 28 Feb. 2017)

Sodium laurilsulfate (0098)

- Harmonised monograph implemented **1st Jan. 2017**
- **Revision** (USP): add IR identification, change colour indicator & solvent in assay

Macrogols (1444)

- **Issues** (USP): IR identification, LC for aldehydes, EG and DiEG (under Identification of Tests?)

POVIDONES

Povidone (0428)
Revision (JP)

- Implementation 1st Jan. 2017
- Addition of IR id. and SST in tests for formic acid and 2-pyrrolidone

Copovidone (0891)
New (JP)

- Phpa 28.2 (until June 2016)
- **Main revision items vs. Ph. Eur.**: IR identification using CRS, tests for pH & 1-vinylpyrrolidin-2-one added, test for 2-pyrrolidone revised

INORGANICS (1)

Sodium calcium edetate (0231)
Revision (JP)

- **Main revision item**: control of imp. nitrilotriacetic acid by HPLC based on Ph. Eur. test (not currently harmo)
- Phpa 28.4 (Oct. 2016)

Calcium hydrogen phosphate (0981)
Revision (JP)

- **Revision item**: content limits
- Phpa 28.4 (Oct. 2016)

Calcium carbonate (14)
New (JP)

- Bilateral JP/Ph. Eur.
- **Issues**: choice of identification tests, policy for elemental impurities testing

INORGANICS (2)

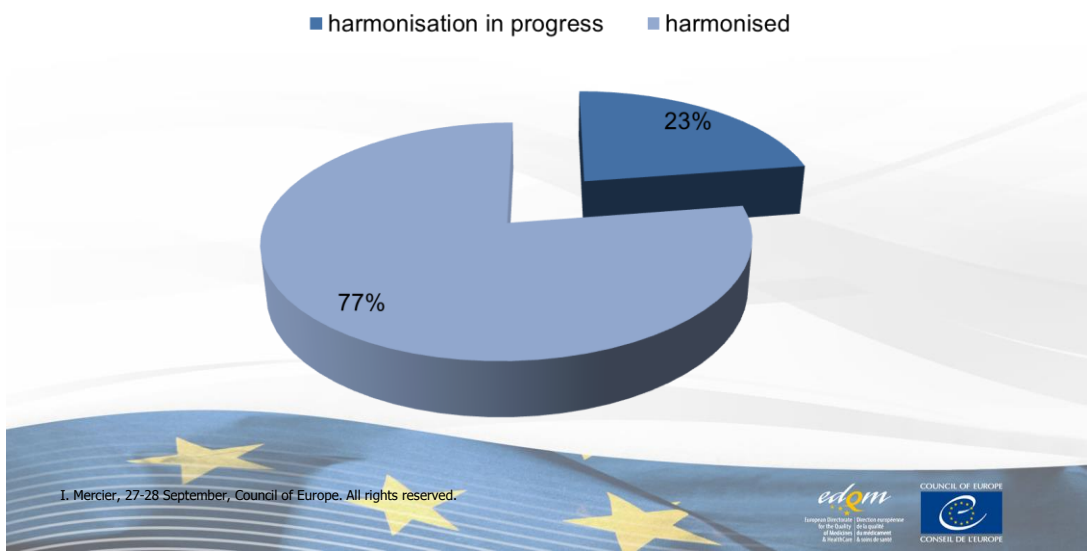
Silica, colloidal anhydrous (434)
Silica, colloidal hydrated (738)
New (USP)

- **Main issue**: identification (by IR ?)
- collaborative trial organised by IPEC to confirm that IR can be used to differentiate both grades – results expected during autumn 2016

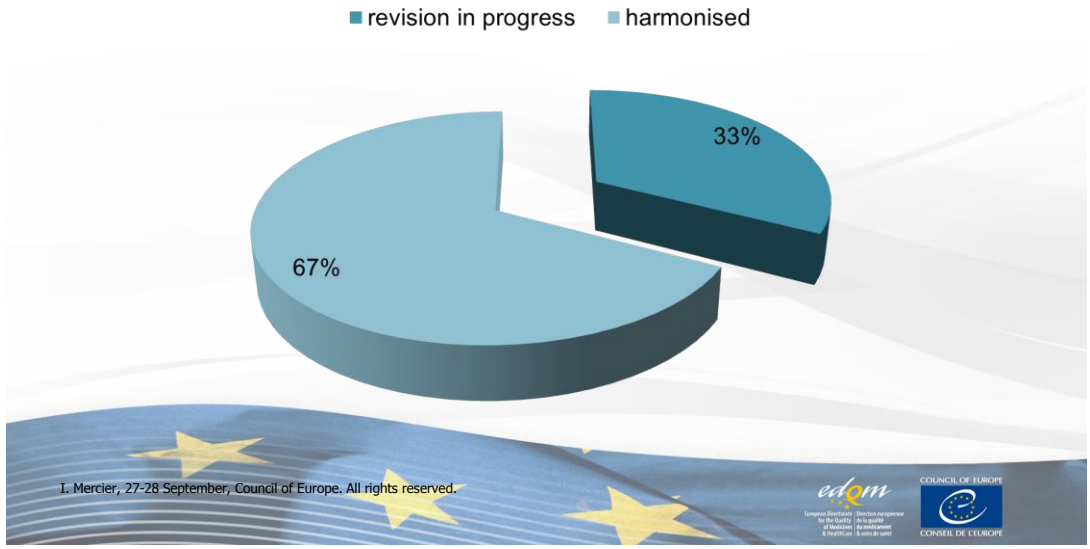
Saccharin (947)
Saccharin sodium (787)
Saccharin calcium (not in Ph. Eur.)
Revision (USP)

- **Issues**: addition of GC method for impurities and an LC method for assay
- Validation data to be supplied by USP

Achievements – texts harmonised
(among 64)



Achievements – texts under revision



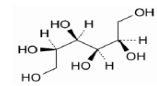
6C-Indication of harmonisation

in monographs and in chapter 5.8

(3) This monograph has undergone pharmacopoeial harmonisation. See chapter 5.8. Pharmacopoeial harmonisation

MANNITOL (3)

Mannitolum



$C_6H_{14}O_6$ [69-65-8] M_r 182.2

DEFINITION

D-Mannitol.

Content: 97.0 per cent to 102.0 per cent (dried substance).

◆CHARACTERS

Appearance: white or almost white crystals or powder.

Solubility: freely soluble in water, practically insoluble in ethanol (96 per cent).

It shows polymorphism (*5.9*). ◆

IDENTIFICATION

First identification: C.

◊*Second identification*: A, B, D.

A. Specific optical rotation (*2.2.7*): + 23 to + 25 (dried substance).
Dissolve 2.00 g of the substance to be examined and 2.6 g of *disodium tetraborate R* in about 20 mL of *water R* at 30 °C; shake continuously for 15-30 min without further heating. Dilute the resulting clear solution to 25.0 mL with *water R*.

B. Melting point (see Tests).◊

C. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *mannitol CRS*.

MANNITOL (0559)

Harmonised attributes

Attribute	Ph. Eur.	JP	USP
Definition	+	+	+
Identification by IR	+	+	+
Appearance of solution	+	+	+
Conductivity	+	+	+
Melting point	+	+	+
Reducing sugars	+	+	+
Related substances	+	+	+
Nickel	+	+	+
Loss on drying	+	+	+
Microbial contamination	+	-	+
Bacterial endotoxins	+	-	+
Assay	+	+	+
Labelling	+	-	+

LEGEND
+: will adopt and implement
–: will not stipulate

Non-harmonised attributes

Characters/Description, Heavy metals, Container and storage/Packaging and storage

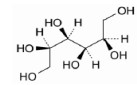
Local requirements

Second identification (specific optical rotation, melting point, TLC) (Ph. Eur.), Absence of *Salmonella* (Ph. Eur.)

(sign-off date: 8 June 2012)

MANNITOL (3)

Mannitolum



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B. Melting point (see Tests).◊

C. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *mannitol CRS*.

Prospective harmonisation

Recently added to the work programme

- Isostearyl alcohol
- Myristyl myristate
- Polysorbate 65
- Sodium cetyl sulfate
- Calcium silicate (major revision for USP)

Conclusions

- Yes, process under control, although sometimes difficult to progress in timely manner due to various regulatory systems in 3 regions and scarce resources
- Cooperation with IPEC is good opportunity to speed up process when upstream contribution and constructive comments received during public enquiry

The WHO Good Pharmacopoeial Practices (GPhP) Initiative

World Health Organization

WHO at a glance

- 194 Member States
- Headquarters in Geneva
- 6 regional offices
- More than 150 country offices
- More than 7000 staff
- More than 700 institutions supporting
- WHO's work:
  - Close partnerships with UN agencies,donors, foundations, academia, nongovernmental organizations and the private sector

Governance of WHO

Governance takes place through the World Health Assembly, which is the supreme decision-making body; and the Executive Board, which gives effect to the decisions and policies of the Health Assembly.

The Organization is headed by

the Director-General,

appointed by the Health

Assembly on the nomination

of the Executive Board.

http://www.who.int/about/governance/en/

What does WHO ? Some examples ..

WHO - The Global Guardian of Public Health

Serves its Member States through, e.g.

- Providing means to communicate information, issue international alerts
- Developing global norms and standards
- Propose global measures, e.g. for supply chain integrity
- Suggest international tools and schemes
- Nomenclature and classifications

What does WHO ? Some examples..

WHO - The Global Guardian of Public Health

Serves its Member States upon request through, e.g.

- Enhancement of convergence among health authorities
- Providing a platform and enabling collaboration among national and regional health authorities
- Provision of assistance to improve capacity building
- Providing a global platform for exchange of information, e.g. International Conference of Drug Regulatory Authorities (ICDRA)

17th International Conference of Drug Regulatory Authorities (ICDRA)
Cape Town - South Africa

Pharmacopoeias: How WHO got involved..

1902 – 1925 Agreements establish a Unified Pharmacopoeia

1929 "Brussels Agreement" stipulates League of Nations should carry out related administrative function

1937 First meeting of "Technical Commission of Pharmaceutical Experts"

1947 Interim Commission of WHO takes over

1948 First World Health Assembly (WHA) approves *Expert Committee on Unification of Pharmacopoeia* to continue this work

1951 WHA renames the *Expert Committee on International Pharmacopoeia* → *The International Pharmacopoeia* published by WHO

Trends towards convergence

International Collaboration towards convergence, including among Pharmacopoeias:

- Pharmacopoeial Discussion Group (PDG)
- MoUs between Pharmacopoeias
- Bilaterial projects among Pharmacopoeias
- Fora and summits to discuss matters of joint interest

Trends towards convergence

Within context of Regulatory Networks, e.g.

- International Conference of Drug Regulatory Authorities (ICDRA)
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- Pan American Network for Drug Regulatory Harmonization (*PANDRH*)

Trends towards convergence

- 1st *International Meeting of World Pharmacopoeias* – hosted by WHO, Geneva, Switzerland, 29 February–2 March 2012
- 2nd *International Meeting of World Pharmacopoeias* – hosted by Indian Pharmacopoeia Commission, New Delhi, India, 18–19 April 2013
- 3rd *International Meeting of World Pharmacopoeias* – hosted by Medicines and Healthcare products Regulatory Agency/British Pharmacopoeia Commission, London, United Kingdom, 10–11 April 2014

Trends towards convergence

- 4th *International Meeting of World Pharmacopoeias* – hosted by Council of Europe/European Pharmacopoeia Commission, Strasbourg, France, 8–10 October 2014
- 5th *International Meeting of World Pharmacopoeias* – hosted by United States Pharmacopeia, Rockville, USA, 20–22 April 2015
- 6th *International Meeting of World Pharmacopoeias* – hosted by Chinese Pharmacopoeia Commission, Su Zhou, People's Republic of China, 21–23 September 2015

Trends towards convergence

- **7th *International Meeting of World Pharmacopoeias* – hosted by Ministry of Health, Labour and Welfare / Pharmaceuticals and Medical Devices Agency /Japanese Pharmacopoeia in Tokyo, Japan, 13–14 September 2016**

Some impressions 1st meeting

Some impressions 1st meeting

Who participates ?

- Usually between 40-60 representatives from world pharmacopoeias, including Argentinian, Brazilian, British, Chinese, Czech, European (representing its 37 Member States and the European Union), Indian, Indonesian, International (WHO), Iranian, Japanese, Kazakh, Korean, Mexican, Russian, Spanish, Ukrainian, United States and Vietnamese pharmacopoeias → *representing about 50 pharmacopoeias and pharmacopoeial authorities worldwide*

- *Since 2nd meeting followed by special events organized by the host pharmacopoeia* : stakeholders and users

What is the focus ?

- Opportunity for greater collaborative work
- Opportunity for sharing of information between world pharmacopoeias
- Development of good pharmacopoeial practices (GPhP), in addition applying WHO's standard-setting processes and procedures
- Outcome presented to WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) → through ECSPP also to WHO's 194 Member States

Purpose and scope of good pharmacopoeial practices (GPhP)

- Primary objective: "*to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization*"
- GPhP describe set of principles providing guidance for national and regional pharmacopoeial authorities to facilitate appropriate design, development and maintenance of pharmacopoeial standards
- Main GPhP published for pharmaceutical substances and FPPs, although principles may also apply to other products (*Ref: WHO Technical Report Series (TRS), No. 996, 2016, Annex 1)*
  http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex01.pdf?ua=1

Meeting agenda of 7th International meeting

- Review of feedback and comments received on additional chapters to GPhP as identified during the 6th international meeting of world pharmacopoeias on:
  - Compounded preparations
  - "Herbals"
  - Glossary
- Discussion on possible future supplements to GPhP and on new strategies /next steps to continue efforts towards convergence among pharmacopoeias

Outcome of the 7th International meeting

Roadmap with next steps and future actions for:

1. **GPhP new supplements on Compounding and Herbal medicines + Glossary**
2. **Identification of "hot topics" having potential public health impact**
3. **Survey on impact and value of new GPhP**
4. **Planning of next meeting(s)**

1. GPhP new supplements

- on **Compounding** and **Herbal medicines** + **Glossary,** planned actions and timeframe:
  - Drafting of additional paragraphs and circulation of updated version among the pharmacopoeias
  - Collation of feed-back
  - Review of comments during the 8th international meeting of world pharmacopoeias
  - Public consultation phase
  - Presentation of update to the WHO Expert Committee on Specifications for Pharmaceutical Preparations
  - Publication

Outcome of the 7th International meeting

2. **Identification of "hot topics" having potential public health impact,** planned actions and timeframe:

- Drafting of a proposal by current and future hosts
- Review by world pharmacopoeias for discussion during the 8th meeting

3. Survey on impact and value of GPhP, planned actions and timeframe:

- Drafting of survey questions and review by pharmacopoeias
- Mailing to stakeholders and users
- Data analysis and discussion during the 8th meeting

4. Planning of next meeting(s)

- **8th *International Meeting of World Pharmacopoeias* – hosted by Agência Nacional de Vigilância Sanitária (ANVISA)/Brazilian Pharmacopoeia,** *dates and site tbc*
- **9th *International Meeting of World Pharmacopoeias* – hosted by NIDQ/Vietnamese Pharmacopoeia,** *dates and site tbc*
- **10th *International Meeting* hosted by …**

International future prospects

- *International Arena: keep momentum,* the global initiative, international forum to discuss challenges and future synergies to serve all pharmacopoeias and their users
- *WHO related:* input from stakeholders and collaboration with partners to define future strategies for WHO activities and recommendations to WHO Member States

- *+ In the focus:* … benefit for patients : improved access to quality medicines worldwide

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¡muchas gracias!

Thank You!

Merci beaucoup!

Спасибо