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Setting Global Specifications for Excipient Standards and Test Methods

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Note : In the winter 2000 Edition of European Pharmaceutical Review a first contribution on the above topic by Dr T. Chowhan was published. The following article addresses the same topic from a different perspective.

1 . Introduction

A reliable quality characterisation (=selection of testing criteria) and standardisation (= definition of specifications) of starting materials used in a production process is a crucial corner-stone in all routine industrial production to reproducibly obtain finished products of consistent quality.

Excipients are used to make active drug substances into medicines for human and veterinary use. In many dosage forms the amount of excipients far exceeds that of the active ingredient(s), especially in the case of highly potent drugs. Practical experience has shown that the quality of excipients can have a major impact on safety and efficacy of drug products due to direct or indirect interaction with active drug substances, with other excipients in a given formulation (e.g. cross-linking of gelatin due to traces of formaldehyde in macrogols or other excipients, leading to changes in the dissolution rate pattern of drug products), or due to carry over of critical impurities.

Excipients are derived from a large number of different classes of chemical substances. They are manufactured from a great variety of source materials using a broad spectrum of different process technologies and production methods. Pharmaceutical excipients are manufactured in facilities of various industries. In many cases pharmaceutical use represents a very small percentage of the total production output. The materials are predominantly designed and used for other applications. To optimise processing properties in these other applications, technical grades often contain other materials (e.g. additives) as well as by-products or other impurities at levels that can create considerable problems for pharmaceutical use . Typical examples for such technical grades are, for instance, the use of:

- glyoxal (classified in Europe as a class 3 mutagen and known as a source of stability problems observed with drug products) in cellulose derivatives
- a broad battery of additives in titanium dioxide (see table 1) to improve for instance the resistance of paint against weather impact.

Table 1 – Production of Titanium Dioxide

Processes	Two
Sulphate	Ore + sulphuric acid / precipitation
Chloride	Ore + chlorine / vapour phase
Crystal modifications	Two (Anatas, Rutil)
Surface coating ^a	
Inorganic	e.g. Ti, Zr, Si, Na, K, Al, B, Sn, Zn, Mn, Ce, Sb, V – compounds
Organic	Silicones, amines, organophosphates, alcohols, alkylphthalates
Producers	Approx. 50 worldwide
^a Purpose of the various coating processes is to achieve optimal application properties for the individual applications	

Source: Ref. 1

The use of technical grade materials in pharmaceutical (and food) preparations can have serious consequences, as e.g. the Haitian glycerol, the Nigerian propylene glycol and the Spanish olive oil incidents have shown and are clearly a major risk source in the manufacture of medicines for human and veterinary use. It is therefore from our perspective indispensable to address this topic adequately in the design of pharmacopoeial monographs for excipients, especially in view of the procurement of such substances from an increasingly global market. Reliance on a binding GMP Code – which in fact does not exist today for excipients – alone is insufficient. A pharmacopoeial monograph which reliably defines a pharmaceutical grade excipient taking account of its manufacturing process(es) and its intended pharmaceutical application is, in our view, a necessary prerequisite in this field.

In drug product registration excipients are requested to meet the requirements of pharmacopoeial monographs with the understanding from regulatory authorities that these monographs represent state of the art in science and technology and it is up to the pharmacopoeias to match with this expectation.

2. Setting global quality standards for excipients: problems, chances, achievements

The project for international harmonisation of pharmacopoeial quality standards for excipients, started by the PDG in 1989 with great expectations from all partners involved in the manufacture and use of excipients as well as drug regulatory authorities turned out to be much more complicated than was originally anticipated. The main reasons for these difficulties are:

- big differences at the level of product specific monographs with regard to testing criteria, specifications and test methods
- substantial differences at the level of general test methods referenced in a large number of product specific monographs

- realising that a considerable number of excipient monographs are far below state of the art in science and technology and standard practice in the supplying industry (e.g. capillary GC for fat derivatives, AAS/OES in the inorganic industry and industries supplying the food sector)
- differences in the understanding of the purpose of a pharmacopoeial monograph for excipients
- different philosophies on how to set limits .

The following cases from the harmonisation practice are exemplary for the above problems and how such problems can be overcome with simultaneous upgrading of a monograph to a state of the art level:

2.1 Ethanol

When the European Pharmacopoeia as the co-ordinating pharmacopoeia for this substance started the harmonisation activities on this widely used excipient back in 1994 harmonisation for the monographs on ethanol was not even realised at the European Pharmacopoeia level because of the national state monopoly for alcohol in many European countries.

A comparison, including the British Pharmacopoeia (BP), the German Pharmacopoeia (DAB), the French Pharmacopoeia (FP), the Swiss Pharmacopoeia (Ph. Helv.), the JP and the USP, valid at that time is compiled in table 2 (Ref. 2).

Table 2 – Ethanol / Comparison of Pharmacopoeial Monographs

	USA	Japan	Switzerland	Germany	UK	France
1.Identity						
1.1. Colour reaction with Nitroferricyanide/ Piperazin	+	-	+	-	+	+
1.2. Jodoform reaction	+	+	+	-	+	+
1.3. Ethyl acetate reaction	-	+	-	-	-	-
1.4. Distillation range	-	-	77.8-79.0°C	78.0-79.0°C	-	78.0-79.5°C
1.5. Colour reaction with Nitroferricyanide/ Piperidin	-	-	-	+	-	-
1.6. Melting point derivative with 3.5-Dinitrobenzoyl chloride	-	-	-	90-94°C	-	-
2.Relative density	0.812 – 0.816 (at 15.56°C)	* 0.814 – 0.816 (at 15.0°C)	* 0.8064 – 0.8089 (at 20.0°C)	0.804-0.809 (at 20.0°C)	-	0.8050-0.814 (at 20.0°C)

3. Acidity	max. 0.90ml 0.02 N NaOH/50ml	* max. 0.10ml 0.1 N NaOH/20ml	various limits using different colour indicators	* max. 0.4ml 0.01 N NaOH/50ml	* max. 0.2ml 0.1 N NaOH/20ml	* various limits using different colour indicators
4. Residue on evaporation	max. 0.0025%	max. 0.0025%	max. 0.001%	max. 0.0015%	max. 0.005%	max. 0.002%
5. Aldehydes/ Foreign substances	n.d.	* n.d.	* n.d.	* n.d.	* n.d.	-
6. Amyl alcohol / non volatile carbonisable substances	n.d.	-	-	-	-	-
7. Fusel oils	n.d.	* n.d.	-	* < colour standard	-	-
8. Acetone / Isopropanol	not more intense as colour standard (~10 ppm)	see 15.	-	-	-	-
9. Methanol	n.d.	* n.d.	-	* max. 500ppm	-	-
10. Assay (via density)	92.3-93.8% w/w 94.9-96.0% v/v	- 95.1-95.6% v/v	93.8-94.7% w/w 96.0-96.6% v/v	93.8-95.6% w/w 96.0-97.2% v/v	93.8-94.7% w/w 96.0-96.6% v/v	92.0-94.7% w/w 94.7-96.6% v/v
11. Aqueous solution / Clarity	-	clear	* clear	-	clear	clear
12. Alkalinity	-	n.d.	n.d.	* max. 0.1ml 0.01 N HCl/15ml Bromocresyl green	-	n.d.
13. Chloride	-	n.d.	-	-	-	max. 1.25ppm
14. Heavy metals	-	max. 1.2ppm	* max. 0.3ppm	max. 2ppm	-	max. 0.25ppm
15. Ketones, Isopropanol, t-Butanol	-	n.d.	-	-	-	-
16. Clarity, tel quel	-	-	clear	clear	-	clear
17. Colour, tel quel	-	-	colourless	colourless	-	colourless
18. Fluorescence	-	-	< Standard	-	-	-
19. Foreign odour	-	-	n.d.	-	-	-
20. Aldehydes and Ketones	-	-	max. 100ppm (Oximreaction)	-	-	=max. 100ppm Acetaldehyde
21. Methanol, Homologous Alcohols and Esters (GC)	-	-	max. 0.01 % v/v Methanol max. 0.02 area % other impurities	-	- * max. 0.04% in sum	max. 0.02% Methanol max. 0.03 area% other impurities
22. UV Absorption	-	-	5cm: 240nm: max. 0.35 250-260nm: max. 0.20 270nm: max. 0.12	1cm: 220 nm: max.0.30 230nm: max.0.18 240nm: max.0.08 270nm: max.0.02	-	1cm: 240 nm: max.0.10 250-260nm: max.0.06 270nm: max.0.03
23. Furfural	-	-	-	n.d.	-	-
24. Zinc	-	-	-	n.d.	-	-
25. Iron	-	-	-	n.d.	-	-
26. Density (absolute)	-	-	-	-	803.8-806.3 [Kg m ⁻³]	-
27. Benzene	-	-	-	-	max. 2 ppm	* max. 5 ppm
28. Reducing substances	-	-	-	-	< colour standard	-

* = Method different, results not comparable/convertible.
n.d. = not detectable

The equivalence between results for a number of nominally identical testing criteria in the above table cannot be judged owing to different test methods (e.g. whereas the BP test for aldehydes uses fuchsin, the DAB uses 3-nitrobenzaldehyde and aniline, the FP dinitrophenylhydrazine, the Ph. Helv. hydroxylamine, the JP and the USP different versions of a permanganate test). As a result 47 different tests had to be run to confirm compliance with the 6 pharmacopoeias referenced above.

A team of specialists from the users and the producers side (including the 2 fundamentally different production processes, i.e. fermentation from various natural source materials and synthesis from ethylene) approached the harmonisation of the monographs in close co-operation with the EP ANM Expert Group from the following platform (Ref. 3).

Facts to be considered essential in the reliable quality characterisation and standardisation of ethanol are

1. Ethanol is globally negotiated as a commodity. By far the largest percentage of the world production is used for technical applications and only a very minor part is used as a pharmaceutical excipient.
2. Ethanol is produced by a large number of different processes. Basically one must distinguish between fermentation processes and synthesis on basis of ethylene.
3. Fermentation processes start from many different sources, frequently from directly fermentable materials such as sugar cane or sugar beet as well as their molasses. Other source materials must first be converted into a fermentable form by means of enzymes, such as various starches, or even waste materials such as lignocellulosic compounds contained in the waste water of cellulose produced by the sulphite process.
4. For ethanol sold on the global market, approximately 70% is obtained by fermentation with consecutive distillation and approximately 30% is produced by synthesis with consecutive distillation.
5. Water-free ethanol (>99% purity) is produced by azeotropic distillation. Benzene, toluene and cyclohexane are among the solvents used for this purpose.
6. Ethanol is subject to a state monopoly and tax system in most countries. As a consequence, one is confronted with a large number of national standards, requirements, and different grades of material.
7. Because of taxes, denaturation plays an important role and a considerable number of denaturation agents (methanol, isopropanol, ethyl acetate, methyl ethyl ketone, denatonium benzoate [at 5-10 ppm only], sucrose octaacetate, *t*-butanol, crotonaldehyde, acetone) are used, varying from country to country.
8. Crude products contain numerous impurities, which vary in species, number and concentration, depending on the source material or production process.

A monograph for a reliable purity standardisation of ethanol must cover, in particular, the detection and limitation of toxic by-products (e.g. benzene or methanol) ; the detection and

limitation of impurities that may interact with active substances (e.g. acetaldehyde or diacetal) the differentiation between pure and denatured grades. A highly effective GC method, together with testing of the substance by ultraviolet (UV) and infrared (IR) spectroscopy are the core elements for such a monograph.

A monograph developed in the light of the above facts and on the basis of a highly selective GC method, UV and IR spectroscopy as the core elements was applied to 28 samples of ethanol from different sources all over the world, stemming from a broad spectrum of source materials and production processes. Based on the comprehensive practical experience gained in these investigations the group came up with the following proposal:

Identification

- A. Oxidation to acetaldehyde + colour reaction (*USP/BP* method)
- B. Iodoform reaction (*USP/JP* method)
- C. Relative density (d 20/20):
 - Ethanol absolute: max. 0.794
 - Ethanol 96%: 0.804 to 0.813
- D. IR Spectrum

If identification test D is carried out, tests A and B can be omitted.

Tests

1. Appearance (clarity and colour) clear and colourless (*LS* method)
2. Acidity or alkalinity (*JP* method)
3. Related Substances (GC)
 - Methanol: <0.02% (v/v)
 - Total amount of impurities other than methanol: max. 0.03% (area%)
4. Acetaldehyde (GC): max 10 ppm (v/v)
5. Acetaldehyde diethyl acetal (GC): max 30 ppm (v/v)
6. Acetaldehyde – equivalents (sum 4+5) (GC): max 10 ppm
7. Benzene (*BP* UV method): max 2 ppm (v/v)
8. UV – absorbing compounds 235-340 nm, 5 cm cell (modified *USP* method): Absorption
 - 240 nm: max. 0.40; 250 nm: max. 0.30; 260 nm: max. 0.30; 270-340 nm: max. 0.10
9. Residue on evaporation: max 0.0025% (m/v)

After 2 public survey cycles the above monograph was adopted on a European level by the European Pharmacopoeia Commission with some minor modifications in June 1997. It cuts down the number of lab tests from 47 to 8 and facilitates the work of all parties involved tremendously.

Approval in the USA and Japan is still pending but is expected in the near future.

2.2 Talc

Talc, widely used in the manufacture of drug products, is from our perspective another interesting example how to combine harmonisation with upgrading of a monograph to a state of the art status and to simultaneously reduce the overall testing workload.

Table 3 –Pharmacopoeial Requirements for Talc

		Ph. Eur. II	USP XXII/ NFXVII	JP XII
1.	Identity test A	+	-	-
2.	Identity test B	+	+	+
3.	Identity test C	+	-	-
4.	Identity test D	-	+	-
5.	Identity test E	-	-	+
6.	Iron, soluble in 1 M H ₂ SO ₄	max. 250 ppm	-	-
7.	Magnesium, “	max. 0.4 %	-	-
8.	Calcium, “	max. 0.6 %	-	-
9.	Calcium, insoluble in 1 M H ₂ SO ₄	max. 500 ppm	-	-
10.	Carbonate	not detectable	-	-
11.	Chlorides, soluble in 2 M HNO ₃	max. 140 ppm	-	-
12.	Readily carbonisable substances	not detectable	-	-
13.	Loss on drying, 180°C	max. 1 %	-	-
14.	Microbes/g	-	max. 500	-
15.	Loss on ignition, 1000°C	-	max. 6.5 %	-
16.	Loss on ignition 450-550°C	-	-	max. 5.0 %
17.	Acid soluble substances (3N HCl, 50°C)	-	max. 2 %	max. 2 %
18.	Aqueous extractables (100°C)	-	max. 0.1 %	max. 0.1 %
19.	Aqueous extract, pH	-	neutral	neutral
20.	Water soluble iron	-	not detectable	not detectable
21.	Arsenic, acid soluble (0,5 N HCl, 100°C, 30 Min.)	-	max. 3 ppm	-
22.	Arsenic, acid soluble (H ₂ SO ₄ 10 %, 100°C ca. 1 Min.)	-	-	max. 4 ppm
23.	Heavy metals, acid soluble	-	max. 40 ppm	-
24.	Lead acid soluble	-	max. 10 ppm	-

The above table 3 (Ref. 4) represents the status of Talc monographs in the EP, the JP and the USP when a team of specialists from the suppliers, users and university fields took up the harmonisation activities in close co-operation with Group of Experts No. 9 of the EP, which was the co-ordinating pharmacopoeia for this excipient. A review of table 3 leads to the surprising result that the EP and the USP have - with the exception of one identity test - nothing in common. The 2 Pharmacopoeias apply completely different testing criteria to define the quality of the same substance!

When comparing the 3 pharmacopoeial testing sets in table 3 with the 1987 technical data sheet for pharmaceutical grade talc of one of the world leading talc manufacturers (see table 4).

it is evident:

- that all 3 pharmacopoeial testing sets are far from presenting the state of the art in science and technology
- that talc manufacturers have to run a huge battery of redundant tests for pharmaceutical certification purposes.



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Pharmaceutical talc of a very lamellar structure, stable as well as physically, chemically and biologically inert, from our deposit in the French Pyrenees.

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WHITENESS

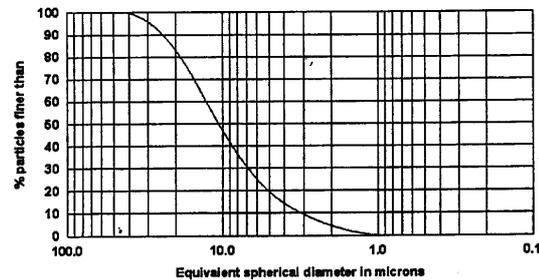
Elrepho Mat DRC 5
(NF Q 03-068)

FMY/L..... 89.8%

PARTICLE SIZE DISTRIBUTION

Dry screening (Alpine)
> 40 microns: max. 2%

- < 20 microns 82%
- < 10 microns 47%
- < 5 microns 19%
- < 2 microns 4%



PHYSICAL PROPERTIES

SCOTT volumeter
NF T 30-042
B.E.T.
Weight loss at 110°C
NF T 30-035

Real density 2.78
Loose bulk density 0.45
Tapped bulk density 0.87
Specific surface area 3.5 m²/g
Moisture content max. 0.5%
pH..... 9.2

CHEMICAL AND MINERALOGICAL ANALYSES

X diffractometry and thermogravimetric analysis
Atomic Absorption Spectrometry

Talc 89%
Chlorite 9%
Dolomite 1%
SiO₂ 60%
MgO 32%
Al₂O₃ 2%
Fe₂O₃ 0.8%
CaO 0.9%
Loss on ignition à 1050°C 5.7%

Traces

Pb..... 15 ppm Sn..... < 10ppm
Cu..... < 5ppm Sb..... < 50 ppm
Ab..... < 3 ppm Cd < 1 ppm
Bi..... < 10 ppm Hg 10 ppb
As..... < 1 ppm

This talc conforms to the European Pharmacopoeia (2nd edition).

PHA/E 887/88

The data presented here are mean values resulting for a statistical processing of regular production samples. They cannot be considered as binding.

Table 4

Talc (theoretical chemical formula $\text{Mg}_3(\text{Si}_4\text{O}_{10})(\text{OH})_2$) is obtained from mineral deposits. The mineral is simply mined (most frequently in open mining), dried and milled. Composition of the mineral between different deposits, but also within the same deposit, can vary drastically depending on the concomitant minerals in the deposit (e.g. dolomite, magnesite, calcite, chlorite.) Contamination with asbestiform minerals from the amphibole or serpentine group cannot be excluded completely either. Talc suitable for pharmaceutical use (approx. 90% $\text{Mg}_3(\text{Si}_4\text{O}_{10})(\text{OH})_2$) is, as a rule, specifically selected in the mines. In view of this situation the group of specialists started its work on the development of a harmonised monograph from the following platform (Ref. 5):

From the 2 options to characterise the composition of talc:

- X-ray diffraction in combination with thermogravimetry (TGA),
- Chemical analysis via AAS,

chemical analysis was preferred according to a public survey at stage 3 of the harmonisation procedure. Consequently this option was pursued in the further elaboration of the monograph. The chosen combination of testing criteria for total magnesium, total aluminium, total calcium and residue on ignition at 1050°C , together with the applied limit set, reliably characterises the composition of pharmaceutical grade talc. This has been confirmed in parallel investigations by X-ray diffraction and TGA and is based on 23 samples of pharmaceutical grade talc from different origins. Exclusion of a potential contamination with asbestiform minerals is covered by a Production Section in the monograph. This obliges the manufacturers to continually monitor their mineral deposits for asbestiform minerals by state of the art technology (X-ray diffraction in combination with specific optical microscopy).

The monograph based on the above criteria has been adopted by the European Pharmacopoeia Commission in 1998 coming into force by 1 January 1999. It has not yet been adopted by the USP and the JP. However, recent discussion in the USA in connection with a potential listing of talc as a carcinogen came to the conclusion that the current USP monograph is significantly out of date and that the present EP monograph appears to reflect current knowledge and science. As a result of this, action has been initiated to adapt the USP monograph to that of the EP.

Finally, in this context, we would briefly like to address one additional item, which has already been discussed and decided by the PDG some time ago but is – with a very few exceptions – not yet implemented: functionality related testing, which means in fact physical characteristics of a substance like e.g. particle size distribution, specific surface area, bulk density (see e.g. table 4). Relevance of such parameters for drug product manufacture and drug product performance has been correctly raised by drug formulators some time ago. A suitable form for the inclusion of functionality related testing into pharmacopoeial monographs is still under consideration by the PDG.

2.3 Magnesium stearate/ Tests for nickel, cadmium and lead

The above topic – as already pointed out in the preceding article by Dr. Chowhan – led to comprehensive and controversial discussions.

This matter cannot be treated as an isolated case but must be seen and assessed in the light of the insufficiency of the current general pharmacopoeial heavy metal test and the consequences to be drawn from this fact. Over the years, thousands of samples of several hundred substances have been investigated by numerous companies without detection of a contamination. On the other hand, problems occurred in a number of cases with materials that passed the pharmacopoeial heavy metal test but were in fact contaminated, sometimes significantly with heavy metals. Examples (Ref 6) include:

440 ppm tin in polylactic acid,
30 ppm platinum in a lactam (antibiotic precursor),
30 ppm nickel in a polymeric amine,
108 ppm cadmium and 215 ppm nickel in magnesium stearate,
High concentration of cadmium and nickel in several other magnesium stearate samples,
2500 ppm zinc in a magnesium stearate sample,
52-530 ppm tin in cetylparmitate.

From the examples presented above it is obvious that the present pharmacopoeial heavy metal test is not suitable to reliably detect and assess an existing contamination. This is underlined by the results of an atomic absorption spectrometry (AAS) investigation with spiked samples of hydroxypropyl methyl cellulose, using the sulphated ash procedure for matrix decomposition (see table 5) and the conclusions which have to be drawn from this data.

Table 5 – Determination of Heavy Metals in Hydroxypropylmethylcellulose (Ref 7)

Element	% Recovery after ignition ^a		Precipitation	Colour
	USP	EP		
Sn	66	0	Yes	Dark
As	63	70	Yes	Yellow
Hg	0	0	Yes	Dark or red
Sb	57	61	Yes	Orange
Cd	60	57	Yes	Yellow
Pb	56	46	Yes	Dark
Bi	62	56	Yes	Dark
Cu	69	54	Yes	Dark
Cr			No	
Ni			No	
Fe			No	

This requires a change in thinking how to handle the test for heavy metals in future. An assessment of the production processes of an individual substance for a realistic contamination risk, together with an adequate data set, is considered a scientifically sound basis to decide whether the classical heavy metal test can be deleted completely or is to be substituted by element specific testing using suitable techniques like AAS, ICP-OES, XRF in combination with modern matrix decomposition techniques to exclude loss of analyte. Several Expert Groups of the European Pharmacopoeia have initiated this process some time ago and the EP is now in a transition stage. According to the practical experience gained so far, the heavy metal test can be dropped in many cases, in other cases a switch to specific element testing (e.g. nickel in hydrogenated fat derivatives) is necessary. Main sources for heavy metal contamination in pharmaceutical preparations are:

- Starting materials (predominantly excipients) of mineral/natural origin
- Catalysts used in the synthesis of starting materials, predominantly active ingredients but partially also excipients, like for instance nickel in the hydrogenation of fat derivatives and polyols or tin in the transesterification of fat products.

As expressed above, we clearly share the opinion that only process related and product decomposition related impurity tests should be included in a monograph. From a global perspective there is an obvious risk for contamination of stearates with nickel (source: catalyst in the hydrogenation of the fatty acid fraction) as well as cadmium and lead (source: carry over from multipurpose use of equipment). Consequently, when attempting to set **global** specifications tests for these elements must be considered as an integrating part of the monograph.

The decision to exclude a test solely on the basis of toxicological considerations and to set limits exclusively on the basis of toxicological calculations is not in line with agreed ICH and regulatory guidelines, which request that limits are also based on specific pharmaceutical quality aspects (e.g. GMP, risk of degradation of the drug product due to interaction of impurities with drug product components). This has once again been confirmed specifically for heavy metals in the recent CPMP draft on catalyst residues (Ref. 8).

2.4 Recent Status of the harmonisation project

Above examples illustrate the nature and dimension of problems which had (and in a number of cases will still have) to be overcome and the extent of detail work necessary to get to meaningful harmonised monographs.

As a result of constant and systematic work within the PDG and the involved expert and working groups, the project has now reached a status which permits finalisation of the work on a number of excipients. In order to profit from the most recent status of the harmonisation work, the PDG decided to base their “sign-off procedure” in future on “harmonisation by attributes”. This makes it possible to officialise already monographs where most of the work, except some single pending items, has been finalised and agreed upon.

The following monographs have been signed off by the PDG or are ready for sign-off and their inclusion into the pharmacopoeias is in progress:

Signed-off

- benzyl alcohol

Ready for sign-off

- citric acid, anhydrous
- citric acid, monohydrate
- potato starch
- wheat starch
- sodium chloride

As an example of the reduction of the overall testing workload associated with harmonisation, table 6 shows the status of benzyl alcohol before and after the harmonisation.

Table 6 – Pharmacopoeial requirements for Benzyl Alcohol

		Ph. Eur. II	USP XXII/ NF XVII	JP XI	Harmonised Monograph
1.	Identity (KMnO ₄ + H ₂ SO ₄)	+	+	+ (performance different)	-
2.	Identity IR	-	-	-	+
3.	Aqueous solution, clarity	+ (clear)	-	+ (clear)	+ (clear)
4.	Aqueous solution colour	-	-	colourless	colourless
5.	Acidic substances	max. 1.0ml 1.0MNaOH/10ml, Phenolphthalein	Identical to Ph.Eur	max. 0.2ml 0.1MNaOH/10ml, Phenolphthalein	Max. 1.0 ml 0.1MNaOH/10ml, Phenolphthalein
6.	Relative density (20°C)	1.043-1.049	1.042-1.047 (25°C)	1.043-1.053	-
7.	Refractive index n ²⁰ D	1.538-1.541	1.539-1.541	1.538-1.541	1.538-1.541
8.	Peroxide value	max. 5	-	-	max. 5
9.	Benzaldehyde (GC)	max. 0.15/0.05*%	Max. 0.2% (HPLC)	-	max. 0.15/0.05*%
10.	Other related substances (GC)	max. 0.2/0.1*%	-	-	Cyclohexylmethanol: max. 0.10% total of other peaks with retention time less than that of benzyl alcohol: max. 0.04/ 0.02*%; total of other peaks with retention time greater than that of benzyl alcohol : max. 0.03/0.2*%
11.	Halogenated compounds	max. 300 ppm Cl	max. 300 ppm Cl	not detectable	-
12.	Evaporation residue	max. 0.05%	max. 0.05%	-	max. 0.05%
13.	Assay (by means of hydroxylvalue)	97.0-100.5%	97.0-100.5%	min. 98.0%	min. 98.0%
14.	Boiling range	-	-	202.5-206.5°C/96%	-
15.	Sulphated ash	-	max. 0.005%	max. 0.005%	-
16.	Aldehydes	-	-	Not detectable (dinitro-phenylhydrazin)	-
17.	Organic volatile impurities	-	Meets general USP requirements	-	-

* second figure applies to parental use

The harmonised monograph does not only cut down the overall testing workload considerably, it simultaneously separates impurities arising from the various production procedures for benzyl alcohol. It further eliminates the reproducibility problems of the former EP GC method (benzaldehyde artefacts because of benzyl alcohol oxidation on packed columns).

3. Testing of excipient batches/ extent and frequency

Concerns have been raised that adaptation of excipient monographs to state of the art in science and technology, like those for talc and magnesium stearate described above, would lead to a strong increase in the workload for batch testing, not justified from a cost /benefit point of view.

With regard to batch testing the EP and the USP make the following statements in their “General Notices” section:

EP

“An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls. Parametric release in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia”.

USP

“Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopoeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopoeial standards”.

In other words: Pharmacopoeial monographs define, what has to be understood as pharmaceutical grade material, without requesting full analysis of every batch, provided that compliance with the monograph can be verified from other suitable sources. Reliable quality assurance measures for excipients built on elements such as adequate evaluation of a supply source including auditing and process validation, use of suppliers’ certificates of analysis, periodic testing, data trending and consequent follow-up of deviations, permit to keep lab testing at a reasonable level.

Aims of the project on international harmonisation of pharmacopoeial excipient standards are to facilitate drug product registration and drug product trade on a global scale and to reduce the overall workload in lab testing for both excipient users and excipient suppliers. The above examples clearly show that these goals have been achieved for a number of excipients or can be achieved in the near future, even where single points in a monograph are not yet harmonised. To conclude from a comparison between harmonised monographs and their preceding EP or JP or USP version that the workload increased is a misunderstanding and misinterpretation of the aims of the harmonisation process.

In view of the above facts and from a scientific perspective we cannot share the view not to adapt excipient monographs to state of the art in science and technology for questionable cost/benefit considerations.

4. Conclusions

As a result of the systematic work within the PDG, considerable progress has been made in the extremely difficult field of harmonising pharmacopoeial excipient standards. The recent decision of the PDG on harmonisation by attributes will permit to profit in future from further progress in the harmonisation work more rapidly.

Examples like those discussed above for ethanol, talc, magnesium stearate and benzyl alcohol clearly show that sound science has been applied in the design of harmonised monographs and we cannot, by any means, share the view that this was not the case. Differentiation of pharmaceutical excipients from technical grade material requires adequate consideration in the design of pharmacopoeial excipient monographs. Integration of functionality related testing into monographs in a suitable form must be pursued.

Unless safety considerations require more stringent specifications, limits should be based on typical results found for commercial materials, but with a reasonable safety margin to cover normal process variation (e.g. 3s approach). It appears that availability of sound data compilations as a decision basis is a certain problem in this part of the harmonisation process.

Pharmacopoeial monographs for excipients define what has to be understood as pharmaceutical grade material, taking account of the various production processes of excipients and their pharmaceutical application(s). From a pharmacopoeial perspective batch-by-batch testing against all criteria of a monograph is not required. Reduced testing on basis of adequate quality assurance measures is considered acceptable.

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