

*Excipients:
Classical quality requirements
and functionality
related testing*

Brussels, Belgium, 4-5 April 2002



PROCEEDINGS

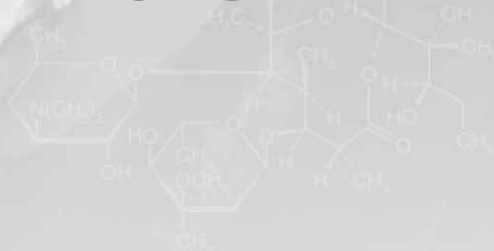


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OPENING REMARKS

Prof. H. G. Kristensen, Chair of the European Pharmacopoeia Commission

On behalf of the European Pharmacopoeia Commission and the European Directorate for the Quality of Medicines (EDQM), I am pleased to welcome all of you to this conference on excipients. I will, in particular, welcome the speakers and moderators and thank you for your willingness to contribute to the conference and its success. Among the speakers are representatives from the Japanese and the United States Pharmacopoeias.

The conference has been organised in response to the growing interest in the field of excipients among manufacturers and users of excipients as well as regulators. The question on how to design and develop pharmacopoeial standards meeting the needs of manufacturers and users is an important issue for the Pharmacopoeia Commission. During the conference you will be presented to recent decisions taken by the Pharmacopoeia Commission, for example on the introduction of what we call functionality-related characteristics into the monographs of the European Pharmacopoeia. It is very important for the Commission to have these decisions discussed at this conference and to learn from your experiences and recommendations on future developments.

In my opening address I will draw your attention to three fields of importance for the standardisation of excipients, namely the classical quality specifications including the control of impurities, the introduction of functionality-related characteristics and the international harmonisation among the three pharmacopoeias, the European Pharmacopoeia (Ph. Eur.), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP).

Impurities in substances for pharmaceutical use have become a hot issue for the Pharmacopoeia Commission because of the revised ICH Q3A guideline on impurities and because of the globalisation of the market for raw materials calling for new solutions to the problems in the identification and control of impurities. The 4th Edition of the European Pharmacopoeia, put into force by 1st January 2002, contains a new general monograph on 'Substances for Pharmaceutical Use'. It has to be applied together with the monographs on drug substances as well as excipients. The section 'related substances' presents the principles for the control of impurities in active substances, which are in good accordance with the Q3A guideline. Nothing is mentioned, however, in the general monograph about the control of impurities in excipients apart from cross-references given, for example, to tests for residual solvents. There is an obvious need to establish some general principles for the control of impurities in excipients. They should take into account that many excipients are manufactured in the facilities of various industries and that the pharmaceutical use frequently represents only a minor percentage of the total production. Great many excipients are of natural or semi-synthetic origin and may consist of a mixture of homologues. I would expect that the concern we have about related substances in the monographs on active substances is not valid in case of excipients because the impurities including degradation products and additives do not necessarily present the same risk for the users of drug products as the impurities in active substances do. They may, however, influence the functionality of the excipients. I do hope that we can have this issue discussed during the conference.

Excipients : Classical quality requirements and functionality related testing

The primary purpose of the Pharmacopoeia is to safeguard the users of drug products. Focus in the monographs is therefore given to the chemical profile comprising identity, purity tests and assay. In recent years we have discussed the possibilities to include functionality testing in the pharmacopoeia monographs because the degree of functionality may have a significant effect upon the product attributes and thereby on the safety and efficacy of the final product. Later this morning I will present the background and the intentions of the Pharmacopoeia Commission in fitting functionality-related characteristics into the monographs. By so doing, the Pharmacopoeia Commission wishes to meet the needs of excipient manufacturers and to assist the drug manufacturers and regulators in the setting of product specific specifications. Although, the tests and methodologies will be included in a non-mandatory section of the monograph, there is certainly a risk that the introduction of 'functionality-related characteristics' will lead to additional testing of excipients. We will have a possibility to discuss this field during one of the workshops.

The international harmonisation of widely used excipients has been on the agenda since the International Pharmaceutical Excipients Council (IPEC) was established in the late 80'ies. The Pharmacopoeial Discussion Group (PDG), was established in 1989 among the European, Japanese and United States Pharmacopoeias with the aim to harmonise monographs on excipients. About 50 excipients are included in the working programme, and some monographs are close to harmonisation. It can be said without any reservation that the European Pharmacopoeia Commission strongly supports the harmonisation work and hope that it can be extended by harmonisation also of general methods for analysis of excipients.

The programme for the conference will allow for discussions of the items I have addressed, in particular during the two workshops to be held this afternoon. Quality assurance and testing of excipients and the international harmonisation will be addressed tomorrow morning and finally we will have a general discussion based on the reports from workshops. It is of outmost importance for the Pharmacopoeia Commission to learn from you about your experiences and proposals on the future development of excipient monographs.

Finally I wish for all of us that the conference will be successful and characterised by a lively discussion of the standardisation of excipients for pharmaceutical products.

Once again, welcome to the conference and thanks to all of you for your interest and participation.

SESSION I:

CLASSICAL QUALITY SPECIFICATIONS FOR EXCIPIENTS

The supplier's perspective

Cellulose excipients

Mr S. Goode, Dow Chemicals (USA)

Fat derivatives

Dr M. Mir, Uniqema (E)

The user's perspective

Prof. H. J. De Jong, Institut de Recherches Internationales Servier (F)

The regulatory's perspective

Dr M. Morris, Quality Working Party (EMEA)

Session I: Classical quality specifications for excipients

THE SUPPLIER'S PERSPECTIVE
Cellulose excipients

Mr S. Goode, Dow Chemicals (USA)

Introduction

The title of this presentation indicates I am to present the supplier's perspective. In reality, I can present only the perspective of The Dow Chemical Company, the largest supplier of modified cellulose excipients. Dow, and our various subsidiaries, supply methyl cellulose, hypromellose, ethyl cellulose, and hydroxyethylcellulose to many hundreds of customers, in over 80 countries. Dow is an integrated company, focused on the essentials of life. We also deliver other excipients such as propylene glycol, polyethylene glycol, glycerin and polyethylene oxides. Dow's manufacturing expertise and global scope allows us to also manufacture raw materials for pharmacological actives and with recent acquisitions, we deliver solutions for the development of new active ingredients. In short, Dow has the scope of interest and breadth of impact to present the supplier's perspective regarding both classical quality specifications and functionality-related testing of excipients.

How do suppliers meet the current monograph requirements for excipients?

This is an important question and it deserves a clear and precise answer. The clear answer is that we meet the current monograph requirements with a lot of hard work and consistent operating discipline. The precise answer is that Dow, and other suppliers, work diligently to assure that we train our workers, validate our processes, test our raw materials and products, monitor our processes and open our operations for audit and inspection.

The classic product monograph specification tests are those that we agree will prove the objectives of a monograph: identity, purity, and quality

- The identity of an excipient is proven through appropriate tests that confirm that what is presented as an excipient product, is in fact that excipient product.
- Purity tests demonstrate both the amount of the excipient and the absence of adulterants or contaminants.
- Quality arises from both the properties of the excipient product and the process of manufacturing. The proper documentation of the quality of an excipient will include the product label, and a certificate of analysis or certificate of compliance attesting to the quality of the excipient.

When tests for identity, purity, and quality are repeated and are repeatable, then there is a basis for statistical analysis to predict and control of the manufacturing process. This is the basis for a number of sampling protocols and for improvement activities using tools such as Six Sigma, that Dow has adopted.

So, the classical quality specifications for excipients provide the firm basis for assuring the identity, the purity, and the quality of an excipient while allowing statistical control of the manufacturing process.

We, as Dow, oppose/resist the addition of functionality-related testing in pharmacopoeial product monographs for 3 reasons.

We believe these reasons are significant, valid, and important to users and regulators as well as to us as suppliers.

- First, we oppose/resist the addition of functionality-related testing as a requirement in product monographs because a single excipient may have multiple applications and thus multiple functionality-related properties. A single excipient may be used as a granulation aid, tablet compressibility additive, processing aid, a taste mask agent or to provide any number of other performance-related characteristics such as controlled release to a formulation. These properties may not be known or intended when a drug product is being developed - their discovery and importance can become known only late in the development cycle. What this means is that neither we the supplier, nor you the formulator, nor the compendial authorities can predict which functionality-related testing will be significant for identifying and accepting an excipient.
- Second, we oppose/resist the addition of functionality-related testing as a requirement in product monographs because there are many formulations that depend on a given functionality-related property. So even a robust functionality-related test protocol may not provide sufficient predictive power to guide excipient selection, nor lot acceptance. We, as suppliers, have the additional concern that there are production processes where the relationship between a process-control parameter and the excipient's functionality-related properties is not absolute. For example, we have a case where we applied additional statistical control techniques to reduce the variability of an excipient's properties for one specification test item. At the request of, and with the assistance of a customer, we reduced our intra-batch and inter-batch variability for one test item while continuing to meet the existing specification. Our customer suddenly discovered that this "more consistent excipient" would not let them process their formulation as they expected. The property we controlled had an unintended consequence of changing a functionality-related property our customer needed. Neither we nor our customer predicted this problem.
- Finally, we oppose/resist the addition of functionality-related testing as a requirement in product monographs because functionality-related testing of raw materials shifts the burden of efficacy of the finished product from the formulator to us, the excipient supplier. The current regulatory framework under which we all work demands that control of the formulation, including control of efficacy and fitness for intended purpose, rests with the formulator.

Suppliers and formulators now conduct some functionality-related testing as part of investigations when quality-control and quality-assurance testing indicates a variance from the expected properties and performance. These tests can be highly specific, and give useful information, for a particular case. Extrapolating from investigative procedures to process control or other requirements demands caution and a high degree of co-operation between formulators, regulators, and suppliers. All sides must work judiciously with any changes to affect only the property expected. Change in functionality can impact other properties.

Excipients : Classical quality requirements and functionality related testing

To repeat, we, as a supplier, believe that the classical quality specifications provide assurance of the identity, purity, and quality of an excipient. We oppose/resist the inclusion of functionality-related testing in product monographs for 3 reasons.

- First, that a single excipient may have many functional properties.
- Second, a single functionality-related property may be demonstrated in many different formulations.
- And finally, we resist the shifting of the burden for efficacy of the final product from the formulator to the excipient supplier.

Regardless of our opposition/resistance to functionality-related testing being included in product monographs, we know that such testing has a role in investigating improvements in the final formulation of drugs. Dow has a long history of cooperating in the development of successful new formulations. We intend to continue our commitments to Responsible Care for our products, and to our customers.

Session I: Classical quality specifications for excipients

THE SUPPLIER'S PERSPECTIVE

Classical quality specifications for oleochemical derivatives

Dr M. Mir, Uniqema (E)

Introduction

Excipients are substances other than the drug substance in a drug product which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug product during its manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use [1].

Excipients have not pharmacological actions themselves but they may play a major role on the active ingredient delivery as they bring the desired functionality to the medicinal formulations and therefore can have a major impact on the safety and efficacy of pharmaceutical final dosage forms.

The effect on the safety is mainly related to the possible carry over of substances that may have significant undesirable biological activity. The effect on the efficacy is related to possible changes in the functionality of the excipient from batch-to-batch which may affect the properties of the medicinal product (changes in bioavailability, in stability, ...).

Excipients specifications

Specifications should be chosen to confirm the quality of the product rather than to establish full characterisation and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the product [2]. Therefore, excipient specifications should focus on the characteristics that may bring the desired functionality to the final dosage forms, i.e. chemical composition and physical properties related to functionality.

Excipients functionality on medicinal products

Monitoring of the excipient composition has been the main goal of most monograph specifications. On the other hand, monitoring of physical properties related to the functionality of the excipients is also desirable. Nevertheless, excipients can fulfil a variety of different functions and may be used in different types of final dosage forms (oral, topical,...). Thereby is not easy to find suitable test methods and specifications to satisfy both manufacturers and users of excipients.

Both safety and efficacy are the result of an adequate control of the composition and physical properties of the excipient. It is worth to note that consistent excipient composition is a prerequisite to achieve consistent functionality as physical properties are the result of the excipient composition.

Excipients : Classical quality requirements and functionality related testing

Therefore excipient specifications should be able to control the excipient chemical composition and eventual batch-to-batch variations.

Functionality related tests and specifications should be agreed between manufacturers and users case-by-case depending on the final dosage form and its manufacturing process. The first step to agree functionality requirements is to have well-defined, accepted test methods able to reliably characterise and standardise excipient functionality.

Fatty acids

Fatty acids are medium/long chain saturated or unsaturated carboxylic acids that are generally obtained by splitting of natural fats and oils yielding glycerine and fatty acids.

Fatty acids from the splitting process are mixtures representing nearly the full spectrum of fatty acids present in the raw material (see attached table).

After the splitting, they are further processed to obtain more pure fractions by crystallization and distillation. Nevertheless a commercial fatty acid is generally a mixture of different fatty acids.

Table: Fatty acid composition of natural fats and oils

Fatty acid (trivial name)	Carbon no.	Coconut oil	Palm kernel oil	Rapeseed oil (C22 rich)	Sunflower oil	Olive oil	Soybean oil	Corn oil	Palm oil	Beef tallow	Castor oil	Fish oil
Caproic acid	C6:0	0 - 1	tr									
Caprylic acid	C8:0	5 - 10	3 - 6									
Capric acid	C10:0	5 - 10	3 - 5									
Lauric acid	C12:0	45 - 53	40 - 52					0 - 1				tr
Myristic acid	C14:0	15 - 21	14 - 18	0 - 1	tr	0 - 1	tr	0 - 1	0 - 2	1 - 6		4 - 10
Palmitic acid	C16:0	7 - 11	6 - 10	2 - 5	3 - 10	7 - 16	7 - 12	8 - 19	38 - 48	20 - 37	2 - 3	9 - 16
Stearic acid	C18:0	2 - 4	1 - 4	0 - 3	1 - 10	1 - 3	2 - 3	0 - 4	3 - 6	15 - 30	2 - 3	0 - 3
Arachidic acid	C20:0			0 - 2	0 - 1	0 - 1	0 - 3		0 - 1	tr		
Behenic acid	C22:0			0 - 1	0 - 1		tr					
Lignoceric acid	C24:0			0 - 1	tr							
Myristoleic acid	C14:1											0 - 1
Palmitoleic acid	C16:1			tr	0 - 1		tr			1 - 9		5 - 15
Oleic acid	C18:1	6 - 8	9 - 16	11 - 60	14 - 65	65 - 85	20 - 30	19 - 50	38 - 44	20 - 50	4 - 9	8 - 25
Gadoleic acid	C20:1			0 - 14	tr		0 - 1					
Erucic acid	C22:1			2 - 52	tr							
Ricinoleic acid	C18:1OH										80 - 87	
Linoleic acid	C18:2	1 - 3	1 - 3	12 - 24	20 - 75	4 - 15	45 - 58	36 - 62	9 - 12	0 - 5	2 - 7	2 - 8
Linolenic acid	C18:3			6 - 15	0 - 1	15 - 1	4 - 10	0 - 2		0 - 3		0 - 3
Unsaturated fatty acid	C20:(2 - 6)									tr		15 - 30
Unsaturated fatty acid	C22:(3 - 6)											10 - 28

Oleochemical derivatives used as pharmaceutical excipients

Fatty acids are used as raw materials for the manufacture of a high variety of excipients:

- fatty acid salts: magnesium stearate,
- glycerides, medium chain triglycerides, suppository bases: glycerol monostearate, hard fat,
- lower alcohol fatty acid esters: ethyl oleate, isopropyl myristate, ...
- Ethoxylated fatty acid esters: macrogol stearates, macrogol oleates,
- Ethoxylated alkyl ether: macrogol lauryl ethers, macrogol oleyl ethers,
- Sorbitan fatty acid esters: sorbitan laurate, sorbitan oleate,
- Ethoxylated sorbitan fatty acid esters: polysorbate 20, polysorbate 80,.....
-

Such excipients are used in different types of formulations fulfilling a variety of different functions: lubricants, coating agents, oleaginous vehicles, emollients, emulsifiers, solubilizing agents, Some of them are able to increase the absorption rate of some lipophilic drugs [3]. During last years there is an increasing interest for such type of excipients in relation to formulation strategies for active ingredients with inadequately solubility in water [3, 4].

Classical tests methods and specifications for oleochemical derivative excipients

Classical tests methods for oleochemical derivative excipients are focused on the control of the chemical composition of the excipient.

Oleochemical derivative excipients monographs include several indirect composition test methods that are specific of this kind of excipients and that are able to monitor the quality and batch-to-batch consistency of such products.

The main information given by these methods is the following:

- Acid value

Is a measure of the free fatty acid content and of the extent to which hydrolysis has liberated the fatty acids from their ester linkage.

It may be a critical parameter if the final dosage form may be affected by pH changes.

- Saponification value

Is an indicator of the mean molecular weight of the substance.

- Hydroxyl value

Is a measure of the number of free hydroxyl groups present in the substance.

It is worth to note that hydroxyl groups might interact with some active ingredients.

- Unsaponifiable matter

Is a measure of the substances contained in the raw materials and that remain as impurities in the excipient like mineral oils, sterols, tocopherols, carotenoids or pigments.

- Iodine value

It expresses the concentration of unsaturated fatty acids and the degree of unsaturation.

- Peroxide value

Is a measure of the peroxides present in the substance.

The most common degradation pathway of oleochemical derivative excipients is oxidation through a free-radical chain process. The first products formed by the oxidation process are hydroperoxides. The peroxide value test is able to detect the initial stages of the oxidation mechanism during the induction period, before the propagation step.

In addition to these methods, oleochemical derivative excipient monographs include several direct composition tests intended to monitor their composition (gas chromatography, size-exclusion chromatography,) and the eventual presence of specific impurities (heavy metals, total ash, water content,....).

Excipients : Classical quality requirements and functionality related testing

Due to the nature of commercial fatty acids, oleochemical derivative excipients are generally mixtures of derivatives of several fatty acids. Fatty acid composition may have a strong impact on the functionality of the excipient and therefore a first approach to characterise the functionality of such excipients is to make a distinction of different grades based on the chemical composition.

Current trends on new/revised Ph. Eur. monographs are

- Introduction of state of the art tests methods intended to monitor the composition of the product (size-exclusion chromatography, ...)
- Differentiation of excipients with different composition covered by a single monograph (i.e. Macrogol stearate type I or II, Ph. Eur 4th Edition)
- Introduction of tests for specific potential impurities (i.e. nickel in hydrogenated oleochemical derivatives)

Conclusions

Specifications should be able to monitor the chemical composition of the excipient in order to assure consistent batch-to-batch performance.

Extremely detailed specifications should not eliminate materials already used in marketed medicinal products.

Functionality related requirements should be agreed between the purchaser and supplier case-by-case on the basis of well-defined, accepted test methods able to reliably characterise and standardise excipient functionality.

References:

- [1] Definition of excipient included in the IPEC GMP's guide for Bulk Pharmaceutical Excipients (1995).
- [2] ICH Q6A guide on Specifications For New Drug Substances And Products. *Chemical Substances*. (1999).
- [3] Bowtle, "Lipid formulations for Oral Drug Delivery", *Pharmaceutical Technology Europe*, 20-30 (September 2000).
- [4] L. Collins-Gold, N. Feichtinger, T. Wörnheim, "Are lipid emulsions the drug delivery solution?". *Modern Drug Discovery*, 44-48 (April 2000),

Session I: Classical quality specifications for excipients

THE USER'S PERSPECTIVE

Prof. H. J. De Jong, Institut de Recherches Internationales Servier (F)

Medicinal products

Active ingredients, Excipients and the Manufacturing Process are the essential components in the making of Medicinal Products. The Quality, Safety and Efficacy of the Medicinal Product is determined by the choice, quality and performance of these components.

Excipients allow for correct handling of the medicinal product (right dose, hygiene, storage ...), they permit large scale industrial manufacturing and they often play an important biopharmaceutical role (immediate release, modified release, targeting).

Ideal excipients

Ideal excipients should be inert towards the active ingredient, the other excipients, the machinery and packaging materials. They should be without regulatory problems (accepted worldwide ?), easily available from several sources and, last but not least, be not expensive.

During new drug (product) development in the pharmaceutical industry, the formulator will study the possibilities and limits of the active ingredient in so called preformulation studies. Many characteristics and parameters related to the active ingredient and excipients need to be taken into account at a moment where still little is known about the behaviour of the new active ingredient, as well as about the final biopharmaceutical requirements (dose, size, dose frequency ...) of the drug product.

Excipients in medicinal products

Developers have a choice among approximately 1200 "inactive" ingredients that are already in use in marketed Medicinal Products and thus implicitly "authorized". From these, about 240 have monograph(s) in at least one of the three "big" pharmacopoeias : USP, JP, Ph. Eur. International harmonisation is ongoing for the "top 51" of these excipient monographs. A large majority is concerned with solid oral dosage forms.

A low risk approach for product developers is to make use of these well known "almost harmonised" excipients. This avoids technological and regulatory surprises. More innovative projects, making use of novel excipients, meet a lot of hurdles. A real new chemical entity requires a full development (quality, safety and functionality should be documented) and carries the risks of discovery (e.g. long term stability problems, interactions, acceptability).

Excipients for worldwide operations

For our company exporting to 130 countries and having production facilities in 12 countries, there is a need for industrial optimisation. This has to be taken into account during product development.

Ingredient selection

In the optimisation effort, the formulation itself, the production processes available and the supply possibilities of ingredients and components have to be taken into account.

There is a strong preference for compendial ingredients. In supplier selection, a number of important items should be checked :

- what overall quality is produced,
- what is intended use,
- what type of production / quality control,
- what quality system in place.

Satisfactory answers to these questions and appropriate reference to a Pharmacopoeia open the possibility of acceptance of this supplier.

For new ingredients, ICH and regional guidances should be followed. The "template" of a compendial monograph for a similar chemical class of substance can be very helpful in setting quality specifications. Main difficulties are found in specifying functionality related characteristics.

A close collaboration between manufacturer / supplier and user (pharma industry) is essential for a valid set of specifications. The functionality related items should not be specified in compendial monographs since they are strongly product related. Compendial General Methods for measuring functionality related characteristics are highly desirable : they promote good cooperation / business between supplier / user and allow for recognition by regulatory authorities.

Session I: Classical quality specifications for excipients

THE REGULATORY'S PERSPECTIVE

Dr M. Morris CPMP/CVMP Quality Working Party (EMEA)

I work for the Irish Medicines Board but I am representing the Quality Working Party of the CPMP. This is the body responsible for developing guidelines with regard to applications for marketing authorisations.

Excipients: EU Regulatory Overview

Over the last ten years we have focused on the importance of excipients in the finished products and, various guidelines mentioned here, have been developed over the last ten years to look at different aspects relating to excipients amongst other things. To go back to the regulatory basis, which many of you will be aware, comes from Directives such as 65/65/EEC and subsequently 75/318/EEC, which lays down the requirements for marketing authorisation in the annex. I am particularly focusing here on the requirements in the quality dossier (the chemistry pharmaceutical manufacturing part of the dossier). However, the Directive is fairly silent in regard to requirements for excipients. The reference to part II, section 3 of the annex lays down the basic requirements for the starting materials which would cover active substances and excipients. Primarily, this has always focused on the active substances.

Regulation of excipients

The revised version of the Directive is now the new codified Directive 2001/83/EC. As far as I am aware, nowhere in any of the Directives is there given a definition of what is intended by an excipient – therefore, I have just considered that “an excipient is any component of the product other than the active substance or any element of the packaging materials.’

I would also like to stress the point that in regard to established excipients, we have the requirement from the European Pharmacopoeia monograph, of the Pharmacopoeias of the member states where there is no European Pharmacopoeia monograph, and of course, it is expected that any excipient will comply in terms of its quality standards (with the monographs of the European Pharmacopoeia).

Note for guidance (Excipients in the Marketing Authorisation Dossier)

Taking into consideration the lack of statutory guidance on excipients, it was decided to develop a Note for Guidance, particularly looking at the excipients in the marketing authorisation dossier to try and focus on those parts of the dossier where the excipients are mentioned. An attempt was made in 1994 to draft such a guideline which is now under revision, principally because of the implementation of the common technical document. Nevertheless, the focus has been mainly on the active substance but the Quality Working Party is aware of the fact that the medicinal products that patients take, consist not only of active substances, but in many cases, perhaps 90% or more of the product, consists of excipients.

Composition

Firstly, in the composition section of the Quality Dossier we would normally expect to see what excipients are present in the product.

These should be described by the common name rather than using brand-names. However, in some cases, it is necessary to use a brand name and a specific grade.

The quantitative declaration of the material of the excipients should be given, the references to the appropriate Pharmacopoeial standards and also an indicator of the various functions of those excipients.

Finally, where we have mixed excipients present, we would expect to see information on the composition of the mixture.

The Development Pharmaceutics Section

The Development Pharmaceutics Section, requires information on the choice and function of the excipients present in the medicinal product. This is covered by the separate guideline, "Note for Guidance on Development Pharmaceutics", which was first developed at the end of the '80s and was revised a couple of years ago. Here, this goes into more detail, apart from quality standard, to ask for complementary information, to explain and describe what is the actual function of the each of the excipients present in the product – why do they need to be there? Once the excipient function has been declared and the excipient choice is supported, the question is raised as to "has the correct concentration of that excipient been used"? The company should indicate why they used that particular concentration to ensure that the optimum concentration is used, what goes into deciding on the choice of the quality or a particular grade of an excipient, and again this needs to be explained in the dossier. Will that excipient have any impact on the manufacturing process for the ultimate product? Are there any additional parameters which need to be considered?

Further information, which is looked at in the development section of the dossier, concentrates on things like compatibility studies – the possibilities of compatibility or incompatibilities which may exist between proposed excipients and the active substance. Or proposed excipients with other excipients that are in the formulation – these are very important.

Finally, are there any compatibility issues relating to incompatibilities with the excipients and packaging materials?

What about the physico-chemical properties of the formulated product? Does this in turn have some kind of negative impact on excipients? Examples may be pH across the proposed range that is likely to be encountered within the formulation. Also the particle size and does this have any impact on excipients?

I have not alluded at this point to new excipients – I am concentrating on existing excipients. As we have heard, there are large numbers of well-known, well-established excipients many of which are monographed in the various Pharmacopoeias. In the case of new excipients, which have not previously been administered to human beings, clearly this is a completely different situation and a whole new dossier is needed with a complete package of safety data as well as quality data. This, obviously, is a significant amount of work. We rarely encounter those in practice – we have had a few with the CFC replacements but there have been relatively few to date.

Preservatives

One of the areas which we focused on in the Quality Working Party was the impact on preservatives because these are a special category of excipients which can be permitted in various products. These are primarily anti-microbial preservatives and chemical or antioxidant type preservatives. These can be used for certain types of formulations particularly multi-dose formulations where repeated sampling is likely and where there is likely to be a risk of potential chemical degradation and microbial spoilage. Anti-microbial preservatives may be used in multi-dose formulations - antioxidants where there is the risk during the use of the product of chemical degradation and an anti-oxidant maybe used (in itself may be sacrificially degraded during the lifetime of the product).

For these kinds of products, there is a special kind of guideline, again which is under revision, and the current proposal would be that this should be combined with the standard excipients guideline to make a single new guideline.

The suitability of those preservatives, whether anti-microbial or chemical needs to be justified, both from the point of view of the choice of the particular quality of preservative as well as the choice of the concentration. In order to do this, it would be necessary to provide some kind of evidence of the validity of the use of that particular excipient or particular preservative that it is able to carry out the particular function that it is playing. Secondly, that the anti-microbial properties are accepted and that the anti-oxidant properties are accepted. From those particular criteria, one can start to determine what would be the specification for the individual preservatives. Finally, how much impact on the specification of the final product do these have?

For finished products containing preservatives, some degree of performance testing of the formulated product would also be necessary by determining the content of the preservative at release and throughout the shelf-life of the product as well as an indicator of the effectiveness in the overall development study to demonstrate that the anti-microbial preservative effectiveness, for example, is retained following Pharmacopoeial methodologies.

Specifications and testing

In regard to the specifications and test-methods for the finished product – notwithstanding the requirements to develop clearly defined monographs and specifications with appropriate testing for the excipients themselves. Once we have formulated the products containing those excipients and active substances, there is a range of test methods and specifications which need to be addressed and these are covered by the ICH guideline Q6A and also by some residual European Note for Guidance on Specifications and Test Procedures.

As far as identity is concerned, it is important that key excipients would be identified in the finished product, if this is considered to be necessary, this can be asked from time to time although usually, it is not required.

One area where identity testing of excipients in the finished product is needed, is in regard to colorants. Where colorants are used, it is usually expected that these would be an identity test available, but not conducted routinely, to determine the colorant in the finished product

A content value of + or –10% on the content of antimicrobials would be acceptable in the finished product throughout the shelf-life.

As regards antioxidants, a value of + 10% would be considered to be reasonable; a lower limit is much more difficult to predict routinely because of the sacrificial degradation of these

Excipients : Classical quality requirements and functionality related testing

materials is likely to be significantly less than –10% - so that is something which needs to be established on a case-by-case basis, in the development of each individual product.

There may be certain performance attributes which need to be determined on the finished product to reflect the function characteristics of a particular excipient and in particular, this would relate to excipients determining release. For example active substances from solid dose forms unless, this could be adequately addressed, for example, by dissolution test on the solid dose forms.

Purity tests are important and we must remember that excipients also contribute to unwanted impurities such as residual solvents and heavy metals; As we have heard, excipients can be contaminated with these and contribute to the total residual solvents or heavy metal burden on the finished product.

These maybe other specific impurities which emanate from the use of particular excipients. These need to be considered in the finished product testing.

Finally, a group of other tests – osmoality, viscosity, suspendibility for certain types of formulation, these are reflected in the Q6 guideline and may well be largely imparted by the use of particular excipients which are added for those particular purposes. Again, the final determination that the excipient is doing its job can be done at the level of the finished product.

A reminder: for all these specification attributes, there will be release and shelf-life criteria. In some cases, the shelf-life criteria may be wider and justification must be presented under these circumstances.

Specific excipients

The guideline on excipients mentions examples of specific excipients with particular issues: where we have mixed excipients, it is important that the characteristics which are desired for that particular mixture are carefully addressed and depending on the functions of that particular excipient in the finished product. Some excipients will be chemically treated starting materials: these need to be carefully defined, how is the transformation arrived at? Are these naturally derived materials or synthetic materials, both are subject to certain chemical treatments and these need to be carefully controlled. We know the problems related to certain biologically sourced materials whether these come from animal, human or plant origin. We have issues related to transmissible agents being present therefore Transmissible Spongiform Encephalopathy (TSE) safety needs to be established. We also have to look closely at the manufacturing processes which are being used to extract these types of products in order to ensure batch-to-batch consistency and safety.

The Summary of Product Characteristics (SPC)

The summary of the product characteristics in the finished product part of the dossier, which is like the ‘data sheet’ requires information on excipients (declared in section 6.1). It requires a qualitative declaration only and not a quantitative declaration. In particular, the attention is drawn to certain types of excipients which may be present in the product, particularly with solid dosage forms where there may be use of printing inks. For example, in the case of transdermal patches the components of the adhesive or patch structures needs to be declared and in general terms, the INN needs to be used where one exists, and certainly the common name as opposed to the brand name.

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It is also mentioned in Section 2 of the SPC where it simply says in the composition section you are to declare the active substances and cross-refer to the relevant section as mentioned.'

Labels and package leaflets

Labels and package leaflets, again the reference here to the Note for Guidance on excipients and labels and package leaflets 'where all excipients should be declared on the labels for certain types of products dose forms, such as parentals, topicals ophthalmic – whereas for other products, other types of dose forms only the significant excipients' – and examples are given in the table in the annex.

For package leaflets where more space is available, all excipients need to be declared by name and once again, you are reminded about ingredients in capsule shells, printing ink, pH adjusters that may be used in the formulation, and in the case of herbal extracts it may be necessary to use diluents.

Conclusions

In conclusion, we have focused primarily on marketing authorisation dossiers in determining classical quality attributes by really referring to Pharmacopoeial monographs and we have not mentioned the word functionality related testing deliberately but this is the reason for this conference and I think that from the Regulatory perspective, we look forward to seeing more information presented in the dossiers in regard to functionality type parameters. Any such parameters would help to control the quality of the medicinal products which are administered to our patients.

SESSION II:

FUNCTIONALITY RELATED TESTING

Fitting functionality – related tests into pharmacopoeia monographs:

Introduction and background

Prof. Dr H. G. Kristensen, Chair of the Group of Experts 12 (Galenical products) of the European Pharmacopoeia

Excipient functionality / impact on product quality and process performance

Dr S. Marrer / Dr U. Völker, Hoffman – La Roche (CH)

The viewpoint of an excipient manufacturer

Dr A. Janssen, DMV International (NL)

Discussions Sessions I and II

Session II: Functionality related testing

**FITTING FUNCTIONALITY –
RELATED TESTS INTO PHARMACOPOEIA MONOGRAPHS:
INTRODUCTION AND BACKGROUND**

Prof. Dr H. G. Kristensen, Chair of the Group of Experts 12 (Galenical products) of the European Pharmacopoeia

The European Pharmacopoeia presents a definition of excipients for drug formulations in the Glossary contained in the section on dosage forms. According to this definition an excipient constitutes any component other than the active ingredient present in a medicinal product. The intended function is to act as a carrier, or a component of the carrier, and in so doing to contribute to product attributes such as stability, biopharmaceutical profile, appearance and patient acceptability and the ease with which the product can be manufactured. Thus, excipients are used in pharmaceutical formulations for a variety of purposes. Although inert as such, pharmaceutical excipients may have a profound effect upon the safety and efficacy of the final dosage form.

The function of an excipient in a given drug formulation should be straightforward. It should serve a physical, chemical or biological function by acting for example as a tablet filler, a lubricant, an anti-microbial agent, a surfactant or an agent added to improve the manufacturability of the formulation. In contrast, the functionality of an excipient is more difficult to characterise because it depends on the properties of the molecule and the physical form of the excipient material as well as interactions with other components of the formulation, the processing method and, in some cases, even the purity of the material. The specification for an excipient to be used in a given formulation has, therefore, to be established during the development work.

In 1994 the USP organised a joint-pharmacopoeial conference on functionality testing to discuss the possibilities for including functionality testing into pharmacopoeia monographs. In order to clarify the European viewpoints, a European workshop was organised the following year in Strasbourg. The conclusions from the workshop were clear. Functionality testing is a field for manufacturers of drug products for the reasons stated above. The Pharmacopoeia can, however, serve the manufacturers by the provision of commonly accepted and standardised methods for the testing of the physical and physico-chemical attributes of excipients and for the setting of internal, product specific specifications. The Pharmacopoeia may provide a non-mandatory list on the critical properties of an excipient in connection with the intended use and, as far as possible, to make reference to general methods for the testing. Pharmacopoeial specifications should not be established. It should be left to the manufacturers to give such information by labelling.

Shortly after, the Pharmacopoeia Commission decided that a non-mandatory section on functionality-related characteristics should be included in the monographs on excipients. The General Notices were amended accordingly. The general monograph on Substances for Pharmaceutical Use published in the 4th Edition of the Pharmacopoeia, includes statements on functionality-related properties of excipients.

A work programme on the development of a few general methods was established as a result of the above mentioned workshop. The work programme was, however, speeded up as a result of discussions held at the conference on international harmonisation of general methods in Sevilla 1998. At present a range of general methods for powder characterisation is in Stage 3 or 4 of the international harmonisation run by the Pharmacopoeial Discussion Group. Most of these methods represent a retrospective harmonisation among the JP, Ph. Eur. and USP, but the three general methods on particle size measurement by laser diffraction, X-ray crystallography and mercury porosimetry are subject for a prospective harmonisation.

At its November Session last year, the European Pharmacopoeia Commission discussed again the inclusion of functionality-related properties in excipient monographs. The Commission confirmed its previous decision to include functionality-related characteristics in a non-mandatory section of the monographs and to establish a list on critical characteristics in relation to the typical uses of the concerned excipient. Further, it was decided to initiate work on 89 monographs in a collaboration between the secretariat and members of the Group of Experts on Dosage Forms. The aim of the work is to draft the section on functionality-related characteristics. The selection of monographs for this work was based on the criterion that different grades of the substance are available on the market and that the grades can be distinguished by tests on physical and physico-chemical characteristics. The list includes organic and inorganic substances. The next issue of *Pharmeuropa* presents proposals on the drafting of anhydrous lactose and magnesium stearate. They are published in order to get comments from users on proposed format.

The Pharmacopoeia Commission considers that the majority of excipients belongs to the classes of

- (i) fats/fat derivatives,
- (ii) cellulose/cellulose derivatives,
- (iii) starches/starch derivatives, and
- (iv) polymeric excipients.

These excipients will be dealt with by Working Parties and in the case of fats and fat derivatives by the Group of Experts 13H. The Working Party on polymeric excipients is new. It has been allocated work on some synthetic polymers and is asked to consider the need for additional, general methods for the characterisation of polymeric excipients. The aim of the Commission is to update the monographs on polymeric excipients to today's technological standard.

The consistency of excipient monographs may be affected by the fact that the monographs are drafted by different groups of experts and working parties. It will therefore be most important to develop a chapter for the Technical Guide on the design of excipient monographs. This chapter will be drafted on the basis of proposals from the new Working Party on polymeric excipients and the experiences gained by the secretariat in the work on the above mentioned monographs to be amended with a section on functionality-related characteristics. A position paper presented to the Pharmacopoeial Discussion Group by the three IPEC's on pharmacopoeial standards for excipients will also be an important basis for the drafting on the Technical Guide.

Thus, the work on functionality-related characteristics of excipients seems to be in good progress. A significant number of general methods has been drafted and are at present in public inquiry. I have no doubt that additional, general methods are needed, in particular in the field of polymers.

Excipients : Classical quality requirements and functionality related testing

Excipients monographs are subject to the international harmonisation among the JP, Ph. Eur. and USP. It is my hope that the Pharmacopoeial Discussion Group will discuss the inclusion of functionality-related characteristics in the harmonised monographs.

In conclusion, I will ask the participants of this conference to discuss the proposed inclusion of functionality-related characteristics in a non-mandatory section of the monographs. It is of outmost importance to have your viewpoints and concerns. The main question to be answered is whether the proposed system can assist manufacturers of drug products in the setting of specifications for excipients. Will it facilitate co-operation between manufacturers of excipient materials and drug products, or will it just mean additional testing?

Session II: Functionality related testing

EXCIPIENT FUNCTIONALITY / IMPACT ON PRODUCT QUALITY AND PROCESS PERFORMANCE

Dr S. Marrer (text presented by Dr U. Völker), Hoffman – La Roche (CH)

Introduction

“Excipients are any substances other than the active drug or product which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.” [1, 2]

Drug products consist of active pharmaceutical ingredients and excipients. Excipients usually have one or more of the following functions in a drug formulation:

- solvent
- emulsifier
- anti-foaming agent
- salt-forming agent
- thickener
- antioxidant
- preservative
- binder
- disintegrant
- filler
- lubricant
- drying agent
- taste agent
- colorant
- solubilizer
- wetting agent
- buffer
- gel former
- coating agent
- etc.

These functions are vital for the quality, safety and efficacy of drug products. The careful formulation of the drug composition during development significantly influences these performance parameters. Afterwards, during large-scale routine production, the drug manufacturers are highly dependent on the excipient manufacturers/suppliers, which have to assure that excipients are continuously delivered in constant quality based on reliable quality standards.

Appropriate specifications and test methods must be established and applied for identification tests, purity and impurity tests including limits, physical characteristics, etc. In some cases it may be useful to include functionality-related tests fulfilling the needs of the customer's processes.

Most Pharmacopoeias and excipient suppliers ignored up to now functionality-related tests for excipients. This is now rapidly changing. In this paper an industry's perspective to excipient functionality is given.

Definitions

Functionality Testing of an excipient means direct testing of the concerned function in a particular formulation and manufacturing process.

In addition to such real functionality tests, manufacturers apply *Functionality-Related Tests* in their control of physical and physicochemical properties of raw materials.

A *Performance Test* for a drug product is a test for critical properties of the drug formulation.

Case study: quality issues with a drug product

The data of the case study were generalized, but are representative for the case.

A large number of batches of a drug product was manufactured without failing dissolution testing. A new production campaign indicated failing dissolution tests. A thorough investigation was carried out in order to find the root cause for the failing dissolution tests. The investigation included a detailed review of manufacturing process steps, process validation, batch records, equipment qualification, analytical method validation etc.

As final root cause, an increased content of CaCO_3 in calcium silicate – an excipient of the drug formulation – was found. The increased amount of CaCO_3 impacts the performance of the dissolution test. During the dissolution test, the particles of the disintegrated drug product usually remain in the bottom area of the dissolution vessel. The turbulence of the stirrer results in the release of the active pharmaceutical ingredients from the drug product and/or its disintegrated particles. The dissolution test is carried out with an acid medium which releases CO_2 from CaCO_3 . The ascending bubbles of CO_2 causes the floating of disintegrated drug product particles to the surface of the medium.

At the surface of the dissolution medium, the drug release process is much less efficient than in the turbulent area at the bottom. This effect finally results within the given time interval of the dissolution test in decreased dissolution data.

The increased content of CaCO_3 in calcium silicate could be attributed to the age of the used excipient batches. During storage, the content of CaCO_3 increases continuously.

In order to resolve the root cause the following measures were implemented:

- A validated method to test for the content of CO_2 in calcium silicate (calculated as CaCO_3) was developed and implemented.
- The content of CaCO_3 in calcium silicate was limited to 3%.
- The primary packaging of calcium silicate was improved (switch to air-tight packs).
- The shelf-life was limited and shortened.

After the implementation of these measures the product quality proved to be successfully re-established with a large number of batches.

The case study shows that excipients' quality can have a significant impact on product quality.

The industry's expectation – Ph. Eur.

The Pharmacopoeia is the relevant reference book in the drug registration process. Similarly structured as a dictionary, it lists the specific requirements for a large number of active pharmaceutical ingredients and excipients. The specifications for the individual active substances and excipients are summarized in monographs. The monographs define the

Excipients : Classical quality requirements and functionality related testing

materials, specify the quality criteria and describe with which methods the quality should be tested. The methods are adapted thereby constantly to the scientific status. They become accordingly ever more complex. The qualitative and quantitative chemical quality of excipients are usually well described in the respective monographs. For excipients not listed in a relevant Pharmacopoeia, the drug manufacturers develop their own monographs.

Besides the chemical characterization, the functionality of excipients depends both on their physical properties and on the drug product formulation and the manufacturing process. This indicates that excipient functionality may very strongly depend on the unique drug product and process technology applied for a particular product. Specifications for functionality-related testing criteria must therefore be based on the needs of drug manufacturers. Therefore, it is recommended that such tests are not included into the mandatory part of the monographs. They rather should be included in a non-mandatory part. Although functionality related testing criteria shall - if tested - be included in a non-mandatory part, the excipient manufacturers and suppliers are expected to include the respective analytical data in the batch-specific Certificate of Analysis together with the analytical methods applied.

As an example the following monographs could require to include non-mandatory functionality-related testing criteria:

<i>Excipient</i>	<i>Functionality related testing criteria</i>
<ul style="list-style-type: none">• Fillers and diluents	Particle size distribution Loose and tapped bulk density Hausner index
<ul style="list-style-type: none">• Lubricants	Particle size distribution Specific surface area
<ul style="list-style-type: none">• Binders	Viscosity (single/multiple point measures)

The list of functionality-related testing criteria shall be extendable based various types of products and applications they are used for. It is obvious that this will require a close cooperation between the partners involved in this process (excipient manufacturer, drug manufacturer and pharmacopoeias).

The industry's expectation – excipient manufacturers & suppliers

As given above, excipients are essential constituents of drug formulations. They are not only ingredients other than the active pharmaceutical ingredient. Excipients contribute unique functionalities to drug products, thereby determining the product's quality, safety and efficacy. Since excipients play such an important role, it is obvious that drug manufacturer have to require from excipients manufacturers adherence to adequate Good Manufacturing Practices (GMP). Such a concept shall assure that the excipient itself possesses the quality, safety, purity and suitability for use that it purports to have.

Examples of relevant GMP guidance for excipients are e.g. published by IPEC [1], WHO [2], or USP [3]. It is obvious that based on the huge variety and source (e.g. minerals, animals, plants, synthetic) of excipients, some GMP requirements may not be suitable for certain types of products and processes.

It is the responsibility of the drug manufacturers to assure the quality of purchased excipients. By auditing he can check whether an excipient manufacturer has appropriate controls in place

to ensure that excipients are consistently produced with uniform chemical and physical characteristics [4]. In order to reduce the audit work load and costs for excipient and drug manufacturers, the development and implementation of a world-wide accepted audit certification program should be considered [5].

The review of the change control systems should usually be an important topic in GMP audit. The excipient manufacturer should establish and maintain an adequate system for controlling changes within production processes. The needs of the customers should be appropriately considered within process changes. In some cases it might be adequate to communicate process changes to customers. In other cases, the possible impact of excipient process changes on drug product quality and drug process performance should be proactively assessed by the excipient manufacturer in cooperation with drug manufacturers. In order to assess possible impact of changes on product quality and process performance, the drug manufacturer has to carry out functionality and/or performance tests.

Some process changes might also have regulatory impact and must be filed as variation to the Health Authorities [6, 7]. It remains within the responsibility of the holder of the Marketing Authorization to provide the Health Authorities timely with technical documents supporting these changes. In order to fulfil this requirement, drug manufacturers must rely on the process control and communication system of the excipient manufacturers.

Conclusion

Excipients are important constituents of drug products. Often they make up to 99% of a formulation and, therefore, directly influence the drug product quality and the process performance. Today's pharmacopoeial monographs focus mainly on standards for chemical product characteristics. The consideration of functionality-related testing criteria - which might have an impact on product quality and process performance - in the non-mandatory parts of monographs will be a significant next step in setting reliable quality standards for excipients.

- [1] The International Pharmaceutical Excipient Council (IPEC), Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients (1997)
- [2] Good Manufacturing Practices: Supplementary Guidelines for the Manufacture of Pharmaceutical Excipients, *WHO Technical Report Series No. 885*, (1999).
- [3] Good Manufacturing Practice for Bulk Pharmaceutical Excipients <1078>, *USP 24*.
- [4] The International Pharmaceutical Excipient Council (IPEC), Good Manufacturing Practices Audit Guideline for Bulk Pharmaceutical Excipients (1998).
- [5] A GMP audit certification scheme for excipients could e.g. be designed based on the concept and ideas of the "USP Dietary Supplement Verification Program". The USP program will indicate to consumers that dietary supplement manufacturers have developed a quality system for producing dietary supplements that assures compliance with the United States Pharmacopeia and the National Formulary (USP-NF) General Chapter on Manufacturing Practices for Nutritional Supplements and FDA's Advance Notice of Proposed Rulemaking for good manufacturing practices (ANPR GMP) (www.usp.org).
- [6] Sam T., Regulatory Implications of Excipient Changes in Medicinal Products, *Drug Information Journal*, **Vol. 34**, 875-894 (2000).
- [7] De Jong H., Harmonizing Regulatory Requirements for Pharmaceutical Excipients, *Regulatory Affairs*, 48-50 (March 2001).

Session II: Functionality related testing

THE VIEWPOINT OF AN EXCIPIENT MANUFACTURER

Dr A. Janssen, DMV International (NL)

Introduction

I am sure that several speakers will lead you to the heights of science and of regulatory possibilities. Let me be your guide for the next 25 minutes in the basement of common sense.

I will divide my presentation into four parts:

- Presentation of DMV International
- The viewpoints of DMV International on functionality related testing
- Some functionality related tests as performed by DMV International
- Conclusions

Presentation of DMV International

DMV International is a division of DMV International, one of the largest dairy companies in Europe. This is important to know because our products are born as food products, they go their way as a food product and at a certain point they become “pharmaceutical ingredients”. There is a huge difference in approach between the legislation on the food side and on the pharmaceutical side. I think that it would be good when those parties would communicate more often with each other.

DMV International is an important manufacturer of products like lactoferrin, caseinates, toppings, coffee whiteners and lactose. For caseinates and lactose we possess large manufacturing sites on a world scale.

On May 28th we will open our new lactose manufacturing site for lactose for direct powder inhalation (DPI). We are currently in the process of implementing a quality system based on the GMP for active pharmaceutical ingredients.

Viewpoints of DMV International on functionality related testing

In this part some ideas, thoughts and viewpoints are presented.

Lactose is extensively used in very different dosage forms (i.e. in powders, tablets, capsules, inhalation) powders. It is evident that the customer requirements will be very different in all these situations. The customer requirements are of course the primary requirements to be looked for; functionality related parameters are only the technical translation of the customer requirements. In the case of excipients we have several supplier-customers relationships in the supplier chain. Involved parties are the pharmaceutical industry, the doctor, the patient and the regulatory authorities. Here we will mainly concentrate on the pharmaceutical manufacturer as a customer.

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One of the important properties of lactose is the combination of a good price and a high quality. The cost of excipients is a very small part of the cost of the manufacturing of medicinal products. However, in discussions with customers we sometimes get a different impression!.

An important requirement for functionality related tests is that they should provide information that facilitates the optimum choice of the excipient. Furthermore, they should provide data to compare excipients.

The customer requirements can be expressed in terms as "good mixing properties", "should contribute to a good content uniformity", "compatible with our current manufacturing configuration", "chemical compatibility with other components", "should have good binding properties", "should yield good tablets", "should be cost effective". When collecting these requirements one should listen very careful to the customer and not jump to conclusions. During a survey of Toyota Motor Company on customer requirements for a sports utility vehicle (SUV) "speed" was mentioned to be very important. However, their current SUV was the fastest on the market but was not considered to fulfill this requirement. More in-depth analysis showed that "speed" should be interpreted as "impression of speed". Mounting springs under the chairs fulfilled the requirement!

There exists a formal technique to link "customer requirements" with "functionality" related parameters the so-called Quality Function Deployment (QFD). This technique was used for the first time at Kobe shipyards in the early seventies. QFD provides a formal framework to discuss design requirements (in our case functionality related parameters) with customer requirements. In our case this technique may be used to decide which functionality related tests give the greatest piece of information with respect to "customer requirements" ("the voice of the customer"). It is our opinion that a minimum set of functionality related parameters should be selected. One should bear in mind that the voice of the customer can not be built into a standard pharmacopoeia monograph. Furthermore this technique can be used in the discussions between suppliers and customers to optimise product development. The figure below gives an example of the central matrix of the QFD.

Qualitätsmerkmale

Legende:

- 9 = starker Zusammenhang
- 3 = mittlerer Zusammenhang
- 1 = schwacher Zusammenhang

Kundenanforderungen	Produktpräsentation	Versicherungsbedingungen	Prämien	Service	Antragsbearbeitung	Schadenbearbeitung	Ergonomie	Einheitlicher Seitenaufbau	Wenige Clicks für Aktionen	Schnelle Erflebarkeit	..	Kundenanforderungsgewicht (%)
Informationen												
über Versicherungsprodukte		9	3									21,7
über Wichtiges im Umfeld												18,3
Kauf												
Individuelle Prämienberechnung			9									13,3
Vertragsabschluss		3	3		9							8,3
Bedienbarkeit												
Einfache Bedienung								9	9	3		10,0
Schutz privater Daten												6,7
...												

Excipients : Classical quality requirements and functionality related testing

On the requirements site we should also mention (validation) parameters like “robustness”, “accuracy”, “precision”, “cost of maintenance”, “cost of maintenance”.

The guiding principle for standardising of methods should be the unambiguous communication between supplier and customer!

One should not forget that sometimes a test may only be used during the design phase and not in routine QC testing. This is particularly true if there is a close relationship between one functionality related parameter (e.g. particle size distribution) and other parameters.

Some functionality related tests as performed by DMV International

The current practice is to perform the following tests:

- Particle size distribution (sieve analysis, laser diffraction)
- Specific area
- Rugosity
- Hausner ratio
- Angle of repose
- Scanning Electron Micrography
- Differential Scanning Calorimetry as developed at DMV International.

Currently only the sieve analysis is done in the Quality Control routine.

Conclusions

- DMV International is in favor of standardising the generic functionality related tests
- Standardisation of tests is desirable to provide a basis for unambiguous communication between suppliers and customers.
- It should be recognised that many functionality related tests are not used in QC routine.
- Methods to be standardised should be a minimum number to obtain the maximum amount of information while avoiding excessive cost.
- Specific tests for specific applications should not be included in a pharmacopoeia monograph but should be established between the supplier and the customer.
- The “voice of the customer” should play a role in determining the set of tests to be included in the pharmacopoeia.
- Our prime candidates are simple tests like particle size distribution, specific area, Hausner ratio and angle of repose.

Session I: Classical quality specifications for excipients

Session II: Functionality related testing

DISCUSSIONS

Prof. S. J. Vessman: We would seem to have a bright future for functionality related tests and there are a lot of methods produced by the EDQM (reference to the conference 'reference' document), especially concerning powder characterisation. For polymeric excipients what is the future?

Prof. H. G. Kristensen: There is no doubt that the existing monographs on polymeric excipients need to be updated and adapted to modern technology and analytical methods. This is a reason why we established a new Working Party and asked this new body to review the need for general methods. In the long term therefore this is positive however, it still needs a lot of discussion and clarification around this subject by the new Working Party.

Prof. S. J. Vessman: Dr A. Janssen is in favour of introducing a number of simple tests, particle size measurement with laser diffraction. Is this simple?

Dr A. Janssen: This was a summary of what we do within DMV. However, for inclusion in the monograph I suggest simple tests which can be used in any place.

Prof. S. J. Vessman: Dr A. Janssen also mentioned having the differential scanning calorimetric method for observation purposes – how does that method you use comply with the one that is presented in Pharmeuropa. Do you think that European Pharmacopoeia's approach is acceptable?

Dr A. Janssen: I am not an expert therefore I cannot give you the details. However, our technique is very easy to use, I am not sure if this fully complies to the European Pharmacopoeia.

Prof. S. J. Vessman: Question to Dr U. Völker: your case studies, indicate that many manufacturers are faced with batches which are compatible and suddenly there is an outlier – this is very difficult to foresee when you make a formulation. You do not have many batches and therefore you do not have the variety from the excipient manufacturer, therefore, this is a good example. A test for carbon dioxide in an excipient can be considered to be a functionality related test.

Prof. H. J. De Jong: One of the problems during product development is to have access to materials with sufficient variability from suppliers, because they make a standard material which is very well controlled. Therefore, how do you study the parameters that you may be able to push one way or another to see what impact this has. First you need to identify what the relationships are. I do believe that we need a strong collaboration between the suppliers of these materials and the users in developing knowledge on these materials for the intended use by the pharmaceutical company. There should also be a collaboration when creating special batches which are 'out of specification', meaning the standard specifications to check what the influences are. At present we are guessing these and sometimes we test for years and never discover anything – we need to act on this.

Prof. S. J. Vessman: When I was in Japan we had problems with certain excipient and I was very eager to get samples with different properties than the regular ones, however the Japanese firm told me that 'they do not produce things like that, we always have one policy'.

There was no possibility of getting qualities outside a specification but this is important as then we know where we are.

Dr U. Völker: We have a lot of excipient suppliers and they have a huge experience and know-how internally comprising technical development teams and know-how. However, it is important to share this information – some do this as it is the entrance to bring their products into the market and therefore into the drug products and this is beneficial. We need to increase this exchange of information and it clarifies who has experience and who does have as much. If we are talking about costs, this could also be a reason why we attain higher costs for a specific excipient where we know that there has been a lot of work done on the excipients supplier's side – if it is reasonable and saves time, pharmaceutical industries will be interested and if the excipient suppliers can help with their experience this is beneficial.

Prof. H. G. Kristensen: I am sure that the question and problem raised by Prof. H. J. De Jong is correct. However, I would like to stress that it has very little to do with functionality related testing as we do in the European Pharmacopoeia. If you wish to characterize particle size, use this general method and use the figures of this. However, you could have a lot of different qualities. Simple methods: I was interested to hear that we need to use a series of simple analyses and not for example laser diffraction method.

Prof. S. J. Vessman: Such methods should be in the European Pharmacopoeia, even if they are not prescribed in monographs. They should be there as a reference. Dr U. Völker mentioned exchange of information between the pharmaceutical manufacturers and the producers of excipients but you are not against auditing?

Dr U. Völker: Not against it no but I would like to see auditing reduced. An example of this is when I was inspecting a global supplier and they have a least one inspection per week; if this is their routine, I think that this is exaggerated. What is the benefit for all of us and I have my doubts on this.

Prof. S. J. Vessman: I think that auditors may not be the most experienced in formulation problems and this should perhaps be done at another level or at least by people who are involved in this exchange of information. As I know the excipient manufacturers have a lot of knowledge and they should contribute to these problems.

Dr A. Janssen: You could also include multi-functional teams in the early phases of development where the supplier and the customer will come together to set the limitations. It would then be possible for quality audits to look at development items and settling these problems as this is not what auditors generally do.

Dr U. Völker: If we talk about the exchange period during development, this is the critical time phase where we should develop these functionality-related tests. Somehow we need to develop these together – it should not be just the pharmaceutical company which should say that 'this is the one which we need' because then excipient suppliers will have to perform on average about 10 additional tests. On the other hand, if they have the experience about their material they could share this for the benefit of all.

Dr J. P. Lopez: We all know that the harmonization of the JP, EP and USP is of utmost importance. It would seem to me that Europe has the leading role in implementing the functionality test objective. How compatible is this test with the harmonization effort?

Mr P. Castle: At the moment, functionality relating testing has not been included within the scope of international harmonization. It is a new subject for the European Pharmacopoeia,

therefore, when we have been working on these monographs, we have not included these tests. They are in some of the United States Pharmacopeia monographs. The current emphasis is to have harmonised methods for functionality related testing. For example, if you look at the monograph on lactose in USP they do have some statements about the particle size distribution and I am sure that we will be moving in that direction in the European Pharmacopoeia. I am not aware that the Japanese Pharmacopoeia intends to do so but it may be that within the Pharmacopoeial Discussion Group we do come to a consensus in the future to actually bring this within the scope of harmonisation.

Dr S. Kopp-Kubel: I would like to refer to two points made by Dr U. Völker. Firstly, the WHO have published a GMP test for excipients and this was established and developed in very close collaboration with IPEC Secondly, certification process and scheme: we are currently working on a model scheme which could be used for all starting materials in the future. This should apply for APIs and also for excipients and will be based on the GMP and/or audits which have been performed. It is not easy and this is still under discussion but there is a concept that whenever there is a national inspection that national GMP certificate or model could be used as a certification. When there is no national system in place, you could refer either to international audit system that is used giving the address of the respective authority and/or give the reference to another national authority inspecting in that country.

Prof. S. J. Vessman: Question to Dr S. Goode: what is your opinion on functionality-related testing. I saw in your presentation that there was some resistance – do you not agree that it would be of value for a producer to have a general method in the Pharmacopoeias and have this as a discussion document between manufacturers and your own production?

Dr S. Goode: From a manufacturing stand point, when we talk about functionality we look at the various formulations. I think that functionality plays a part in the formulation and I think that we have to have tests to test for and specify functionality where we can, but coming to the audit situation, one of the reasons why we started developing harmonisation of the requirements for auditing was because on one account you would have a company that would audit you and say ‘this is a fantastic system’ however, two days later when we come in and say that this is no good, it does not work because they are looking at it for their particular formulation. This is the dilemma which we work with. We agree that functionality related tests are necessary, and beneficial however, we have to have a scope wide enough to play in so that all the companies using the products can make formulations.

Prof. H. J. De Jong said that it would be nice to have some materials not in specification before we fix the formulations. The driving force, and particularly from the pharmaceutical industry is that we want you to have good control on your processes. Therefore, if you have very good control on your processes then you do not make that product which is so variable. Again, formulations in the pharmaceutical industry have to be robust enough to be able to take that normal variation and in the products which we produce, but when we start trying to specify specific formulation dependent functionalities, this becomes very difficult.

Prof. S. J. Vessman: Even if this is non-mandatory?

Dr S. Goode: If this is non-mandatory, then I think that we should talk to the customers to have the inter-relationship of what you are doing and what the customer needs (this was mentioned by Dr A. Janssen). We do this on the customer specifications now.

Prof. S. J. Vessman: Does this mean that you would prefer to have the individual companies come to you and visit?

Dr S. Goode: This is not a preference and we should not be over-audited. When we fix the functionality based test, we need to think very seriously on the simple tests (and this does not mean a test which is not sophisticated, it should be one which everyone has access to) when we have those tests, those tests will have to be specific enough and broad enough in scope to cover a number of the typical formulations. When you have a specification in a monograph that you can have 60% to 90% purity, if I decide to make 65% and another supplier makes 85% how are we going to control this? We have to talk to the customer.

Dr J. P. Lopez: Remark to Dr S. Goode: I see a real difficulty for excipients which have multiple functionalities. If you take some cellulose derivatives, which some of us know very well, some of them are binders and have many other functions. The same product used in different contexts and different formulations can have a totally different function. Therefore, for one product you should evaluate differently from the other. Some have very complex set of analyses on the producer label, which certainly adds a lot of additional costs to the final product.

Dr U. Völker: I think that we should not challenge the principle direction with extreme cases. You are right in saying that if we have multi-functional excipients then we will be in a far more difficult situation however, we should move towards the same common agreed methods then this would help both the pharmaceutical industries and excipient suppliers – this is where we should start the discussions and then the more complex excipients.

Prof. H. G. Kristensen: I get the impression from many discussions which I have been involved in on the functionality related testing that in particular manufacturers of excipients are afraid that we are discussing specifications. The proposal made by the Pharmacopoeia is that we introduce and make reference in the monographs to standardised commonly accepted methods which will be a help when you mention data on the label of your product. You can make any limits, this has no relation to the Pharmacopoeia. What the Pharmacopoeia does is to say, for example, lactose is a filler, therefore you should consider particle size, the bulk density, content and adsorbed water etc. The Pharmacopoeia allows that if you wish to make a particle size characterisation, we have the possibility to use laser diffraction, sieve analysis or microscopy and these methods are described in the European Pharmacopoeia and are standardised. It is accepted by the regulators that these are relevant methods once you have validated these. The Pharmacopoeia does not put in specified cases or limits for these properties. We need to have better discussions between excipient manufacturers and drug manufacturers.

In my opinion it would be very difficult to include functionality related tests as such in international harmonisation. It would also be very difficult to include in the certificates of the EDQM Certification Scheme. This is because they are reference methods (we do not give specifications) and therefore we cannot harmonise any specifications between the three Pharmacopoeias – we cannot give a certificate for compliance with a specification which does not exist. We can give good recommendations on methods on commonly accepted analytical techniques.

Prof. S. J. Vessman: It is very clear that excipients are becoming more high-tech and I urge the manufacturers of excipients that we need to treat them as such also from a characterisation point of view. There are many methods available and if we could have them in the European Pharmacopoeia then I think that we could meet those two statements. Viscosity was mentioned as being tested laboriously in the production of the cellulose ethers. Viscosity is just an average value. You could mix high and low viscosity and have an average value,

however this would not function. Twenty years ago I was a member of a group who investigated problems, and one was mixing – this is no longer allowed.

If you are in the R&D environment, it is very different to when you are in the quality control laboratory. In the R&D you have to go into details to understand why certain excipients do not function – separation methods and structure elucidations might be their case but in the quality control laboratory the importance is that the product conforms with the specifications and that the products are the same. For this we need different types of methods. The Pharmacopoeia offers a lot of these.

Mr P. Castle: Question to Dr M. Mir: glycerol monostearate – you may have noticed that this is one of the new monographs which will be added to the harmonisation programme with JP and USP. In the European Pharmacopoeia monograph which Dr M. Mir outlined, you pointed out that we have added a test for fatty acid composition of glycerol monostearate. Is this a classical quality requirement to give a necessary control of the chemical composition or is it a functionality related test for this product?

Dr M. Mir: The test for the composition of fatty acids is one of the methods for the control of composition that may be also useful to control their functionality. Dr U. Völker has shown us an example in his presentation, stearic acid used as a lubricant for tablets, where the composition has a clear impact on the performance of the product.

Mr P. Castle: It seems to me that we have tests which cannot be divided simply into chemical tests and functionality related tests. We have said that we are going to put functionality related tests in a separate section at the end of the monograph. For some tests we will still have to decide – in this case there are limits and we have said that we will not have limits for functionality related tests. This means that we are going to keep it in the classical part of the monograph even though we realise that it does have functionality related aspects. To Dr S. Goode: When we are working on harmonisation on these monographs we are very much aware that as Prof. H. J. De Jong said, compared to the overall market for these products we are peanuts. Are the qualities that we are demanding, usually special grades and does this mean extra testing for you. How do you manage these in your overall quality system?

Dr S. Goode: Normally we do have what we call ‘premium grades’ (USP or EP grades) and we do have industrial materials. A chemical company such as ours (Dow Chemicals) makes products which go into many, many markets with specialised products (very few products) and these products meet the parameters that pharmaceutical companies need. If we stick to methodology; harmonisation of methods to test these parameters will be a good thing.

Prof. H. J. De Jong: GC test for fatty acid composition is this functionality related or is this classical? I think that there are many cases in many monographs where we have tests where we have a new approach and ask the question should it remain where it is. For certain cases yes but for others no as this is sometimes part of a general characterisation of a material which is needed for the overall quality for all applications and in certain cases it is too specific. In the past our thinking on this was different and we need to reconsider.

Second comment to Dr J. P. Lopez question: We all agree that to have general methods that are identical world-wide described in such a way that they can be reproduced in laboratories the world over, the answer is yes. The interest of everybody is the same and this avoids conflicts on details of techniques which are different. We also agree that the setting of specifications is a question between supplier and the user and it is a business contract. There is a baseline of quality requirements which should be specified in a public book like the European Pharmacopoeia – so that this source can say that this material fit for use in humans

Excipients : Classical quality requirements and functionality related testing

by a route of administration, oral or injectable etc depending on the category. We also agree that functionality is a product related item and for many applications it is one-product related – it does happen that one company, who makes through a specific process a special grade of material, and this is business, deal with 1, 2 or 3 suppliers. Is it necessary, is it useful, is it justified? What do we need to treat the condition, what should the product do, and what are the different ingredients which are important to this product? We should have optimised minimum baselines, then extras are sometimes possible but these have a cost.

Dr J. P. Lopez: Your conclusion is correct – if the industry is prepared to pay for the additional requirements, we shall see if it is feasible and then inquire on the price.

SESSION III:

QUALITY ASSURANCE AND TESTING OF EXCIPIENTS

Quality systems

Dr C. Mroz, Colorcon Ltd (UK)

Supplier audits

Dr T. Riedo, Novartis Pharma AG (CH)

Dr P. Rafidison, IPEC Europe

Viewpoint of the inspectorate – GMP and GDP inspections in France

Dr O. Gross, AFFSAPS (F)

Discussion session III

Session III: Quality assurance and testing of excipients

QUALITY SYSTEMS

Dr C. Mroz, Colorcon Limited (UK)

Introduction

The intention of this presentation is to give a broad overview of a Quality System, why the manufacturer of a pharmaceutical excipient would want to deploy one, what it should contain and the benefits it could provide.

In today's business climate, which includes price control and competitiveness, the prudent use of a Quality System is good business practice. The Quality System can be used as a tool to control the product being manufactured and to manage the interface between seller and buyer to facilitate customer satisfaction. This presentation concentrates mainly on Quality Systems and how they relate to the product.

This presentation deals with the motives for use of a Quality System, what activities it should include and suggest a framework around which it could be based.

Purchaser requirements

When a pharmaceutical company purchases a quantity of material, which it intends to incorporate into a medicinal product, that company then takes the liability for that material. If the material is itself inherently defective or it causes a defect in the final medicinal product that is not picked up during in-process testing or final release then the purchaser takes legal responsibility. In the worst case this could cause injury or even be fatal to the end user, the patient. Hence the purchaser needs to have confidence in the material purchased in relation to quality (safety) and performance.

Quality

Quality can be defined in terms of a chemical specification and can be verified by Quality Control testing on receipt. The purchaser can perform testing of every batch of material against every parameter listed on the specification. However this is expensive and requires a large amount of resource, thus it is desirable that the material can be released for use based on reduced testing, parametric release or even on the basis of identity testing only. This can only be done if the manufacturer (and supplier in the case of a distributor) employs a Quality System which the purchaser feels confident will protect the quality of the product.

Performance

Performance of an excipient can be defined in terms of a chemical or physical specification, but in many cases unspecified characteristics such as particle size distribution, polymorphism or trace components can affect the way an excipient performs. What the purchaser is looking for is consistency from batch to batch of the material in question. Proper use of a Quality System can assist consistency.

Pricing, efficiency of suppliers

A Quality System can also control processes to reduce the risk of product failing specification and being rejected, directly helping to increase efficiency and control costs. There are other commercial benefits associated with the use of Quality Systems, however these are not addressed here.

There are many good reasons why the manufacture and supply of pharmaceutical excipients be performed under conditions controlled by a Quality System. The Ph. Eur. specifies in its general monograph on Substances for Pharmaceutical Use that they are manufactured by procedures that are designed to ensure a consistent quality.

What is a quality system

A Quality System is fundamentally a philosophy adopted by a company that defines the way it does its business. Written Quality Systems can easily be purchased from a variety of sources, but these have no real value unless their principles are integrated into the company culture. The Quality System can be broken out into four main areas:

- 1) a high level quality policy, formulated by senior management
- 2) a series of procedures available to all relevant personnel which if followed achieve the objectives defined in the quality policy
- 3) a system of training to ensure employees are able to use the procedures
- 4) records to give evidence demonstrating compliance with the Quality System

Which activities a company wishes to include in the scope of the Quality System are the choice of the company itself. For the manufacturer of an excipient this should include as a minimum:

- 1) Procurement of quality impact materials and services, subcontractors
- 2) Quality Control, raw materials, in process and finished goods
- 3) Production/packaging, process validation, cleaning, process control, implementation of corrective actions
- 4) Maintenance (planned and unplanned)/ calibration of equipment
- 5) Change control
- 6) Traceability

These are all Good Manufacturing Practice items, however the company may want to include other activities such as design, technical support and other parameters which contribute to customer satisfaction. The scope of the Quality System should clearly specify what is included.

Quality systems model

One of the most widely recognised models for a Quality System is ISO 9001:2000. Recent revision of the standard has increased emphasis on continuous improvement, monitoring customer satisfaction and the measurement of quality parameters. This standard has advantages in that it is subject to external assessment and for many companies this is the only

time that they are subject to outside audit. One often quoted disadvantage is that the standard is not industry specific. However if the company chooses its assessment body carefully then the value can be fully exploited.

Using a framework such as ISO 9001 is just that, a framework. The detail enclosed within that framework still needs to be defined. In relation to the GMP related activities, there are no legal or regulatory requirements which need to be met. Therefore the use of voluntary guidelines such as the International Pharmaceutical Excipients Council Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients can assist in formulating the quality procedures.

Other useful tools

Many materials used as pharmaceutical excipients find their main use as foods or food additives. Hence it is not unreasonable for the manufacturers to align their Quality Systems in line with their key market. For example the association, the American Institute of Baking (AIB) has published its own guidelines which focus on safe production of foods and food ingredients. The AIB will inspect companies against these guidelines. Anecdotal reports of these inspections indicate that should a company meet the requirements, then they will satisfy most requirements for pharmaceutical applications as well.

One other technique widely used in the food industry to complement GMP in a Quality System is Hazard Analysis Critical Control Points (HACCP). This is basically a risk assessment tool which identifies key points in a process and requires suitable strategies be adopted at those points to reduce risk.

WHO have recently published a position statement on the use of HACCP in association with drugs and other pharmaceutical products. Additionally, in the United States, the FDA requires the use of HACCP in some food safety areas.

Summary

In summary there are several benefits which can be gained by a company by the use of a well constructed Quality System, and the system can also go a long way to demonstrate suitability of a product to a prospective purchaser. However use of a Quality System in itself does not guarantee that a company manufactures products under suitable conditions of control, there must be a link between the Quality System and appropriate Good Manufacturing Practices.

Session III: Quality assurance and testing of excipients

SUPPLIER AUDITS

Dr T. Riedo, Novartis Pharma AG (CH)

Regulations

Most pharmaceutical companies have a comprehensive supplier audit programme in place, but interestingly enough there is no Good Manufacturing Practices (GMP) requirement asking them to do have one. Neither the European Guide 91/356/EWG for the manufacture of drug products for human use nor 21 CFR 210/211 (“GMP for Finished Pharmaceuticals”) nor the ICH Q7A Guide (“Good Manufacturing Practice for Active Pharmaceutical Ingredients”) ask for supplier audits. It’s required, however, that starting materials must originate from approved suppliers. An approval of suppliers requires a supplier qualification system.

In the case of Active Pharmaceutical Ingredients and of drug products national and international guidelines define standards for manufacture, analysis, storage, distribution and documentation. For excipients such authority guidelines are not available though in solid drug products such as tablets or capsules they can easily make up to more than 90% of the total mass. There is no authority guidance because excipients are considered to be inactive principles in a drug product formulation. Excipients should have no pharmacological effects.

Excipients manufacturers have established their own guideline, the IPEC GMP Guide for BPE (Bulk Pharmaceutical Excipients). This guide documents what industry considers to be reasonable GMP standards. However, this is also the shortfall of the document: It was published by industry, not by or together with an authority. As the guide is not an official authority document, it is not enforceable.

The need to qualify excipients manufacturers and the lack of GMP guidance for their manufacture creates an unsatisfactory situation: The supplied pharmaceutical company has to define acceptance criteria without having a binding regulatory basis for a decision making. Qualification and audits of excipient suppliers are therefore often done in an arbitrary manner. Different pharmaceutical companies will choose different approaches which can make the live for an excipient supplier quite cumbersome.

Novartis approach

Basis of our Supplier Qualification Programme is the Supplier Questionnaire. New suppliers need to send samples for analytical purposes and sometimes additional use tests are performed. We have three levels of acceptance: Approved, qualified and certified. Material can only be used in production if originating from a supplier classified according to our Qualification Programme. In the case of excipients, supplier audits are required for key excipients. In our understanding, key excipients are those excipients that play an important role in some of our drug product formulations.

Each delivery of an approved supplier is fully analysed. If an approved supplier keeps a predefined level of quality or even surpasses it, he may become qualified. In this case, we reduce the analysis and omit a number of tests. Reduction to identity testing is only possible if a qualified supplier becomes certified. In all cases where reduced testing is planned an audit is required.

Supplier audits

When we perform an audit, we want to verify whether the supplier has all the necessary systems in place to guarantee that he constantly provides material meeting specifications in a reproducible way.

During an audit, we use a top-down approach. We look at the quality management structure and - of course – a system like ISO 9000 facilitates an audit in an ideal way. We will review the systems: quality, facility & equipment, material handling, production, packaging & labelling and laboratory control. We very much follow the approach the Food and Drug Administration (FDA) has recently taken. We are less and less focussed on the product but rather review the systems in place. Do these allow sufficient control to keep variability low? Are there any grey zones, particularly at the interface of different departments? Are key elements of GMP such as change control, deviation handling or contamination/cross-contamination addressed in an appropriate way and throughout the company?

In case of complaints or problems we do on-the-spot discussions and/or verify whether the corrective actions are implemented.

Actual and future issues

One of the most critical actual issues is the Transmissible Spongiform Encephalopathy (TSE) situation and it will remain a top level problem for quite some time. The TSE certification is reviewed critically, in particular if an excipient is not of synthetic or vegetable origin. In addition, emphasis will be put on the route of synthesis. An important point is to verify that also the auxiliary material used during a manufacturing process is not of animal origin. I remind you in this context that activated charcoal is quite often made out of animal bones and mainly bovine bones are used.

The unsatisfactory situation of having no enforceable GMP guide for the excipients manufacture has to be addressed. We need a harmonized GMP Guide comparable to the ICH Q7A Guide for APIs. Such a guide will add to the benefit of both excipients suppliers and supplied pharmaceutical companies. In his foreword, the IPEC GMP Guide highlights the similarity of the manufacturing processes for APIs and BPEs. Quite rightly so and in our opinion similar processes ask for similar standards. The ICH Q7A is a reasonable standard as it is accepted by health authorities. In addition, it is an excellent document as it gives guidance in a pragmatic and reasonable approach.

Clearly, excipients manufacturers are important partners of the pharmaceutical companies. Only close co-operation allows us to offer reliable medication in the best possible way and for the benefit of patients who are in need of it.

Session III: Quality assurance and testing of excipients

SUPPLIER AUDITS

Dr P. Rafidison, IPEC Europe

Introduction

An excipient is defined as ‘any substance in a pharmaceutical product other than the active drug’. Mostly, excipients are used as the vehicle that carries the few milligrams of drug to the body, but they can also aid processing, enhance stability (as preservatives, and antioxidants etc), or add colour and flavour. They usually remain in the final formulation and may be identified in the final dosage form. Although they represent about 99% of the formulation, excipients are the “Cinderella” of the drug dosage form, and have never really captured the attention of the pharmaceutical industry. Exceptions to this are the novel excipients; these represent real breakthroughs in the technology, bringing new patents, or simply being a key excipient replacement such as CFC.

Active ingredients and excipients: what is the difference?

Excipients are different from active ingredients. They have multiple usages in the industrial world where customer’s needs and self-regulation is the base for the quality systems. Excipients are often sourced from food, food additives, or cosmetics industry where the market is large volume/low value. In the contrary, active ingredients are more likely to be low volume/high value product, mainly dedicated to the pharmaceutical industry, which make GMP enforcement easier to resource and implement.

Auditing the suppliers of excipients

Pharmaceutical industry carries the primary responsibility for the quality and safety of raw materials that enter a medicinal product. This obligation has consequently led our customers to adopt a comprehensive audit programme at our facilities.

The supplier’s challenge is to be able to address the concerns around the “appropriate” quality system valued by the customer, and address potential non-conformities in an affordable manner. It has to be recognised that other industries standards (food, cosmetics.) may be acceptable for the pharmaceutical industry and are part of the supplier’s credentials. However, beyond the manufacturing of the product, the total supply chain is to be evaluated to address traceability, which raises the global trade environment with different players, brokers, different ordering mechanism such as internet.

IPEC GMP guidelines

- In 1995, IPEC sets itself the challenge to create a single voluntary harmonised GMP standard, revised in 2001 to reflect the ISO 9000 series update. This would bring the following key advantages:
- Increased transparency on excipients sourcing
- Product traceability
- Improved guarantee on excipient purity, safety and consistency
- And mastering the supply chain.

The format used for this guide is based on ISO 9000 series quality systems. These are the most used Quality standards in the suppliers industry, and can address the excipients source diversity. The key expectation was to improve the dialogue between the producer and end-user and install reasonable GMP standards based on common ground.

Finding a common language

The real difficulty faced during the auditing process was certainly to realize that industrial practices don't always match with the pharmaceutical world. From non cost effective practices to more paper and more documentation, we had to achieve consensus to satisfy both worlds. For example the terms "cross-contamination, validations, complete label reconciliation, and stability programs" etc caused much debate and different interpretation. When you make sugar, starch, or other large volume products in the food, cosmetics industry for example, you need to figure out how to satisfy these types of requirements, without compromising the flow of your activities. You also need to conclude 'non-feasibility' before incurring any major costs. All of these issues, and more, needed to be addressed and resolved using an appropriate supplier/customer partnership.

Key auditing considerations

Whenever an audit is planned, ingredient nature and complexity should be understood. Process used, closed or open, type of processing, and degree of exposure to the environment is key to assess the extent of GMP to be required. Documentation evaluation, batch history, complaints files, audits, recalls, and product master file will give a general indication of the level of compliance to the organisation's procedures. The existence of a formal quality system in place is an indication of a quality discipline, ISO 9001 certification will ensure that management is effectively involved in quality, documentation system is in place, process controls reviewed and documented, and training plans and internal audits are a routine. A third party audits this quality system twice a year, and records of such audits are retrievable.

Area of potential concerns

The excipients' supplier may be organised differently than pharmaceutical companies, the Quality unit being not necessarily independent from the manufacturing leader. The general design of building and layout may not be optimal to prevent mix up and cross contamination, which may be of a concern for a multipurpose facility. Some process and storage may occur outdoors in an entirely closed system. The nature and extend of documentation may not fit the pharmaceutical definition, however, during the audit, these records may be easily retrievable. Expectation on validation programme may differ between auditors; in the excipients world, process capability data or statistical analysis are the current practices in place. General housekeeping and cleaning program are places where some improvements need to be made, keeping in mind the potential exposure of the product. Management of changes may not be understood the same way: change is one the improvement tools use in the industry, and may occur often. Notification of customers may be seen as a burden if regulations are not understood.

General industry good practices such as recycling may not be suitable to the excipients without the appropriate controls.

A lot of these potential concerns can be addressed through behaviour changes and training, however some of these gaps may need substantial investment, which will need a proper benefit/reward balance analysis.

Conclusion

In conclusion, reasonable good practices can be implemented using common sense, and accepting other industry's practices as a start. Audit of suppliers has a cost and the use of a third party certification would be an encouraging signal to go towards better manufacturing practices. Such experience has started in the United States of America using the IPEC GMP guidelines as a reference; voluntary inspection of raw materials suppliers is carried out in France and United Kingdom at least, more needs to happen in Europe to encourage suppliers to operate to the principles of GMPs.

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Session III: Quality assurance and testing of excipients

VIEWPOINT OF THE INSPECTORATE

GMP and GDP Inspections in France

Dr O. Gross, AFFSAPS (F)

Introduction: Quality and safety of medicinal products

In most of the European countries, the legislation on medicinal products requires that manufacturers and distributors observe a quality assurance system including Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP). It requires also competent authorities to carry out repeated inspections to monitor compliance with GMP, GDP and relevant legislation.

To be in line with the general principle of quality assurance, which is that quality should be built into the product, Good Manufacturing Practice should be applied by:

- The manufacturer of medicinal products and
- The manufacturer of the pharmaceutical starting materials.

And, to make sure of the quality and safety of medicinal products Competent Authorities should carry out repeated inspections of:

- The manufacturers and wholesalers of medicinal products and
- The manufacturers and distributors of the pharmaceutical starting materials.

Legislation: Pharmaceutical starting materials and pharmaceutical excipients

The pharmaceutical legislation defines pharmaceutical starting materials as all of the components of medicinal products:

- The active ingredients
- The excipients, also called “non active”

The legislation requires that both ingredients, which are intentionally included in medicinal products, should have been appropriately evaluated for safety and functionality. But, up to now there is no requirement concerning quality assurance, conformity of production, consistency of specifications for the pharmaceutical starting materials.

In most of the European countries, the current pharmaceutical legislation for pharmaceutical starting materials:

- Does not require an authorisation to manufacture pharmaceutical starting materials.
- Does not provide a legal base for inspection of manufacturer, or distributors.
- Does not enforce an official binding GMP or GDP regulation for starting materials.

In this matter the pharmaceutical legislation is unfortunately very poor and it is obvious that today, neither the manufacturing nor the distribution chain of excipients are considered by the pharmaceutical legislation as important topics for the quality and safety of medicinal products.

Because of the weakness of the community legislation some countries like France decided to create their own legislation on pharmaceutical starting materials.

Inspection of pharmaceutical excipient manufacturers

In 1998, France amended its national legislation to introduce by law requirements for pharmaceutical starting materials, active ingredients and excipients. Today a new competent authority, the French Agency for the safety of health products (AFSSAPS) monitors compliance with the new law, inspects and certifies manufacturers or distributors of pharmaceutical starting materials.

The law requires Good Practice for the manufacture and the distribution of starting materials. It includes an official declaration of such activities by companies operating in France. GMP or GDP certificate can be obtained by voluntary companies.

This legislative base is enough to carry out several inspection programmes of starting material manufacturers and distributors. One of this programme is focused on excipients manufacturers.

The inspection reports of the inspections conducted within this programme show that most of the deficiencies found are related to the following chapters of the Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients (IPEC 2001):

Personnel : Competency Awareness and Training (6.2.2.)

Purchasing : Verification of Product (7.4.3.)

Production : Contamination Prevention (7.5.1.4)

Testing and Batch Release (7.5.1.14)

Validation of Processes for Production (7.5.2.)

An other programme is focused on distributors and traders. The activities carried out by the inspected distributors are, distribution of API and excipients, importation of API and excipients and manufacturing activities as re-packing, re-labelling

The guidelines used during the inspection are Good Distribution Practice for Starting Materials (national guide) and Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH guide)

Most of the deficiencies found during this inspection programme are related to :

- Facilities, especially re-packaging and re-labelling areas.
- Re-packaging and re-labelling operations, which are in fact manufacturing activities.
- Receiving and storage operations.

Excipients : Classical quality requirements and functionality related testing

- Shipping operations, transfer of information and traceability.
- Laboratory controls, certificates of analysis.

These results should only be considered as spot test results. The number of inspected sites and the geographical area covered are too small to allow us to conclude.

Nevertheless, it seems that, to ensure the safety and the quality of medicinal products, it will be important, in the future, for the Competent Health Authorities, to be able to carry out regular inspections to monitor compliance with:

- Good Manufacturing Practice for excipients manufacturers.
- Good Distribution Practice for distributors.

Session III: Quality assurance and testing of excipients

DISCUSSION

Dr P. Rafidison: We need as excipient suppliers to be clear on what an impurity is as we take it for granted that everybody understands what we look for. Excipients are mixture of things, for example polymers, therefore the definitions that apply to pure chemicals do not always apply to some excipient ingredients. This is the reason why we at IPEC developed guidance explaining what these are or may be to help suppliers. The real issue which we face is that our customers would like to rationalize the questions. Specifications are set for active ingredients and we are then asked to provide similar information for excipients. These are templates and people who fill in these papers do not necessarily understand pharmaceutical regulation or consequences behind it. They only want to please their customers and therefore tick a box. Authorities should contribute in making clear what is sufficient and taking out the non relevant as our customers are often saying 'this may not be relevant but we have to have a regulatory statement saying that it is not relevant'!

Prof. H. J. De Jong: Question to C. Mroz: I know that in the United Kingdom there have been some volunteer operations between the MCA and several companies could you comment on these ventures?

Dr C. Mroz: The Medicines Control Agency Inspectorate in the United Kingdom understand that as things move forward, the regulation on starting materials will become compulsory at some point. The MCA would like to expose itself to the excipient part of the starting materials and has set up a volunteer scheme where companies can volunteer to be inspected by the Medicines Control Agency (MCA). It has no legal basis because there are no official GMP set of guidelines against which they can inspect; the company which pays my salary did undergo such a voluntary GMP inspection. This took two days and there was a fee and the check-list used was a combination of ICH and Q6,7A, the IPEC guide and the WHO guide. From my company's point of view, this was a very useful exercise to do and I think that the MCA benefited from seeing the industry's point of view. If I am correct, only half a dozen companies have as yet volunteered to go through this. Those that have, have seen this as a benefit.

Dr A. Artiges: As regards this lack of legal basis, on one hand you Dr Rafidison said that you visited the European Commission in order to ask them why they were so hesitant in preparing their revision of their directive. The answer is because this field is so complex. Many excipients used in the pharmaceutical field represent a small proportion in comparison to other activities such as food, cosmetics etc. On the other hand, we have seen that from discussions and experience there is a lack of directives. It is because you have pressure coming from the pharmaceutical industry and the consumers that you will receive the pharmaceutical regulation which is not completely adapted to your needs. In the end, it is the manufacturer of excipients who is interested, therefore do you intend to rediscuss within IPEC or other manufacturer's associations and other excipient field, food for example, in order to try and make other proposals? If not, you will have more and more deficiencies.

Prof. H. J. De Jong: There are mixed feelings. Not only on the European Commission level but also inside the pharmaceutical industry as well as the excipient manufactures. Some people think that we should not have any further regulations as the whole field of medicinal products. It is already over-regulated and others that say that if you see the behaviour of the

individual pharmaceutical industry that is, at the end, responsible for the quality of its products under the actual laws in place, then it is up to the suppliers much more today to be inspected against a generalised standard. If France has a top interest for x and Germany for y then you can get a unbalanced, non-economic and non-efficient operation. This was the driving force behind ICH that set the rules which are acceptable and that are productive for everybody and therefore everybody plays by the same rules. The ball game is constantly changing and it was said by several speakers that sometimes they get a fantastic report after a visit and sometimes it is disastrous and the product cannot be used. The route to take is somewhere in between these. What we would like to promote is one day obtaining an international standard, and I think that ideally a Q7B for excipients would be the answer, however, it would have to be particularly well-worded. We cannot take the document Q7A and change the words API by excipients. In this document we should include good rules which already exist in the food and other industries and different expertise than what generated the Q7A.

In the answer from the European Commission, it was mentioned that 'exceptional' cases could be taken out to make a specific regulation and there, it was referring to contamination with prions or dioxins (high risk excipients). This is not a good route to go down and I would be more in favour of one framework and add on specific cases than to start with the specific cases.

Dr A. Artiges: Certification of suitability of a European Pharmacopoeia monograph; This means that this system is only possible if there is a monograph in the Pharmacopoeia. For products with TSE risk to answer the requests of the European Commission and EMEA we have extended the scheme to the general monograph on products with TSE risk. For the time being, this is only applied for this general monograph but the concept could be adapted depending on public health needs. As regards a system like GMP, the quality system is of major importance and it has been included in the requirement of the procedure itself. This means that the company who is applying for a certificate should commit itself to explaining what kind of quality system is in place, as there is no legal general basis, and this could be any one which is in place in the country concerned, and should be open to inspection from the competent authority. For the time being, we do not want to have our own system – we would like to participate in a common system of inspection in Europe. We have started on a voluntary basis as we think that there is an urgent need for this; This is a good base as we have already learnt a lot from the companies and from the national inspectorates. We have good results and this voluntary scheme has been extended to not only voluntary companies but we have identified, based on the request of national authorities or assessors, to voluntary national inspectorates and this also in the field of excipients; At present we have relatively few certificates for excipients referring to specific monographs (10%) however, as regards TSE risk it is the opposite (90%).

SESSION IV:

**INTERNATIONAL HARMONISATION OF EXCIPIENT
MONOGRAPHS**

The purpose and content of Pharmacopoeial monographs for excipients

Dr U. Kettenring, IPEC Europe

USP perspective on excipient harmonisation

Dr S. Harris, the United States Pharmacopeia (USA)

JP perspective on excipient harmonisation

Dr M. Uchiyama, Japanese Pharmacopoeia (J)

European Pharmacopoeia perspective on excipient harmonisation

Mr P. Castle, Secretary of the European Pharmacopoeia Commission

Discussion Session IV

Session IV: International harmonisation of excipient monographs

**THE PURPOSE AND CONTENT OF PHARMACOPOEIAL
MONOGRAPHS FOR EXCIPIENTS**

Dr U. Kettenring, IPEC Europe

I would like to present to you the Tri-PEC position paper: The title is “The Purpose and Content of Pharmacopoeial Monographs for Excipients”

Background of the Position Paper

In 1989 the Pharmacopoeial Discussion Group (PDG) was created. The PDG, in turn is comprised of three member groups:

- The Japanese Pharmacopoeia (JP)
- The United States Pharmacopeia (USP)
- The European Pharmacopoeia (Ph. Eur.)

Each pharmacopoeia is represented by several members.

The PDG was created at the initiative of the leaders of the three main Pharmacopoeias on the basis of the detected non scientifically justified disharmony between these books.

In 1990 the ICH (International Commission on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use) started with industry and regulators represented from the three regions. The PDG activities are more or less incorporated in the effort with the Quality topic Q4: Pharmacopoeial Harmonisation.

At present the PDG works on the task of harmonising selected general chapters as well as selected individual monographs.

Harmonisation on an international level is rather difficult, since next to numerous technical discrepancies also cultural, political and legal differences are involved and must be overcome.

Definitions must be set: (e.g. as to the meaning of the word harmonised (here again you will be dealing with legal issues, such as what is defined as “equal” what is defined as “equivalent”) etc. The PDG must decide how they want to proceed e.g. regarding the use of hazardous reagents and regarding the use of specific methods that may not be known or available for all three member regions.

Several groups are involved in providing support to the PDG, in particular in an effort of facilitating and accelerating the harmonisation process:

- CEFIC (European Chemical Industry Council) an organisation of starting materials manufacturers only,
- EFPIA (European Federation of Pharmaceutical Industries Associations) an organisation of pharmaceutical manufacturers only and
- IPEC (International Pharmaceutical Excipients Councils).
- IPEC is made up of representatives of excipient manufacturers, distributors and users (pharmaceutical companies). This is the only organisation where users and producers actually sit down together to discuss issues and to find joint solutions.

This document is a Tri-PEC-Position Paper this means it is a consensus paper of the International Pharmaceutical Excipients Councils of America, Japan and Europe.

This position paper itself is a “harmonised” document as it has been approved by IPEC-Japan, America and Europe.

Purpose of the document

In numerous discussions within IPEC it turned out, that considerable differences in the understanding of the purpose and the content of a pharmacopoeial excipient monograph is one of the major obstacles in the international harmonisation process.

This document is therefore considered as an important element to overcome the existing problems and to facilitate the ongoing harmonisation process of the three main pharmacopoeias, namely these are JP, USP and Ph. Eur.

This document helps to define a harmonised standard for excipient monographs. Tri-IPEC’s goal is to establish a baseline how an excipient monograph for the 21st century should look like.

There are still many differences among the three main pharmacopoeias. With this paper Tri-IPEC wants to give the PDG a template for monographs. Tri-PEC members, that is excipient producers and users on a global level already agreed on this template. The paper was and is widely discussed with the PDG in order to produce a document that the Pharmacopoeias will also be able to approve. Active discussions with the PDG are extremely crucial because we know, if the Pharmacopoeias don’t agree on this document, it will be only of academical use. We want and hope that the PDG will also be able to approve our position paper, and that we can this way push ahead with renewed speed in the global harmonisation process.

Now I would like to give you a brief summary of the contents of the position paper:

General Background of Excipients

- Excipients are derived from a multitude of sources:
- Natural substances (e.g. talc, NaCl)
- Animal sources (e.g. shellac, gelatin, fat derivatives like Magnesium stearate, lactose)
- Vegetable sources (e.g. starches, cellulose’s, fat derivatives like Magnesium stearate)
- Semisynthetic origin (e.g. Cellulose derivatives like hydroxypropylmethylcellulose (HPMC))
- Synthetic origin (e.g. polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (PEG), Poloxamer, Crospovidone)

Excipients must possess consistent physico-chemical properties to ensure reproducible performance during manufacture and use of a drug product.

Purpose and Content of an Excipient Monograph

- The purpose of a pharmacopoeial excipient monograph is to provide an appropriate set of tests and specifications that allows the user to reliably characterise (i.e. selection of testing criteria) and standardise (i.e. definition of specifications) excipient quality.
- The pharmacopoeial tests should insure the quality and safety of excipient use.

The specific tests and specifications should address

- Appearance
- Identity
- Chemical purity
- Micro/biological purity
- Physical characteristics associated with the chemical structure of a substance (e.g. Optical rotation for enantiomeric purity)

The tests and specifications should consider

- Manufacturing process
- Potential impact of impurities on safety and efficacy of a pharmaceutical product
- Excipient degradation products
- Differentiation of pharmaceutical versus technical grade (e.g. TiO₂, NaCl, sodium starch glycolat, citric acid)
- Specific requirements for the type of dosage form (e.g. forms for inhalation or for parenteral use)

These above items address the “quality related” properties of the excipient itself. The next item addresses functionality-related properties.

- Differentiation of physical grades in the non-mandatory part and for information only (e.g. microcrystalline cellulose, lactose)

Quality-related properties pose a potential risk for the patient. The functionality-related properties pose a potential risk for the manufacturing process of the drug product itself as well as consistent drug product performance.

However, the extent of the risk depends on the formulation of the individual drug product and the production process used.

Therefore, we are urging that these tests and specifications will be placed in the non-mandatory part of the monograph and for information only. This issue will not be easy to implement in the pharmacopoeias because there is still not definitive word on how the JP can deal with non-mandatory parts.

As the treatment of functionality-related properties is of great interest to excipient producers and excipient users alike, we are including separate discussion material regarding for this topic as part of the appendix to the paper.

To set the limits and methods the following should be considered

- The safety evaluation of impurities should be based on risk assessments rather than analytical capabilities.
- Safety, stability and functionality considerations have to be taken into account.
- The limits should be based on typical results found in commercial materials and are known to be non-critical for the product.

Excipients : Classical quality requirements and functionality related testing

- Specifications should be included for all likely impurities
- Any tests, methodologies and limits should be appropriate in terms of their underlying science and technology.
- Wherever appropriate, newer, more precise, more specific and safer-to-use analytical technologies should replace older, outdated, non-specific methods as well as methods that use hazardous reagents.
e.g. substitutions of the very unspecific and unreliable heavy metal test by sulphide precipitation by specific element determination using atomic absorption spectrometry (AAS) or atomic emission spectrometry (AES), but exclusively where the origin / production process of an excipient involves a realistic contamination risk with the element under discussion.
- Specific tests are preferred to non-specific tests
- Tests that produce numeric results are preferred to simple pass/fail tests

Functionality related properties

- Functionality-related properties are for instance particle size distribution, specific surface area, crystal modification.
- Functionality-related properties have to be controlled to ensure the efficient and reproducible production and consistent performance of the medicines.
- Functionality-related properties should be given in the non-mandatory section of the monograph and on the label for informational purposes only.
- Preferably they should refer to one of the general methods of the pharmacopoeia
- Overall functionality-related tests like compaction or powder flow should not be included in a pharmacopoeial monograph.

Family versus Individual Monographs

The possibility of family monographs should be considered (e.g. for different grades of polymers like macrogols and poloxamer)

Outlook

We are not intending to authorise this document, however we would like to have the document published in the Pharmeuropa (Scientific Notes) and/or Pharmacopoeial Forum (Stimuli Article).

If the PDG considers defining this document as a standard for the following harmonised excipient monographs, it will be a big reward for all of us and the work and many hours of discussions we conducted over the past one and a half year. IPEC is convinced that the design of pharmacopoeial excipient monographs in line with this document will not only

- facilitate the international harmonisation process but will simultaneously lead to
- monographs representing the current knowledge in science and technology and
- are acceptable as such by regulatory authorities in the drug registration process.

Session IV: International harmonisation of excipient monographs

USP PERSPECTIVE ON EXCIPIENT HARMONISATION

Dr S. Harris, The United States Pharmacopeia (USA)

This presentation will provide an overview of some of the requirements in the development of an excipient monograph. It describes the role of *USP* with the Pharmacopeial Discussion Group (PDG) in the harmonization process together with *EP* & *JP*; a brief description of the PDG harmonization process for monograph and general chapters, and the current status of the 51 monographs undergoing harmonization and outlines the lead pharmacopeia for each of these monographs. Information and update on the proposed joint ICH-PDG harmonization process and the next steps expected.

Session IV: International harmonisation of excipient monographs

JP PERSPECTIVE ON EXCIPIENT HARMONISATION

Dr M. Uchiyama, Japanese Pharmacopoeia (J)

I will be talking about the current attitude of the Japanese Pharmacopoeia (JP) towards excipient harmonization in the revision process leading up to the fifteenth edition, in my capacity as Chairman of the JP Committee.

As you are well aware, the need to harmonize excipient standards had already gained wide acceptance by the time the PDG was formed in Tokyo, back in 1989. The fundamental activities of the JP to accomplish international harmonization are focused, at present, on efforts to harmonize excipient monograph standards and related test methods as soon as possible for as many monographs as possible.

Priority setting

As everyone interested in pharmacopoeia well knows, the PDG has a different purpose to the ICH, and consequently has different priorities. Pharmacopoeial harmonization aims to facilitate international circulation of drugs, including excipients, and to improve overall quality. The purpose of the ICH, on the other hand, is to facilitate the approval of new drugs. Such differences inevitably bring with them substantial differences in the priority of subjects for harmonization. That is to say, the PDG has placed a high priority on the monographs of major excipients that can be used commonly for a number of new drug products, in addition to important general test methods irrespective of classical quality assurance or functionality-related tests. Conversely, ICH gives higher priority to general test methods such as dissolution, content uniformity and the like, which are frequently employed in dossiers for new drug applications.

Basic premise

To clarify the intended goal of harmonization to which the PDG adheres, we have to remember the basic premise established by the PDG as a general policy for harmonization and announced publicly in each Forum in 1995. This premise states that harmonization of monographs means agreement based upon “objective comparability” and a clear statement of any differences. Analytical methods where different tests or methods yield the same results are covered under provisions by the three pharmacopoeias to allow alternate methods. The JP believes that these concepts remain valid as a basic premise, and intends to follow these concepts in our future actions towards international harmonization.

Monograph standards

Regarding our perspective on the harmonization of monograph standards, I would like to say that positive recognition of the above-mentioned “objective comparability” is required before anything else. A significant part of the non-harmonized attributes will become mutually acceptable by enforcing objective comparability, particularly in the establishment of acceptance criteria. I firmly believe that excipients that have been on the market of a certain region for many years should not be excluded by the establishment of harmonized monograph standards.

At the same time, harmonization of monographs is closely connected with harmonization of testing methods. In fact, significant numbers of non-harmonized attributes seem objectively comparable, but cannot be harmonized due to discrepancies in test procedures or conditions in general chapters. Monograph harmonization cannot be attained unless we first obtain harmonized, or at least interchangeable, test methods in general chapters. This is particularly true for basic, classical methods for quality assurance. We should lose no time in increasing harmonized or interchangeable general methods and utilizing these in concert with our overall harmonization efforts.

Moreover, it is essential for each regulatory authority to recognize as equivalent those test procedures that have been harmonized and adopted as interchangeable by the PDG. This means that discussions on pharmacopoeial harmonization will finally converge on the relationship between technical agreement among the pharmacopoeias and drug review criteria of the regulatory authorities in each member nation. We should strive towards understanding from regulatory authorities of what we aim to accomplish and the rational basis of mutual acceptance of interchangeable testing methods as an ultimate measure to cope with present difficulties – such an understanding would no doubt solve many sticking points. The incorporation of these concepts into the general chapter of each pharmacopoeia is well worth considering.

Functionality-related attributes

Let's consider the treatment of functionality-related attributes in excipient monographs. Functionality-related attributes are essential to express the distinctive physical properties and advantageousness of excipients. In addition, it might be a good idea to emphasize noteworthy physical features as an aid to discriminating excipients from each other. Needless to say, we still do not fully understand how the physical properties of excipients impact the actual functional performance of products in the final dosage forms, so we need not be overly concerned with the functionality of final products. To clarify the relationship between physical parameters of excipients and the functionality of products in detail, further investigations by academics and manufacturers are required.

Functionality-related specification is therefore an important attribute to show the merit and value of an excipient. However, when the drug master file (DMF) system is applied to excipients in the drug regulation process, those attributes concerning characteristic features of physical properties will become more suitable for incorporation in DMF data as protected company data. Consequently, it is not necessarily appropriate to specify functionality-related attributes of excipients in terms of definite numerical values in the monograph standards. Since functionality-related physical properties should be evaluated based on intended purpose by the user of the excipient, these should be stipulated as labelling in the monograph with acceptance criteria, and not as specifications. In these cases, acceptance criteria can be expressed as an allowable range with respect to labelling indications. However, when a difference in physical properties might exert a substantial influence on the safety and stability of drug products, physical properties should then be fixed as specifications, taking safety and stability equally into account. The above-mentioned concepts are quite compatible with the proposals outlined in the recent Tri-PEC position paper.

Functionality-related test methods

Label claims are important as parameters for maintaining useful functionality and ensuring desirable quality at the stage of release or acceptance of an excipient product. Given this, and irrespective of the treatment of functionality-related specifications within individual monographs of excipients, harmonization of functionality-related test methods will assume even greater importance in facilitating unimpeded circulation of excipients in the global market.

Despite the advances in harmonization brought about by the PDG agreement, sticking points still occur in various cases. Sticking points often occur when different results are obtained for the same specimen from two different methods, and each method is based on different principles, has been employed for a long period in different regions, and has been satisfactorily validated. In such cases, would it be possible for both methods to be adopted together in the general chapters or in each monograph? This is simply a proposal, but I dare to say that in such cases monographs should list alternative methods along with original methods, even if this other alternative will provide a different result when employed. Monograph specifications or label information could then be expressed in terms of a numerical indication for each of the specified test methods. Such procedures to solve various apparently insoluble sticking points could be modified in diverse ways according to the extent of difficulties encountered. I hope and expect to see more detailed discussions in PDG meetings among the three pharmacopoeias regarding such ideas.

Reference standards

Under these circumstances adequate reference standards are needed in order to verify that alternative test methods actually provide the expected results.

A desirable characteristic of reference standards in these situations is to provide a constant physical property, regardless of purity or homogeneity, much as the reference standard provided by USP for dissolution tests. I certainly hope that the leading manufacturers of excipients could be expected to provide robust materials to attain specific objectives within their capacity and specialty. For instance, to the best of my knowledge, Shin-Etsu will be able to offer hydroxypropylmethylcellulose phthalate (HPMCP) or hydroxypropylmethylcellulose (HPMC) for use in viscosity adjustments.

Entry of excipients in JP

The revision process for the JP has shown no change in the number of entries for excipients from the previous edition, at 273. I believe that the inclusion of excipients in the pharmacopoeia brings several advantages to both manufacturers and consumers of excipients. It ensures adequate quality, provides the desired functionality and safety, and promotes smoother circulation on a global scale, resulting in preference over other excipients unlisted in the pharmacopoeia. These advantages will, as a matter of course, facilitate the approval process with respect to quality and safety issues.

The JP Committee established a policy of increasing the number of excipients included in the JP as one of the primary goals in the action plan for the next revision. One of the reasons why the number of excipients in the JP has remained unchanged is the existence of voluntary

standards for excipients, the Japanese Pharmaceutical Excipients (JPE), published by the Pharmaceutical and Medical Safety Bureau, which contains 436 monographs. The JPE has been treated as a quality standard in regulatory procedures for new drug applications, just as the JP. However, since the only official compendium is the JP, only items in the JP are subject to international harmonization. In other words, international harmonization of excipients through the PDG works as an effective measure to incorporate unlisted excipients into the pharmacopoeia. Typical recent examples are calcium disodium edetate and crosprovidone.

On the other hand, you may be aware that we have the Pharmaceutical Excipients Dictionary (PED) edited by the JPEC in cooperation with the Ministry of Health, Labour & Welfare. This dictionary contains a total of 1178 monographs with a precedent of domestic use. Therefore, irrespective of coverage as subjects for harmonization through the PDG, we will continuously endeavour to increase the number of excipients in the JP by transferring appropriate items from the JPE or PED.

In the practical endeavour to incorporate new monographs of excipients, the drafting of monographs for each candidate excipient is highly dependent on manufacturer experts. The liaison member from the JPEC has proved extremely effective and has supported the activities of the JP Committee by preparing data needed for the evaluation or validation of proposed specifications, and by drafting proposals of monograph standards. The activity of the JPEC in these matters is fully appreciated.

Conclusion

When we look back to the reports or minutes of various conferences and meetings in which we have discussed subjects concerning pharmacopoeial harmonization of monographs and test methods, we find that we have consistently reached similar understandings and agreements to those reached today. This reveals that the subject itself involves many obstacles along the path of obvious progress. However, I believe the situation has been steadily improved in recent years by the continued efforts of the PDG. We should continuously strive and cooperate to overcome our present difficulties in mutual recognition of comparability and interchangeability of monograph standards and general test methods. I can say that I am ready to inform the JP Committee members of today's enthusiastic discussion. I will ask them to continue their efforts towards accomplishing our common vision in collaboration with other pharmacopoeia by making full use of every means at their disposal in the revision process for the forthcoming edition.

Session IV: International harmonisation of excipient monographs

Ph. Eur. PERSPECTIVE ON EXCIPIENT HARMONISATION

Mr P. Castle, Secretary of the European Pharmacopoeia Commission

I have been closely involved with international harmonization within the PDG for almost three years. The PDG was founded twelve years ago, therefore this represents 25% of the time. What I would like to present is a personal view of my experience over these three years. As the work programme has already been looked at by my colleague, Sue Harris, I will not go into that side of things.

Although the full story of the PDG is not excipients, it is also other items, I will concentrate on the work on excipients.

The mission of the Pharmacopoeia

We have to remember that before we started on international harmonisation we had our own mission to carry out. We must not forget that the real mission of a pharmacopoeia is to safeguard public health by provision of suitable standards – standards which are usable by the people who, once they get into the Pharmacopoeia, have to apply them. This means the regulatory authorities, manufacturers, official control laboratories. When we try and harmonise our monographs, the other Pharmacopoeias have the same mission. You may think that harmonising monographs is an easy job, but is harmonisation compatible with our basic mission? We have to ensure that is compatible. The PDG is an informal group, however, we all have our own constitution in which we have to work so that we have to ensure that harmonisation is carried out in a way that preserves our essential aims. We have to remember that a Pharmacopoeial standard is valid within a given regulatory system. A Pharmacopoeia cannot exist in a vacuum; it is one of the pillars which holds up the whole building of quality and safety of medicines.

The regulatory systems in which we exist within the three regions are different. The way that the Pharmacopoeia fits into those regulatory systems is different which is one of the sources of difficulties that we had to realise within the PDG. Medicines legislations is developing all the time in the three regions so that we should not be surprised that the regulatory structure is not the same within the three. Since ICH has existed, there has been a move towards each other in the three regions. Nevertheless, ICH has limited itself to new products so we have not seen the regulatory systems move completely together because of ICH.

This means that when we are harmonising we have to ensure that the product that we get out of harmonisation will fit into our regulatory system just as USP and JP has to ensure that the monograph that we get out of harmonisation fits into their systems.

Why harmonise

Why should we harmonise the monographs? The benefits are for multi-national industry and we should realise that harmonisation means change for everybody. Harmonisation means that we will all have to change something in our Pharmacopoeias. This means that there are some users of the Pharmacopoeia who have to experience change in the monographs where there is little in it for them. If they are not operating in a multi-national environment, then they will derive no benefit from that. The benefit of international harmonisation is that you are having to question your own positions. Why is our monograph different? This gives us an occasion to rethink the monographs, to modernise them and to improve them.

The harmonisation work which we do will not be limited to the three regions – other people use the European Pharmacopoeia, Japanese or United States Pharmacopoeias. The benefits will seep out and concern other regions.

Why not harmonise

Are there any reasons why we should not harmonise? I have felt that there is one good reason not to harmonise and that is that harmonisation is a lot of additional work with no additional resources.

At a time when the European Pharmacopoeia is being asked to expand its standardisation activities and to take on new projects within the strictly European aspects of the work, allocation of resources has to be made in a rational manner and we have to ask whether international harmonisation outside of the European sphere is the priority for resources.

In addition, harmonisation with the USA and Japan is not relevant for all of the users of the EP so that we have to weigh the interests and needs of everyone in allocating resources and most of all to remember our primary mission in the safeguard of public health.

What does harmonisation mean?

The first assumption has always been that harmonisation leads to exactly the same monograph or method in all three regions. From a pragmatic point of view, an important aim is to reach a monograph which avoids having to test twice or three times for the same purpose. This means harmonisation of specifications and methods. There may be additional tests in the monograph of one region, for example, EP and USP often include tests applicable when a substance is used for a specified purpose (injectables, etc.) whereas JP does not usually include these special “grades” in the monograph but has them as a part of the specification for the preparation. Such differences are more apparent than real and do not imply duplicate testing. More recently, the PDG has decided that the benefits of harmonisation, even if not complete, should be made available to users as soon as possible. This has led to the use of “harmonisation by attribute”, whereby sticking points that cannot be resolved within a reasonable time are declared, temporarily we hope, as non-harmonised. It will be important to give full information on these residual differences but there can be no doubt that harmonisation by attribute will be of benefit to users and can be an opportunity for a new start. This should not however distract our attention from the fact that the ideal harmonised monograph is one that is interchangeable, so that when the monograph is used as part of the common language of quality specifications, reference to one pharmacopoeia is equivalent to reference to all three.

How do we harmonise?

The working procedure of the PDG is an informal document, in the same way that the PDG itself is an informal organisation. However, experience has taught us that following the working procedure is the only way to avoid misunderstandings in the complex processes that lead to harmonisation. Each pharmacopoeia has to respect its existing procedures, which for EP means consultation of the groups of experts, publication for comment in *Pharmeuropa* and final adoption by the European Pharmacopoeia Commission.

As in all our work, input from users of the pharmacopoeias is essential and the PDG is constantly striving to enhance this input. To achieve this users must feel that they are involved in the work and can usefully contribute.

Who is involved?

The European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopoeia are central to the process. Since a large part of the work programme is on

excipients, involvement of the excipient councils (TriPEC = IPEC Americas, IPEC Europe and JPEC) has been essential and is increasingly important. The main partners are from the three ICH regions and the need for pharmacopoeial harmonisation has been recognised by ICH as essential for full application of some guidelines, notably Q6A on specifications. WHO has observer status within the PDG. Input from other parties is possible at the level of forum publication.

What to harmonise?

For monograph harmonisation, the PDG recognised the advantages of beginning with excipients, which are of interest to the vast majority of users. The first programme of 50 monographs was based on proposals from users and with hindsight it has to be said that the programme was established more with a view to what was desirable than to what was possible. Harmonisation of general chapters was secondary to the work but is now receiving more attention because it is a source of recurrent sticking points.

The first programme included:

organics	24 monographs
inorganics	8 monographs
celluloses	14 monographs
starches	4 monographs

See complete list in Appendix.

Where are we now?

Over the last year or two, 12 excipient monographs have been signed off by the PDG and are published or in the process of publication by the three pharmacopoeias. Many but not all of these have residual differences. Five general chapters have been signed off. The PDG will now make a special effort to move a large number of monographs to sign-off applying harmonisation by attribute where necessary.

Spin-off: the additional benefits.

The work on harmonisation and the regular meetings that this has involved have brought some benefits that were not initially expected. For the first time a forum has been created for wider discussion of the aims and status of pharmacopoeias at the end of the 20th and beginning of the 21st centuries. There has been an opportunity twice a year to exchange ideas on pharmacopoeia policy and for us all to learn about the position of the other pharmacopoeias in their region. The PDG has also created a wider international perspective on pharmacopoeial work. JP Forum was created as a direct response to harmonisation work and now all three pharmacopoeias have a specific section on international harmonisation in their forum publication.

Sticking points

The work on harmonisation has in many cases progressed well to the point where the clear majority of attributes are harmonised but after many years' work less than a quarter of the work programme has been signed off. The main reason is the occurrence of sticking points. Shakespeare told us that we should "screw our courage to the sticking point and [we]'ll not fail". Well the first thing has been to identify these points and the reasons for their occurrence.

Where the sticking point has its origin in the regulatory environment within which the pharmacopoeia operates this can lead to insurmountable difficulties, particularly where the regulation in question is not specifically directed to medicines.

Differences in general policy can also be hard to circumvent. Requirements for residual solvents are an example of this. EP applies the ICH approach for all products. USP has its own policy and JP expects this aspect to be dealt with during licensing not by the monograph.

General chapters can be a source of sticking points, particularly the more well established ones that are applied in many existing monographs and where it is not possible to revise them without extensive validation work. The tests for heavy metals and loss on drying are examples. The test methods for microbiological quality are being harmonised but until harmonisation is achieved these attributes have to be declared non-harmonised, even if the limits applied are the same.

Local traditions, for examples for reagents, and policies related to use of toxic reagents can be a source of sticking points. The methods used in a pharmacopoeia for many years may appear to be robust until they are transferred to another region. It has frequently occurred that robustness breaks down for unexpected reasons, for example reagent quality.

Finally, the issues involved are not always clear cut. When a choice has to be made between using a toxic reagent and using a method that gives less information on the quality of the product, the decision is to a certain degree arbitrary and inevitably the three pharmacopoeias will not always have the same perception.

How to move forward?

Harmonisation by attribute will be an important factor in more rapid progress. Enhanced co-operation with TriPEC, which has now been established, will be of great importance for the future work programme and for resolution of sticking points. TriPEC has presented an action plan to the PDG based on examination of existing data, and where this is not sufficient collaborative testing, to demonstration equivalence of methods and to test their robustness. The PDG is now examining where this kind of contribution by TriPEC would be of most benefit. A pilot exercise carried out by TriPEC in 2001 showed that progress can be achieved in this way.

It will be essential for the co-ordinating pharmacopoeia to make a realistic assessment of the comments and status of harmonisation at each stage of the process so that sticking points are resolved wherever possible before the final stage. This means solving problems not shelving them.

Excipients: the poor relation?

Much of the emphasis in recent years in pharmacopoeias may appear to have been on active substances as the regulatory requirements have become more precise and demanding in a way that has not applied to excipients. However, international harmonisation has focused our attention on the complexity of standards for excipients, including functionality-related properties, and this has underlined the importance of pharmacopoeial monographs for this group of substances.

The future

The PDG will now move on to define a new work programme since a number of monographs have been signed off. Past experience has taught us that we have to pay more attention to time management if we are to meet the expectations of our users. Delays in harmonisation tend to be cumulative, each pharmacopoeia has its own lead times for publication etc. and advanced planning is essential.

As harmonisation by attribute is applied increasingly, it will be necessary for each pharmacopoeia to make clear to users what the harmonisation status of each monograph is. For EP this will be via an information chapter on pharmacopoeial harmonisation. The

possibility of indicating harmonisation status directly within the monograph is also being examined.

For the future, the question of functionality-related characteristics within the harmonisation will have to be examined.

New work programme

The top ten items proposed by TriPEC for the new work programme are:

carmellose; calcium carbonate; copovidone; gelatin; glucose/dextrose; glyceryl monostearate; mannitol; nitrogen; sodium lauryl sulphate; starch, pregelatinised.

Ph.Eur. can support these items, with a qualification for nitrogen, where the scope of the monograph needs to be defined first.

Appendix PDG Work Programme on Excipients

Alcohol
Alcohol, Dehydrated
Benzyl Alcohol
Calcium Disodium Edetate
Calcium Phosphate, Dibasic
Calcium Phosphate, Dibasic Anhydrous
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Croscarmellose Sodium
Microcrystalline Cellulose
Cellulose, Powdered
Cellulose Acetate
Cellulose Acetate Phthalate
Citric Acid, Anhydrous
Citric Acid, monohydrate
Crospovidone
Ethyl Cellulose
Hydroxyethylcellulose
Hydroxypropylcellulose
Hydroxypropylcellulose, Low Substituted
Hydroxypropylmethylcellulose
Hydroxypropylmethylcellulose Phthalate
Lactose, Anhydrous
Lactose, Monohydrate
Magnesium Stearate
Methylcellulose
Methyl parahydroxybenzoate
Petrolatum
Petrolatum, White
Polyethylene Glycol
Polysorbate 80
Povidone
Saccharin
Saccharin, Sodium

Excipients : Classical quality requirements and functionality related testing

Saccharin, Calcium
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Chloride
Sodium Starch Glycolate
Starch, Corn
Starch, Potato
Starch, Rice
Starch, Wheat
Stearic Acid
Sucrose
Talc
Titanium Dioxide
Ethyl Paraben
Propyl Paraben
Butyl Paraben
Glycerin

Session IV: International harmonisation of excipient monographs

DISCUSSION

Prof. H. G. Kristensen: International harmonization has been on the agenda for 12/13 years. Dr Kettenring has given us the understanding that harmonization is very difficult. Nevertheless all three Pharmacopoeias have a very positive standpoint on harmonization with strong expectations for the future for progress in this field.

To Dr Kettenring: In your presentation of the IPEC proposal, you showed a slide on quality-related properties and you stressed that there was a need to make a differentiation between pharmaceutical and technical grades mentioned on titanium dioxide as an example. I have seen in the last 2 or 3 years a survey of titanium dioxide samples taken from the European market. There was a surprisingly high number, approximately forty. This was analysed for the content of heavy metals which was very variable and also very high, not acceptable for pharmaceutical use. Do you think that we should focus on the problem of titanium dioxide because it would be very difficult to obtain samples for pharmaceutical use if you follow the principle made in your proposal.

Dr U. Kettenring: With titanium dioxide you have practical problems because you have a monograph for titanium dioxide and it is also an E substance so you need to take into account the EU directive on these. However, these are specifications and there are no methods. Nevertheless we need to use material which covers the EU directives as well as the monograph – these are tough and the materials are very interesting. This is without question a different quality than if you use it as in paint. We would like to see this in the European Pharmacopoeia monograph so that you have reliable methods which you can use and not only specifications where you have to invent your method and validate it etc.

Prof. H. G. Kristensen: Dr Harris presented the PDG process and we are in the situation now where a number of monographs are harmonized and they are going to be published. What about for revisions however?

Mr P. Castle: Within the European Pharmacopoeia we have a well defined revision process and we will have to stick to this. However, within our informal working procedure and informal agreement, that we will harmonise monographs together. This means that if we see the need to revision a monograph we will not only notify the European Pharmacopoeia Commission we will also notify our PDG partners and expect that then we will appoint a coordinating Pharmacopoeia for that revision work and I would expect that this would go through the PDG process, probably skipping some steps but nevertheless it would be handled within the PDG. This would mean that in the end, we should, as within Europe, implement the monograph on the same day – if we do not do this, people will one day have a harmonised monograph and the next day a non-harmonised monograph.

Dr P. Vree: Peter Castle told us that it is the mission of the European Pharmacopoeia to safeguard public health and Dr Kettenring told us that according to the TriPEC opinion there should be a rationale for all the safety tests. If not, as is sometimes the case for tests performed by tradition, tests can be deleted. My question is: is there at present enough data to introduce that rationale. The principle sounds very good, however, in older times the Pharmacopoeias had good reasons to set those limits for impurities. How do we safeguard

public health if we want to delete a test? How much data is needed? Is the same principle true for multi-source excipients?

Dr U. Kettenring: This is something that we are looking at within the Harmonisation Committee. We do have other issues, not only the monographs which should be harmonised. IPEC does have the possibility of asking the users and the producers which gives us a wide field of collecting information and data from American, Japan and Europe. With this you have enough to start work and see how far you will go with the data collected and how you can give a good reason to say that this or that test will be eliminated. Our members will provide us with data – sometimes this takes time but we do get the information.

Mr P. Castle: There are some particular cases where we do not get the ‘hard’ data. You have some but not all of it. Nevertheless in the end you have to make a decision concerning the standard, decisions about the monograph. We set the limit stricter than it needs to be so therefore if it fails, it fails ‘safe’. This means that the limits are tighter than they perhaps need to be.

Dr K. Goode: Peter Castle mentioned that prospective harmonisation is easier than retrospective harmonisation and that was related in general when he talked about the test methods. There are quite a number of excipients with monographs in one or two Pharmacopoeias but not in all. Quite often it is the case that where another Pharmacopoeia decides to elaborate a monograph, it will produce a monograph which is different to that of the pre-existing monograph. Could I ask that the Pharmacopoeias in general should look to try and adopt pre-existing monographs wherever possible as it would be much easier. If you are using or have been using a US monograph for something for the last twenty years, and you get an EP monograph which is different, then you have a major problem in trying to ensure that you comply with all of the requirements.

Mr P. Castle: It is very interesting the idea that instead of embarking out on our own, try and do some prospective harmonisation for this kind of excipient. We should look at that in our future work programmes. This would mean putting it onto the PDG programme as a mixture between prospective and retrospective harmonisation. You should remember though that a 20-year-old monograph may be due for updating.

Prof. H. G. Kristensen: On the general methods there is prospective harmonisation.

Question to Dr Uchiyama: you mentioned the need for reference standards to verify alternate methods in the control of excipients. This idea is new to me, do you mean reference standard of the excipient material which allows you evaluate and verify other analytical methods than those described in the Pharmacopoeia monograph. This is not the ‘normal’ situation where we need reference materials.

Dr M. Uchiyama: I was speaking about reference materials which are not the materials used so far in excipient monographs. If you wish to compare and verify the results of the different methods, you can use any chemical substance or material having robust and have constant physical properties. It is not necessary to use the excipient as a reference standard.

Prof. H. J. De Jong: Is it more like creating calibrators, setting a temperature scale or for particle size scale?

Dr M. Uchiyama: Yes.

Prof. H. J. De Jong: Therefore it should be a suitable material however it can be any material which has a particle size distribution that can be measured by laser galinometry to set the methods.

Dr M. Uchiyama: This is similar with reference standards for dissolution test produced by the United States Pharmacopoeia.

Dr U. Kettenring: If we put in the Pharmacopoeias different or alternative methods, that are not equivalent but we know that with this particle method in the particular region it is safe and in the other region the other method was also safe. How do the authorities treat this question?

Prof. H. G. Kristensen: The field in which I am experienced is dissolution testing. Here the Pharmacopoeia presents several apparatus to be used after the choice of the drug manufacturer. The Pharmacopoeia states that one of the methods is preferable in general, but the choice has to be made by the manufacturer and in the end approved by the regulators.

Mr P. Castle: I do not think that we would put the European regulators in that situation – this would only be passing the problem to somebody else and not solving it ourselves. This is our problem therefore, if we can demonstrate equivalence of alternative methods, then we should have the courage to choose one or the other method. Alternatively we could publish a scientific article where it is demonstrated that the methods are equivalent but actually putting the two in our Pharmacopoeia would be difficult and the Commission would not adopt this as an approach.

ROUND TABLE DISCUSSION

Prof. Dr H. G. Kristensen, Chair of the European Pharmacopoeia Commission; **Dr A. Artiges**, Director of the EDQM; **Mr P. Castle**, Secretary of the European Pharmacopoeia Commission; **Dr M. Morris**, CPMP/CVMP Quality Working Party (EMEA); **Prof. H. J. De Jong**, International Pharmaceutical Excipients Council (IPEC); **Dr M. Uchiyama**, Japanese Pharmacopoeia; **Dr C. Mroz**, Colorcon Limited;

Workshop 1: Classical quality specifications for excipients

Conclusions

Mr P. Castle: After yesterday's session, we have prepared this summary in the form of very brief statements of the points which were raised during the workshops. Having gone through the report which we made yesterday, it is clear to me that many of the items are action items which the European Pharmacopoeia will have to follow-up – this we will do within the next few months.

Residual solvents: it was pointed out that there is an illogicality in that option 2 for dealing with residuals solvent is not applicable on paper at the moment to class 3 and we cannot see why. This is a point which needs to be followed up. As far as the application of options is concerned, of course, excipient manufacturers do not know the final use of their excipients. For them, these options do not mean anything. This means that it is only in negotiations and contacts with their users can those options actually be applied.

Problems with expression of limits: in the General Chapter on residual solvents, because limits are expressed in ppm and we cannot agree on what a significant figure is, 5000 ppm can be interpreted differently, and I did not agree with the Chair of the Commission on how many significant figures there were there; if you have 0.5% then I think that you will all agree that there is only one significant figure, but should a batch fail if you find 5020 ppm – is this a reasonable approach? To be followed up by the European Pharmacopoeia.

The idea is that there is some tolerance on stated limits. Well there is no tolerance on the stated limits, but there is divergence of interpretation on what the limits mean in that General Chapter. Flavours are sometimes added to preparations in solvents that are included in the list. The requirements should not apply to those – this maybe needs to be made clearer.

Some specific items – monographs which are giving problems and need to be followed up.

Glyceryl monostearate, mannitol and aluminum magnesium silicate.

For bulk and tapped density: method 1 cannot be used for specifications between supplier and customer. If that is not clear in the draft at present, then we must make this clear that this is a test which is useful in development but will not be used for routine characterization of excipients and which cannot be used as a means of having a common language between the supplier and the customer.

Viscosity and cellulose derivatives: there is a plea for simple methods for example the Brookfield viscometer. I told that participants yesterday that this is at present on the work programme of the European Pharmacopoeia so that we will be introducing these methods into the Pharmacopoeia and I guess that these will also be applied to celluloses in the near future.

Excipients : Classical quality requirements and functionality related testing

For the Karl-Fischer determination of water, to allow the use of non-toxic reagents. At present the General Chapter does allow the use of non-toxic reagents on condition that you validate but we do not give much guidance about the validation. For us the next step to give guidance on how to validate these alternatives. At the moment, the suppliers of the reagents that do not contain pyridine do have validation packages for a lot of substances and you can obtain them from the supplier of those reagents, but not for all substances.

We had some discussion on the heavy metals test which seems to be a recurring theme of every conference organised by EDQM. People would like to see this test replaced by instrumental methods, atomic spectrometry and inductively coupled plasma spectrometry. In the European Pharmacopoeia will be introducing a new General Chapter on ICP. Replacing a heavy metals test, which is a general test with a test for a specific metal is not so easy, unless you are sure what the heavy metals presents are.

The relevance of the test was questioned. If you are testing hundreds of batches and you have never found any heavy metals in there, is it really a relevant test? Again, it is seen as a possibly useful test for materials which are manufactured in conditions where you not really sure of what the conditions are. For example, substances which come from outside Europe where the manufacturers may not be inspected.

Some manufacturers have pointed out that for their products, they would prefer to do skip testing – maybe testing every ten batches. There was a suggestions that we could deal with heavy metals contamination in a general monograph, to leave some flexibility for testing for people who are really sure of the risk of contamination of heavy metals.

Similarly, the test for arsenic was questioned. This was almost a traditional test because of the possibility of arsenic getting into the product from sulphuric acid. I think that there is a general agreement with the products manufactured in Europe that arsenic is not going to be a problem any longer; but products do not just come from Europe.

With fat-based excipients, we are now introducing more and more chromatographic tests for characterisation of these products. The relevance of the traditional methods such as acid value, iodine value, hydroxyl value was questioned. Do we really need these traditional tests for fat-based excipients now that we have the chromatographic tests? Again this is a point for the European Pharmacopoeia to follow-up.

Colouring matter: in general we do not have monographs on colouring matter in the European Pharmacopoeia. We do not have monographs because at the first attempt this proved too difficult, this is the reason. The excuse is that we do not have monographs because they are covered by EU Directives – covered may not be the ‘word’ as the EU Directives give a list of things that should not be in there and a list of things which should be in there but it does not give any methods for determining whether they are in there or not. One exception is that we do have a monograph for TiO₂ because it is not just used a colouring matter it is also used as an excipient and possibly also as an active. Therefore, we do have a monograph on TiO₂ and of course it is not the same as the EU Directive. Manufacturers have to comply with both. We have been told that monographs for colouring matter would be useful in the European Pharmacopoeia – may be we should try harder than the last time.

As far as oils are concerned, it was suggested that we should have a test for rancidity, instrumental methods exist for this. There may be a problem if there is only one instrument for determining and there is just one supplier.

For croscarmellose, a manufacturer pointed out that the assay which we inherited during the harmonization process, is in fact a duplication of other tests and gives no extra information. In addition to that, it is very difficult for the users of croscarmellose to carry out the test, which is not very robust. The manufacturers can do the assay because they are used to doing it and they do it several times a week, or day. They are well trained in that and have no problems with the method but they end up in the position of dispute with their customers who are getting out-of-specification results, probably not related to the batch but more often related to the robustness of the method.

We discussed the monograph on substances for pharmaceutical use. A hand survey in workshop I A, revealed that 25% of attendees of this conference have actually read the monograph on substances for pharmaceutical use. We looked at its relation to individual monographs and I did my best to explain that it complements the individual monographs. It does not overrule them and it does not contradict or conflict with them.

It seems that quality assurance people do not always understand that this applies to excipients as well as to active substances. It does apply to excipients, it is just the paragraph of related substances and the paragraph on impurities which does not apply to excipients. It was pointed out that in some cases, there are conflicts between the limits for residual solvents given in the General Chapter which is enforced by the monograph on substances for pharmaceutical use and the specific monographs on those products – this is something that we will have to check within the European Pharmacopoeia.

For polymeric excipients, there is a desire on the part of users to have information on the additives which may be present in these polymeric excipients and when these monographs are in the European Pharmacopoeia you should only be allowed to use the title of the European Pharmacopoeia if it is stated in the definition of the monograph that additives may be included in the product. Otherwise, if you put an additive in there and the definition does not allow an additive, then that is not Pharmacopoeia material. In any case, the additives should be stated on the label.

There was quite a strong plea in the workshop for having a monograph on empty capsules. This was seen as being an interesting and useful standard in the Pharmacopoeia. There was such a monograph in the 10th Edition in the French Pharmacopoeia (1983) but this is not in the current edition of the French Pharmacopoeia. Again, another point for the European Pharmacopoeia to follow-up.

Certificates of analysis: The Pharmacopoeia allows the use of validated alternative methods if you prefer to use this as opposed to the European Pharmacopoeia's method. A number of people felt that this should be mentioned on the certificate that if you have a certificate stating compliance with the European Pharmacopoeia then, if in the test for ions for example you did not do the European Pharmacopoeia's test but a validated alternative, then you should state this on the certificate.

It was noted that IPEC is at present preparing a guidance document dealing with all issues related to certificates of analysis. Many people would like to see on the certificates the actual numerical value of the test – where the test gives a numerical result, rather than simply stating on the certificate “complies”. People feel that they are being cheated of a bit of information which would be of interest and useful in comparing batch to batch what the results could be and somebody pointed out to us that in her certificates of analysis, she gives more information than simply required by the analysis of the Pharmacopoeia and this can sometimes cause

problems because, you then start getting questions about the extra information from the regulatory authorities.

We looked at harmonisation by attribute and I was pleased to notice that people thought that it was something of a step forward but of course, they do need to have a clear statement of what the harmonisation state of these monographs is and they want to have that in the most user-friendly method possible. They would also like to see information on advancement of the work programme on international harmonisation and I can tell you that the three Pharmacopoeias have agreed to have, on their respective websites, a section devoted to international harmonisation by the PDG and that is where we will now give regularly updated information on the work programme.

We had a discussion about manufacturing, retest and expiry date. Some users insist on knowing the manufacturing date. They want to have this information. In any case, the retest or expiry date is needed and for some people putting the expiry date, for them implies that there has been stability testing and the results of that stability testing will be available on request.

Finally, having gone through all these complex issues related to the Pharmacopoeia, to standards and to excipients then people told us that it is so complicated that we need to run training sessions on good use of the Pharmacopoeia.

It would seem that we will now have to recycle ourselves as professors of the Pharmacopoeia!

Workshop 2: Case studies for functionality-related tests

Conclusions

Dr C. Mroz: The way which we report the outcome of workshop II is by using the five questions which were the framework of the three sessions.

What are present industrial practices to standardise functionality-related characteristics?

The outcome of that is that current industrial practice is to agree specifications between supplier and customer. For functionality-related tests, examples of which are viscosity, degree of substitution, particle-size distribution, manufacturers have their own preferred method and each purchaser also has a preferred method; therefore you have a whole matrix of different methodologies used. Typically these extra parameters which do not form part of the current chemical specification are not quoted on the marketing application.

Also, functionality-related characteristics are controlled by validation of processes used in the manufacturer of excipients. If the manufacturer of the excipient is quite good, making a single product for many years and has good control over the process and validation, they do tend to achieve a degree of consistency. So batch 1 would be the same as batch 2 and the same again a year later, hence reducing the need to look at functionality-related parameters as these can be taken for granted if that specific manufacturer does have good control on the process and also good control over starting materials. If you are trying to make a consistent product, then you need something consistent to start with in the first place.

One thing which we did come up with was sampling. If you are buying an excipient in bulk (10 tonnes) and you are doing particle-size analysis – how best to do that? What sampling regime do you use. Do you take one sample from one drum and take that as being typical for the batch? Bearing in mind that some segregation or particle movement will happen during transit. There needs to be an agreement between supplier and customer on the actual sampling regime and the number of replicate samples that are going to be done, and in the case of things like particle size, how is this sample going to be prepared? Are you going to use ultra-sonification, a mortar and pestle or are you going to keep testing until you get the result you want?

Which excipients, which criteria, which analytical methods?

Which excipients? was a difficult question. If you look at the type of medicinal products which have the potential of being influenced by the excipients it covers everything – solid dosage forms, especially modified-release, liquids, topicals, inhalation products. There is a wide range of medicinal products which could potentially be affected by the quality or the performance of the excipient. Hence, almost any excipient could have the need for functionality tests to be identified. As you have such a wide range of materials, the criteria that need to be covered are also very wide and varied.

As a specific example, we need to standardise on tests for viscosity, which came up in the previous group, which could cover newtonian and non-newtonian liquids. A test method for gel strength for those that form matrixes or those that form gels for topical application.

The idea of test-methods – should you use something simple or should you use something state of the art. Again, this is a subject for debate but the Pharmacopoeia would be at its most useful if the test methods that are being prescribed for the non-mandatory parts were based on equipment which is commonly available provided that these methods provided reliable and robust results. If an individual users wants to use a state-of-the-art piece of apparatus, instead of something more routine, that is fine and that is permitted provided that some cross-validation is performed.

As with any test method, calibration standards, and again this was mentioned this morning, should be specified. Especially for polymeric excipients, there is the question of how to characterise their functionality-related properties. Polymeric excipients were seen as a special case because with a complex molecule you have a range of variable parameters and especially in pre-formulation when you are using examples at the extremes of the specification range, high, medium and low. This is fine if you are looking at one parameter. If you have more than one variable parameter, say that you have three or four then to have a high parameter 1, low parameter 2 and mid parameter 3 you end up with a very complicated matrix. This does not stop some customers asking for these sort of samples to be supplied which can be 27 or 36 different samples of material. There are ways of statistically designing a model.

This is not the role of the Pharmacopoeia but it was expressed that there is a need for the user of an excipient to have a full understanding of the excipient manufacturing methods. We talked yesterday about cutting the number of audits and maybe this is the case but perhaps instead of audits there should be some sort of mechanism where the user of an excipient can communicate with the producer, understand the manufacturing method, see what the variables are and hence come to a conclusion on whether those variables could potentially have an impact on the actual use of the material that is being discussed.

Specifically again on polymeric excipients there is a need for a method to determine molecular-weight distribution which can be applied to certain polymers in very specific applications.

Prof H. G. Kristensen: The last part of the discussion was focusing upon the presentation of the approach of the European Pharmacopoeia.

The starting point is what are you doing in industry today in specifying testing and reporting? It became clear that regulators generally accept the indicated function according to the European guidelines and they make reference to the monograph in the Pharmacopoeia. There are a very few specific cases where there is a need to pay a little more attention to certain properties. Generally this is the level of control. I think that it was reflected during this morning presentations that this has been the situation until the present but we will now pay more attention to the controls on some impurities, for example, according to the general monograph on substances for pharmaceutical use. This means that for the manufacturers the current specifications on physico-chemical properties are established as in-house standards and are not included in marketing authorisation applications. They are not included the specification which needs to be approved by the regulatory authorities before marketing.

This situation whereby it is not, in most cases, included in the marketing application authorisation produces some fear when considering what will happen if the Pharmacopoeia established a non-mandatory section on functionality-related characteristics. It was clear in the view points in the groups from the participants that many asked the question : when you have a list of such parameters of characteristics or properties in the monograph, even if it is non-mandatory, will regulators require internal specifications stated in the marketing authorisation application. How will these be dealt with by inspectors?

Personally, I have the feeling that there is a fear from the manufacturers of drug products when you put more into the Pharmacopoeial monograph, which is usually accepted by the regulatory authorities. If you put more items into this even though it is a non-mandatory section it will be reflected and will have some consequences when we consider the relations with the regulatory authorities and the inspectors. One example was given by one of the participants who asked ‘what happens if we have put the in-house specification into the licensing file and our excipient supplier makes a change in their manufacturing process?’ Does this mean we need to alter our internal specification? Do we then make an application for a variation, when new problems will arise.

Concerns were expressed in relation to multi-functional excipients and I take it as an expression that even though we state that this is a non-mandatory section, it may have a semi-mandatory function.

Introduction of this system calls for the training of all the involved parties, not only the regulators but also the inspectors, manufacturers of excipients, manufacturers of drug products. These concerns are legitimate and it is understandable that now, for the first time you are presented with a proposal for specific monographs, ie lactose and magnesium stearate, that you begin think of what the situation will be.

I had the impression that at the beginning, when in the early days we were discussing functionality testing and later on functionality-related testing, IPEC and manufacturers of excipients were pushing the ideas. The impression which I had yesterday, and this was confirmed by the moderators in the two other groups, were that the people who are representing the drug manufacturers were generally more positive than the excipient manufacturers. Therefore it was a pleasure for me to hear Dr Kettenring’s speech giving a

clear recommendation from IPEC and TriPEC to include functionality-related tests in a non-mandatory section.

The European Pharmacopoeia approach is supported by most, however, it needs to be applied with caution. We need to include the “simple” tests and we have to keep these tests to a minimum. “Simple” tests should be tests which are used in most of the industries but can be highly sophisticated when looking at the instruments. Some participants do not support the European Pharmacopoeia approach in having functionality related tests stated in a non-mandatory section. This is because of what it means in the regulatory process for drug products. The argument is that ‘why do you need to make a cross-reference to a general method for particle size’ – we know very well that we need to test lactose for particle size and therefore this list of tests in the monograph is not needed. Instead, you could put this into a General Chapter in the Pharmacopoeia and make a description or presentation for what is need for functionality-related testing.

We have the possibility, if we put it into the non-mandatory section in the individual monographs, to give more detailed information about the testing of each property. For example, for the magnesium stearate, where a test for specific surface area is mentioned here we can say something concerning the pre-treatment, or the method, method 1 from the General Monograph on surface area determination by Brunauer, Emmett & Teller. We do have this possibility of being more precise in the individual monographs.

From drug manufacturers it was mentioned that they are seeing an increased degree of collaboration between excipient manufacturers and users. This collaboration is needed for setting of specifications. It is a help for both parties if we have the general methods stated and functionality-related tests stated in the Pharmacopoeia because then we can work on a common basis. If you, as a drug manufacturer, are negotiating and dealing with two different manufacturers you will benefit from the Pharmacopoeial standards (non-mandatory) by making reference to the same methods of analysis and you can then immediately compare the results. This was seen as a benefit of the introduction of the European Pharmacopoeia approach. The European Pharmacopoeia can therefore support this collaboration but I think that we could even support the collaboration with the licensing authorities and the inspectors, simply because when we start putting general methods into the Pharmacopoeia we are on one level but there is another level training the inspectors and the regulators who meet and discuss the subject. This has always been a very important part of Pharmacopoeial work for the different countries to meet and discuss and reach consensus in their interpretation whether it is for analytical methods or in a general monograph.

Roundtable Discussion

General Comment and Questions

Dr A. Artiges: The purpose of this meeting was to put in place all the partnerships and I think that this has been the result of the workshops. This has proved to be very productive. Sometimes we receive a proposal or suggestion to go in one direction, however, we are not always able to have a clear picture of what will be all the possible consequences of that decision. I think that during this meeting we have a clearly perception of what is needed but also precautions and warnings we should take.

Dr M. Morris: It is very helpful to have this kind of dialogue where representatives of excipient manufacturers together with the users, i.e. the people that we usually deal with, the finished product manufacturers, and regulators and pharmacopoeial authorities are all together so we get the opportunity to hear some of these issues with which we do not normally have a direct communication line – we do not normally have direct communication with manufacturers of excipients. There are some issues which have arisen and I would generally support what I have heard, certainly in relation to the workshops which I attended.

There are a few things which give me a slight cause for concern and a slight feeling that I should discuss these with colleagues in the Quality Working Party. There are some areas of misunderstanding. I am also concerned to hear that there is a general worry amongst the manufacturers of finished products and excipient manufacturers that information on useful additional parameters over and above standard excipient monograph tests, should in some way be withheld from regulatory authorities that this is something that the regulators do not need to know about. I would have taken the opposite view that in the developments of the pharmaceutical section of the dossiers, the opportunity for companies making applications to indicate particulars, not only function and the appropriate optimal concentration of excipients; but also to indicate whether there are any particular parameters which may need to be controlled for a given product. I do not see that the introduction of functionality -related type testing into the monograph as it is proposed, giving general methods and references to methods within the Pharmacopoeia and further useful information is threatening to the manufacturers of the products and their suppliers. I think that this helps to improve the confidence of the regulatory authorities that the manufacturers of the products really have good control over what they are producing on a batch-to-batch basis. It will help to overcome problems that we all too often encounter. I am in the process of dealing with four different ones this year, problems where companies were manufacturing products and suddenly a problem arises and what was routine production goes wrong. It is a big job for the companies to investigate why this went wrong. Where we see information, up front in a dossier to say 'yes, we know from our development work that we need to control this particular parameter over and above simple compliance with the pharmacopoeial monograph': it is very reassuring from the regulator's point of view.

Clearly, any additional functionality testing would be seen to be on a product-by-product basis and the same excipient with multi-functional properties could result in different tests being applied for use in different circumstances.

The whole concept is very helpful. What is being proposed, I feel, is the right way forward and I think that this symposium has been successful in identifying issues and concerns so that we can take them back to the Pharmacopoeia Commission and the regulatory authorities within the European Union to do something to be a bit more transparent and more reassuring to our customers.

Prof. H. J. De Jong: It is not the aim to just add on extra tests but to do this in a selective way and where it is relevant and identify the critical and non-critical issues and act accordingly. I think that this is the way that I would defend this approach.

Dr S. Kopp-Kubel: This forum has been very positive in having the different parties to discuss, not only specifications, but also the more general quality-related issues. It was also encouraging to see that efforts which are currently on-going at WHO, triggered by the World Health Assembly are known but I would like to inform you of the new activities which are being worked on: HACCP has now been adopted by the expert committee who are overseeing all the activities and give recommendations to the Director General and to the Member States on quality assurance. The concept of HACCP is now recommended for pharmaceutical production. WHO has two projects in the area of starting materials, the first is the certification scheme for the quality of products for production for GMP and audit related and the second is a document in preparation on trade and distribution. These two documents will hopefully be available soon.

Prof. H. J. De Jong: This is will very useful, not only distribution but trade, brokers etc as these people play an important role and this may help us get a clearer view and voluntary rules or recommendations.

You may have seen a paper from the CPMP Quality Working Party which is out for comment concerning European drug master files. There is a drug master file guideline and it was thought that it needed to be updated. Therefore, you have a possibility to react before the end of August 2002, however, in the preamble of this document a number of questions and suggestions are being asked and made. One is a topic mentioned by Dr Robert, Chairman of the Quality Working Party when we had the meeting in November last year, where he suggested that certification for substances which have a monograph in the European Pharmacopoeia should become mandatory in the future. It has now also been proposed for active ingredients. Concerning excipients: should the master file system be opened to novel excipients and plastic materials? This is a request to give comments.

Both of these suggestions, if taken up, would result in a need for change in the legal framework in Europe. The European Commission in Brussels is interested to know if they will need to revise their position or not, therefore, they too are asking for your comments too.

IPEC have been working for a long time trying to create interest for excipient master files. Excipient master files being packages of data, not only on quality in the specifications and the making of the materials but also, for the new ones, on the safety package. This represents a huge investment which can be figured between 20 and 30 million dollars where, if it has been paid for by a maker company or a combination of a maker and user company, it contains a lot of confidential information. It is obviously not in the interest of the companies who do this innovative work to put it out to the general public - there is a confidentiality period with this and a master file system could be an excellent safe conduct system to communicate between the makers and the authorities. If you have the 'open' and the 'closed' part you can also deal with the pharmaceutical companies wanting to use that ingredient.

The European master file system is very different to that in the United States and Japan is thinking of creating a master file system but this means a change in the law and this is still ongoing. When the law is being voted, then there will be technical committees that will deal with the scope and the orientation of this.

Dr M. Morris: In regard to the proposal for revision of the drug master file the Quality Working Party have spent a lot of time discussing this and I think that the general consensus has emerged that people are in favour of widening the scope to allow information on excipients or even packaging materials to be presented in a drug master file format. It was not a unanimous view, some people did have reservations about this but clearly there is, at present, a legal barrier to this approach because the directive 75/318 EEC only permits 'third parties' to provide data on behalf of applicants in the case of active substances. Some member states felt so strongly about this that they resisted the idea of having a European-wide drug master file system until that directive has been modified to remove the legal barrier. Prior to that, many member states including Ireland quite happily received drug master files for excipients and other components. I say 'happily' in the sense that we were prepared to facilitate those companies who wish to provide drug master files on new packaging materials which were used, for example, for a range of different products – it makes it easier to produce one set of files where potentially a large number of marketing authorisations were involved. I do not know on what legal basis we used to do this but we did not have a problem. To be strictly correct, however, the directive does not really permit this.

The big concern which was raised at the time, quite rightly so, is that in some way when a regulatory authority accepts a drug master file on behalf of an applicant for marketing authorisation they are, in a way, taking the responsibility away from the marketing authorisation applicant by assessing the data on behalf of that applicant, rather than the applicant themselves taking the responsibility for satisfying themselves about the source and the quality of the material coming from their suppliers. The outcome of it was that the drug master file procedure as operated currently and operated for the last ten years works very well as it focuses everybody's responsibility where drug master file was submitted, the owner to the drug master file, the active ingredient manufacturer had to provide the relevant information both to the authorities and in the 'open' part to the applicants for marketing authorisation. Therefore, each of the three parties took their responsibility and I think that this has worked very well. The position which we will be looking to, is to see if we could have where necessary a similar facility available for excipient manufacturers to provide similar kind of data in a drug master file;

Looking at this from a practical point of view, if we have a situation where we have a new excipient, previously unregistered within the European Union, then a package of data is going to be necessary anyway, and we saw this with the new CFC replacement propellants, even though the same legal barrier was in place then it was quite reasonably circumvented and we had a very good pan-European assessment of the those two new, previously un-used excipients which involved safety, efficacy and quality assessment and it was done in a parallel version of a mutual recognition procedure with a lead authority taking responsibility and preparing assessment reports and everybody participating in the discussions. This did work very well. These are the only two obvious examples which I can think of – we had one or two others but by and large not as important as these cited.

Then these are the excipients which are well established but are not covered by a Pharmacopoeial monograph. For these, the drug master file route may be of use if significant

information is needed. In general terms, particularly for the Pharmacopoeial excipients, the assessment which is done in most authorities, and certainly this is my own personal experience that there is very little focusing on excipients other than compliance with a pharmacopoeial monograph, and as I have indicated if there are any additional tests which need to be done to control a particular use of an excipient then we can expect to see those tests as well.

This leads me on to the certification procedure. Firstly, the Quality Working Party is 100% behind the certification procedure. It is seen as the best mechanism for delivering a single assessment of a starting material. Up until now, primarily active substances but now that the facility is available for excipients, we would certainly and strongly encourage everybody to use the certification procedure as this takes away the need for supplier auditing etc. It is now done as a single approach, up-front. A document is issued at the end of this by the EDQM which everybody, including regulatory authorities can be quite happy to accept. We are very anxious to encourage the certification procedure, certainly for active substances as well as for excipients. As Prof. De Jong has indicated, we have gone even further and suggested, that we make this process mandatory. The idea would be to use the European Pharmacopoeia certification scheme and as an alternative, to open up the drug master files for those excipients where that kind of additional data would be needed. The numbers of drug master files would be fairly few.

Prof. H. J. De Jong: The number of really new excipients is small and will remain small as this is firstly a huge investment and you need to have a good reason to use them. However, if we look at the new products, meaning the gene-derived biotech products there is a need for quite sophisticated additional materials that would be probably polymeric constructs and nanotechnologies. You need to have a system with all the valuable information which needs to be generated around these to be evaluated in a correct way and to get a procedure in place within the system.

Personally, as well as some of my colleagues in IPEC, I think that for novel, new excipients it would be beneficial to have a master file system where the evaluation of the quality and the manufacturing safety and functionality (because efficacy can only be tested in a medicinal product), could be evaluated in a drug master file type procedure. This would be a paying system but you would get a provisional approval in the sense that intrinsically this is an ingredient that can be used by oral, injectable, inhalation etc routes where the data package has been generated for these, with a daily dose stipulated.

Then you would have a tool which could be used by the pharma industry to be included in complete formulations and the final judgment would come from the marketing application and the full evaluation of the programme. Following this, there should be a confidentiality period for ten years for example. After they become well established, they are fit to be included in the Pharmacopoeia, like the actives they would be taken up as a monograph and would be open to certification procedure, with an inspection system in the future. Please give your opinion on this to IPEC, we would like to hear your feelings but also to the authorities as is requested.

Dr P. Rafidison: New excipients – are these products which have never been used in human being? We still face the issue of the excipients which do already exist but that have no monographs but require additional information. For example, you have a cosmetic product which has never been used in a medicinal product, the question is that you have no monograph, you have no system to submit your drug master file as there is no process for it or

the framework. Where should those products go? Our preference, from experience, the use of a certificate of suitability.

Prof. H. J. De Jong: Let us take the category that is already in use in pharmaceutical products within the European market, meaning that they have already gone through the approval process – safety and quality have already been evaluated but there is no monograph in the European Pharmacopoeia. The user and/or the producer should make a proposal. What has already been suggested is that you make reference to the monograph on pharmaceutical substances, to open up the procedure. However, as a producer you should be willing to work with the European Pharmacopoeia to deliver data and methods, samples and proposals for specifications. This can then be picked up in the work programme of the European Pharmacopoeia and simultaneously you can then start with the certificate procedure. However, there must be an initiative, you cannot have a certificate if there is not a monograph.

Dr P. Rafidison: We opened up a big door with the risk assessment of TSE source material, allowing non-monograph products to be assessed! Therefore, is it possible to open up the door with other types of excipients? Why not do this systematically as a preventative measure for better quality?

Dr A. Artiges: We will take note of the concerns and suggestions which you have. It would be good to receive a position paper to identify the various situations which have come up, the status of such products - are they already on the market, what use do they have, what experience do we have on these, are they in Europe or another country? We can then take these on board and take a multi-disciplinary decision which would discuss this with the Quality Working Party, possibly with the national authorities and the inspectorates and IPEC. We could then give you adapted proposals. The question is of high importance but is so big that we are unable to solve this now.

Dr P. Rafidison: I would like to highlight that it is a huge workload getting a monograph through the system and in my experience it can take up to 6 years. If you have an immediate need of data and you would like to protect your know-how, you would have to provide something which treats the information within a year. I think that it is a great concept if you are really dedicated to pharmaceutical industries and want to provide and create new monographs, which is certainly the best way to address this problem. However if you want to register your product quickly, there is no way other than giving away know-how to customers as we want our excipients to be used.

Prof. H. J. De Jong: We need two systems, one is a system to transmit a full data package including the safety evaluation which is not the job of the Pharmacopoeia because they do not have the expert groups to do that type of evaluation (only in the certification and that is after evaluation). But if it is a first evaluation, for a new chemical entity or an entity which has never been appreciated or evaluated for pharmaceutical use, you need to go through the system with the adequate expert groups. Once you have that acceptance then the Pharmacopoeias is completely available to give a judgment on the quality. If it is an ingredient used in one product, in one country within the European Union I think that the priority is very low. If you have a product which is used in several pharmaceutical products in all of the European Union, then you are much higher priority to be taken up on the work programme. If you have adequate data available, this can be speeded up and the 'five-year period' would be reduced. If you are in a situation where there are several competitors with slightly different specifications and test methods, this could create a long debate to give attention to all the parties – we cannot in the Pharmacopoeia have a preference for

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manufacturer A, B or C if they have equivalent but not identical approaches to the problem etc.

The interested parties should signal their wishes through a policy statement, a general letter or citing a number of examples of topics which they are interesting in, to get feed back and to get the development of policy with the European Pharmacopoeia Commission and its institution.

BIOGRAPHICAL NOTES

Dr Agnès Artiges graduated in pharmacy and has a PhD in the same subject, as well as a degree and a PhD in law, the latter from the University of Paris, France. In her postgraduate law degree she specialised in European Institutions. She was Assistant and Assistant Instructor in the Toxicology Laboratory of the Faculty of Pharmacy of Bordeaux before joining the French Ministry of Health in 1971. During her career with the Ministry, she has held the posts of Head of the French Pharmacopoeia, Head of the Registration Authority for Medicinal Products for Human Use and Head of the Sub-directorate of Scientific and Technical Affairs. In addition, she was Chairman of the European Pharmacopoeia Commission from November 1989 to November 1992 and a member of the former Quality Working Party of the Committee for Proprietary Medicinal Products (CPMP) of the EC and was Chairman of this Working Party from December 1991 to March 1993. Dr Artiges left the French Ministry of Health in April 1993 to take up the post of Director of the European Directorate for the Quality of Medicines (European Pharmacopoeia and European Network of Official Medicines Control Laboratories/OMCL) - Council of Europe.

Mr Peter Castle graduated in biochemistry from Cambridge University, England in 1968. He worked on drug metabolism and determination of drugs in body fluids at the Pharmaceutical Society of Great Britain for three years before joining the animal health division of Smith Kline & French in the licensing department, working on veterinary vaccines and anthelmintics. Since 1974 he has worked in the Technical Secretariat of the European Pharmacopoeia, now a division of the European Department for the Quality of Medicines (Council of Europe, Strasbourg). He is Secretary to the European Pharmacopoeia Commission and head of the division dealing with development of monographs and general chapters.

Prof. Henk J. De Jong is Director of International Scientific Relations with Servier, France, since 2000. Between 1994 and 2000, he managed worldwide regulatory affairs and before this, he was head of preclinical development with the same company (1984-1994). Previously he was professor of pharmaceutical analysis and analytical chemistry at Leiden University, The Netherlands. He is a member of the French and European Pharmacopoeia Commissions, honorary professor at Leiden University, The Netherlands and visiting professor at Hoshi University, Tokyo, Japan. He is an active member of IPEC-Europe. Prof. De Jong received his masters degree in chemistry and physics from Leiden University (1970), PhD same university (1973) and did a post-doc at Faculté de Pharmacie Université de Montpellier, France.

Dr Dries De Kaste obtained his degree in pharmacy from the State University of Groningen, The Netherlands, in 1979. He studied for his PhD at the University of Amsterdam and the State University of Utrecht, The Netherlands. He obtained his PhD in 1990. From 1990 till 1991 he was chemical-pharmaceutical assessor for human and veterinary products at the National Institute for the Quality Control of Drugs (RIGO, Leiden, The Netherlands). Since 1991 he has been head of the department Quality Control and Pharmacopoeial Affairs at the Laboratory for Quality Control of Medicines of the National Institute for Public Health and the Environment (RIVM-LGO, Bilthoven, The Netherlands). He was member of Expert Group 11 (Organic chemistry, natural products; 1991-1999) and Expert Group 11S (Sugars; 1997-2001) of the Ph. Eur. Commission. Since 1991 he is member and secretary of the Dutch

delegation of the Ph. Eur. Commission. In June 2001 he was elected as the 1st vice chairman of the Ph. Eur. Commission. He is rapporteur (since 1992) and chair of the Technical Advisory Board (since 1998) and member of the Steering Committee (since 1999) of the Certification Procedure of the EDQM.

Mr Sidney Goode is with Dow Chemical's corporate Environment, Health and Safety Function. He has been an active participant in the development of GMP and pharmacopeial requirements for excipients. Mr. Goode has led committees developing both industry and regulatory initiatives. Within Dow, he has consulted and directed compliance programs for many products.

Dr Olivier Gross is Doctor in pharmacy. Since 1992 civil servant inspector of the French Ministry of Health, and since 1997 head of the Inspection Unit in charge of the pharmaceutical starting materials at the French Agency for the Safety of Health Products.

Dr Sue C. Harris is the Director for Non-Complex Actives and Excipients, Information and Standards Development (ISD) for the United States Pharmacopeia. Her responsibilities include oversight of the three Excipient Expert Committee Groups and two Non-Complex Actives Expert Committee Groups. Ms. Harris joined the United States Pharmacopeia in June, 1999. She previously held positions of Stability Manager/Project Leader for Midwest Research Institute. Ms. Harris received her B.S. in Agronomy/Chemistry from the University of Arkansas in 1979.

Dr Armand Janssen obtained his degree in pharmacy from the State University of Utrecht in the Netherlands. He studied for his PhD at Leyde University, the Netherlands. During the period 1983-1987 he was a research assistant at the Leyde State University. After this period he held several positions in the pharmaceutical industry in the field of Quality Management and Regulatory Affairs. Since 2001 he has been Manager Regulatory Affairs (Food & Pharma) at DMV International.

Dr Undine Kettenring, obtained her degree in chemistry from the university of Freiburg in Germany. She studied for her PhD at the university of Basel in Switzerland. She obtained her PhD in 1993. She developed her career as head of the quality control of a pharmaceutical company (Medichemie) in Switzerland. She is currently working for Novartis Pharma AG in Basel where she leads the unit for excipient release. Since 2001 she chairs the harmonisation committee of the International Pharmaceutical Excipients Council Europe.

Prof. Henning G. Kristensen obtained his degree in pharmacy from the Royal Danish School of Pharmacy in 1963. He obtained his PhD degree in 1968 and DSc in 1981 both within particle technology. He has since 1978 been professor of pharmacy and from 1982 to 1988 Rector of the School of Pharmacy. His field of research is the formulation design, processing and quality control of oral solid dosage forms. In recent years, the research has been directed towards the biopharmaceutical aspects of poorly soluble drug substances and the role of lipids for drug absorption. He has been the Chair of the Danish Pharmacopoeia Commission and a member of the European Pharmacopoeia Commission since 1976. From June 2001 he is Chair of the European Pharmacopoeia Commission. He has chaired the Group of Experts on Dosage Forms since 1993 and chaired several Working Parties, e.g. Standard Terms, Sterilisation Methods, Inhalations.

Dr Stephan Marrer obtained his degree in pharmacy from the University of Bern in Switzerland. He studied for his Ph.D. at the Free University of Berlin, Germany, where he obtained his Ph.D. in 1988. From 1988 to 1990 he was scientific assistant at the Department of Pharmacy, Free University of Berlin, at the University of Southern California, San Diego and at Biosym Technologies, San Diego. Since 1991, Dr Marrer works in the pharmaceutical industry. Currently he holds the position as Vice Director of Galenical Manufacturing, Quality Control & Quality Assurance at Hoffmann-La Roche, Basel. In addition to his industrial activities, he is Lecturer for Pharmaceutical Quality Assurance at the Pharma Center, University of Basel, and at the Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology Zürich.

Dr Miquel Mir obtained his degree in Organic Chemistry from the University Autònoma de Barcelona (Spain) and a PhD degree from the same university. After a one-year post-doctoral stay at the Chemistry Department of Loughborough University (UK), he worked during four years for a generics API manufacturer in Spain where initially he was in charge of scale-up and validation of manufacturing processes and then held the position of head of the Quality Assurance (GMP's) & Regulatory Affairs Department. Since May 2001 he is working at Uniqema as Healthcare Technical Service Manager.

Dr John Michael Morris received his degree in pharmacy and his PhD from the University of Manchester, UK, in 1973 and 1981 respectively. After his bachelor's degree he became a research pharmacist at Sterling Winthrop, in the United Kingdom but then moved to the hospital service where he subsequently specialised in quality control, and quality assurance. After eight years he moved to regulatory affairs, in Ireland, where from 1987 to 1995 he was Senior pharmacist at the National Drugs Advisory Board and then was appointed to his current position of Pharmaceutical Director at the Irish Medicines Board in Dublin. In his capacity of Pharmaceutical Director he is responsible for supervising and co-ordinating pharmaceutical activities including assessment of applications for marketing authorisation of human and veterinary medicinal products, applications for clinical trials and other activities with particular reference to the quality of medicines. He was a member of CPMP Working Parties on Quality of Medicines and Biotechnology/Pharmacy. and is currently Vice Chairman of CPMP/CVMP Quality Working Party, and a member of the European Pharmacopoeia Commission.

Mr Carl Mroz graduated in Chemistry in 1982 from Kingston Polytechnic, United Kingdom. He has been involved with the pharmaceutical industry for 25 years in a variety of roles including Production, Quality Control, Regulatory Affairs and Quality Assurance. He is currently Global Quality Assurance Director at Colorcon, a company which produces compounded excipients used in conjunction with solid dosage forms. He is also a current board member and past Chairman of the International Pharmaceutical Excipients Council (IPEC) Europe.

Dr Patricia Rafidison is PhD pharmacist, from Paris XI with 20 years of experience in implementing Quality Assurance programme both in pharmaceutical and chemical companies. She is currently the Global Quality and Regulatory Manager for Life Sciences at Dow Corning where she has implemented ISO 9001 certification and is in charge of maintaining GMPs initiative and compliance. She is dealing with risk management for Life Sciences applications as part of her activities. Prior to joining Dow Corning, she was in charge of Quality Assurance management implementation then pharmaceutical development in Boehringer Ingelheim, France. She is acting as the IPEC GMP chairperson for GMP Committee for Europe and has participated in the development of GMP and safety guidelines for excipients.

Dr Theodor J. Riedo studied chemistry at the University of Basel, Switzerland, where in 1978 he obtained his PhD. After a postdoctoral fellowship at the Faculty of Inorganic Chemistry at the University of Basel, he started his industrial career in 1980 in a middle-sized Swiss pharmaceutical company where he became head of QC. In 1989, he joined Sandoz who in 1996 merged with Ciba-Geigy to become Novartis. He held various positions within QA and has a long experience in supplier qualification and supplier audits. In 2000, he was appointed head of the Compliance department within Novartis Pharma Chemical Operations Switzerland.

He worked for EFPIA as an expert on the EFPIA/CEFIC Guide “GMP Guideline for API Manufacturers” and on the new ICH Q7A Guideline “Good Manufacturing Practice for Active Pharmaceutical Ingredients”.

Dr Mitsuru Uchiyama graduated from the Faculty of Pharmaceutical Sciences, University of Tokyo, Japan, where he earned his B.S. (1953) and PhD (1958). He joined the School of Pharmacy, Tohoku University (Sendai) in 1959, and was Professor of Hygienic Chemistry from 1968 to 1974, after which he joined the National Institute of Health Sciences where he served as Head of the Food Division (1974 to 1984), Head of the Drug Division (1984 to 1987) and Deputy Director General (1987 to 1991). He was appointed as Director General in 1991. After retiring from government service in 1995, he became the Chairman of the Board of Directors, Japan Pharmacists Education Center and has devoted his efforts to the promotion of continuing education for pharmacists in Japan.

He is currently the Chairman of the Pharmaceutical Affairs and Food Sanitation Council of the Ministry of Health Labour and Welfare, concurrently with the Chairman of the Committee on Japanese Pharmacopoeia.

Prof. Jörgen Vessman, born 1933 got his license as pharmacist 1961, and a PhD in analytical pharmaceutical chemistry 1971 (Professor Göran Schill as supervisor). He was adjunct professor at the University of Uppsala, Faculty of Pharmacy between 1975 and 1998.

He has had positions with Kabi from 1964-77 (Analytical Chemistry, Research Department) and with Astra Hässle (now AstraZeneca) from 1977 to 1995 as head of Analytical Chemistry, Pharmaceutical and Analytical R&D. From 1995 to his retirement in 2001 he acted as a Senior Research Adviser in that organisation. Jörgen Vessman is member of the Swedish Chemical Society (chairman Analytical Division 1980 –1985), the Swedish Pharmaceutical Society (member of the board 1984-1998), the American Chemical Society, the Federation of European Pharmaceutical Societies (EUFEPS) and the American Association of Pharmaceutical Scientists (AAPS Fellow 1995). He was member of the Swedish Pharmacopoeia Committee from 1989 to 2001 and in the Swedish Delegation to the European Pharmacopoeia (Ph. Eur.) from 1993 to 2001. He was a member of the Ph. Eur. experts groups 4 (1978 –90) and 11 (1990-95). From 1995 he was chairman of group 10C in the Ph. Eur.. Between 1994 and 1999 he was chairman of the Committee on Industrial Relations within EUFEPS. Since 1991 he is a member of the Royal Swedish Academy of Engineering Sciences, division IV Chemical Engineering.

Dr Uwe Völker obtained his degree in pharmacy and his Ph.D. from the University of Heidelberg in Germany. Since 1989, Dr Völker works in the pharmaceutical industry in various positions in the area of QC and QA. Currently he holds the position as Head of GMP Compliance, Global Quality at Hoffmann-La Roche Headquarter, Basel. He is a 'specialist in pharmaceutical analytics' according to German Pharmacist Association.

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