

**Implications of the new
CHMP Guideline on the Pharmaceutical Quality
of Inhalation and Nasal Products**

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vorgelegt von

Dr. Herta Reile

aus Eichstätt

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Betreuerin und 1. Referentin: Dr. Susanne Keitel

Zweiter Referent: Dr. Usfeya Muazzam

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List of Abbreviations

CFC	chlorofluorocarbon
CMC	chemistry, manufacturing and controls
COPD	chronic obstructive pulmonary disease
DPI	dry powder inhalers
FDA	U.S. Food and Drug Administration
IPAC-RS	International Pharmaceutical Aerosol Consortium on Regulation and Science
JP	Japanese Pharmacopoeia
OIP	orally inhaled products
Ph.Eur.	European Pharmacopoeia
pMDI	pressurized metered dose inhalation products
QbD	quality by design
SmPC	summary of product characteristics
USP	U.S. Pharmacopeia

1 Introduction

Medicinal products for inhalation consist of a great variety of technical systems and are used by a large number of patients, mainly with asthma or COPD. The advantage of inhalation products for these indications is the drug delivery directly to the site of action. At earlier times products for inhalation were mostly pressurized metered dose inhalers (pMDI) containing CFCs. Based on the Montreal Protocol, the international treaty regarding protection of the stratospheric ozone layer by determining the production and consumption of compounds that deplete ozone in the stratosphere (e.g. chlorofluorocarbons (CFCs), halons) [1], the development of dry powder inhalers and non-CFC containing pressurized metered dose inhalers as replacements of CFCs containing products have been boosted.

In the meantime there is a great variety of technical systems on the market. Beside medicinal inhalation products used for asthma and COPD and for other lung diseases like locally acting antibiotics and antiviral drugs for lung infections, the development of innovative lung delivery devices was triggered by the findings on pulmonary delivery of drugs to the systemic system. Especially for drugs with low oral bioavailability inhalation therapy is an attractive route of administration bypassing the need for parenteral administration. Inhalation products and nasal products have been developed for systemic delivery via the lungs or nasal mucosa. Due to the advantages of nasal and pulmonary drug delivery over conventional drug delivery routes (e.g. fast onset of action, avoidance of hepatic clearance, avoidance of GI digestion of proteins, improved convenience and compliance) these types of products gain growing importance [2].

The aspects of pharmaceutical quality of inhalation products are very complex since they generally consist of a drug product formulation together with a delivery device implicating many different parameters influencing product performance. First regulatory guidance on medicinal products for inhalation have been developed during the early 1990s in parallel by several competent authorities worldwide which had very diverse views on risk assessment of such products [3]. As a consequence regulatory requirements for inhalation products vary significantly throughout the world. Since such complex medicinal products

are mostly developed for an international market divergence in regulatory requirements is a large drawback for product development.

As an effort on harmonization as well as an update of existing regulatory requirements and in order to cover newer types of devices the new CHMP Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products has been compiled and came into effect in the European Union on 1st, October 2006 [4]. As it was recognized that EU and Health Canada regulators have similar approaches to the assessment of these types of products the guideline has been developed in collaboration with Health Canada since 2004 based on an already existing Canadian draft [5] and represents a harmonized guideline for both regions [6]. Prior to this new guideline there was no guidance on nebulisers and nasal sprays in the European Union.

In this thesis the changes of regulatory requirements on pharmaceutical quality specific to inhalation products (pMDIs and DPIs) within the EU and the impact of this new guideline on international drug development in this area are discussed. Topics with the need for further harmonization of requirements in EU/Canada and US are outlined.

Other quality aspects generally to be considered for all kind of medicinal products are not addressed here. Further regulatory requirements and issues specific to medical devices in general [7, 8, 9] are out of scope of this thesis.

2 Overview of Regulatory Environment in EU and US

This is an overview of the current regulatory environment on pharmaceutical quality related requirements which are specific for inhalation and nasal medicinal products demonstrating the important position of the new guideline.

European Union

The new CHMP Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products [4] replaces the guidelines on

- pMDIs (CPMP Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalation Products) [10] and
- DPIs (CPMP Note for Guidance on Dry Powder Inhalers) [11]

and is complementary to the CPMP Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) [12].

For detailed guidance on pharmaceutical development study designs (e.g., priming studies) and the analytical procedures used primarily for inhalation and nasal products (e.g., cascade impactor analysis) the guideline refers to other publications (e.g., United States Pharmacopeia, European Pharmacopoeia, ISO standards [4]). Further requirements on pharmaceutical quality like impurities, process validation, specifications, and stability testing are described in other EU guidance documents, including ICH guidelines.

The European Pharmacopoeia which is legally binding includes several chapters regarding regulatory requirements for medicinal products administered nasal or by inhalation:

- Preparations for Inhalation (5.6/04/2005:0671) [13]
- Preparations for Inhalation: Aerodynamic Assessment of Fine Particles (5.6/04/2005:20918 corrected 5.2) [14]
(International harmonization with USP and JP [15, 16])
- Pressurised pharmaceutical preparations (5.6/01/2005:0523) [17]
- Nasal Preparations (5.6/01-2007:0676) [18]

USA

The FDA has published the following Guidance for Industry which had been considered when drafting the new EU guideline:

- Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products [19]
- Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation [20]
- Guidance for Industry on Integration of Dose-Counting Mechanisms into MDI Drug Products [21].

There are two further guidance documents which, however, are still in draft:

- Draft Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation, which is in draft status since October 1998 [22]
- Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action [23].

The USP (U.S. Pharmacopeia) contains the following monographs regarding current requirements for medicinal products administered by inhalation:

- Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers, General Chapter <601> [24] (Particle size section under revision/ international harmonization) [15]
- Pharmaceutical Dosage Forms, General Chapter <1151> [25]
- The Biocompatibility of Materials used in Drug Containers, Medical Devices, and Implants, General Chapter <1031> [26]
- Minimum Fill, General Chapter <755> [27]
- Uniformity of Dosage Units, General Chapter <905> [28]

However, the USP has not the status of 'law' like the European Pharmacopoeia in EU and FDA's view is not necessarily in line with the USP.

Japan

For Japan no specific guidance on orally inhaled and nasal drug products (OINDP) exists so far [29].

3 New Guideline on Inhalation and Nasal Products

3.1 History of the Guideline

The need for revision and update of the previous CPMP Notes for Guidance on DPIs and pMDIs [11, 10] which came into force in December 1998 and October 2002, respectively, was addressed in a concept paper in April 2004 [6]. Recent significant international developments like the development of new dry powder inhalers, technological innovations in pMDIs, and a variety of single breath liquid systems (non-pressurized metered dose inhalers) needed to be reflected in regulatory guidelines. For nasal products, products for nebulisation, and hand-held nebuliser products no CPMP guidance was available. These developments have been included already in updated general chapters in the European Pharmacopoeia.

In the US the FDA had adopted one updated Guidance for Industry (July 2002) and released a second updated guideline as draft (April 2003) in this area [19, 23].

The Draft Guidance for Industry ‘Pharmaceutical Quality of Inhalation and Nasal Products’ released by Health Canada in November 2003 demonstrated that EU and Health Canada regulators have similar approaches to the assessment of these types of products [6]. This presented the opportunity of developing a harmonized guidance based on the Canadian draft for which the FDA guidance documents and EU guidelines and pharmacopoeial requirements had been considered and incorporated where applicable [16]. The EMEA Quality Working Party and Health Canada started the collaboration on a joint guideline in May 2004 [30].

The first draft guideline of this cooperation was published for consultation in February 2005. Comments from Industry and Health Authorities were received, discussed at a public meeting in October 2005 and considered for the final guideline on the pharmaceutical quality of inhalation and nasal products which was released in April 2006 coming into force in October 2006 in both regions. [4, 31]

3.2 Scope

The CHMP guideline on inhalation and nasal products [4] outlines the specific requirements of quality aspects of new human medical products intended for drug delivery to the lungs or nasal mucosa evoking a local or systemic effect.

New marketing authorization applications for innovative medicinal products as well as generics should comply with the specified requirements. Although the pharmaceutical quality of existing products is not in scope of this guideline, the general principles should be considered for changes of these products.

The guideline does not specifically address clinical trial materials, but drug substance and drug product batches used for pivotal clinical trials need to be extensively characterized in accordance with the guideline as these batches outline the quality of the product proposed for marketing.

The new guidance has been developed for products with drug substances of synthetic or semi-synthetic origin, but the general principles should be considered also for other inhalation or nasal products.

Specific quality aspects are described for inhalation products delivering drug substance to the respiratory tract like

- pressurized metered dose inhalers (pMDI)
- dry powder inhalers (DPI) (device-metered, pre-metered)
- products for nebulisation (single-dose, multi-dose)
- non-pressurized metered dose inhalers (= metered dose nebulisers)

and nasal products like

- pressurized metered dose nasal sprays
- nasal powders (device-metered)
- nasal liquids (single use or multiple use drops, non-pressurized multiple use metered dose spray).

Liquid inhalation anesthetics and nasal ointments, creams and gels are excluded. [4]

3.3 Content Overview

The following section provides an overview of the content of the CHMP guideline on inhalation and nasal products.

Drug Substance

Specific drug substance specifications are addressed for products containing a drug substance which is not permanently in solution during drug product manufacture, storage and use. An appropriate particle size test and acceptance criteria should assure a consistent particle size distribution, expressed as the percentage of total particles in a given size range. Justification of acceptance criteria should be based on particle size distribution of relevant batches whereas process capability and stability data may also be considered.

Drug Product Pharmaceutical Development

General guidance on pharmaceutical development is given the ICH guideline Q8 where it is stated: *The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls* [32].

This importance is also reflected in the CHMP guideline on inhalation and nasal products since the main focus of the guideline is put on the pharmaceutical development of the product. Emphasis is placed on characterization of the drug substance, the drug product, and the device via pharmaceutical development tests ensuring ‘quality by design’ with less emphasis on end product testing. The investigated parameters deliver also information related to efficacy, safety and/or usability of a medicinal product.

In general, development tests should be performed on two different product batches including two different batches of inhalation devices (where applicable) to account for batch variability. Matrixing and/or bracketing design may be acceptable with appropriate justification.

The section on drug product pharmaceutical development is divided in requirements for inhalation products and for nasal products. In each part there is an overview table with development tests normally conducted for characterization of the different product types. Which tests are required depends on the type of product, however, it is stated that not all listed tests might be needed for each product and for some delivery devices even more tests relevant to the performance might be necessary. In this respect high flexibility is provided acknowledging the vast variety of different technical systems.

The overview table on inhalation products lists 21 topics of pharmaceutical development studies and indicates their applicability for pressurized metered dose inhalers, dry powder inhalers (device-metered or pre-metered), products for nebulisation (single-dose or multi-dose), and non-pressurized metered dose inhalers. Following the overview table each topic is explained in more details in the guideline. In order to limit the scope of this thesis Table 1 summarizes the pharmaceutical development studies relevant for inhalation products without further annotations.

Table 1: Overview on pharmaceutical development studies which might be necessary for inhalation and/or nasal products

Pharmaceutical Development Studies for	
Inhalation Products	Nasal Products
(a) Physical characterization	same
(b) Minimum fill justification	same
(c) Extractables / Leachables	same
(d) Delivered dose uniformity & fine particle mass through container life	(d) Delivered dose uniformity through container life
(e) Delivered dose uniformity & fine particle mass over patient flow rate range	no
(f) Fine particle mass with spacer use	no
(g) Single dose fine particle mass	no
(h) Particle / droplet size distribution	same
(i) Actuator / mouthpiece deposition	same

(j) Drug delivery rate and total drug delivered	no
(k) Shaking requirements	same
(l,m) Initial & repriming requirements	same
(n) Cleaning requirements	same
(o) Low temperature performance	same
(p) Performance after temperature cycling	same
(q) Effect of environmental moisture	same
(r) Robustness	same
(s) Delivery device development	same
(t) Preservative effectiveness / efficacy	same
(u) Compatibility	no

Regarding the development testing for generic products and the information coming from pharmaceutical development studies to be included in the SmPC, it is referred to the region specific appendices 1 (generic products) and 2 (SmPC).

The overview table on nasal products indicates the applicability of 16 topics of pharmaceutical development studies (see Table 1) for pressurized metered dose nasal sprays, nasal powders (device-metered), and nasal liquids (single use drops, multiple use drops, single use sprays, and non-pressurized multiple use metered dose sprays). For further details it is referred to the studies discussed for inhalation products.

Drug Product Manufacture

The manufacturing process including all filling and packaging operations have to be described and the filling process has to be validated ensuring formulation homogeneity throughout the routine production. In-process controls are required on correct fill volume/weight, container closure implementation, and performance testing on actuation release mechanism of each unit (where applicable).

Excipients

In addition to the usual pharmacopoeial requirements further tests should be included in the specifications for excipients, such as suitable particle size tests for lactose used in dry powder inhalers. The limits of such tests should be qualified via batches used for pivotal clinical studies. However, *in vitro* studies (like multistage impaction / impinger) might also prove suitability of the limits. In case physical properties of an excipient are important for the drug product performance but are not easily controlled the limitation to a single, validated supplier might be necessary.

For any excipient without well-established use in inhalation and nasal products the safety in the new route of administration has to be shown. It is recommended to seek scientific advice on this issue.

Drug product specifications

Like in the chapter 'Drug Product Pharmaceutical Development' also the section on drug product specifications is divided in specifications specific for inhalation products and for nasal products. Overview tables list drug product specification tests normally included in the specifications of the different product types of inhalation products and of nasal products. In the overviews it is indicated which specification is requested for which type of product. Following the overview tables each topic is explained in more details. The following Table 2 shows a comparison of specific drug product specification tests which might be necessary for inhalation and nasal products.

Table 2: Overview on drug product specification tests which might be necessary for inhalation and/or nasal products

Drug Product Specification Tests for	
Inhalation Products	Nasal Products
(a) Description	same
(b) Assay	same
(c) Moisture content	same
(d) Mean delivered dose	same
(e) Delivered dose uniformity	same
(f) Content uniformity / Uniformity of dosage units	same
(g) Fine particle mass	same
(h) Leak rate	same
(i) Microbial / microbiological limits	same
(j) Sterility	same
(k) Leachables	no
(l) Preservative content	same
(m) Number of actuations per container	same
no	(n) Particle / droplet size distribution

Additionally, for some nasal products testing of the particle / droplet size distribution is required.

Container closure system

Beside the standard specifications for closure systems the reproducibility of drug delivery by the device has to be demonstrated (where applicable). The composition of all components of the container closure system, including coatings and any additives should be provided and have to comply with relevant standards (where appropriate).

Stability

Among the usual stability-indicating tests also weight loss should be examined where appropriate. In case the storage orientation could influence the product quality stability data on different orientations should be presented. If a secondary packaging is used for protection from light and/or humidity the period of time the product may be used after removal of the secondary packaging have to be supported by appropriate stability data at the end of the product's shelf life.

Appendices

Region specific requirements on generic products, the SmPC, and spacers and holding chambers (EU only) are outlined in 3 region specific appendices. Since these requirements could not be harmonized between EU and Canada the guidelines issued in the two regions have different appendices. As an example, in contrast to EU legislation a generic product in Canada must have an identical qualitative composition compared to the reference and the quantitative composition of the excipients may vary only within $\pm 10\%$ of the amount of the excipient in the reference product [30]. As a consequence the requirements for generics could not be harmonized.

In the following only the CHMP guideline has been taken into consideration.

Appendix I: Generic Products

For generic products therapeutic equivalence to the reference product must be demonstrated by *in vivo* and/or *in vitro* studies [12]. For all generic inhalation and nasal products the comparability with the reference product has to be shown with the *in vitro* studies as outlined in this appendix.

Appendix II: Information for Consumers and Health Care Professionals

In appendix II it is stated what specific information from the pharmaceutical quality of inhalation and nasal products should be included in the SmPC sections '2. Qualitative and Quantitative Composition', '4.2 Posology and Method of Administration', and '6.4 Special Precautions for Storage'. For example for products with new chemical entities or with known drug substances used in inhalation products for the first time the dose per actuation should be expressed as delivered dose. Since this is the dose actually reaching the patient

the delivered dose is considered important. For existing products the metered (ex valve) or delivered dose (ex actuator) may be used according to national current practice, however, clearly specified which parameter is used.

Appendix III: Devices including Spacers and Holding Chambers (European Union only)

In the last appendix requested information on medical devices in general and in particular on spacers and holding chambers are defined. Reference is given to the requirements in Council Directive 93/42/EEC [7] which all medical devices have to fulfill.

4 Changes in EU

The new CHMP ‘Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products’ consolidates the updated requirements on the pharmaceutical quality of the various types of inhalation and nasal products in one documents as it replaces the previous guidelines on pMDIs [10] and DPIs [11] and remedies the former lack of guidance on nebulisers and nasal sprays in the European Union. This allows a convenient overview of the requirements on all inhalation and nasal products.

As all requirements on nebulisers and nasal products are newly introduced only changes of the requirements on the pharmaceutical quality of pMDIs and DPIs are discussed in the following.

Drug Substance specification

The requirements for the drug substance regarding particle size testing remain basically unchanged. The new guidance provides more details on appropriate acceptance criteria including considerations on process capability and stability data. The topic of alternative sources of drug substance is also addressed.

Drug Product Pharmaceutical Development

In the new guideline specifics on the number of batches of drug product and the delivery device used for pharmaceutical development are introduced.

Minimum fill justification is added to the required pharmaceutical development testing.

The new guideline now clearly distinguishes between the requirements on extractables and leachables. Whereas an extractable profile should be determined only for non-compendial plastic and rubber container closure components of pMDIs coming into contacts with the formulation during storage, leachable profiles should be investigated for compendial and non-compendial parts.

Delivered dose uniformity is now combined with fine particle mass control throughout container life, which demonstrates the importance of the latter parameter. The reproducibility of the delivered dose and the particle size distribution are the most crucial

attributes of inhalation products. Not only consistency of the emitted dose which reaches the patient (delivered dose) but especially consistency of the fraction which actually reaches the lower airways (fine particle mass) is significant for product efficacy. Also drug safety may be influenced by the fine particle mass. At the one hand systemic side effects might be caused by the amount of drug absorbed via the lungs, at the other hand a change in the fine particle mass results in a changed oropharyngeal fraction, which could affect safety as well.

Besides the testing throughout the container life (inter- and intra-inhaler) for DPIs the consistency of these parameters have to be tested now also over the patient flow rate range. This represents an important test because the fine particle mass of some DPIs could differ by a factor of almost two when the flow rate is increased from 30 L/min to 90 L/min [16]. Due to this fact the minimum, median, and maximum achievable rates should be investigated.

For pMDIs which may be administered with a spacer or holding chamber there is the new requirement to show consistency of the fine particle mass before and after cleaning of the spacer/holding chamber. This requirement was introduced since it has been shown that cleaning instructions for spacers and holding chambers could influence the fine particle mass *in vitro* and the efficacy *in vivo* [16].

In case a pMDI contains a suspension the appropriate shaking before use and any effect of extensive shaking on the delivered dose uniformity has to be evaluated.

Regarding the priming and re-priming of pMDIs it is now requested to store the container in various orientations prior to priming studies and to perform re-priming studies at multiple time points throughout the container life.

Regarding the justification of cleaning requirements the new guideline stipulates that instead of the unchanged aerodynamic particle size distribution rather data providing evidence of no change in delivered dose uniformity and fine particle mass or droplet size distribution have to support appropriate cleaning procedure.

Evaluation of the effect of low and high temperatures on the performance of pMDIs was already included in the former guidance. However, in the new guideline more details are

specified like the required temperatures, storage periods, the justification for re-priming, and test such as leak rate, weight loss, delivered dose uniformity, fine particle mass, related substances and moisture content.

Description of the delivery device development is explicitly requested in the new guideline including changes of design or performance characteristics implemented during product development (e.g. changes of component material, delivered dose, fine particle mass). In case prototype devices have been used for clinical studies their equivalence with the product intended for marketing must be shown. Besides the request for a dose counter or other fill indicator for device-metered DPIs this is now also encouraged for other multiple dose products.

Drug Product Manufacture

New requirements on the formulation are the inclusion of the concentration of the drug substance, the fill amount and the target delivery amount.

In addition to the filling procedure also packaging operations should be validated. Specifics on the number of necessary batches used for process validation are omitted and thus the general requirements on process validation step in.

Excipients

Beside other tests the control of microbiological quality of excipients is now requested and, where applicable, justification has to be provided for omission of routine microbiological quality control.

Drug Products Specifications

In the new guideline a description of the formulation including the delivery device is asked for in the drug product specifications.

Regarding the mean delivered dose now a common limit of $\pm 15\%$ of the label claim is mandatory. In the former guidelines the specified limits for DPIs and pMDIs were 20 % and 15 %, respectively [10, 11].

For pMDIs the need of a test and qualified limits for leachables is explicitly requested, dependent on the results of the drug product pharmaceutical development.

Drug Product Container Closure System

Now the reproducibility of drug delivery by the device has to be demonstrated additionally, where applicable. The composition of all components of the container closure system, including coatings and any additives should be provided. If coatings are employed the procedure including process controls have to be provided.

Definitions

The chapter with elaborate definitions facilitates the exact comprehension of the requirements. This is especially important for such harmonized document valid for several countries/regions to avoid misunderstandings due to deviating meanings of expressions.

Appendix I: Generic products

The requirements on generic products have not been specified in the previous guidelines [10, 11]. Besides the reference to the 'Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products' [12] the *in vitro* studies necessary for all generic inhalation and nasal products regarding the comparability with the reference product are explained. For generic pMDIs and /or DPIs comparability must be demonstrated in terms of

- a complete individual stage particle size distribution profile
- the delivered dose
- extractables / leachables
- delivered dose uniformity & fine particle mass over patient flow rate range
- particle / droplet size distribution
- pharmacopoeial excipients.

In summary there are now more requirements in the new guideline specified in a higher level of details than in the preceding EU guidance giving comprehensive and scientifically sound guidance. More emphasis is laid on characterization via extensive testing during pharmaceutical development which is in line with the ICH guideline on pharmaceutical development (Q8). However, acknowledging the vast variety of different technical systems in this area high flexibility of many requirements is provided.

5 Comparison of CHMP and FDA Requirements

In this thesis the comparison of specific requirements in EU and US has been concentrated on some important issues of pMDIs and DPIs not taking into consideration nasal products and products for nebulisation.

The US requirements specific for pMDIs and DPIs are summarized in the ‘Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation’ which is still a draft since October 1998 [22]. In general FDA guidance documents imply a higher level of details with more stringent acceptance criteria than EU guidelines and ask for additional tests and characterization studies. Furthermore, FDA guidance is not necessarily in line with pharmacopoeial compendia like USP. The new CHPM guideline contains higher flexibility and offers case by case approach in terms of tests needed and related acceptance criteria. However, also the FDA guidance states that alternative approaches may be used and applicants are encouraged to discuss these with the appropriate FDA division prior to implementation [22].

Drug Substance

In addition to the EU guideline the FDA guidance asks besides the control of particle size distribution as specific drug substance specification also for the control of crystalline forms (e.g. shape, texture, surface) of the drug substance.

Drug Product Pharmaceutical Development

The following section describes additional or divergent requirements of the FDA guidance compared to the EU guideline (see also section 3.3 Content Overview, Drug Product Pharmaceutical Development).

In general the FDA guidance states that development tests should be performed on three instead of two different product batches.

The characterization of the **plume geometry**, and tests after **microbial challenge** are additional tests not requested in the EU guideline.

For products with different strengths ***in vitro* dose proportionality** should be characterized in terms of emitted dose content uniformity and particle size distribution, whereas in EU proportionality of fine particle mass has to be shown which is the more relevant parameter regarding product efficacy and safety.

In case a pMDI may be administered via a **spacer** the emitted dose content uniformity and particle size distribution at different flow rates and after increasing waiting periods should be evaluated. In EU the fine particle mass is the performance indicating parameter which has to be evaluated, additionally in connection with cleaning instructions.

For DPIs the effect of the **performance over a flow rate range** has to be evaluated in terms of emitted dose content uniformity and particle size distribution instead of the delivered dose uniformity and the fine particle mass like in the EU guideline.

As additional tests for DPIs the evaluation of dose build-up and flow resistance are required. Instead of determination of the device's flow resistance the EU guideline requests investigation of minimum delivered dose and fine particle mass at the minimum, median, and maximum rates achievable by the intended patients population which provides more relevant information on product performance related to efficacy and safety in practical use.

In summary, there are some additional tests for drug product pharmaceutical development requested in the FDA guidance. On the other hand several tests which are specified as drug product specifications are not indicated for pharmaceutical development like in the EU guideline. However, all quality indicating parameters have to be evaluated during pharmaceutical development to assure consistent product quality. Prior to using a parameter for quality control of the finished product it has to be investigated in details which should take place during development. Further on, there are also some tests missing in the FDA guidance which are requested by the EU guideline, like fine particle mass, actuator/mouthpiece deposition (for DPI), re-priming through container life, effect of low temperature on performance and delivery device development. These are very important parameters defining the product performance and have to be analyzed for pharmaceutical development. Regarding a dose counter or other fill indicator which is requested in the EU

guideline there is a separate FDA guidance on integration of dose-counting mechanisms into MDI drug products [21] but not for DPIs.

Excipients

Further to requirements for excipient specifications in EU (see section [3.3 Content Overview, Excipients](#)) the FDA guidance requests extensive routine testing on all excipients like for a drug substance. Drug master files should be submitted for major and non-compendial excipients. The request of broad routine testing is comprehensible for non-compendial excipients; however, for compendial excipients the additional requirements specified in the new EU guideline seem sufficient and more adequate to assure continuous high product quality.

Drug product specifications

In addition to the EU requirements for drug product specifications (see section [3.3 Content Overview, Drug product specifications](#)) specific to inhalation products the FDA guidance requests for more tests, as presented in Table 3. There are also tests with the same name (e.g. drug content (assay)) but with different meaning. However, there are also tests required in EU which are not listed in the FDA guidance (see Table 4).

Table 3: Specific Characteristics for Inhalation Drug Product Specifications in the US

(* Additional parameter compared to EU requirements)

Characteristics	pMDIs	DPIs
Appearance and Color	yes	yes
Identification	yes	yes
Microbial Limits	yes	yes
Water or Moisture Content	yes	yes
Dehydrated Alcohol Content *	yes (if alcohol is used as co-solvent)	no

Net Content (Fill) Weight *	yes	yes
Drug Content (Assay) *	yes (concentration in entire container)	yes (amount in dosage unit for pre-metered and in reservoir for device-metered)
Impurities and Degradation Products	yes	yes
Dose Content Uniformity	yes	yes
Dose Content Uniformity through Container Life *	yes	yes
Particle Size Distribution *	yes	yes (of Emitted Dose)
Microscopic Evaluation *	yes	yes
Spray Pattern *	yes	no
Leak Rate	yes	no
Pressure Testing *	yes	no
Valve Delivery (Shot Weight) *	yes	no
Leachables	yes	no

Table 4: Specific Characteristics for Inhalation Drug Product Specifications not requested in the US

Characteristics	pMDIs	DPIs
Mean Delivered Dose	X	X
Fine Particle Mass	X	X
Number of Actuations per Container	X	X

A specific assay and appropriate limits for **dehydrated alcohol content** have to be included in the drug product specifications for pMDIs in case alcohol is used as co-solvent.

Net content (fill) weight correlates with minimum fill in EU, however, the latter should be performed within the pharmaceutical development studies and is not part of the drug product specifications. Regarding the acceptance criteria the FDA guidance refers to the USP chapter <755> 'Minimum Fill' [27] which states that none of the 10 tested containers should contain less than the labeled amount. In EU the acceptance criteria are the same as the drug product specifications for delivered dose uniformity and fine particle mass (see below; 13).

Regarding **drug content (assay)** the FDA guidance implies the drug substance concentration in entire container (pMDI), the drug substance amount per dosage unit (pre-metered DPI), or in the whole reservoir (device-metered DPI) whereas in EU the amount per weight or volume unit, or for single dose products per dosage unit is requested. FDA sees this test not so much as a performance criteria of the drug product but as an assurance of consistency of manufacture (e.g. formulation, filling, crimping, and sealing). As an alternative the EU guideline requests determination of the **number of actuations per container** in the specifications. Combined with other specifications (e.g. delivered dose uniformity and mean delivered dose) this criteria is more important for product quality control and, finally, for patients than the drug content in the entire container or net content (fill) weight.

Furthermore, a consistent manufacturing process should be ensured via an appropriate process validation rather than extensive routine testing of the finished product.

Control of **dose content uniformity** is regarded by the FDA as the overall performance evaluation of a batch by assessing the formulation, manufacturing process, valve and the actuator. The acceptance criteria have been partly harmonized recently between USP and Ph.Eur. but since the draft FDA guidance has been released in 1998 the new, less stringent criteria are not yet incorporated in the FDA guidance. Ph.Eur. and USP specifications employ the same sets of limits but the requirements are not identical regarding the base for calculating the specified percentages. In USP chapter <601> [24] criteria are based on the labeled claim whereas in Ph.Eur. [13] the criteria are based on the mean value of the results (mean delivered dose). On the other hand the EU guideline additionally requests the evaluation of the **mean delivered dose** within the drug product specifications and indicates that the mean delivered dose should be within $\pm 15\%$ of the label claim.

The FDA guidance requests as specification the **dose content uniformity throughout container life**. The EU guideline asks for this test within the pharmaceutical development but not explicitly as control test for each product batch. However, according to the section on Preparations for Inhalation [13] the Ph.Eur. also requests evaluation of delivered dose content uniformity also throughout the container life.

In contrast to the EU guideline the control of **fine particle mass** (which actually reaches the lower airways) is not demanded by the FDA guidance as specification criterion, although this parameter is very important regarding product quality, affecting product efficacy and safety. The specification for particle size distribution which is requested in the FDA guidance should be replaced by the superior parameter fine particle mass.

Microscopic evaluation is requested by the FDA but not in EU. In the FDA guidance this examination is justified with provision of additional information (presence of large particles, changes in morphology of drug substance and/or carrier particles, extent of agglomerates, crystal growth, and foreign particulate matter). As routine testing for batch release the control of the fine particle mass is considered much more meaningful than microscopic evaluation rendering the latter unnecessary.

Further additional US specifications for pMDIs are **Spray Pattern** (shape and size) which evaluates the performance of valve and actuator, **Pressure Testing** for pMDIs using a co-solvent or more than one propellants (which verifies the proper propellants or propellants mixture ratio), and **Valve Delivery (Shot Weight)** which evaluates the valve-to-valve reproducibility. In EU the latter is requested as a specification of the container closure system but not of the final drug product. Like the tests for Spray Pattern these tests are important in pharmaceutical development but are not effective tests for routine testing of the final product. Quality affecting factors of components like size and shape of the actuator orifice or valve performance have to be tested and controlled within the incoming components acceptance tests. Therefore, as specification for testing of the final product these tests are redundant and less sensitive to product performance changes than dose delivering testing [34]. Parameters which are already assured during product development and components control should not be required for the testing of finished product.

In general, it is preferable that a regulatory guideline does not stipulate detailed specifications on pharmaceutical quality but rather outlines a process for setting specifications which are product specific and data driven.

Drug Product Container Closure System

In the FDA guidance the requirements on the drug product container system are outlined in details whereas the EU guideline mainly refers to the relevant Ph.Eur. chapter. The differences are not further discussed here.

6 Considerations for Future Harmonization

Since most pharmaceutical manufacturers of inhalation and nasal products intend to operate in more than one region nearly all such products are international developments. Global harmonization of regulatory requirements is important for a streamlined global development process enabling fast and cost-effective development and availability of new and safe inhalation products to patients.

The new CHMP Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products [4] represents a harmonized up-to-date guidance within EU and Canada which has already taken into consideration FDA requirements. As a consequence, compared to the former EU guidance, the requirements in the new guideline are closer to the FDA requirements concerning the characterization level. But, at the same time, due to case by case approaches higher flexibility is provided in terms of which parameters need to be evaluated and the related acceptance criteria.

In the previous section (5. Comparison of CHMP and FDA Requirements) the differences of the requirements in EU/Canada and in US are outlined. There are several topics discussed which are indicated for further harmonization, such as the differing acceptance criteria for dose content uniformity, whether the fine particle mass (EU) or the particle size distribution (US) is considered as the performance indicating parameter, the divergent specifications and details for tests on the effect of low temperature and temperature cycling on product performance, the acceptance criteria for minimum fill, the different definitions of drug content (assay), the number of actuations per container, microscopic evaluation, spray pattern and shot weight. The draft FDA guidance requests many individual tests for routine quality control of the finished product. However, an excessive number of tests at the release of a finished product may be redundant and meaningless. Modern quality control theories emphasize that quality cannot be "tested into the product" but rather, should be "built in". The goal of this concept is characterizing a new product via extensive development studies and applying that information to select appropriate control tests for the finished product maximizing the value of characterization and control testing and minimizing redundant testing. [34]

Further aspects which are not yet covered in a harmonized guideline are the conditions under which *in-vitro* studies can be used to waive clinical trials (as specified in the CPMP points to consider on the requirements for clinical documentation for orally inhaled products [12]) together with the acceptance limits for *in-vitro* equivalence for which no consensus is reached yet even within the EU. [33]

The FDA follows a totally different concept of the review of a new drug application (NDA) and appears to have a different risk perception and risk management regarding manufacturing and quality aspects of inhalation products [3]. The FDA draft guidance on Metered Dose Inhaler (pMDI) and Dry Powder Inhaler (DPI) CMC documentation, published in 1998, contains quite exact specifications which are more stringent compared to previous FDA requirements and also to existing public standards. As a consequence, the draft guidance was met with public criticism raising significant concerns with FDA's regulatory approach to inhalation drug products and indicating that certain tests recommended by the draft guidance were not scientifically justified [36]. Since the pharmaceutical manufacturers had difficulties to comply with the more stringent requirements they formed a consortium (IPAC-RS, International Pharmaceutical Aerosol Consortium on Regulation and Science) to pool their financial and intellectual resources and to discuss their proposals together with the FDA. Their major topics are delivered dose uniformity, foreign particulates, supplier quality controls, microbiology, leachables and extractables, particle size distribution profile comparisons, cascade impactor, and mass balance [3]. Beside other scientific platforms IPAC-RS tries to stimulate constructive dialogue of scientists and regulators from FDA, international regulatory agencies, industry, academia, USP and other stakeholders to develop a common realistic view on appropriate requirements aiming to updated (new draft) FDA guidance with a higher degree of international harmonization. [35]

At the IPAC-RS conference last November one of the main topics in addition to the international harmonization of regulatory requirements was the conversion from the old approaches to the new Quality by Design (QbD) concept which is outlined in the harmonized ICH guideline Q8 [32]. The QbD concept emphasizes enhanced product and process understanding gained through pharmaceutical development. This is the basis of

control strategies and less emphasis is laid on end-product testing but more reliance put on process control and in-process monitoring. Global acceptance of the Quality by Design concepts will facilitate global developments. Internationally harmonized solutions are needed for many issues on how development, manufacture, control and risk management of inhalation and nasal products could change under this new model [35]. A pre-requisite for further harmonization in this direction is the updating of guidelines to incorporate the principles of the ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality Systems). Especially the ICH guideline Q6A on Specifications - Test Procedures and Acceptance Criteria (CPMP/ICH/367/96) needs to be brought in line with key aspects of QbD, e.g. Process Analytical Technology (PAT). [29, 32]

Updating of the draft FDA 'Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation' with the concepts of Quality by Design might dispose the requirements for some unnecessary and redundant quality control tests on the finished product and put more emphasis on pharmaceutical development. This would be a beneficial step for international harmonization of the requirements for inhalation products.

The new CHMP guideline which is harmonized within EU and Canada and took also the US requirements into consideration could serve as a good basis for an urgently required update of the FDA draft guidance from 1998 to align with recent progress in scientific and regulatory developments.

7 Summary

Medicinal products for inhalation are commonly used for asthma and COPD, but also as locally acting antibiotics and antiviral drugs for lung infections. Recently, inhalation and nasal products gain growing importance due to the advantages of nasal and pulmonary drug delivery to the systemic system over conventional drug delivery routes. These types of products consist of a great variety of technical systems and the aspects of pharmaceutical quality are very complex since these products generally are composed of a drug product formulation together with a delivery device. This implicates many different parameters influencing product performance.

As an effort on harmonization as well as an update of existing regulatory requirements and in order to cover newer types of devices the new ‘Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products’ has been jointly developed by the EMEA Quality Working Party and Health Canada and came into effect in both regions in October 2006. It replaces the previous CHMP guidelines on pMDIs and DPIs and remedies the former lack of guidance on nebulisers and nasal sprays in the European Union.

In this thesis the changes of regulatory requirements on pharmaceutical quality specific to inhalation products (pMDIs and DPIs) within the EU and the differences to FDA requirements are discussed. Topics for further harmonization between EU/Canada and US are outlined.

In the new CHMP guideline emphasis is placed on characterization of drug substance, drug product, and the device via pharmaceutical development tests ensuring ‘quality by design’ with less emphasis on end product testing which is in line with the ICH guideline on pharmaceutical development (Q8). In the section on pharmaceutical development and the section on drug product specifications tables with development tests normally conducted for characterization and with tests normally included in specifications give a concise overview on the requirements for the different product types. It is stated that depending on the type of product not all tests (or additional tests) might be required providing high flexibility acknowledging the vast variety of different technical systems. In

the new guideline there are now more requirements specified in a higher level of details giving comprehensive and scientifically sound guidance.

The US requirements specific for pMDIs and DPIs are outlined in the 'Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation' which is still a draft since October 1998. Compared to the new EU/Canadian guideline there are some additional tests for drug product pharmaceutical development requested in the draft FDA guidance, but there are also some important tests for product development missing. An essential difference for instance is that the evaluation and control of fine particle mass (the fraction which is actually reaching the lower airways) is not requested by the draft FDA guidance for pharmaceutical development and as specification criterion, although this parameter is very important regarding product quality, affecting product efficacy and safety. The test for particle size distribution which is the corresponding parameter requested in the draft FDA guidance should be replaced by the superior parameter fine particle mass.

The draft FDA guidance requests many individual tests for routine quality control of the finished product including parameters which are already assured during product development and components control, and which should not be required for redundant testing of finished product. Modern quality control theories emphasize that quality cannot be "tested into the product" but rather should be "built in". The goal of this concept is characterizing a new product via extensive development studies and applying that information to select appropriate control tests for the finished product maximizing the value of characterization and control testing and minimizing redundant testing.

Updating of the draft FDA guidance from 1998 with the concepts of Quality by Design might dispose the requirements for some unnecessary and redundant quality control tests on the finished product and put more emphasis on pharmaceutical development. This would be a beneficial step for international harmonization of the requirements for inhalation products.

The new CHMP guideline which is harmonized within EU and Canada and already took the US requirements into consideration could serve as a good basis for an urgently

required update of the FDA draft guidance from 1998 to align with recent progress in scientific and regulatory developments.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Dr. Herta Reile