ICH Q8: Pharmaceutical Development. Regulatory Requirements Directed by the New Note for Guidance (EMEA/CHMP/167068/2004) in Comparison to the Previous Guideline (CPMP/QWP/155/96). A Critical View from the Generic Pharmaceutical Industry.

Wissenschaftliche Prüfungsarbeit
zur Erlangung des Titels
"Master of Drug Regulatory Affairs"
der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Wilhelms-Universität Bonn

vorgelegt von
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Bonn 2007

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List of abbreviations

API	Active Pharmaceutical Ingredient
CHMP	Committee for human medicinal products (replaces the former term CPMP)
CVMP	Committee for Veterinary Medicinal Products
CMS	Concerned Member State
CP	Centralised Procedure
CPMP	Committee for proprietary medicinal products (replaced by CHMP)
CTD	Common Technical Document
DMF	Drug Master File
DP	Decentralised Procedure
EEC	European Economic Community
EC	European Community
EMEA	European Medicines Agency
EU	European Union
EWP	Efficacy Working Party
GMP	Good Manufacturing Practice
FDA	Food and Drug Administration
HMP	Herbal Medicinal Product
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
MRP	Mutual Recognition Procedure
NDA	New Drug Application
NCE	New Chemical Entity
NtA	Notice to Applicants
PAT	Process Analytical Technology
Ph. Eur.	European Pharmacopoeia
PIL	Patient information leaflet
PSUR	Periodic safety update report
QA	Quality Assurance
QC	Quality Control
QWP	Quality Working Party
RMS	Reference Member State
RoW	Rest of the world
SmPC	Summary of Product Characteristics
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

Introduction

In November 2005 the new "Note for Guidance on Pharmaceutical Development" (EMEA/CHMP/167068/2004) was approved by the EMEA (European Medicines Agency) and came into operation on 1 May 2006. This guideline follows the previous "Note for Guidance on Development Pharmaceutics" (CPMP/QWP/155/96) from July 1998 although this has not explicitly been mentioned in the new guideline[1, 2].

The new guideline is the transition by the CHMP (Committee for Human Medicinal Products within the EMEA) of the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Topic Q8 (Q = quality) with the identical title "Pharmaceutical Development", which was finalised (Step 4) in November 2005 [3].

The Pharmaceutical Development section in the quality Module 3 itself provides a summary and overview of the components of the drug product, its manufacture and quality control with the special focus on the development aspects of the drug product from early initial galenical stages towards a high qualitative product as intended for the market.

The aim of this thesis is to compare the requirements as presented by the new guideline (EMEA/CHMP/167068/2004) in comparison to the ones directed by the previous guideline (CPMP/QWP/155/96). A special focus is laid on the needs and requirements for the generic pharmaceutical industry with respect to pharmaceutical development and a reflection of its conversion in the near future.

The history and development of the new guideline ICH Topic Q8

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines [4].
In the sixties and seventies of the 20th century a rapid increase in legislation, regulation and guidelines for reporting and evaluation the data on quality, safety and efficacy of new medicinal products was observed [4, 5]. The detailed technical requirements had diverged in different regions over time to such an extend that the industry found it necessary to duplicate many time-consuming and expensive test procedures in order to market new products internationally. These conditions required for harmonisation. The first harmonisation of regulatory requirements was achieved by the European Community in the 1980s.
Eventually the ICH was founded in April 1990 by representatives of the regulatory agencies and industry associations of the three regions, European Union, Japan and the USA, which

have been involved since then [4]. ICH is comprised of Six Parties that are directly involved and three Observers and IFPMA. The Six Parties are the European Commission (presented by the CHMP), the Ministry of Health, Labour and Welfare in Japan (MHLW), the US Food and Drug Administration (FDA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japan Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The ICH Observers comprise the World Health Organisation (WHO), the European Free Trade Association (EFTA, represented at ICH by Swissmedic) and Canada (represented by Health Canada). IFPMA is the International Federation of Pharmaceutical Manufacturers & Associations.

At first the ICH steering Committee was established. Topics for harmonisation are divided into Quality (Q), Safety (S) and Efficacy (E). Six-party Expert Working Parties (EWPs) for each topic have been established. These meet in the same week as the Steering Committee and report their progress.

Six international conferences took place in the meantime between 1991 and 2003. The aim is to remove the need to duplicate clinical and preclinical studies, harmonise the requirements for applications and eventually to introduce new medicines sooner to the markets by harmonised requirements. Initially, ICH guidance was predominantly intended for "New Chemical Entities" (NCE) but since the developed guidelines can be regarded as state of the art in pharmaceutical science, these are applicable to all other kind of products as well.

Each topic of harmonisation follows the five ICH steps from the first discussion of a given topic for harmonisation towards its final implementation into national legislation or guidance in the tripartite regions [4].

Step 1: Consensus building.
Technical Discussions in the Expert Working Parties (EWP).

Step 2: Confirmation of six-party consensus.
A consensus text is released for consultation. This process is predominantly industry-driven.

Step 3: Regulatory Consultation and Discussion.
Performed by the involved authorities.

Step 4: Adoption of an ICH Harmonised Tripartite Guideline.
Available after signing by authorities, lawyers and the Steering Committee

Step 5: Implementation.
To be performed on regional basis.

The advantages of the ICH are obvious. The improved regulatory cooperation provides an atmosphere of mutual confidence and trust. A globalisation of standards shall be reached and a scientific perspective provided. ICH guidelines are robust and thus of great scientific value for applicants in comparison to pure national guidance. These efforts will result in better trade effects like better market penetrations in the other regions, political perspectives like the involvement of the EU and the reduction of duplicated testing and resources. Finally the ICH developed guidances are also accepted on other countries as scientific standard, e.g. Australia.

The harmonisation of requirements for pharmaceutical development was one of the ICH topics among others and resulted in the guideline Q8.

With the switch from the former "NtA" format [6] towards the CTD (Common Technical Document) structure in 2001 (ICH M4, (M = multidisciplinary) [7]) and its final implementation within the EU in July or November 2003 [8, 9], the guideline CPMP/QWP/155/96 was no longer up to date since it basically reflects the former structure of "Part II A.4 Development Pharmaceutics" of the chemical pharmaceutical part of the application dossier.
However, a simple adaptation to the new CTD structure "3.2.P.2 Pharmaceutical Development" with its six subsections 2.1 – 2.6 was not the predominant reason and does not justify a new guideline but at most only a revision. ICH M4 provides already a summary of basic description and requirement to the CTD sections 3.2.P.2.1 – 2.6, which are only partially comparable and compatible with the previous guideline on "Development Pharmaceutics" (CPMP/QWP/155/96).

The starting situation for pharmaceutical development was different in the tripartite regions before ICH Q8 was initiated [10]. In the USA there have been different opportunities to submit information on development. One possibility is the submission of the Investigational New Drug dossier (IND). Other companies use the EU CTD section 3.2.P.2 for submission. Finally, the information on development is distributed in the new drug application (NDA) but less combined. However, the American CTD is more focussed on future regulatory commitments and the applicant does less focus on the description how the product was actually developed. The current "Development Report" puts more emphasis on the successful Pre-Approval Inspection (PAI). In Japan there have been limited expectations on development and increased information has been requested for more complex formulations only. However, since Japan focuses more on Module 2 (as the successor of the former GAIYO) but less on the quality Module (3) itself, the information on development is usually summarised to a limited amount.
This general view is different in the EU. The section "Development Pharmaceutics" has traditionally been used to describe the development of the formulation, critical attributes of the product and the development of the manufacturing process [10]. The EU supports the definition of requirements for specific dosage forms on top of the information, which has already been required for the key central document. Studies on the pharmaceutical development are regarded as the basis of a proper and successful development of a drug product. These data shall prove that a risk analysis has been conducted on the suitability of the formulation and the manufacture of the presented medicinal product. Critical aspects shall be detected by these studies in order to provide sufficient proof that the required quality can be maintained during the routine manufacturing process of the drug product. Therefore, a specific guideline on "Development Pharmaceutics" (CPMP/QWP/155/96) was already in place since 1998.
In this context it is of central focus for the industry to avoid largely different application dossiers within these regions. These different approaches to the presentation of developmental

studies in the tripartite regions required for harmonisation. It was therefore agreed within the CTD-quality international working group that a harmonised guideline is beneficial especially in view to a consistent approach for providing and evaluating developmental data across the three regions. This guideline was meant to be developed to describe 'what' shall be discussed in the CTD section 3.2.P.2 but not to define the 'how', i.e. the details of necessary studies to be carried out [11].

Eventually the harmonisation initiative for pharmaceutical development in the tripartite regions was started in October 2003 with Q8 as an ICH topic. After four meetings of the involved Expert Working Party (EWP) Step 2 was reached in November 2004 and the transmission of the draft guideline to the CHMP for public commenting was conducted. After the transmission to the interested parties the following month, the final approval was achieved in November 2005. Finally, the guideline is now implemented or adopted since May and September 2006 in the tripartite regions, respectively [4].

What is the outcome of this international initiative? ICH Q8 is not only a replacement or addition of the previous (solely European) guideline but it is more, it is the joint initiative of the tripartite regions, the USA, Japan and the European Union. It is therefore an adaptation to the requirements of all ICH regions to harmonise the requirements on pharmaceutical development and is the reflection to an increased knowledge in pharmaceutical science. The applicant is invited to give better insight into his developmental studies leading to the formulation as intended for the market. Furthermore, ICH Q8 provides an offer to combine the pharmaceutical development studies with quality risk management and quality systems as described and outlined in ICH Q9 and Q10.
The new guideline focuses in more detail which kind of developmental data are today required with focus to the CTD, which are also referred to as the baseline expectations [10]. However, the main reason within the harmonised view towards this new guideline was to give the applicant more "freedom" or better "space" to demonstrate the suitability of the chosen product formulation, its development to the final presentation and the manufacturing process as intended for the market. Finally, the newly introduced term "design space" offers the opportunity to "provide assurance of quality" instead of following and maintaining a specific list of requirements to be demonstrated and fulfilled by the applicant for the chosen formulation. An ICH Q8 Annex is planned for the future, which will contain requirements for specific dosage forms [10, 12].

The contents and requirements according to the new guideline

In the following section the contents of the new guideline shall be closer reviewed. For each subsection the same numbering is used as in the note for guidance.

1. Objective and Scope

The objective of this guideline is to describe the suggested contents for the section 3.2.P.2 "Pharmaceutical Development" of a regulatory submission / quality dossier in the current ICH M4 Common Technical Document (CTD) format.
According to the new guideline this section is regarded as an opportunity for the applicant to present the gained knowledge of scientific approaches and quality risk management during the development and manufacturing process of a pharmaceutical product intended for marketing. This section shall provide a comprehensive understanding of the product and its manufacturing process for official reviewers and inspectors in order to understand easier the final selection of the pharmaceutical dosage form, its manufacturing process and packaging material. Furthermore, this guideline names areas for more flexible regulatory approaches based on the presentation of a greater understanding and relevant scientific knowledge about the medicinal product gained by the applicant.

This guideline gives general guidance on the contents of the section 3.2.P.2 for drug products within the Module 3 of the Common Technical Document according to the ICH guideline M4 [7, 8]. Although the guideline does not directly apply to contents of dossiers during the clinical research stages of drug development (so called "Investigational Medicines Product Dossiers", IMPD), their principles should be regarded during those stages as well.

2. Aim of Pharmaceutical Development

It is the aim of the Pharmaceutical Development section to demonstrate that a medicinal product of the required quality and intended performance has been created. Pharmaceutical development studies and the gained manufacturing experience are intended to provide the establishment of the design space, the product specifications and the manufacturing controls (in-process controls).
Here the ICH uses for the first time the term "design space", which is defined as the "multidimensional combination and interaction of input variables, process parameters and the assurance of quality for the intended product".

The term "design space"
It is especially interesting that working within the design space is not considered as a post-approval change. Hence, the movement out of the presented design space is considered to be a change, which will usually initiate a regulatory post approval variation process as described in the Guideline on Dossier Requirements for Type IA and Type IB Notifications or a type II variation [13, 14, 15]. Thus, the definition and development of a design space (which will be

evaluated and approved by the regulatory authority) can provide the opportunity for the applicant to alter his medicinal product during the marketing phase without the need to initiate post-approval variations to the medicinal product.

In this context it is important to understand that the quality of the pharmaceutical product "cannot be tested into products but quality should be built in by design" [1]. Therefore the pharmaceutical development shall provide information for the basis of quality risk management. Changes in the formulation and manufacturing process during the development of the product including unexpected results and further lifecycle management steps shall be regarded as opportunities to achieve additional knowledge and understanding of the product and provide the frame for the establishment of the "design space." This term will be discussed in more detail in an own section below.

The Pharmaceutical Development section shall include the knowledge and justification for the selected type of dosage form and the proposed formulation; both should demonstrate that the selected formulation is suitable for the intended use of the product. It shall be demonstrated that the development of the drug product and its manufacturing process can be well understood by reviewers.
Therefore, this section shall contain at least all aspects of drug substances, excipients, container closure systems and manufacturing processes, which are critical to the product quality, and control strategies to observe these shall be justified. These aspects are regarded as critical as long as their variation can have an impact on the drug product quality.

The Pharmaceutical Development section is especially intended as an opportunity for the applicant to demonstrate his enhanced knowledge of the product performance depending on a wider range of material attributes, manufacturing processes and process control parameters. This knowledge demonstrated by the applicant gives an overview about his degree of process understanding and facilitates the establishment of an extended design space.
These can include

- risk-based regulatory decisions
- manufacturing process improvements within the approved design space described in the dossier
- reduction of post-approval submissions and
- real-time quality control which leads eventually to a reduction of end-product release testing

The appropriate use of quality risk management principles can lead to additional development studies in order to collect additional knowledge.

It is important to realise that the developed level of gained knowledge, and not the volume of data per se, provides the basis for science-based submissions and their regulatory evaluation.

The current guideline gives an overview and guidance on all sub-sections of the Pharmaceutical Development and it is fortunately subdivided in the same way as section 3.2.P.2 described in the ICH M4 guidance. This includes:

1. Introduction
2.1 Components of the Drug Product
    2.1.1 Drug Substance
    2.1.2 Excipients
2.2 Drug Product
    2.2.1 Formulation Development
    2.2.2 Overages
    2.2.3 Physicochemical and Biological Properties
2.3 Manufacturing Process Development
2.4 Container Closure System
2.5 Microbiological Attributes
2.6 Compatibility

In the following the new guideline shall be closer reviewed. For each subsection the same numbering is used as in the note for guidance.

2.1 Components of the Drug Product (3.2.P.2.1)

2.1.1 Drug Substance (3.2.P.2.1.1)

Since the physicochemical and biological properties of the drug substance can influence the performance and manufacturability of the drug product, theses properties should be identified and discussed e.g. solubility, water content, particle size, crystal properties, biological activity and permeability. ICH Q8 refers here to another ICH guideline, Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products, and their included decision trees #3 and #4 for further guidance on the potential effect of physicochemical properties of the drug substance on the drug product's performance [16]. The gained knowledge here can be used to justify elements of the drug substance specification laid down in section 3.2.S.4.5.

Furthermore, the compatibility of the drug substance with the used excipients for the selected formulation should be evaluated. Finally, if more than one drug substance is contained in the finished product, their compatibility between each other must be evaluated as well.

2.1.2 Excipients (3.2.P.2.1.2)

Since the chosen excipients, their concentrations and their characteristics can influence the drug product performance like stability and especially bioavailability and also the

manufacturability of the product, their choice should be discussed individually in relation to their intended function within the formulation. This evaluation should also include processing aids like granulation fluids.
It is also necessary to reflect the compatibility of the excipients with each other. The intended functionality of excipients like antioxidants, penetration enhancers, disintegrants, release controlling agents and especially preservatives must be demonstrated – not only at the product's release but also throughout the intended shelf life.
Information about the performance of excipients (e.g. antioxidants of preservatives) can be used to justify the drug product specification (in section 3.2.P.5.6) where appropriate.

2.2 Drug Product

2.2.1 Formulation Development (3.2.P.2.2.1)

In this section the applicant should provide a summary on the development of the formulation for the intended usage and route of administration. Formal experimental designs can be useful to identify variable parameters, which might be critical or important to the drug product's quality.
This summary should describe the evolution of the drug product formulation from initial concepts to the final design including the choice of drug components like drug substance, excipients, container closure system or any relevant dosing devices. If appropriate, the knowledge with similar drug product(s) can also be used to reflect the selected formulation.
Any excipient ranges in the batch formula (3.2.P.1) should be highlighted in this section and justified on the experience achieved during the relevant manufacturing development.

Often the formulation between initial batches e.g. used in clinical safety and efficacy or bioavailability studies and the composition proposed for the final commercial product has changed and improved. In this section the applicant should provide an overview and rationale about the differences and the justification of the formulation development changes.
In this context any information from comparative in vitro (like dissolution) or in vivo studies (bioequivalence) should be summarised and a reference to the study batches should be provided. The successful correlation of in vitro/in vivo studies should be provided in this section as well. This correlation can support the selection of appropriate dissolution acceptance criteria or eventually reduce the need for further bioequivalence studies when changes to the product or its manufacturing process are intended.

Finally, all special design features of the drug product like tablet score lines, overfill, anti-counterfeiting measures etc. should be described and justified in view to the intended use of the pharmaceutical product.

2.2.2 Overages (3.2.P.2.2.2)

Overages of the drug substance compensating for degradation during the manufacture or shelf life are generally discouraged by authorities since these can negatively influence the safety and efficacy of the product.
If an overage of the formulation is used, any information about the amount and reason of the overage and the justification for the amount of overage should be provided. The overage should be fully included in the batch formula (3.2.P.3.2).

2.2.3 Physicochemical and Biological Properties (3.2.P.2.2.3)

If physicochemical and biological properties like physiological implications of the drug substance and formulation attributes are relevant to safety, performance or manufacture of the drug product, these should be discussed in this section, e.g. studies on the development of a test for the respirable fraction of an inhaled product can be included. Otherwise, any information supporting the selection of disintegration versus dissolution testing to assure drug release together with a suitable test should be provided and justified. This discussion should cross-reference to any relevant stability studies in the stability section (3.2.P.8.3). Reference is provided to the ICH Q6A "Specifications" guideline with its decision trees #4 and #7 or the ICH Q6B guideline [16, 17].

2.3 Manufacturing Process Development (3.2.P.2.3)

In this section the applicant has the opportunity to explain the selection, the control and any improvements of the manufacturing process as intended for the commercial production and as described in the manufacturing section (3.2.P.3.3) in the CTD format.
The appropriateness of the components and the used equipment should be discussed in consideration of critical formulation attributes. Process development studies, its improvement, the process validation and continuous process verification and any process control requirements should be provided and should include microbiological and physical and chemical attributes as well where appropriate. These aspects can be used also to justify the drug product specification in section 3.2.P.5.6.
It is important to identify the critical process parameters, which should be monitored or controlled to ensure the desired product quality.
The applicant should describe differences in the manufacturing processes of the pivotal clinical trial batches (for safety, efficacy, bioavailability and bioequivalence), primary stability batches and the product intended for marketing as described in 3.2.P.3.3. This should include the summary of the differences on the performance, manufacture and quality of the product and should be presented in a comparable format of the manufacturing processes and batch analysis data, e.g. presented in section 3.2.P.5.4. Typical characteristics of these batches like batch size, manufacturing site, intended use (e.g. bioequivalence study batch number) and manufacturing design differences should be included as well.

The description of measurement systems, which monitor critical attributes or process end-points, is useful as it provides flexibility for future process improvements. The collection of process monitoring data enhances the understanding of the process. Finally, all strategies of process control and the resulting process adjustment should be enlisted in order to control all critical manufacturing attributes.
The applicant is invited to provide an assessment of the process reliability under different operating conditions, at different scales or with different equipment. This understanding of process robustness can be useful in risk assessment and risk reduction especially together with the use of risk management tools (according to ICH Q9 Quality Risk Management) [18] in order to support future manufacturing and process improvements.

2.4 Container Closure System (3.2.P.2.4)

In this section the choice and rationale should be discussed for the used container closure system of the commercial product. Special focus should be placed to the intended use of the drug product and the suitability of the primary container for storage and transportation including also the storage and shipment containers for the bulk product. The applicant should reflect the choice of materials e.g. in view to protection from moisture and light and he should demonstrate the integrity of the container closure system. Further attention should be paid to possible interaction between the pharmaceutical product and container components (e.g. sorption to container or leaching) and the safety of the used materials. A justification for the secondary packaging material should also be included.
Finally, if a dosing device like a dropper pipette, measuring spoon, pen injection device, dry powder inhaler etc. is used, the reproducible dose of the product should be demonstrated as far as possible simulating the intended use of the product by the patient.

2.5 Microbiological Attributes (3.2.P.2.5)

In this section the microbiological attributes of the drug product should be discussed including the rationale for performing or not performing microbial limit tests for non-sterile products (according to the decision tree #8 described in ICH Q6A Specifications) [16].
If antimicrobial preservatives are used in the formulation, its selection and effectiveness must be demonstrated. This includes products that are inherently antimicrobial. The antimicrobial preservative effectiveness should be demonstrated during development and the lowest concentration providing the required level of efficacy throughout the intended shelf life should be investigated and used for the product. Where relevant, a microbial challenge testing under simulated patient use as far as possible should be performed and demonstrated.
If products are intended to be sterile, the integrity of the used container closure system and the prevention of microbial contamination must be demonstrated.

2.6 Compatibility (3.2.P.2.6)

If the drug product is intended for use with reconstitution diluents (e.g. infusion solutions), its compatibility with these solutions should be demonstrated. These investigations should cover admixture and dilution prior to administration, the recommended in-use shelf life of the mixture at the recommended storage temperature and at the likely extremes of concentration.

Comparison of the current guideline ICH Q8 with the previous guideline

In January 1998 the Committee for Proprietary Medicinal Products (CPMP, today Committee for Human Medicinal Products, CHMP) published and adopted the "Note for Guidance on Development Pharmaceutics" with the shorthand expression CPMP/QWP/155/96, which came finally into operation in July 1998 [2]. This guideline reflected the data requirements of the section "A.4 Development Pharmaceutics" within the chemical-pharmaceutical quality documentation Part II. This section is one part of the application according to the requirements for the analytical, toxicological and pharmaceutical, medicinal and clinical documentation according to the Directive 75/318/EEC from 20 May 1975 as amended, for the data required for the granting of a marketing authorisation. Here, this guideline is referred to as the "*previous* or *preceding* guideline" in the following (in comparison to the *new* ICH Q8).
A similar EU guideline exists already for veterinary medicinal products, the "Note for Guidance: Development Pharmaceutics for Veterinary Medicinal Products", EMEA/CVMP/315/98, which came into operation on 1 March 2000 [19]. This guideline shall not be regarded here in closer detail. Furthermore, no veterinary equivalent is planned at the moment as a VICH Q8; however, the VICH is considering Q9 and Q10 [12].

The Note for Guidance on Development Pharmaceutics, CPMP/QWP/155/96 is divided in a very similar way as the new ICH Q8 guideline into the following sections:

1. Introduction
2. Components of the Product
   2.1 Active Substances
   2.1.1 Compatibility
   2.1.2 Physico-chemical Characteristics
   2.2 Excipients and other non-active constituents
3. Formulated Products
   3.1 Overages
   3.2 Physico-chemical parameters
   3.3 Liquid and Semi-solid Formulations
      3.3.1 Components of the formulation
      3.3.2 Compatibility with other products
   3.4 Solid dosage forms
      3.4.1 Homogeneity
      3.4.2 Performance Testing
         3.4.2.1 Disintegration Testing
         3.4.2.2 Dissolution
            a) Conventional release preparations
            b) Modified release preparations
   3.5 Other Dose Forms
      3.5.1 Transdermal Patches
      3.5.2 Pressured Metered Dose Preparations for Inhalation
      3.5.3 Dry powder for inhalation
4. Packaging Materials
   4.1 Sorption to container
   4.2 Leaching
   4.3 Dose reproducibility
5. Manufacturing Process
6. Conclusion

This table of contents of the previous note for guidance makes already clear that the focus of this guideline was much more specific than the new note for guidance. Table 1 compares the contents of both guidelines.

Table 1 Comparison of the contents of the previous and new guidelines on Pharmaceutical Development.

Previous Guideline CPMP/QWP/155/96	Current Guideline EMEA/CHMP/167068/2004
1. Introduction	1. Introduction
2. Components of the Product	2.1 Components of the Drug Product
2.1 Active Substances	2.1.1 Drug Substance
2.1.1 Compatibility	(in 2.1.1 Drug Substance)
2.1.2 Physico-chemical Characteristics	(in 2.1.1 Drug Substance)
2.2 Excipients and other non-active constituents	2.1.2 Excipients
3. Formulated Products	2.2 Drug Product 2.2.1 Formulation Development
3.1 Overages	2.2.2 Overages
3.2 Physico-chemical parameters	2.2.3 Physicochemical and Biological Properties
3.3 Liquid and Semi-solid Formulations	-
3.3.1 Components of the formulation	-
3.3.2 Compatibility with other products	2.6 Compatibility
3.4 Solid dosage forms	-
3.4.1 Homogeneity	
3.4.2 Performance Testing	
3.4.2.1 Disintegration Testing	
3.4.2.2 Dissolution	
a) Conventional release preparations	
b) Modified release preparations	
3.5 Other Dose Forms	-
3.5.1 Transdermal Patches	
3.5.2 Pressured Metered Dose Preparations for Inhalation	
3.5.3 Dry powder for inhalation	-
4. Packaging Materials	2.4 Container Closure System
4.1 Sorption to container	(Sorption
4.2 Leaching	Leaching
4.3 Dose reproducibility	Reproducibility)
5. Manufacturing Process	2.3 Manufacturing Process Development
	2.5 Microbiological Attributes

Legend: - not included as such

Interestingly, the both topics “Formulation Development” and “Microbiological Attributes” have been introduced into the new guideline and were not present per se in the previous guideline.

It is already obvious by the direct comparison of the tables of contents that the preceding guideline contains more topics than the newer one.

The direct comparison of topics indicates already that the previous guideline is focused much more on detailed guidance especially for specific dosage forms (e.g. liquid and semi-liquid dosage forms, solid dosage forms, transdermal patches and different inhaler types). These are obviously no longer regarded in detail in the current guideline. However, this observation is only superficial. Both guidelines have roughly the same extend. Although the current guideline does no longer provide specific guidance on the content of the Pharmaceutical Development section for these dosage types, much of the general guidance is also applicable to these specific dosage forms. It is now left to the applicant to decide how much understanding, data and gained scientific knowledge to be generated and presented in the section 3.2.P.2.
Furthermore, additional notes for guidance for specific dosage forms are today in operation [20, 21, 22, 23, 24], which were not present in 1998 when this guideline was published.

In the following the sections of the previous guideline shall be reviewed. For an easier orientation the same numbering (in brackets) is used as in the guideline.

(1.) Introduction

The previous guideline points out that pharmaceutical development studies are necessary to establish that the selected type of dosage form and formulation are satisfactory for the intended purpose. Crucial formulation and processing aspects for the batch reproducibility should be monitored routinely. Whereas this note is primarily focussed on chemical active substances, it may be applicable to other types of products as well.

In comparison to the above introduction, the current guideline focuses on the opportunity of the applicant to present the gained knowledge, scientific approaches and quality risk management which shall prove his comprehensive understanding of the product and manufacturing process for reviewers and inspectors.

Although both objectives appear to be quite different, they obviously focus into the same direction. The previous guideline is much more focused on specific details to be described whereas the current guideline makes an appeal to the self-responsibility of the applicant to present his comprehensive understanding and knowledge of the pharmaceutical product, which finally resulted in the presented formulation.

(2.1) Active Substance

The preceding guideline requests compatibility studies of the active substance(s) with the excipients and on the compatibility of fixed combination products, which can be performed e.g. by presentation of preliminary stability studies.
The guideline points furthermore to the physico-chemical characteristics of the active substance including solubility, water content, particle size and crystal properties. If these are variable and critical for the quality of the product, it needs to be controlled appropriately and

acceptance criteria and limits need to be defined. Sometimes additional tests beyond the ones laid down in a pharmacopoeial monograph are necessary.

The new guideline names these physico-chemical properties as well and points out the significance to evaluate the potential effect of the drug substance's physicochemical properties on the performance of the drug product. Whereas the previous guideline gives no further advice or link here, the current one directs to ICH Q6A *Specifications* with its decision trees #3 and #4 [16].

(2.2) Excipients and other non-active constituents

The previous guideline requests an explanation and justification of all constituents regarding their function in the formulation. Experimental data are required for preservatives or the compatibility of excipients e.g. in a dual preservative system where appropriate. Full information on the composition, function and safety is requested for novel constituents like e.g. a new matrix of a prolonged release preparation, a propellant or permeability enhancer. Reference is given to the Note for Guidance on Excipients [25].

The current guideline is not as explicit in its requirements for the selected excipients but focuses more on the discussion of the product performance and manufacturability caused by each excipient in the composition.
However, the demonstration that selected excipients (e.g. antioxidants, penetration enhancers, disintegrants and release controlling agents) can provide their intended functionality is also requested.

(3.) Formulated Products

This section with its subdivisions forms about two third of the previous guideline and gives detailed advice to the requirements of developmental stages of different dosage forms. Whereas section "3.1 Overages" and "3.2 Physico-chemical parameters" focus more on general aspects of a formulated product (drug product), the following sections 3.3 – 3.5 review the requirements for the specific dosage forms "liquid and semi-solid formulations" (section 3.3), "solid dosage-forms" (section 3.4) and "other dose forms" (section 3.5) like "transdermal patches", "pressured metered dose preparations for inhalation" and "dry powder for inhalation".

The new guideline places emphasis on "Overages" (section 2.2.2) and "Physicochemical and Biological Properties" (2.2.3) but does no longer provide detailed requirements for the formulation development of the specific dosage forms (liquid formulations, solid dosage-formulations, transdermal patches, metered-dose inhalers, dry powder inhalers etc. This is explainable as individual notes for guidance are now present for these special dose forms [20, 21, 22, 23, 24], which were not in operation when the previous guideline was released

in 1998. Furthermore, an ICH Q8 Annex is planned for the future, which will contain requirements for specific dosage forms [10, 12].

(3.1) Overages

The previous guideline discourages the use of overages in the formulation because of the risk of overdosing soon after release. An overage on grounds of instability of the active substance in order to maintain or extend shelf life should not be used beyond 10 % but it is better to reduce the shelf life. An overage to cover losses during manufacture (manufacturing overage) is regarded less critical. In each case the usage of an overage should be justified with special view on the safety and efficacy of the product.

Overages (section 2.2.2) are also regarded by the current guideline basically with the same view as in the previous guideline. However, the new guideline is a little more stringent: any overage of the drug substance to compensate degradation, to maintain or to extend shelf life is discouraged regarding safety and efficacy of the product. An overage based on expected and documented manufacturing losses is not as critical. Information is requested about the amount, the reason and justification for the amount of overage, the latter must be included in the batch formula.

(3.2) Physico-chemical parameters

The previous guideline focuses on the pH range specified in a formulation, which should be properly investigated especially regarding its effect on the active substance, the excipients or antimicrobial preservatives and bioavailability of the product. Other parameters like dissolution, redispersion, particle size, distribution, aggregation, rheological properties, etc. or tonicity adjustments, globule size of emulsions, changes in crystal form, viscosity or syringeability for parenteral products should be considered in pharmaceutical development studies. Syringeability of a preparation should be clearly demonstrated where appropriate.

ICH Q8 does not focus on specific physicochemical and - newly introduced - biological properties per se but reflects these more in general. These properties should be identified and discussed where relevant to the safety, performance and manufacture of the formulation. An example is provided by the development of a test for the respirable fraction of an inhaled product. The development and suitability of other tests to assure drug release is encouraged. Finally reference is provided to ICH Q6A “Specifications” with its decision trees #4 (Part 3) and #7 (Part 1) and ICH Q6B [16, 17].

(3.3) Liquid and semi-solid formulations

CPMP/QWP/155/96 requests the demonstration by experimental results that key components like antimicrobial preservatives, antioxidants and other components like surfactants, solvents,

chelators, permeability enhancers, tablet lubricants, release modifiers etc. are appropriate for the formulation.
The suitability of antimicrobial preservatives, which are foreseen only for non-sterile formulations, should be considered regarding storage conditions, reconstitution, dilution before use and multi-dose usage. The testing of its efficacy is required according to the European Pharmacopoeia level A criteria, if not otherwise justified and a validation of the test procedure is required. The assignment of "an in-use shelf life" is necessary and should be demonstrated by appropriate testing results as well. The preservative content shall be included and controlled according to the shelf life specification. Extended shelf lives must be justified and further challenge tests may be necessary. Reference is provided to the so-called "note for guidance on preservatives". This guideline is actually called today "Note for guidance on inclusion of antioxidants and antimicrobial preservatives in medicinal products" (CHMP/CVMP/QWP/115/95) [26].
Since antioxidants may be sacrificially degraded during the manufacture or shelf life of products, the level of which should be justified and sufficient activity must also be demonstrated throughout the shelf life.
The compatibility of intravenously applied products (parenteral products) with relevant reconstitution solvents or diluents should be provided. This includes recommended storage conditions and the limitation of possible extremes of concentration.

Although ICH Q8 less stringently focuses on any possible requirements for specific dosage forms, it does reflect the topic compatibility. This is consistent with the CTD section "2.6 Compatibility". Basically the same requirements have to be fulfilled by the applicant regarding compatibility studies as already outlined in the previous guideline.

The new guideline also deals with antimicrobial preservatives. This is not regarded in a section for liquid and semi-solid formulations as in the preceding guideline but within the section "2.5 Microbiological Attributes". Here, the topic is no longer specified only for liquid and semi-solid formulations but more in general for any products, which are inherently antimicrobial. Its effectiveness shall already be demonstrated during the development and the testing shall be included in the drug product specification as also required in the preceding guideline. The new guideline focuses stronger on the lowest effective preservation concentration in view to efficacy and safety as well as testing conditions, which simulate patient use as far as possible. These two points are new and were not regarded in the previous guideline.

(3.4) Solid dosage forms

The preceding guideline requests appropriate compatibility studies of any solid dosage forms if these are mixed or diluted with liquids before administration. However, in this chapter most emphasis is laid on homogeneity and performance testing of bulk or unit-solid dosage forms.
In order to ensure even distribution of the active substances, homogeneity studies already at the development stage and confirmation by validation should be presented in the dossier. It is

necessary for the applicant to demonstrate the unit solid dose form by uniformity of distribution between batches and also within one batch. Therefore the uniformity is also addressed in the product specification and is valid for each batch. The routine testing shall be supported by development studies, especially in case of highly potent substances present in low concentrations in a selected formulation.
The demonstration of the divisibility of tablets and the uniformity of the halves should be performed where the applicant can justify the administration of tablet halves.

Although the new guideline does no longer focus on developmental requirements for specific dosage forms the inclusion of any special design features of the drug product (e.g. tablet score line) and its rationale for the intended use must be made evident according to this guideline as well. Divisibility studies of tablet halves are not directly requested by this general formulation but the applicant is safe if the rationale of tablet score lines are supported by adequate breakability data which confirm the dosage uniformity in these cases. Again the new guideline does less specifically demand named developmental studies (here breakability test data) but offers the opportunity to the pharmaceutical industry to demonstrate the adequate justification of the chosen formulation including their special design features. Furthermore, breakability must be proven according to the European Pharmacopoeia monograph “Tablets” (07/2007:0478).

Performance testing
The performance of a drug product can be regarded as an indicator of the delivery of the active substance from the dosage form to the target site. This process depends on the dose form and the route of administration and may be immediate (suppositories, conventional release tablet) or modified in form of prolonged or delayed release. The performance monitoring is usually carried out by disintegration and dissolution studies.

1. Disintegration Testing: This test is applied to each finished batch of oral solid dose forms and furthermore to suppositories or to uncoated tablet cores before final coating. It shall demonstrate the effective break-up of the solid formulation and an individually validated limit needs to be selected within the limits of the pharmacopoeial monograph. A routine disintegration test can be replaced by a dissolution test with acceptable discriminatory power in the release specification. This test procedure should be performed as described in the Pharmacopoeia.

2. Dissolution testing: Although the in-vivo in-vitro correlation of drug release by dissolution testing is difficult, such testing provides a useful measure to determine the actual amount of drug liberated from its dosage form into an aqueous medium. Therefore, dissolution testing should be applied to all solid dosage forms during the development phase. It shall be carried out with the equipment described in the European Pharmacopoeia and the use of deviating devices needs to be justified.

For conventional release preparations dissolution tests should be carried out during development and stability studies in order to establish whether this test needs to be included routinely in the release specification.
For modified release preparations the choice of test conditions and release rates during batch testing shall be adopted to the in-vivo studies and reflect the release and absorption profile of the product. It should therefore consist of an in-vivo in-vitro release rate correlating study. This kind of study is especially important for medicinal products with an active substance with a narrow therapeutic window.

The new guideline does not directly touch the topic disintegration testing but the dissolution topic is included in the section for Formulation Development (3.2.P.2.2.1). The only hint to disintegration is the need to support the selection of dissolution versus disintegration in the section 2.2.3 "Physicochemical and Biological Properties". No differentiation between different solid dosage forms is reflected by the new guideline regarding dissolution. However, information from comparative in vitro studies (here: dissolution) or comparative in vivo studies, which links clinical formulations to the proposed commercial formulation, should be provided. In the same way as was requested in the previous guideline ICH Q8 asks to establish an in vitro/in vivo correlation, which can guide to the selection of appropriate dissolution acceptance criteria. Furthermore, this successful correlation can potentially reduce the need for further bioequivalence studies upon changes to the product or its manufacture.

(3.5) Other Dose Forms

(3.5.1) Transdermal patches

CPMP/QWP/155/96 requests developmental studies of the appropriate combination of physicochemical properties, potency, biocompatiblity and clinical need of drug substances, which are intended to be used in transdermal patches. Special focus should be laid on the matrix reservoir and adhesive materials to exclude the possibility of incompatibilities with the active substance. It is also required to determine the release behaviour of the drug substance with a membrane barrier containing diffusion cell as described in the European Pharmacopoeia "Dissolution test for transdermal patches (2.9.4)" and the transmission rate characteristics need to be defined for the release and shelf-life specifications.

(3.5.2) Pressured Metered Dose Preparations for Inhalation

The guideline requires the examination of the particle size of the active substance and the quality of the co-solvent proposed as propellant and the surfactant. The interaction and combination of these substances in view of the stability and physical and chemical properties of the active substance like particle size, solvation, crystal form etc. needs to be carefully investigated during the developmental phase. Especially the moisture content and the potential for extractables following the interaction with the valve mechanism needs to be

investigated. Furthermore the amount of active substance to be delivered from the valve and mouthpiece and the uniformity of content between doses must be demonstrated. The deposition of the emitted dose should be examined with the apparatus described in the pharmacopoeia. It may be necessary to include some of these parameters into the product specifications. Finally, the correlation between results of in vitro testing and batches used in vivo with acceptable performance should be made. Again, the deposition of the active substance in the mouthpiece may need to be addressed.

(3.5.3) Dry powder for inhalation

For these single dose or multidose preparations the particle characteristics of the drug-excipient mix (like size, shape, rugosity and charge) or other parameters like water content need to be regarded. It is also important to investigate the flow rate in vitro and in vivo and correlate these results of in vitro testing with batches showing acceptable performance in vivo. In the same way as for pressured metered dose inhalers the deposition of the drug in the mouthpiece needs to be investigated.

The new guideline does not reflect the specific dosage forms like dry powder inhalers, transdermal patches or pressurised metered dose inhalers any longer. This is partly understandable since specific guidelines are available for these dosage forms in the meantime (e.g. “Quality of Modified Release Products A) Oral solid Dosage forms, B) Transdermal dosage Forms Section I (Quality)”, CPMP/QWP/604/96 or “Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalers”, CPMP/QWP/2845/00). Other requirements are nowadays included in specific European Pharmacopoeia monographs like “Pressurised Pharmaceutical Preparations” (01/2005:0523)”, Preparations for Inhalation” (04/2005:0671), “Transdermal Patches” (07/2005:1011), “Oral Powders” (07/2005:1165) or 2.9.18 “Preparations for Inhalation: Aerodynamic Assessment of Fine Particles” (04/2005:20918 corrected 5.2). These do partly also reflect requirements for the pharmaceutical development. Eventually, an ICH Q8 Annex is planned for the future, which will contain requirements for specific dosage forms [10, 12].

(4.) Packaging Materials

The previous guideline requires justifying the choice of the primary packaging material. This should include appropriate considerations for the safety of medical personnel and patients during the use of the product. The integrity of the container and closure system should be performed including the need for child resistant packaging where appropriate. With the reference to the “Note for Guidance on Plastic Primary Packaging Materials” [currently: 27] the possible interaction between the pharmaceutical product and its container must be considered. This includes the admixture or dilution of products prior to administration, e.g. when added to large volume infusion containers.

The selected primary packaging materials should also be regarded in view to the manufacturing method; for sterile products a container allowing the optimum sterilisation of the finished product should be used.

(4.1) Sorption to the container

The sorption of active substances and additives (where appropriate) from liquid and semi-solid formulations into container materials like rubber closures, plastic materials and administration sets should be investigated and corresponding data presented. Studies reflecting relevant in-use situations should be performed, e.g. by investigating products at the distal end of a container fitted with an administration device (i.e. by top down storage).

(4.2) Leaching

An equivalent investigation is necessary for any leaching phenomena from any packaging components into liquid or finely divided solid preparations over the shelf life.

(4.3) Dose reproducibility

The dose reproducibility needs to be demonstrated where applicable. This includes dropper pipettes, pen injection devices and others. It needs to be proven by reproducible and accurate dosage of the product under patient-simulated testing conditions as far as possible. Special attention regarding dose reproducibility must be paid to the homogeneous resuspendability of suspensions and lyophilisates into intow-change or two-chamber cartridges according to the relevant patient leaflet instructions.

Whereas significant differences between the old and new guidelines are obvious regarding the description or requirements for specific dosage forms, the demands for container closure system justifications are closely related. This is to some extend not surprising since the ICH Q8 is subdivided in the same sections as is the common technical document and this includes the section “2.4 Container Closure System”.

The new guideline requests the discussion of the choice and rationale for the selected container closure system with regard to the intended use. These are basically the same requirements as in the previous guideline. However, additionally the suitability of the packaging material for the storage, transportation and shipping including shipping containers for bulk products is requested, which was not the case in the CPMP/QWP/155/96.

The choice of the materials should be justified in the same way as in the previous guideline. The same is true for the demonstration of the integrity of the container and closure, which should be supported by studies and the interaction between product and container or label must be considered. The new guideline focuses additionally on the protection from light and moisture where necessary. The compatibility with the materials

of construction with the dosage form including sorption and leaching is reflected also in ICH Q8 but in contrast to the previous guideline specific requirements and tests are not mentioned. Again, the new note for guidance is more generally maintained than the old one. However, the use of any secondary packaging material should be justified where relevant; a requirement not reflected in the previous guideline.
Both guidelines request the reproducibility and accurate dose of the product under testing conditions if a dosing device (like dropper pipette, pen injection device, etc.) is used. In this topic both guidelines are almost identical. Interestingly, this dose reproducibility is the only section where a specific requirement for dry powder inhalers is included. This single dose form is elsewhere not mentioned in ICH Q8. The correct reconstitution of lyophilisates or homogeneous resuspendability of suspensions in cartridge systems is not explicitly mentioned in the newer note for guidance.
The integrity of the container closure system to prevent microbial contamination of sterile products is required elsewhere in the new guideline, included in the section "2.5 Microbiological Attributes".

(5.) Manufacturing Process

The demonstration of the choice of the manufacturing process is required in the development section; it must be explained and justified for the selected dosage. Starting materials of appropriate quality shall be used. Especially the definition (or selection) of adequate specifications with view to assure the quality of the finished product should be indicated by the manufacturing process. Process development studies will direct towards process optimisation and validation requirements. Especially for biological products the development of the manufacturing process is of great importance.
The development and validation studies should address microbiological, physical and chemical parameters and direct to appropriate microbial controls of the finished product.

This chapter focuses also on the need to justify the choice for sterilisation for relevant products (e.g. parenteral, ophthalmic and sterile topical preparations). The choice of an appropriate sterilisation method should be justified and whenever possible, a fully validated terminal sterilisation method as described in the European Pharmacopoeia should be used. If this terminal sterilisation cannot be applied, filtration through a bacteria-retentive filter or aseptic processing may be used and must be justified. This is basically only acceptable for heat labile active substances or other key components of the formulation, which might significantly degrade under heat sterilising conditions. The previous guideline points out that heat labile packaging materials should not be used for otherwise heat stable products but the choice of alternative packing materials should be thoroughly investigated.

As mentioned previously, ICH Q8 often guides more generally and less specifically to many developmental data requirements in comparison to the previous guideline. However, this is not the case for the reflection of the manufacturing process. The new guideline focuses pretty descriptive on necessary documentation regarding manufacturing

development, once in the section “2.2.1 Formulation Development” and furthermore in “2.3 Manufacturing Process Development”. Basically all requirements directed by the preceding guideline are also included in ICH Q8 in the above mentioned sections. Beyond this, it is obvious that the new note for guidance is even more specific than the previous guideline. This is especially true for the development of the manufacturing process, its improvement, critical formulation attributes, available manufacturing process options, appropriateness of components and the used equipment, process development studies, continuous process verification, any improvement programme and critical process control requirements. Differences between the manufacturing processes for clinical trial batches, primary stability studies and the final process described in the manufacturing section (3.2.P.3.3) should be described, summarised and presented in a tabular form, e.g. in a comparative way in the batch analysis section (3.2.P.5.4). The understanding of process robustness is regarded to be useful in risk assessment and risk reduction and can support future manufacturing and process improvements. These points of view are all not or not as thoroughly regarded in the previous guideline. Here, ICH Q8 is a significant improvement over CPMP/QWP/155/96. This is not only obvious by more specific data requirements from the applicant but also by guiding him to an enhanced and better understanding of the manufacturing process development from initial studies over pivotal clinical trial batches towards a comprehensive manufacturing control of the product as intended for the market. In this context the new note for guidance reflects on the description of measurement systems which allow monitoring of critical attributes or process end-points. This requirement is not included in the preceding guideline.

The appropriateness of the method of sterilisation for drug products intended to be sterile needs also to be justified according to the new guideline. However, ICH Q8 does not longer require specifically terminal heat sterilisation per se. Instead, the method of sterilisation needs to be justified. This again leaves more space to the applicant to choose adequate methods but also requires the need to better understand and justify the selected choice (of sterilisation) than directed by the previous guideline.

The previous guideline does also focus on microbiological attributes, but not in a separate chapter, which is now included in the new guideline according to the CTD division. Nevertheless, both notes for guidance focus on the integrity or suitability of the container closure system for sterile products. However, only ICH Q8 does this with the remark to prevent microbial contamination.

(6.) Conclusion

The preceding guideline regards development studies as the vital background, which ensures that a medicinal product can be generated with the appropriate quality as intended for the market. The designed formulation, its manufacture and validation and the test procedures should comply with the principles of GMP and should consistently comply with the finished

product specification. Therefore, any development studies should comply with GMP principles [28] as well although they are usually not part of GMP inspections. Development studies should therefore ensure that the desired characteristics of the product can be consistently achieved and meet the specifications at release and throughout shelf life.

The new guideline does not provide a conclusion as such. Instead, the objective of the guideline (Section 1.1) and its scope (1.2) intend to provide a comprehensive understanding of the product and manufacturing process for the reviewers and inspectors.

Comparison of both guidelines – a summary

As already mentioned before, ICH Q8 is more general than the previous guideline directing to the self-responsibility of the applicant to provide all necessary information and preliminary results to justify the selected formulation in his application. The previous document is more explicit and detailed regarding individual requirements.

In summary the both guidelines differ by far more than the revision of requirements adapted to the former section "II A.4 Development Pharmaceutics" in the former NtA guidance [6] and the current CTD section "3.2.P.2 Pharmaceutical Development" as directed by the current NtA guidance [7, 8]. Both documents deviate by their general requirements on the presentation of development data much stronger than the different structure of the both topics within the quality (pharmaceutical-chemical) documentation would suggest. In the former NtA of 1998 the section on Development Pharmaceutics did not provide explicit subdivision. However, the CPMP/QWP/155/96 intends to set out clearly detailed and specific requirements of developmental data basically for most (if not all) pharmaceutical forms (at least for products with chemical active substances). It requests what kind of data needs to be generated by the applicant and leaves little "space" for deviation or different approaches.
This is completely different with the new guideline. ICH Q8 does not only describe the adaptation of development studies to the now valid CTD format in its current presentation (ICH guideline M4 as of February 2004, [7, 8]), which is already more specific due to its subdivision into six sections (3.2.P.2.1 – P.2.6). However, the new guideline is less demanding in specific requirements for individual data as outlined by the selected comparisons above. The main difference to the previous guideline is that ICH Q8 offers the opportunity of the "design space". This multidimensional combination of input variables and process parameters shall demonstrate the assurance of quality and are regarded as an area of gained knowledge from pharmaceutical development studies and manufacturing experience, which should be provided by the applicant. This information shall demonstrate that a quality product and its manufacturing process have been developed, which consistently deliver the intended performance of the product. ICH Q8 leaves more responsibility to the applicant to acquire and compile the critical input and process attributes of the product and how to control these adequately.
Furthermore, the technical and scientific development of pharmaceutical products has improved over the years. Hence, any relevant guideline(s) need(s) to evolve as well and shall

adapt to modern and contemporary requirements of improved possibilities for any drug formulation and process developments.

It is now up to the applicant to describe and include strategies reflected during the development of the product in the Pharmaceutical Development section of the dossier. However, this does no longer prevent him from providing a clear overview and summary of strategies about the drug components, the manufacture and safety measures of the product.

Eventually the question must arise which guideline to use, the new (= current) one, the preceding one, or both? Comparing both guidelines makes obvious that many analogue requirements exist but also many differences. It must be evident that the new guideline, which came into operation in May 2006 is now the valid one and does therefore apply to the contents of the pharmaceutical development sections in general and this not only in view to the CTD subsections.
However, it remains surprising that no clue has been provided that ICH Q8 replaces the previous guideline. Would this mean that two guidelines on pharmaceutical development are valid simultaneously, the new one and the old one? This assumption is supported by the fact that both guidelines are listed side by side among the Quality Guidelines on the EMEA homepage [29] without any comment that the newer replaces the older one. This does not occur in case of other guidelines, where a "replaced by […]" remark has been provided [25, 30].

Basically, both guidelines do not contradict each other in their contents. Thus, the applicant is always on the right side if he follows the advice provided by the newer guideline. However, in order to design the developmental studies and to demonstrate the appropriateness of the selected formulation of his pharmaceutical product, the applicant can use the previous guideline as well for specific questions regarding special dosage forms. As a result it can be concluded that both guidelines support each other. This will be optimally performed in combination with the relevant current guidances for these formulations provided in the relevant monographs in the European Pharmacopoeia and separate notes for guidance [20, 21, 22, 23, 24]. Furthermore, an ICH Q8 Annex is planned for the future, which will contain requirements for specific dosage forms [10, 12].

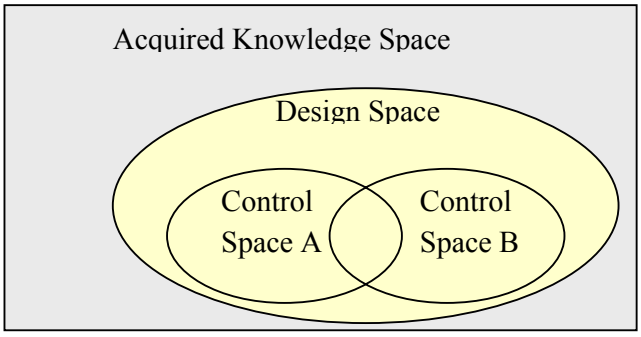
The term Design Space - Integration into ICH Q8, Q9 and Q10

The current guideline defines the "Design Space" as the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.

At the first glance this definition appears to be a little vague and imprecise. So, how to fill this term with meaning and relevance?
The design space is the established range of process parameters and formulation attributes, which have been demonstrated to provide the assurance of quality. It thus forms the linkage between development and the manufacturing design. The applicant is intended to present his science, his manufacturing scheme, which was developed through his science, and shows how both link together.

The central question must arise how to fill this term with relevance, significance and content. In can be summarised that the definition and term for possible regulatory requirements for the concept of "quality by design and design space" are placed very much at its begin. Less than one year after the official introduction of the term "design space" into the guideline ICH Q8 clear visions and expectations already exist. However, the knowledge and experience how to fill this topic or room with specific data and necessary requirements is pretty vague and little. The dynamic and commitments are strong on all sides. Nevertheless, the topic "strategies for reduction or minimising variations" is of major topicality and importance for authorities as well as for innovative and generic companies. Especially, the common understanding of the design space shall not result in additional regulatory requirements. This means that design space applications should be optional [10, 12].
However, the design space is an excellent tool also and especially for the generic pharmaceutical industry in order to lay down the rationale of the intended product, the concepts, experiments and developmental studies leading to the final product as intended for the market. The great advantage of the "design space" as currently understood by authorities and companies is that the applicant can select how much information he likes to present especially regarding his developmental strategies. It is important to realise that the basic requirements are not regarded to be part of the optional design space area. This means that for example justification, studies regarding preservatives, special design features (like breaking scores) etc. must be described in detail and their intended use has to be justified – basically in the same way as before and outlined in the previous guideline.

Figure 1 An illustration of the design space



ICH Q8 provides the opportunity to the pharmaceutical industry to give insight into their decisions during development of the pharmaceutical product. It is widely on the applicant to decide – beyond a minimum or baseline expectation of information – how much data to be generated and presented in the section 3.2.P.2. However, the more data can confirm the scientific knowledge achieved by the applicant about the drug substance, the excipients, the manufacturing process and improvement, the different container closure systems used etc., the more this will eventually provide the desired flexibility for the design space. The usage of a meaningful design space provides the opportunity to reduce the need of post-approval changes procedures and increases regulatory flexibility.

Eventually, it is up to the applicant to describe and include strategies reflected during the development of the product in the Pharmaceutical Development section of the dossier. However, this does no longer prevent him from providing a clear overview and summary of strategies about the drug components, the manufacture and safety measures of the product. Pharmaceutical development should be understood as the description of a learning process, which is based on negative and successful developmental studies in order to prove the design space. Any information from these studies is regarded as the basis for risk management. It is the aim to identify critical attributes and parameters since these are risks to the pharmaceutical product. Critical formulation attributes and process parameters shall be identified. The evaluation of these should give insight how much the alteration (variation) of these attributes can influence the quality of the product. Therefore, the design space can provide regulatory flexibility. Exploring the influence of any (critical) factors creates knowledge. A risk analysis of the result of any change should then be possible. The opportunity to move within the defined area after approval can give the flexibility for continuous improvement without the need for a further variation application.
The subject of reducing the number of variations is of great importance for all parties, industry and authorities. Currently, the Variations Regulations are based on a rather 'prescriptive' approach [31]. Any change and amendment to the marketing authorisation implies a variation, which needs to be filed before implementation. Minor variations (type IA and B) are currently listed in an exhaustive manner. The "design space" model provides a chance to an overall reduction of the amount of variations. Eventually this can contribute to the revision of the current variation model, e.g. by moving from a "tell and do" towards a "do and tell" procedure. It is also proposed to introduce the term "design space" in the Variation Regulations [31]. At least a revision of the Variation Regulations (EC) Nos. 1084/2003 and 1085/2003 is among the regulatory activities of the CHMP and CVMP in the near future [32].

This approach towards a "design space" can only be welcomed and supported not only from the inventing but basically also from the generic pharmaceutical industry on a long-term basis. Nevertheless, at the beginning there will remain some scepticism at least among generic manufacturers against this opportunity since it will result in more effort during the developmental phase. Eventually, the chances to establish for example a design space for

different packaging materials or a stable manufacturing process can become important in the future when several manufacturing locations might once be envisaged in the future.

ICH Q8 should be regarded in conjunction with ICH Q9 (Quality Risk Management) [18] and ICH Q10 (Quality Systems); the latter is currently only in the draft phase.
The tripartite harmonised ICH guideline Q9 was finalised (Step 4) in November 2005. It has already been adopted in the both other tripartite regions, Japan and the USA. Instead, in the EU, ICH Q9 will be implemented as an amendment to the EU GMP Guide and thus part of the European legislation EudraLex [33].
Among the tree ICH topics Q8, Q9 and Q10 the first document finished was ICH Q9 on Quality Risk Management on 9 Nov 2005 and ICH Q8 was finished one day later. The possibilities and opportunities described in Q9 should be regarded as toolbox how risk-based working can proceed. According to the ISO/IEC Guide 51 risk is defined as a combination of probability of harm and severity of that harm, which is itself defined as a damage to health, including the damage that can occur from loss of product quality or availability. This guideline provides a framework that may be applied to all aspects of pharmaceutical quality including development. Several risk management tools are supposed in ICH Q9 together with potential areas of use.
As a conclusion quality risk management provides a useful process which enables both industry and regulators to focus better on what is important for patients. ICH Q8, Q9 and Q10 shall enable together the pharmaceutical community to move towards the desired state of quality management. It is likely that quality risk management is going to result into a ‘best practice guide’ over time.

As already mentioned in the introduction, ICH Q8 has just been implemented in the EU. A Q8 Annex (ICH Q8 (R1)) is intended for the future, which will contain requirements for specific dosage forms [10, 34]. Sections on “Information on medicinal products” and “Information on drug substances” with more precise descriptions are currently in an early planning phase [35]. It is the aim of ICH Q8 to gain a scientific understanding of the processes, which are based on the data evaluation during develospment and manufacture. This understanding will lead to a design space, which shall eventually replace the quite narrow specifications. The authorities have promised a rethinking for this purpose in such a way to accept the obtained scientific data based on good confidence in the applicant. It is the declared aim of this process to reduce registration timelines and to accelerate innovations. This hope gets support because the European Commission (represented by the CHMP) and FDA were involved in the generation of ICH Q8 [35].
No draft document has yet been published on ICH Q10. However, it is intended to demonstrate the cooperation of the teamwork of GMP, quality management and quality by design. In summary all three ICH guidelines are aimed to improve the partnership-like relation between authorities and industry.

It should be the goal of the production to do it "right the first time." However, this is often not the case and some processes have not been improved adequately. Instead, money and time has been invested into quality management systems, which collect data of deviations to a larger extent. Here, an active reorientation from the black box thinking towards a scientific understanding of the manufacturing process is necessary. A major obstacle towards this goal is the general tendency to decreased development times so that not enough data for the "Quality by Design" and PAT (Process Analytical Technology) approach [35, 36] can be collected. However, after the market entry the optimisation of any processes is much more difficult than before. The optimal approach will be if development and production are performed at the same time instead of consecutively one after the other.
As a conclusion the industry must understand their processes in order to achieve good quality in an economic way. The tendency to more refined and higher developed drug systems is observable and the manufacturing processes are also becoming more complex. A rethinking towards a pharmaceutical development with more time for "Quality by Design" with process capability investigations and Process Analytical Technologies (PAT) controlled processes is advisable in order to understand risks better [36]. As a result, shorter approval times and lesser inspections can hopefully be expected from the authorities in the future. [35] Finally, a big chance is laid in real-time quality control, which shall eventually reduce end-product release testing. One example is the usage of parametric release, e.g. by full description and validation of terminal heat sterilisation, which can eventually lead to decreased end-product sterility testing [37].

Requirements of the new guideline for the innovating pharmaceutical industry

Any pharmaceutical company introducing a medicinal product containing a new chemical entity (NCE) for the very first time into the market is named the originator or, synonymously, the innovator of the respective medicinal product. Usually, the new active substance has been immediately patent protected after discovery, and the galenical formulation and the manufacturing process or even specific methods and other aspects may be as well. The application dossier must prove the quality, efficacy and safety of the drug product as required in article 8 (3) of the Directive 2001/83/EC [38] or, if applicable, according to article 6 (1) of the Council Regulation EC No. 726/2004 [39].

The previous guideline and ICH Q8 do not focus or distinguish between selected requirements for the innovating or generic pharmaceutical industry. Basically, all chapters of the current note for guidance are applicable for the originating pharmaceutical industry. This is especially true for section "2.1 Components of the Drug Product" and "2.2 Drug Product".
Since the innovator has to investigate the physicochemical and biological properties of a drug substance, probable targets, preclinical and clinical studies including dose finding studies, the

route of administration and the formulation or, in summary, the whole array of drug development, the current guideline applies to the originator development basically at all stages. The innovator is faced with all requirements directed by this guideline, at least as long as those are applicable to the product.
The investigation of the drug substance is of central importance for the originator, at least as long as this drug substance has not previously been included in any application before. These investigations include characteristics like solubility, dependence on pH, wetability, polymorphism, stability of the drug substance in view to light, oxygen, temperature and other factors. The drug substance should be thoroughly described especially in view to its intended target site(s). The used excipients are also of great importance, especially regarding the selected formulation.
The description of the active substance and the justification for the chosen formulation together with the route of administration are of major importance for any innovating drug product. Especially the interaction of the drug substance with any of the excipients should be investigated. As a result the originator should also focus on the formulation development from initial laboratory scale batches, pilot batches, batches used in preclinical and clinical studies and finally the therapeutically justified formulation as intended for the market.
The manufacturing process development needs also to be reflected, however, this topic is perhaps not as critical for the product's safety and quality as the formulation development. Nevertheless, specific adjustments or alterations of the manufacturing process during upscaling need to be reflected and justified as well.
The container closure system is also within the focus of any newly developed drug product, especially if the route of administration requires special formulations. The container should ensure the quality of the product throughout the intended shelf-life with view to its protective performance and compatibility with the drug product. Furthermore, it should also be usable for the patient. This is of special focus if new types of containers have been invented (like special forms of inhalers, syringes, etc.), which might also be more complicated to apply.
Microbiological attributes and compatibility with any reconstitution media are also of central interest for any new drug product and must be regarded by the originator.
Since special dosage developmental requirements are no longer included in the new guideline, further advice can be found in the relevant monographs and dosage form guidances as already outlined above.

Requirements of the new guideline for the generic pharmaceutical industry

As mentioned in the previous chapter, ICH Q8 does not focus or distinguish between selected requirements for the innovating or generic pharmaceutical industry. Instead, the guideline is designed for all kind of medicinal products containing innovative, generic, herbal products, etc. Therefore, it is up to the applicant to rule out which of the sections are more applicable to his specific pharmaceutical product and which are perhaps less. Basically, all sections and

requirements do apply to any given product, whether it is an innovating development or a generic. The applicant can disregard only special requirements (e.g. for liquids) if this does not apply to his product (e.g. for solids).

General considerations

Generic medicinal products enjoy an increasing importance in comparison to the innovative medicinal products [40]. This tendency was clearly reflected by the review of the pharmaceutical legislation laid down in the Directive 2001/83/EC (article 10 (2)) as amended by the Directives 2004/27/EC and 2004/24/EC from 30 April 2004 [38].
The generic product must be essentially similar to the respective innovator product. Essential similarity in the sense of Directive 2001/83/EC (article 10(2)) [38] means that the generic medicinal products must be comparable with the respective innovator (originator) regarding quality, safety and efficacy. This comparability has to be demonstrated to the regulatory authorities by means of appropriate chemical/pharmaceutical documentation, and, if applicable, toxico-pharmacological and clinical bridging studies submitted with the application for marketing authorisation. Special requirements on substantiating this comparability are applied to generic herbal medicinal products and biopharmaceuticals, because these are not only characterised by their complex therapeutically active principles and pharmaceutical forms, but also by their manufacturing processes.
A pre-condition for each pharmaceutical company to cope with these challenges is the compliance with regulatory demands on standard pharmaceutical products.

Generic pharmaceutical products contribute significantly to the economic provision of medicinal products for the patients because of significant cost savings in comparison to innovator products. However, the generic market is characterised by strong competition and high pressures of time issues (phase-out of patent protection of the relevant innovator product), costs and prices. Therefore, generic companies face the necessity to introduce continuously new products to the market as close as possible to the respective active substance patent expiry dates, in order to achieve maximum market shares, best prices, sales and profits [40].
Within tight timelines a generic product has to be developed essentially similar to the originator's product, registered and launched, while observing numerous patent and registration issues challenging to balance the regulatory stipulations and the economic aspects appropriately.

Innovative medicinal products are almost exclusively protected by patents. A patent is a legal title, which protects a technical invention for a limited period of time. The patent enables its owner to exclude others from using the invention on the territory, for which it has been granted [41]. It is usually valid for 20 years starting from the day of issue. The patent duration can be extended by application for a Supplementary Protection Certificate (SPC) for maximally five years according to the Regulation No. (EEC) 1768/92 [42].

When a patent or SPC of an active substance and/or formulation has expired, the active substance can be used by other pharmaceutical (i.e. generic) companies to manufacture and market a comparable medicinal product with the same dosage strength, pharmaceutical form (galenical formulation) and bioavailability.
The development of a generic drug starts of course earlier ant the time period to develop a generic product varies between 2 – 4 years. With a further 2 – 3 years after application until a marketing authorisation is granted in relevant countries, the overall time period to enter the market of a generic medical product is 4 – 7 years.
When applying for a marketing authorisation of a medicinal product containing an NCE, the originator company has to provide data on the quality, safety and efficacy in form of a so-called "stand-alone" application or full dossier (modules 1 – 5 according to the CTD). With the approval of the innovator's product, the regulatory authority issues a data exclusivity period on the respective dossier preventing generic applicants to refer to it. The data exclusivity period may last from several months, e.g. for paediatric exclusivity in the USA, to 10 years for centrally or nationally authorised products in the EU (or 8 years with the amended Directive 2001/83/EC and Regulation EC No, 726/2004 [38, 39]), calculated from the approval date of the originator product. After the expiry of the data exclusivity period, a generic applicant is allowed to refer to the clinical and preclinical data of the originator without knowing the specific content. He has to submit only quality data of the generic product and has to prove the bioequivalence to the innovator product. Own safety and efficacy data gained by the generic applicant are not required. The marketing authorisation granted by the regulatory authority may, however, only be used after the originator's patents and/or SPCs have expired. Patent issues are not evaluated by the regulatory authorities, but are often subjects of litigations between the originator and the generic companies.

Generic medicinal products are reimbursed and marketed at significantly lower prices than originator products during their marketing exclusivity. These generic prices are depending on national health insurance systems and, therefore, contribute to an economic healthcare provision. Because the prices of generic products decrease rapidly after patent expiry and up to 70 % of the originator's prices in the first year and then up to 25 % in the following years [40], the generic manufacturers are forced to introduce as many new products as possible within tight timelines trying to enter the market immediately after patent expiry wherever possible.

This indicates that generic companies are faced to strong competitive market and price reimbursement issues. These general conditions strongly influence the pharmaceutical development of each new generic product. It is therefore necessary to develop a future medicinal product in a strictly limited timeframe. Furthermore, an optimised manufacturing procedure is necessary in order to keep the manufacturing costs as economic as possible.

Development of a generic pharmaceutical product

Whereas the originator has to find and adapt a formulation according to the physicochemical and biological characteristics of the new drug substance and especially has to develop a suitable route of administration, the generic imitator has to adapt his product to the route of administration of the originator product and has to prove the bioequivalence of both products.

The rationale and development of a generic product is subject to other requirements than for an inventing product as already outlined above. Cost rationale, fast development, aim to be the first to market, optimised production process, availability of drug substance (which can cause e.g. up to 80 % of the total cost), patent issues with the originator product or its different formulation successors are the key challenges to the generic pharmaceutical industry.

When a generic pharmaceutical company (or applicant) starts to develop an essentially similar product, a large amount of knowledge about the active pharmaceutical ingredient (API) has already been collected. This knowledge is presented in the full application dossier of the originator, which is, however, not accessible to the generic applicant. Nevertheless, the most important and comprehensive summary of data is presented in the summary of product characteristics (SmPC) of the innovator product, and this is available to the generic applicant as well. This central key document of the originator's marketing authorisation contains also the description on the dosage form (e.g. solid or liquid) and the qualitative composition of the used excipients. This information is already of great help and the starting point of the generic development.
The next task to do is an intensive literature search on the active substance and the used excipients. It is of central interest what is already known and published about the active substance, its manufacture, its physicochemical and biological properties like solubility, water content, particle size, crystal properties, biological activity, permeability and others.
The literature search by the generic applicant has to be extended to patent searches because often not only the active substance has been placed under patent protection by the originator but also special excipients, special formulations or dosage specialities, e.g. coated particles for the active substance, and even control methods. Thus, the generic industry has to pay attention to the patent situation of the originator product in order to avoid any litigations with the inventor once entering the marketing phase. It is of special importance to rule out these limitations as early as possible in the developmental phase of the generic product in order to avoid false strategies. Aggravating is that some of these patents (especially for specific formulation aspects) have often been granted after the originator product was introduced to the market and the development of a generic product has already been started. Thus, the generic applicant has to focus on a patent non-infringing development.

In the following section the development situation for a typical generic solid oral dosage form is described. Similar approaches exist for other dosage forms and are not regarded here in detail.

The physicochemical and biological properties of the active substance are the most important characteristics for the generic developer. Usually a stability study of the drug substance (under accelerated conditions) is the first developmental step together with the analysis of its pH dependency, pH lability, light and moisture sensitivity. Parallel to this is the development of analytical procedures for the active ingredient, sometimes based on literature data. Binary mixtures of the drug substance with each single excipient are carried out next and are placed on accelerated stability (stress stability, usually 40 ºC/75 % relative humidity) for 4 weeks and longer (4, 8 and 12 weeks, 6 months). These experiments provide already first insights into possible incompatibilities of the active substance with some of the excipients.
Furthermore, the comprehensive analysis of the originator product takes place and typical characteristics are investigated like impurity profiles, changes during stability storage, etc.
The next typical step is to place the originator product on stability, once in its original packaging but also in alternative packaging materials (i.e. other blister foils or containers) and finally also the open product storage without packaging material. These analyses provide excellent insight into the originator product's sensitivity against light, moisture, or oxygen, together with the storage advice given in the SmPC.
The next task is to develop an adequate dissolution method (for solid dosage forms). It is the aim of the generic developer to use the same excipients as the originator if no patent limitations exist. However, some excipients can cause problems or are just out-dated. Each excipient has typical characteristics and functions in a formulation. Thus, its selection by the originator provides already insight in the function, the manufacture (dry mixture or wet granulation processes) of the drug, its disintegration and dissolution behaviour. Some excipients are typical dry binders like calcium hydrogen phosphate, lactose monohydrate, mannitol or sorbitol. Others like povidone, hydroxypropyl cellulose or maize starch are typical excipients used with wet granulation steps. Finally, the tablet breaking behaviour gives an insight whether the manufacturing process contained a simple mixture or granulation step.

It is the general aim of the generic industry to develop a product with a simple formulation, which can be rapidly and easily manufactured e.g. in a free-fall tumble mixer with high performance in order to achieve a most economic production process. Unfortunately, this is not often the case and it is then of central effort to develop a robust manufacturing process.
Some excipients (which the originator still uses) are no longer suitable because they might be out-dated. E.g. polymethacrylates or other polyacrylates are more and more disreputable because the tendency of increased brittleness during the stability causes problems with the dissolution. Today, more evolved excipients based on a fatty matrix (castor oils) or cellulose derivatives can be used instead.
Furthermore, the generic developer is faced to an increasing number of patents (e.g. 27 formulation patents for a specific analgesic, oxycodon), which can limit the choice of useful excipients for his selected formulation. Even analytical methods can be protected by patents like dissolution methods with selected testing time points, and the generic imitator has then to develop a slightly deviating method. Safety data sheets of the originator product can also

provide a useful insight into the initial formulation and some physicochemical characteristics like particle size, higher aliphatic alcohols or melting point characteristics.

The next step during the generic development is the stability investigation of several initial recipes (different mixtures) of the generic product in at least two or more different primary packaging materials. It is the general aim of the developer to start the formulations as broad as possible since usable limitations will independently and rapidly arise. Once first insights into the initial formulations have been achieved, the development of pilot scale batches can evolve, which will eventually be used also for the bioavailability studies. It is also useful to investigate several formulations for bioequivalence to the originator product since special physicochemical characteristics (like micronised drug substance) or different excipients often have a strong influence on the bioavailability.

The upscaling process for the manufacture of pilot scale and especially production scale batches is a further real challenge for the pharmaceutical development. Increased manufacturing time frames due to larger batch sizes, problems with curing effects of fatty excipients, different amounts of binders and liquids during the production often influence the dissolution rate or the impurity levels negatively. Other factors like increased heat during sieving, higher pressure, problems with content uniformity, admixture or melting of fatty matrices can occur since longer machine running periods are necessary to comply with the larger batch sizes. A big challenge is also the coating process since longer processing runs of the coater (several hours instead of few minutes during galenical development) has a significant influence on the moisture of the tablet cores.

Parallel to the development of initial and especially the final formulation as intended for the industrial production, the development or improvement of the dissolution method has to occur. It is of major importance to develop suitable working analytic methods and it can be quite a challenge to develop a discriminating dissolution method, which is mandatory. The method must fulfil that 90 – 95 % of the active will be released again from a tablet after an appropriate time period for the intended product. The time points (specification) are often directed by the release behaviour of the innovator product. Today the dissolution will be investigated at three different pH levels (at pH 1.0, 4.5 and 6.8). The analysis takes place in buffers of different ionic strength and molarity (e.g. in 0.1 and 0.3 molar buffer solutions) and with different ion loading in order to analyse the consequences on the used salt form of the active component. The development of a dissolution method depends also strongly on the solubility characteristics of the drug substance and its sink conditions, which need to be fulfilled. For this purpose the use of a solubiliser in the dissolution method is sometimes necessary.

Basket and paddle dissolution apparatus are investigated at different velocities and with several ion loads. Finally, equipment from different manufacturers is used, which might have a strong influence on the dissolution behaviour (e.g. in the case of Felodipine). The dissolution method needs to be validated. ICH and the USP both include requirements for method validations [43].

Similar approaches are necessary for the development of selective methods for content (assay) and purity of the drug product. A sufficient identification of already known and also

of the possible unknown impurities together with their toxicological qualification (according to the requirements of ICH Q3A and Q3B [44, 45]) is mandatory.

The availability of the drug substance for the generic product is also a major challenge. Will this be produced in-house or purchased from external vendors? It is highly recommended to have alternative drug substance sources of suitable quality on hand and the accurate observation of the market is mandatory.

Eventually, the development studies during the life-cycle management of a generic drug never ends. Excipient sources may discontinue or particle sizes of other excipients sources arise to be critical for the formulation (e.g. magnesium stearate) and alternative sources do often no longer fulfil the requirements of the once established satisfactory formulation. Changes during the routine production like the use of different equipment (mixers, granulators, sieves, coaters, etc.) can result in new limitations for the formulation and need special care and attention. Thus, the development of a given industrial generic product never stops and is in the need of constant improvement or re-evaluation. This typical life-cycle management is a big challenge but also a great chance to use the "design space model". The above mentioned explanation of generic development provides an excellent insight into the gained knowledge and understanding of the input variables (process parameters, starting materials) during the manufacture of any generic product and can be used to justify the "design space". In an optimal case this can already be included in the initial application. Alternatively, the "design space" may be introduced after approval by a type II variation.

Basically, the above mentioned development key factors are not different for any originator product, and the inventor is faced to the same challenges. However, due to the extended timeline for preclinical and clinical studies the originating industry has more time to test and optimise the suitable formulation. Furthermore, the manufacture of the product does not underlie such strict economic pressure as any generic product due to the innovator's market exclusivity and basically uninfluenced product pricing.

Requirements to generic pharmaceutical development according to the new guideline

Developmental studies have often been conducted in the required detail for new chemical entities (NCE) by the innovating pharmaceutical applicant [10]. However, the developmental studies of generic products are limited in many cases to the focus to provide an as similar product as possible without any patent infringement of the originator. Pharmaceutical development studies are eventually the key to understand the approach of the applicant but sufficient information on this approach is often still missing [46]. This has especially been observed with generic applications [10].
So, which guidance provided by the EMEA/CHMP/167068/2004 shall be followed by the generic applicant and which ones need perhaps not? The quality guideline leaves this question

open to the applicant but basically all requirements are applicable not only to the innovator but to the generic applicant as well.
The question must arise whether this makes sense. For the generic industry some topics during development need more focus and some less as described in more detail below. However, since no special guideline for a generic product exists per se, it is on each individual applicant to find out which of any requirements are more directed to him and which ones might be not. If a generic applicant is of the opinion that several requirements are not valid for his generic product, he must justify this choice. This is basically also true for the new guideline EMEA/CHMP/167068/2004. Nevertheless the authorities should not set the same benchmark to the amount of developmental data from the generic industry in comparison to the originator.

The question arises whether all sections and requirements as outlined in the new guideline are applicable also to the generic pharmaceutical applicant. In the following overview a special focus shall be provided as to which of the requirements listed in ICH Q8 should be applicable to the generic development.
The generic product must be essentially similar to the respective innovator. This means that the generic product has the same qualitative and quantitative composition of active substances, the same dosage form as the reference product and the bioequivalence to the reference product was proven by suitable bioavailability studies [38, 47]. Furthermore, the different oral dosage forms with immediate release are regarded as the same dosage form. Finally, the generic applicant does not need to provide bioavailability studies if the relevant criteria outlined in the corresponding guideline [bioclassification system, 47] are fulfilled.
These requirements to a generic pharmaceutical product are also an immense advantage in view to pharmaceutical development studies. The generic industry follows the path of the pioneering task of the originator. Therefore, the main focus of the development of the essentially similar product is the process control and its optimisation. The resources for excipients and the drug substance are also of major focus and studies thereon need to be described.
Since basically the same active ingredient and dosage form is used as for the innovator, special explanations or even justifications are not necessary.
This is especially true for the drug substance (section 2.1.1 in the new guideline), however, the physicochemical and biological properties need to be known and understood by the generic applicant as well. If he cannot provide this knowledge by literature data or even a pharmacopoeial monograph, the relevant studies as outlined in the guideline need to be performed.
This possible exemption is not true for the used excipients (section 2.1.2) as these play a major role in the used formulation of the generic product. Even if the same qualitative composition is used for the generic product as is in the originator product, the applicant needs to justify these and prove the suitability of the used amounts. The new guideline does no longer refer to the “Note for Guidance on Excipients”, which is going to be replaced together with the CPMP “Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products” by a new guideline currently in the draft status [25, 26,

30]. Herein, “an explanation of the choice of the excipient (and grade where necessary)” should be compiled. Furthermore, “the compatibility of excipients with other excipients and active substances should be established”. This is fully compliant with the expectations on excipients described in ICH Q8. This question is of even greater importance since the generic applicant can basically choose other excipients in his “essentially similar” formulation than the originator. Binary mixtures of the API with each excipient can be the first suitable investigation as already outlined earlier. However, it is of special importance to analyse any incompatibilities between API and excipients or among the used excipients themselves. For the complete formulation containing all excipients, the relevant stability studies will provide the best proof of the chosen composition. No question about the necessity that special excipients like antioxidants, penetration enhancers, preservatives, etc. need to be justified in the appropriate manner.

The same is true for the formulation (section 2.2.1); this should be the result of the above mentioned studies on the excipients and is of special focus for the generic product. A justification for any differences between pilot scale batches, batches used in the bioequivalence studies and for the final commercial product is also applicable to the generic applicant, of course. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed where appropriate.

The description and justification of any overages (section 2.2.2) is also not questionable to the generic applicant and needs to be included in the quality documentation.

Physicochemical and biological properties (section 2.2.3) need to be addressed for generic products as well where applicable.

The manufacturing process development (section 2.3) needs also to be reflected. Any improvements, changes and differences between the different developmental formulations must be discussed and justified. The suitability of the used manufacturing process must be provided by the generic applicant; this can be done by the reflection of critical steps or equipment and the adequate control of these, e.g. by suitable in-process controls (IPC). This section is fully applicable to any generic product and is an excellent area to make use of any quality risk management tools described in ICH Q9.

The container closure system (section 2.4) is also within the focus of the generic drug product; however, here a similar container as used by the originator is mostly suitable. Nevertheless, the generic applicant must justify the chosen container and prove its suitability. Again, the results of stability studies will do best justice of this topic. It is especially advisable to analyse different container types throughout pharmaceutical development. An increased knowledge gained on this field by the generic applicant provides an excellent justification for the design space “container” and may be of great help if he once plans to switch to other (related) container types or container components throughout the life-cycle of the product, e.g. for new markets. Additional studies in this area during the developmental phase can later pay off by avoiding new stability studies or even post approval variations during the marketing phase.

Microbiological attributes (section 2.5) such as microbial limit tests or the suitability of antimicrobial preservatives and compatibility (section 2.6) with any reconstitution media are

also of central interest for any generic product and must be discussed and justified by the applicant.
Since special dosage developmental requirements are no longer included in the new guideline, further advice can be found in the relevant monographs and dosage form guidances as already outlined above [20, 21, 22, 23, 24].

The new guideline invites the generic applicant (basically in the same way as the innovator) to lay down the gained knowledge of the pharmaceutical development of his product and not to keep it further hidden or secret to authorities, regulators and perhaps inspectors. This was often the case in older quality dossiers [46]. Furthermore, authorities are nowadays increasingly rejecting the scarce documentation, which is often provided on pharmaceutical development in older dossiers. They expect improved gained knowledge – experienced by positive as well as negative experimental results. This proven knowledge will be the key to an enhanced and better understanding of each input variable (like starting materials, but also process parameters) and offers the chance to broaden the design space in order to provide assurance of quality of the pharmaceutical product also and especially for the generic applicant. It is on him to decide how much use he likes to make of it. However, the minimum of the baseline expectations of this guideline need to be fulfilled [10].

Critical discussion of the new guideline from the viewpoint of the generic pharmaceutical industry

The previous chapter outlined an exemplary way how a typical development of a generic pharmaceutical product proceeds and also which sections of the new guideline are especially applicable to generic products. It made clear that the generic product development underlies different starting points, conditions and expectations than the originator product

In this context it is of major importance for the applicant from the generic pharmaceutical industry to consider and evaluate which changes or improvements might be necessary in the future throughout the life cycle of his product.

Points to consider are:

- Which kind of regulatory requirements might be necessary to consider in the future?
- How to cope with risk management and assessment – ICH Q9?
- Which key markets shall be accessed in the future?
- Are there perhaps different requirements to the product for different markets (e.g. kosher starting materials and manufacturing process) which needs once to be regarded in the future?
- Which are the anticipated batch size requirements in the future?
  Is it once necessary to increase or decrease the batch size?

May it be probably necessary to subdivide the current batch size into smaller sub-batches?

- How does the current manufacturing process may be altered if other drug substance sources have to be used in the future, new vendors?
- Which are the critical parameters of the used starting materials and the process?
- Are critical parameters like particle size, polymorphism, solubility and other critical characteristics of the active substance well investigated and well understood enough so that it does not mess up the manufacturing process?
- Which are the critical excipients like some flavours? Do other excipient or excipient sources have an influence on the manufacturing process of the generic product?
- Upscaling: How stable is the manufacturing process for different equipment, e.g. other or larger granulators, mixers, sieves? How about additional process parameters like other flow rates, drying air or heat (e.g. lability)?
- Which possibilities are feasible to improve (i.e. shorten) single process steps like stirring or mixing? Will the product still maintain the same quality?

Only if the applicant has an idea which of these factors (perhaps all) might influence the manufacturing process development in the future, it is on him to evaluate these influences or to be more precise: risk factors.
It is furthermore obvious that the more of these parameters are considered and included into any developmental studies (e.g. different sources of a specific excipient like cellulose acetate or others) the more knowledge can be gained about the process capabilities, and possible error sources can be ruled out or at least better controlled. This is exactly what the intention of ICH Q8 is about: the generation of a design space and not just a narrow design line that has been proven to be just adequate for a given formulation.

It is obvious that the investigation of these increased factors will not only be time-consuming but also costly. In selected and several cases an improved and more comprehensive formulation and manufacturing development including these factors will eventually pay off in the future. The huge chance to reduce or to circumvent some possible variations in the future can also be a very time- and cost-saving intention. For instance type II variations are not only time-consuming and expensive in larger mutual recognition procedure registrations but even worse if many solely national registrations need to be maintained. Here, a more of developmental data including e.g. studies with different excipient of excipient sources can eventually pay off for the generic pharmaceutical applicant.

From these observations it is also clear that the generic pharmaceutical industry must gain experience with the term “design space” and fill this with significance. Today the experience and knowledge about the design space is still pretty vague. In order to apply for the design space model it is also of major importance to figure out how many conducted studies are necessary during the developmental stage so that the authorities are going to accept this design space to a degree that a specific variation can be avoided, for example the replacement of one excipient by a comparative one. Are the results – or better knowledge, which the

applicant gained – comprehensive enough to define the design space or are the data not sufficient? Only the future will provide experience how this topic can be handled between applicants and the authorities. If the applicant fulfils all possible requirements today for a specific variation and contains these data already in his developmental studies, it is most likely that no variation regarding this topic will be necessary in the future. This requires that the applicant needs to place batches with an altered or different excipient source on stability during development studies and carry out relevant dissolution studies (a priory) in order to avoid a relevant type IB variation (no. 18 according to the Guideline on Dossier Requirements for Type IA and Type IB Notifications [15]) once in the future. This implies that the applicant has already knowledge or a clear vision about possible alterations in the process parameters, which might come up in the future. Often this visionary thinking is just hypothetical. The question remains whether it is realistic and affordable or even feasible in a timely manner to cover all or many future variations already during the developmental phase. Nevertheless it can be a great chance in selected circumstances and can safe money and time. Both are factors of tremendous significance for any generic pharmaceutical product.

The model or usage of the design space makes most sense during the initial pharmaceutical development phase. It makes less sense after introduction of the product to the market since any change and alteration of the quality documentation during the life-cycle of the product automatically implies a post-approval variation process.
Even an update of the pharmaceutical development section, e.g. to include additional knowledge or results on the manufacturing process must be regarded as a variation. Unfortunately, if these changes do not fall into the scope of type IA and IB variations, the update or a possible introduction of the design space is a type II variation. It must be evident that the change to the design space after market introduction is therefore of very little interest especially for the industry. In these cases it makes much more sense to apply directly for a regular variation for a given purpose.
Therefore, the big chance for the design space model and idea should be seen during the developmental phase but less later, and this is the same for the inventing and the generic pharmaceutical industry.

So, which areas are susceptible especially to generic pharmaceutical development and provide a chance for the application of a design space? Basically all sections outlined in ICH Q8; however, a few topics predominantly. The formulation development, examining different excipients (e.g. with the same function in the formulation), different excipient grades or different API sources are a large field, which shall already be investigated during developmental studies. This approach is not only to find the final composition as intended for the market but especially to broaden the scientific understanding of these input variables. If the generic applicant can prove that four different flavours do not (negatively) influence the characteristics of the final product, this provides already excellent justification if he once intends to use a different flavour during the life-cycle of this pharmaceutical product. The same approach can be chosen during the manufacturing development. For instance the use of

different mixing conditions or different granulator types will result in improved process understanding and the determination of critical manufacturing aspects to the formulation. This gained knowledge can be used to justify other similar adjustments later during the industrial scale production. The use of different container types or different parts of the primary packaging systems is also an excellent area suitable for the application of a design space. The investigation of different blisters or foil strengths or different plastic caps used on glass bottles provides an increased scientific approach of the generic applicant towards critical (stability) parameters for the quality assurance of the intended product. Again, a more of developmental studies may be an investment now to reduce possible variations in the future, e.g. for a type I variation on a related packaging material. However, these approaches need to be evaluated and no guarantee can be provided to the applicant at the time of development planning. Here, a consultation of the relevant authority (authorities) might be of good help for specific questions and approaches in form of scientific advice.

ICH Q8 can be regarded as an additional regulation and thus as an additional burden for the industry on the first glance. However, the adaptation of regulatory requirements to the current state of pharmaceutical science is a common and necessary process, which must and will eventually be agreed on both sides, authorities and industry.
Finally, if the applicant includes not only economic strategies into his focus but also the viewpoint of the patients (with their expectations, questions and concerns), the use of quality risk management tools and the "Quality by Design" focus will be much easier in order to provide quality assurance to the customers. Furthermore, this approach offers the great chance to reduce waste batches for some products [48].
ICH Q8 must be regarded as a chance for a basic change. The product quality and performance can be ensured by the development of effective and efficient manufacturing procedures [10]. The batch release specification can be established on grounds of a comprehensive understanding of formulation and processing factors, which can influence the final performance of the medicinal product. Eventually, the continuous improvement of these factors will provide the opportunity for real-time quality control and increase therefore the quality assurance.
The chances are immense also for the generic pharmaceutical industry. A better understanding of the selected manufacturing process opens also the door for new technologies and provides better prerequisites for any change management. Finally, it will result in less failed batches, a topic of huge importance and interest especially for the generic pharmaceutical industry.

Summary and outlook

In November 2005 the new guideline ICH Q8 with the title “Pharmaceutical Development” was finalised. It directly came into operation in the tripartite regions, e.g. in Europe with the “Note for Guidance on Pharmaceutical Development”, EMEA/CHMP/167068/2004 in May 2006 and in the other two regions in May and September 2006 as well.
On the first glance this guideline is the current successor of the already existing European guideline “Development Pharmaceutics”, CPMP/QWP/155/96 from January 1998. But this view is only superficial since no indication can be found that the new guideline eventually replaces the previous one. In Europe it must therefore be regarded that both guideline are in operation and applicable.

ICH Q8 is not just a replacement or addition of the previous guideline but it is more; it is the joint initiative of the tripartite regions, the USA, Japan and the European Union and therefore and adaptation to the requirements of all ICH regions. It is the reflection to an increased knowledge in pharmaceutical science. The applicant is invited to give better insight into his developmental studies leading to the formulation and production process as intended for the market. Furthermore, ICH Q8 provides an invitation to combine the pharmaceutical development studies with quality risk management tools and quality systems as described and outlined in ICH Q9 and Q10.

Comparing both development guidelines makes clear that many analogue requirements exist. But the direct comparison of topics indicates also that the previous guideline is focused much more on detailed guidance. This is especially obvious for the requirements on specific dosage forms (e.g. liquid and semi-liquid dosage forms, solid dosage forms, transdermal patches and different inhaler types), which are now no longer regarded in detail in the current guideline.
The main difference is that the new guideline offers the opportunity of the “design space”. This multidimensional combination of input variables and process parameters shall demonstrate the assurance of quality and is regarded as an area of gained knowledge from pharmaceutical development studies and manufacturing experience, which should be provided by the applicant. This information shall demonstrate that a quality product and its manufacturing process have been developed, which consistently deliver the intended performance of the product. ICH Q8 leaves more responsibility to the applicant to acquire and compile the critical input and process attributes of the product and how to control these adequately.
ICH Q8 provides the opportunity to the pharmaceutical industry to give insight into their decisions during development of the pharmaceutical product and invites them to provide this insight in an improved manner than before. It is widely on the applicant to decide – beyond a baseline expectation of information – how much data to be generated and presented in section 3.2.P.2. However, the more data can confirm the scientific knowledge achieved by the applicant about the drug substance, the excipients, the manufacturing process and improvement, the different container closure systems used etc., the more this will eventually provide the desired flexibility of a design space. The usage of a meaningful design space

provides then the opportunity to reduce the need of post-approval changes procedures and thus increases regulatory flexibility.

The question comes up why the previous guideline may remain in operation. Isn't the new guideline able with the provision of the design space to cover all current requirements on pharmaceutical development, especially in view that additional special dosage form guidelines exist? A clear answer has not been provided by the EMEA, but it is also no disadvantage to keep the preceding guideline in operation, neither for authorities, nor for the industry. Furthermore, the positive response to ICH Q8 on both sides is encouraging further expansion. An ICH working group is developing annexes e.g. on special dosage forms in the future. This implies that the whole subject of ICH Q8 has not been completely finished but can be rather regarded as an ongoing process. Once these annexes come into operation, the ICH Q8 complex might eventually replace the previous guideline on "Development Pharmaceutics".

The generic pharmaceutical industry faces other challenges than the originator, and this can also be regarded during the pharmaceutical development. According to the new guideline, basically the same requirements regarding developmental studies exist for both kinds of pharmaceutical applicants. However, whereas the innovator has to focus mainly on the investigation of the physicochemical and biological properties of a drug substance, probable targets, preclinical and clinical studies including dose finding studies, the route of administration and the formulation finding, the generic applicant has the huge advantage to claim essential similarity with view to the active substance, strength, route of administration and bioequivalence. Thus, the generic focus is more directed to the selection of the drug components, i.e. the active substance sources and different excipients. Besides the formulation development especially the manufacturing process development is of major focus for the generic pharmaceutical development. Due to economic considerations, the availability and replacement of any component sources of the drug product as well as the manufacturing process improvement and optimisation are the main challenges during the life cycle management of any generic product. An increased scientific knowledge gained by suitable studies during the pharmaceutical development, e.g. on different used API and excipient sources or grades, can provide the great opportunity to broaden the design space. This will be evaluated and approved by the regulatory authority and may offer the possibility to reduce the amount of post-approval variations to the medicinal product.
However, the experience on the necessary studies, the evaluation and application of the design space is still low on both sides, authorities and industry. The near future will show how both parties can maintain this desirable approach and deal with it. At least the regulatory framework for this purpose has now already been provided by ICH Q8 and this chance should be taken by the industry.

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Hereby I declare on oath that I wrote this thesis independently and no other than the listed aids was used.