ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, ICH Q10 Pharmaceutical Quality System: vision, concept and their potential impact on industry and regulators – will they foster innovation?

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

AAPS	American Association of Pharmaceutical Scientists
ANDA	Abbreviated New Drug Application
API	Active Substance Ingredient
BWP	Biotechnology Working Party
CAPA	corrective action and preventive action
CCPIE	China Center for Pharmaceutical International Exchange
CDER	Center for Drug Evaluation
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing and Controls
cGMP	current Good Manufacturing Practices
CPMP	Committee for Proprietary Medicinal Products (now CHMP)
CPQ	Council on Pharmaceutical Quality
CTD	Common Technical Document
DoE	Design of Experiments
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EFPIA	European Federation of Pharmaceutical Industries` Association
EFTA	European Free Trade Association
ELD	Evaluation and Licensing Division
EMEA	European Medicines Evaluation Agency
EU	European Union
EWG	Expert Working Group
FDA	Food and Drug Administration
FIP	International Pharmaceutical Federation
FMEA	Failure Mode Effects Analysis
GMP	Good Manufacturing Practices
HACCP	Hazard Analysis and Critical Control Points
IBM	International Business Machines
ICH	International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGPA	International Generic Pharmaceutical Alliance
IND	Investigational New Drug
IPEC	International Pharmaceutical Excipients Council
ISO	International Standards Organization
ISPE	International Society for Technical Professionals in the Health Care Manufacturing Industry
JPMA	Japan Pharmaceutical Manufacturers Association
MHLW	Ministry of Health, Labour and Welfare
NDA	New Drug Application/Approval
NCE	New Chemical Entity
NfG	Note for Guidance
ONDC	Office of New Drug Chemistry
ONDQA	Office of New Drug Quality Assessment
PAT	Process Analytical Technology
PFSB	Pharmaceutical and Food Safety Bureau
Ph.Eur.	Pharmacopoeia Europea
PhRMA	Pharmaceutical Research and Manufacturers of America
PQAS	Pharmaceutical Quality Assessment System

Q	Quality
QbD	Quality by Design
QWP	Quality Working Party
RDPAC	R&D-based Pharmaceutical Association in China
RTR	Real time release
SOP	Standard Operation Procedure
SPC	Supplementary Protection Certificate
US	United States
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organization
WSMI	World Self-Medication Industry

1 Introduction

Manufacturing techniques of medicinal products have not kept up with advances in science and technology. In the Wall Street Journal on September 3, 2003 the following quote appeared: "*The pharmaceutical industry has a little secret: Even as it invents futuristic new drugs, its manufacturing techniques lay far behind those of potato chips and laundry-soap makers*."[1] It astonishes that for pharmaceuticals that have to fulfill high criteria regarding quality, efficacy and safety the manufacturing techniques drag behind those of fast food industry.
In the United States (US) approximately US$ 120 billion a year are spent for total research and development by regulators and pharmaceutical companies. A large number of new molecules have been developed but less attention has been paid to the development of the drug. Most of the investment has been made in basic science and only a small part in developing new manufacturing processes.[2] The reasons therefore are that product complexity did not demand it. Additionally, the regulatory framework discouraged the manufacturers to invest in innovative technologies.[3]
But the situation has changed. More detailed knowledge of the molecular science enables the pharmaceutical companies to develop new complex products such as e.g. hybrid drugs. Complex products are difficult to manufacture. The production of these new products requires novel manufacturing techniques.[4] As the regulatory framework is seen as one of the reasons why the development of novel manufacturing technologies is far behind the development of complex products it is time to change it.

It has been recognized that the quality of applications varies and that many applications lack adequate pharmaceutical development information.[5] The reasons therefore are different. It can be that the applicant does not want to provide all details to the authorities. It is also possible that the required information is not available.
But especially this information included in the quality part of a dossier provides detailed information for the reviewer on formulation and manufacturing processes.

The implementation of improvements and changes in a dossier needs prior approval or at least notification. As result of these regulatory hurdles some pharmaceutical companies have been reluctant to change and/or continuously improve their manufacturing process and therefore to continuously improve the product quality.[5]
But according to Article 23 of Directive 2001/83/EC there is an expectation that industry keeps up with the „state of the art". A marketing authorization holder has to update the dossier in order to *"...take account of scientific and technical progress..."*.[6]
A less restrictive regulatory environment would surely help to meet this requirement more easily.

Considering the above-mentioned aspects a change of the pharmaceutical manufacturing paradigm seems to be necessary.
At the meeting of the International Conference on Harmonisation (ICH) in Brussel, 2003 a new Vision has been agreed. Industry and regulators worked together to develop a regulatory framework that encourages the pharmaceutical industry to enhance their knowledge of product and processes, to implement modern tools for quality risk management and to establish quality systems to produce high quality products to meet the needs of the patients.

Three new ICH Quality guidelines have been developed respectively are under way to finalization to change pharmaceutical manufacturing paradigm:

- ICH Q8 Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality Systems

Regarding the change of the paradigm away from an empirical, data-based approach to a science and risk-based approach the experts are speaking of a (r)evolution in pharmaceutical development.[7]

A large number of workshop sessions with regulatory representatives and members of the ICH Expert Working Groups (EWG) together with the industry have already taken place discussing the topics of ICH Q8, Q9 and Q10 to finally achieve a greater mutual understanding of their objectives and concepts.

2 The Current State of Pharmaceutical Manufacturing

Many companies invest as much money for drug manufacturing as for research and development. Factory utilization is often below 15% because of batch-production processes. For some products waste may top 50%. Sometimes scale-up is difficult and unpredictable. In most cases the pharmaceutical manufacturers do not know the reason for production failures.[8]
Gaps have been recognized in the application of manufacturing science principles.[9]
Less understanding of product and processes is the basic problem. Many product formulations and processes are based upon empirical data and not on knowledge obtained through development studies. It was realized that little knowledge on mechanisms could have a negative impact on product quality.[10]
Decision-making is very often based on the best available knowledge without applying quality risk management tools. In cases where manufacturing processes are not robust product quality varies. That can neither be in the interest of the manufacturer nor in the interest of the patients. Most pharmaceutical companies currently rely on resource-intensive quality control systems to prevent that defective products come to the market. In case of recalls the typical reaction is to increase the corrective actions.[4]
Today's established approach is rather guidance-oriented, fixed on specifications and based on the elimination of "worst practices". The conventional way to proof quality is testing the end-product according to pre-determined specifications (release specification and shelf life specification). The aim is then to meet these specifications.
Under the traditional manufacturing model companies often submit an extensive amount of data in the chemistry, manufacturing and control (CMC) part of the dossier.[8] But most of the submitted data is not directly related to the quality of the product.[5] A large amount of data is not automatically an indication for high product quality. But a large amount of data in any case prolongs the approval time for the marketing authorization.
According to the current variation regulations in the ICH-regions changes of formulation and manufacturing processes need prior review by authorities. That means that resources at the industry but also at the authorities are tied for the approval of variations.

3 The ICH-Vision

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) was formed in April 1990 in Brussels. The core group consists of the regulatory authorities and the research-based industry associations of the European Union (EU) (European Medicines Evaluation Agency [EMEA] and European Federation of Pharmaceutical Industries` Association [EFPIA]), the US (Food and Drug Administration [FDA] and Pharmaceutical Research and Manufacturers of America [PhRMA]) and Japan (Ministry of Health, Labour and Welfare [MHLW] and Japan Pharmaceutical Manufacturers Association [JPMA]).[i] Additionally, a Steering Committee has been established meeting twice a year. [11]
The aim of the ICH is to achieve an "...*increased international harmonisation, aimed at ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner...*"[11]
ICH guidelines are not legally binding, unless incorporated into local law. They represent agreed-upon scientific guidance to meet technical requirements for registration within the three ICH-regions.
Since 1990 a numerous guidelines in the fields of safety, quality, efficacy and multi-disciplinary have been established by the ICH Process[ii].
While discussing the current state of pharmaceutical manufacturing and its opportunities for improvement a new ICH-Vision was "born". The Vision is also articulated as the Desired State for pharmaceutical manufacturing in the 21st century.[3]

At the ICH meeting in Brussels in July 2003 the five-year Vision was agreed:

"Develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management."

The Vision is the outcome of a workshop discussion attended by 60 designated experts from the six ICH parties (EMEA, EFPIA, FDA, PhRMA, MHLW and JPMA), observers (World Health Organisation [WHO], Health Canada and European Free Trade Association [EFTA]) and non-ICH parties (International Generic Pharmaceutical Alliance [IGPA] and World Self-Medication Industry [WSMI]) on a risk-based approach to drug product quality.[12]

For the ICH guideline Q8 Pharmaceutical Development the ICH Q8 Expert Working Group (EWG) articulated the Vision as:[13]

- *Product quality and performance achieved and assured by design of effective and efficient manufacturing processes,*
- *product specifications based on mechanistic understanding of how formulation and process factors impact product performance,*
- *an ability to affect continuous improvement and continuous "real time" assurance of quality.*

The Vision or the Desired State is a mutual goal of industry, society and regulators. Janet Woodcock, deputy commissioner of the FDA described the Desired State as "*a*

[i] Further participants of the ICH: official observers (WHO, Health Canada, EFTA) and global trade associations from the generic and self-medication industries (IGPA and WSMI)
[ii] The drafting of the ICH guidelines follows a five-step process agreed in 1992

maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight".[14]

The Desired State of pharmaceutical manufacturing was characterized in the *Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach: Second Progress Report and Implementation Plan* (February 20, 2003) as:[15]

- *Product quality and performance achieved and assured by design of effective and efficient manufacturing processes,*
- *product specifications based on mechanistic understanding of how formulation and process factors impact product performance,*
- *continuous "real time" assurance of quality,*
- *regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability,*
- *risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process, control strategies to prevent or mitigate risk of producing a poor quality product.*

4 ICH Q8 Pharmaceutical Development

In the pharmaceutical development section the applicant has the opportunity to describe the development of the formulation and the manufacturing process of a medicinal product. There, the application can tell the reviewers "the story of the product". The transfer from data gained through development studies into scientific knowledge on formulation and processes can be discussed.

In the European Union pharmaceutical development data are traditionally the basis for the assessment of the drug. Pharmaceutical companies describe the formulation development, the critical product attributes and the design of the manufacturing process. It is expected that weaknesses in the formulation and in the process are identified and described.[16]
The relevant guideline describing what should be done is included in Section 3.2.P.2 Pharmaceutical Development is the *Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)*.[17]
The information on pharmaceutical development submitted with the application for marketing authorization provides basic information to understand the approach of the applicant, but sometimes they are insufficient.[18] As already-mentioned the reason could be that more detailed knowledge is not available or that the applicant does not want to provide all information, even if they could be of relevance for the assessment.

In the United States the information on pharmaceutical development is submitted to the agency differently. Some companies submit development data via Investigational New Drug application (IND)[iii] other companies provide these data around the New

[iii] IND: The current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

Drug Application (NDA). The level of information given by the companies varies and this is due to the concerns over consistency and questions.[16]
It has been observed that US manufacturers have gained extensive data through development studies but they have been rather reluctant to share them with the regulators.[8] Such a behavior will restrain the new Vision of a science and risk-based approach of the ICH.

In Japan the authorities have a great emphasis on the Overviews and Summaries included in Module 2 of the Common Technical Document (CTD) and less on the single data and detailed descriptions contained in Module 3 (Quality Part), Module 4 (Toxicological Part) and Module 5 (Clinical Part). The pharmaceutical development plays rather an inferior role. Just for complex dosage forms more detailed information on pharmaceutical development is expected.[16]

4.1 History of ICH Q8

Regarding the different regulatory environments in the three ICH-regions a harmonized ICH guideline was needed to achieve a common understanding of regulators and industry on the content of Section 3.2.P.2 Pharmaceutical Development in Module 3 of the CTD dossier.
The development of a harmonized ICH guideline on pharmaceutical development was triggered by the adoption and implementation of CTD in the three ICH regions[19].

Initial discussions on the value of pharmaceutical development to the reviewers in the EU have already been taken place at the ICH meeting in Tokyo in September 1998. The EU proposed to include the pharmaceutical development into the CTD. The FDA offered resistance to this proposal. As mentioned-above so far it was not required by the FDA that the companies provide development data in the drug dossiers submitted for application for marketing authorization. But in the European Union the pharmaceutical development part was already the key element of the drug dossiers.
Finally during the ICH meetings in Tokyo (March 2000) and Brussels (July 2000) a consensus on including pharmaceutical development into Module 3 of the CTD has been achieved.

According to the ICH M4Q(R1) guideline (*The Common Technical Document for the Registration of Pharmaceuticals for human Use: Quality – M4Q(R1); Quality overall Summary of Module 2 and Module 3: Quality)*[iv] :
"*The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate....Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality."*[20]

The problem was then that approaches of the interpretation of the content described in Section 3.2.P.2 Pharmaceutical Development in the CTD dossier have been inconsistent across the three ICH-regions.[16]

[iv] The CTD provides a harmonized structure and format for new product applications. The CTD was agreed upon in November 2000 in San Diego, USA. It is divided into four separate sections. One of these sections is the Quality section (M4Q).

It was the industry that finally required and pushed the development of ICH Q8 Pharmaceutical Development to define what has to be presented in the pharmaceutical development section. The definition of the content of the pharmaceutical development section in a dossier was especially important as information on pharmaceutical development was not required from the FDA by then.

At the ICH meeting in Tokyo in February 2003 the Concept Paper of Pharmaceutical Development was presented to the ICH Steering Committee for harmonization.
At the ICH meeting in Brussels in July 2003 the ICH Steering Committee agreed that the experts of the six parties would further work on the new tripartite guideline Pharmaceutical Development. The ICH Q8 EWG has been established seeking to incorporate elements of *Risk* and *Quality by Design* into the ICH guideline Q8.
On October 8, 2003 the ICH Steering Committee endorsed the final Concept Paper of ICH Q8 Pharmaceutical Development.[21]
ICH Q8 started off fairly on target but during the ICH guidance development process it expanded to describe now more fully how the manufacturers could establish design systems and quality control.[8] ICH Q8 reached Step 4[v] of the ICH Process in November 2005.
In the European Union the ICH guideline Q8 came into operation in May 2006 as *Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068/2004)*.[22]
In the United States the *Guidance for Industry: Q8 Pharmaceutical Development*[23] has been published in the Federal Register, Vol. 71, No 98 on May 22, 2006.
In Japan the ICH Q8 guideline has been implemented in the PFSB/ELD Notification N°0901001 on September 1, 2006. Currently ICH Q8 i s under revision.

4.2 Structure of ICH Q8

ICH Q8 is envisaged as a “Two-Part” guideline. Part 1 of the guideline comprises the core document, describes the baseline approach, the requested optional information, Design Space and regulatory flexibility. Part 2 comprises annexes and examples in addition to the core document. It has been realized that further explanation of ICH Q8 is required. These annexes and examples shall provide further details and shall promote a common understanding and implementation of ICH Q8. They are still under development. Table 1 presents an overview on the structure and content of ICH Q8.

Part 1	Part 2
• Core document	• Annexes relating to specific dosage forms
• Baseline expectations	• Examples of “baseline expectations” versus “optional information”
• Optional information	
• Definition of Design Space	
• Regulatory flexibility	• Appropriate examples of risk management

Table 1 Structure of the “Two-Part” Guideline ICH Q8 Pharmaceutical Development

Source based on the presentation of Susanne Keitel, ICH Q8 “Pharmaceutical Development” – State of Play, Düsseldorf, May 31, 2006 [19]

[v] Step 4 of the ICH Process: adoption of an ICH harmonized tripartite guideline

4.3 Scope of ICH Q8

ICH Q8 applies to drug products (new chemical entities [NCE] and biotechnological/biological products) as defined in the scope of Module 3 of the CTD according to *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q (R1*).[vi] But it may also be applicable for other categories of product such as e.g. herbal products, radiopharmaceuticals, products of fermentation.
It provides guidance on what shall be discussed in Section 3.2.P.2 Pharmaceutical Development: components of the product (drug substance(s) and excipients), the formulation development including overages, the manufacturing process development, container closure system, microbiological attributes of the drug product and the compatibility of the drug with reconstitution diluents.
The guideline does not apply to submissions during the clinical research stages of a product development but it is recommended to consider its principles for those stages.

4.4 Objective of ICH Q8

The goal of pharmaceutical development is to achieve product quality through design and to consistently assure the performance of the product as it relates to the safety and efficacy of the drug throughout the product lifecycle.
In Section 3.2.P.2 Development Pharmaceutical the applicant has the opportunity to describe his experiences gained through development studies and the transfer of that information combined with prior knowledge of the formulation and the manufacturing process. The intention is that the applicant demonstrates a "*comprehensive understanding*" of the product and its manufacturing process. The decision taken for the drug substance(s), excipients, the dosage form or the container material should be based on "*scientific approaches*" and by applying "*quality risk management*".
Section 3.2.P.2 Development Pharmaceutical is initially compiled for the application of a marketing authorization but afterwards it can be revised to implement additionally gained knowledge during the lifecycle[vii] of a product.

4.5 Concept of ICH Q8

ICH Q8 encourages a new pharmaceutical development paradigm. The guideline is considered as an opportunity to switch from a simple data transfer in the development pharmaceutical section of a dossier to a science-based knowledge transfer. The enhanced knowledge (of successes and failures) shall be shared with regulators and inspectors in order to achieve a comprehensive understanding of the drug at both sides.

[vi] Scope of ICH M4Q(R1): "for drug substances and their corresponding drug product as defined in the scope of the ICH Guidelines Q6A ("NCE") and ICH Guideline Q6B ("Biotech")"
[vii] Definition of lifecycle according to *the Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068/2004)*: "all phases in the life of a product from the initial development through marketing until the product's discontinuation."

The key concept is “Quality by Design”. Two key elements of Quality by Design mentioned in ICH Q8 are:

- determination of a Design Space (baseline or enhanced approach)
- application of Process Analytical Technologies (PAT) to enhance knowledge of product and processes

4.5.1 Quality by Design

It has been recognized that quality cannot be tested into a product but has to be designed and built into it from the initial concept through to all elements of manufacturing. But what is “Quality”?
According to ICH Q6A *(Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances”):*
“Quality” is defined as “*the suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity*”.[24]
Product quality assurance comes from process understanding and process control plus compliance with the acceptance criteria.
Quality by Design is not really a new topic. Already in the past pharmaceutical companies had collected information gained through development studies, created space models and monitored their processes. But the companies today in general use only a small percentage of the intellectual capital they own when designing processes, so that there is space for significant improvement.[25]
Moreover, the performance was done differently from company to company and between the three ICH-regions Japan, the European Union and the United States. There was no harmonized approach existing.

Scientific knowledge is the basis to be able to design quality into products. At the beginning of the development of a new drug there is usually only little known about the molecule available. During the development process the manufacturer has to decide on the pharmaceutical form, what excipients can be used etc. There are different possibilities to design a drug but the relevant aspect is the quality. Therefore it is important to understand the relationship between quality attributes and their impact on product quality related to safety and efficacy. Quality attributes are determined on mechanistic understanding of how formulation and process factors impact product performance.

4.5.2 Design Space

Design Space is defined in the glossary of ICH Q8 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. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.“*[13]

It is the aim to define the boundaries for the Design Space wherein material attributes and process parameters can vary without having an impact on the quality. The critical attributes of material and manufacturing processes influencing the product quality need to be fully characterized and monitored.

As working within the Design Space is not considered as a change continual improvement of formulation and processes within the Design Space is expected as one of the potential benefits. There is possibility to optimize manufacturing processes without prior approval. The regulatory burden can thus be reduced. But that presumes firstly that the applicant has established an approved Design Space in the drug dossier and secondly that the improvements are carried out within the Design Space.

The scientific knowledge that is required to be able to define a Design Space can base on established scientific literature or it can be gained through development studies.
More detailed knowledge of product performance and manufacturing process parameters can also be gained by the application of PAT (see section 4.5.5, page 18). Statistically designed experiments (Design of Experiments/DoE)[viii] or scale-up correlation are alternative approaches to define a Design Space.[26]

4.5.3 The Dual System

The implementation of a Design Space into a drug dossier is an option and not mandatory. It is up to the applicant how much resources and at what time in the lifecycle of a product s/he wants to invest in a Design Space concept. The applicant can chose the currently common way. That means that s/he provides data received through the conduct of formal pharmaceutical development studies and nothing more (baseline expectations, see below). Or s/he can decide to perform further development studies to gain more information on the product and the aspects influencing the product quality (optional information, see below).
Which approach the applicant does chose will depend on different parameters, like e.g. size of the company, costs, capacity, type and complexity of the product, already available scientific knowledge.

Baseline expectations - Baseline approach
For a baseline approach at least those parameters of drug substances, excipients, container closure systems and manufacturing processes critical to the product quality as well as the justification of control strategies have to be provided in the pharmaceutical development section of the dossier.
A baseline approach can vary from a very baseline approach without investigations on the impact of varying process parameters and material attributes where every change needs prior approval to a baseline approach with a few additional investigations where most changes need prior approval. A very baseline approach also called “one dimensional” approach[19] does not meet the ICH Q8 definition of Design Space, as Design Space is defined as “*multidimensional combination*”.
Within the EU at least the requirements according to the present *Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)* shall be met.[17]

Optional information - Enhanced approach
Additionally to the information required for a baseline approach the applicant can choose to conduct pharmaceutical development studies to get more detailed knowledge of material attributes, processing options and process parameters. With this “multidimensional” approach all attributes of the formulation and/or

[viii] Definition of Formal Experimental Design according to ICH Q8: a structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as „Design of Experiments“ (DoE)

manufacturing process critical for the quality of the product are considered.[19] An enhanced scientific understanding of the formulation, the manufacturing process and its control can be demonstrated and the boundaries for a Design Space can be defined. This approach provides the opportunity for regulatory flexibility.

4.5.4 Regulatory Flexibility

The degree of regulatory flexibility depends on the level of scientific knowledge and understanding of the product demonstrated in the dossier. An enhanced knowledge on product and process can result in an expanded Design Space. An expanded Design Space in return facilitates regulatory flexibility.

And according to ICH Q8 more regulatory flexibility facilitates:[13]

- "*risk-based regulatory decisions (reviews and inspection);*
- *manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;*
- *reduction of post-approval submissions;*
- *real-time quality control, leading to a reduction of end-product release testing.*"

Figure 1 illustrates the relation between changes within/outside a Design Space and regulatory flexibility/prior approval.
The manufacturer can exchange parameter (a) with other parameters (b or c) being within the prior approved Design Space without prior approval. An exchange of a parameter (c) within the Design Space with a parameter (d) outside the Design Space needs prior approval. Regulatory flexibility is then given when the changes take place within the Design Space (from a-b or from b-c).

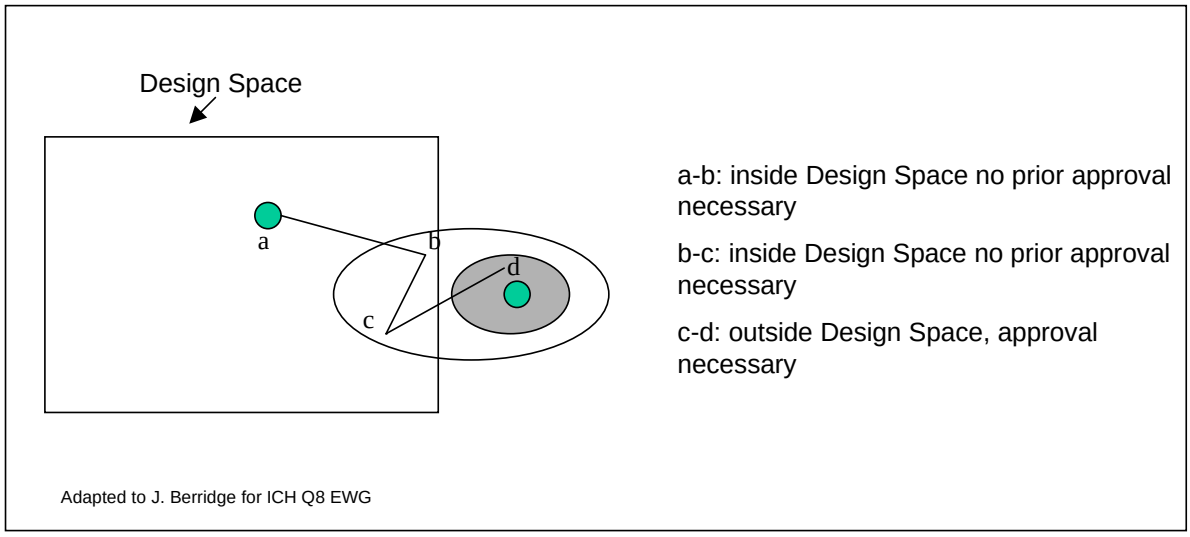

Figure 1 Changes within/outside Design Space and regulatory flexibility/prior approval

4.5.5 PAT

Currently PAT is a buzzword within the industry. PAT is not just new technologies but it can be described as a set of tools and principles that can improve process understanding. PAT facilitates building quality into products and therefore the realization of Quality by Design. PAT is a core component of Quality by Design. It is considered as pivotal to any company achieving manufacturing excellence.
According to the definition of the ICH guideline Q8, PAT is "*a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.*"[13]
The difference to the current practice without PAT is that with PAT processes are variable under qualified control but the output is constant, whereas with the current practice processes are validated. They are fixed but the output is variable.[27]
An EMEA PAT team[ix] has been established in January 2004 to prepare a harmonized approach within the EU for assessing PAT-based submissions and to evaluate the implications of that new approach.[28] In the US the *Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (PAT Guidance)[29] has been established in September 2004. This PAT Guidance describes a regulatory framework that shall encourage pharmaceutical companies to develop and implement innovative approaches on a voluntary basis. It is intended to facilitate the introduction of new technologies or new control tools in the field of pharmaceutical manufacturing.

A lot of activities in the PAT area have already been done. In the European Union the EMEA PAT team has published the *Reflection Paper: Chemical, pharmaceutical and biological information to be included in dossiers when Process Analytical Technology (PAT) is employed (EMEA/INS/277260/2005)* of March 2006 for recommendation on how PAT can be presented in applications or variations to Marketing Authorizations.[30] It is a working paper and feedback from industry is welcome. Such an approach promotes the co-operation of regulators and industry. Both parties can exchange their experiences and can together define how PAT can be included in dossiers.

In June 2005 representatives of the EFPIA developed a discussion document. It is a CTD section called "Mock P.2". This Mock P.2 document supports discussion between industry and regulators with the goal to aim the ICH quality principles. Mock P.2 demonstrates how quality can be built-in during formulation and process development. With a simple example (immediate release tablet, 20 mg active, highly soluble, highly permeable drug) it is demonstrated how Design Space can be developed. The concept includes the use of models and algorithms. Mock P.2 gives an example on how Design Space, PAT and quality risk management can support regulatory flexibility, continuous improvement of the process and the movement to real-time release.
Mock P.2 demonstrates that changes within the Design Space do not influence the manufacturing process and the quality attributes of the finished product. Consequentially, modification within Design Space should be acceptable without prior approval. Furthermore, this example illustrates how to find and to set critical parameters of the process.[31]

[ix] EU PAT team: 4 GMP inspectors, 6 assessors of Quality Working Party (QWP) and Biotechnology Working Party (BWP), EDQM-observer and EMEA secretariat

The Mock P.2 document demonstrates that the use of a Design Space and PAT (ICH Q8) and quality risk management (ICH Q9) enables Quality by Design to achieve the Vision. This Mock P.2 document is surely a good example but it is also just an example and not "reality". The described Design Space concept is very simple but Design Space can be much more complex. It will be important to gain more experiences with the new concepts of Quality by Design. Experiences can be gained if applicants apply these new concepts and discuss them with regulators.

Companies are using different approaches and philosophies. They are at different stages of the progress.[32] Currently several applications containing PAT elements are under review through the EU Centralized Procedure. It has been recognized that additional expertise is needed from the regulators to evaluate innovative methods and maybe new regulatory approaches are required.[8]
Nevertheless, with the introduction of a PAT system advantages like improved product quality, more efficient and effective control, regulatory flexibility, real-time release and the support of continuous improvement are anticipated.[33]
Thus, PAT is a helpful tool or system to achieve the ICH-Vision.

5 ICH Q9 Quality Risk Management

Quality risk management is defined as "*a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle*" (according to the ICH guideline Q9).[34]

Risk Management is neither a new tool nor a new innovative approach for the pharmaceutical world. Principles and tools of risk management are already established in pharmaceutical industry and at authorities but sometimes they are poorly defined. Medical devices have ISO 14971[35] and the food industry uses Hazard Analysis of Critical Control Points (HACCP) in the quality area of risk management. For pharmaceuticals such a structured risk management was missing.[36]

There are already existing guidelines using risk management principles to protect the patient e.g. by ensuring that the quality of the commercial product remains consistent with that of the product used in the clinical phase. The EU Variation Regulations 1084/2003[37] and 1085/2003[38] (trees to identify variations according to degree on risk, evaluation of quality defects) or GMP guidelines like e.g. Annex 15 on Qualification and Validation of the EU Guide to Good Manufacturing Practices[39] use the concept and principles of risk management.
With the adoption of ICH Q9 it is expected from the reviewers and inspectors that pharmaceutical industries not only apply the tools and principles of risk management but that they provide well documented evidence of good quality risk management.[14]

5.1 History of ICH Q9

At the Sixth International Conference on Harmonisation (ICH6) in Osaka on November 12-15, 2003 the ICH Steering Committee agreed on the adoption of ICH Q9 Quality Risk Management as a new topic, part of the ICH initiative on a risk-based approach to drug product quality. The Final Concept Paper[40] and the Final Business Plan[41] have been endorsed on November 11, 2003.

The ICH Q9 EWG then developed the guideline. Among others they worked in close co-operation with the ICH Q8 EWG.
ICH Q9 reached Step 2[x] of the ICH Process on March 22, 2005 (Post Step 2 correction on June 15, 2005). It was approved by the Steering Committee and released for public consultation.
At the ICH Steering Committee meeting in Chicago on November 9, 2005 the ICH Q9 document was adopted at Step 4[xi] of the ICH Process. It was recommended for adoption to the three ICH regulatory bodies (EMEA, FDA, MHLW).
In the European Union the final draft version is recommended for formal adoption into the European regulatory system. Teams have been established to include risk management principles in Chapter 1 of the GMP Guide (Volume 4, Part I, Chapter 1 of EudraLex: The Rules Governing Medicinal Products in the European Union).[42] The part Introduction of the GMP Guide has been amended and a new Annex 20 of the Guide will be published.[43] The European Commission has published the revised Chapter 1 of the GMP Guide for consultation (deadline for comments: April 30, 2007).[42] Furthermore, some documents of the Compilation of Community Procedure[xii] are under revision/development to implement ICH Q9.
In the United States ICH Q9 has been adopted as *Guidance for Industry: Q9 Quality Risk Management*,[44] published in the Federal Register, Vol. 71, No 106, pages 32105-32106, June 2, 2006.
In Japan ICH Q9 has been adopted on September 1, 2006, PFSB/ELD Notification n° 0901004 as "Annex" of the Product GMP Guideline.

5.2 Structure of ICH Q9

The core document of ICH Q9 comprises the objective, the scope, quality risk management principles, the formal risk management process and the risk management tools. The core documents describe "what to do"; the annexes of ICH Q9 describe "how to do it" and "where to do it". Table 2 presents an overview of the structure and content of ICH Q9.

"What to do?" – Core document	"How and where to do it?" - Annexes
• Objective	
• Scope	
• Two Primary Principles of Quality Risk Management	
• Quality Risk Management Process	
• Risk Management Methodology	• Annex I (How to do it?)
• Integration of Quality Risk Management into Industry and Regulatory Operations	• Annex II (Where to do it?)

Table 2 Structure of ICH Q9 Quality Risk Management

[x] Step 2 of the ICH Process: Confirmation of six-party consensus
[xi] Step 4 of the ICH Process: adoption of an ICH harmonized tripartite guideline
[xii] Compilation of Community Procedures on Inspections and Exchange of Information: a collection of GMP inspection - related procedures and forms agreed by the GMP inspectorates of all the Member States and designed to facilitate administrative collaboration, harmonization of inspections and exchange of inspection-related information.

5.3 Scope of ICH Q9

ICH Q9 "*provides principles and examples of quality risk management that can be applied to all aspects of developing a medicinal product, submitting to a regulatory authority, and for manufacturing sites inspections*".[45]

The guideline applies to the pharmaceutical companies but also to regulatory authorities in the fields of pharmaceutical assessment of the quality part of the dossier as well as to the inspectors. The risk management principles and the different suggested tools apply throughout the lifecycle of drug substances, drug products, biological and biotechnological products. ICH Q9 is not intended to apply to risk management used in a pharmacovigilance setting involving safety and efficacy.

5.4 Objective of ICH Q9

The objective of ICH Q9 is "*to offer a systematic approach to quality risk management*".[34] It is the intention to achieve a common understanding and application of quality risk management principles and tools. Therefore, ICH Q9 provides guidance on how to effectively use quality risk management. The overall goal is the protection of the patient.

5.5 Concept of ICH Q9

Products and processes became more and more complex but also new measurements, process controls, new technologies or statistical tools have been developed that improve the ability to predict and assure product performance and quality.
Besides efficacy and safety, quality is an important attribute for pharmaceutical products. Quality is influenced by risks. No effective medicine is without risk and the benefits of medicinal products always need to be balanced against their risks.[46]
Risk is defined as "*the combination of the probability of occurrence of harm and the severity of that harm*" (according to ISO/IEC Guide 51:1990, modified).[47]

The focus of risk management is on product quality and the risks (=critical parameters) influencing the quality. Quality risk management affords the identification of parameters critical for the product's quality, the assessment of those risks and their elimination or reduction. Always having in mind the primary goal to provide effective and safe medicines to patients.
ICH Q9 does not impose new requirements or expectations on the pharmaceutical industry. The guideline has been elaborated to harmonize the different approaches of implementation of risk management, to speak the same language in all ICH-countries. It is flexible and not mandatory. It is more as a document providing principles and tools that can be used to support and promote a risk-based approach.
Although the application of quality risk management is optional it is highly appreciated by the authorities. The reasons therefore are that quality risk management is a valuable element for a robust quality system. Furthermore, the management of risks is an important aspect regarding the safety of the products and finally the protection of the patients. Statements like "*Implementation of Q9 is optional, but quality risk-management is not*" can interpret this.[8] Quality risk management is a quality improvement methodology.[48]

It is a challenge to focus the resources on the high-risk areas. That applies to the industry as well as to the regulators. Therefore a broad understanding of risk-based control models to manage developing and manufacturing issues is needed. It helps to focus the efforts and resources on things that are really important to provide quality assurance to the patients.

The key elements of ICH Q9 are:[34]

- two primary principles of quality risk management
- quality risk management throughout product lifecycle
- a formal quality risk management process
- quality risk management tools
- integration of a quality risk management into existing quality systems

5.5.1 Two Primary Principles of Quality Risk Management

ICH Q9 provides two primary principles of a quality risk management:[34]

1. *The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and*
2. *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.*

The principles clarify that only those risks shall be evaluated having an impact on the product quality. For this evaluation scientific knowledge is needed. That means that experts are required to be familiar with risk management processes. The levels of risks are different, depending on the benefit for the patient. The lower the level of a risk the lesser should be the assessment and documentation of it.

5.5.2 Quality Risk Management Process

ICH Q9 provides a formal model of a typical quality risk management process outlined in a diagram. It is a systematic process for risk assessment[xiii], risk control[xiv] and review of risk[xv] with the aim to coordinate and facilitate decision-making processes.
The responsibilities - especially for the decision makers[xvi] - are described as well as each single step of the process. Details are provided on “what to do” and “who has to do it” (experts from the appropriate areas and individuals familiar with quality risk management processes).

[xiii] Definition of risk assessment acc. to ICH Q9: a systematic process of organization information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
[xiv] Definition of risk control acc. to ICH Q9: actions implementing risk management decisions (ISO Guide 73)
[xv] Definition of risk review acc. to ICH Q9: review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk
[xvi] Definition of decision maker(s) acc. to ICH Q9: person(s) with the competence and authority to make appropriate and timely quality risk management decisions

5.5.3 Risk Management Methodology + Commonly Risk Tools (Annex I)

ICH Q9 provides a short description of tools suitable for the assessment and management of risks to quality. The list of tools is not exhaustive and not every tool is applicable to every situation. Case by case decisions is possible. ICH Q9 provides a source of tools that can be applied flexible and adapted by industry and regulators where the application of quality risk management is appropriate. It has a supportive and not a descriptive character. The tools shall afford a scientific approach to decision-making.

In Annex I of ICH Q9 the most commonly risk management tools, such as e.g. HACCP or Failure Mode Effects Analysis (FMEA) and their potential areas of use are described. For each of the tools a short description (including their strength and weaknesses) and references is provided.
This Annex provides a good overview of available tools. The description of the tools provides an orientation to companies, which one would be most suitable for their product.

5.5.4 Integration of Quality Risk Management into Industry and Regulatory Operations + Areas for Application (Annex II)

ICH Q9 advises industry and regulators to integrate a quality risk management process into (existing) quality systems to be able to make science-based decisions on risk to quality. This can provide regulators with greater assurance of a company's ability to deal with risks.
Potential areas for the application of quality risk management are suggested for industry and regulatory operations (quality management), industry operations and activities (development, facilities, equipment and utilities, materials management, production laboratory control and stability studies, packaging and labeling) and regulatory operations (inspection, assessment).
With quality risk management it is possible to rank risks, to prioritize them and to reduce subjectivity.[36] Thus, through the application of a quality risk management companies can identify activities that require closer monitoring and those that merit less attention. More robust data sets will lead to lower uncertainty at the industry and the regulators. The level of risk to patients determines the level of oversight by the authorities (marketing authorization application, post-approval submission) and the inspectors.

Regarding the quality of a product quality risk management principles and tools as laid down in ICH Q9 are basic elements for the realization of a science and risk-based approach.

6 ICH Q10 Pharmaceutical Quality System

Pharmaceutical Quality System is defined as "*management system to direct and control a pharmaceutical company with regard to quality*." (ICH Q10 EWG based upon ISO 9000-2005[49]). [50]

A lot of quality systems have already been established for instance as reaction on the global trading that became more commonplace or to meet the demand of the need for an international recognized model for operating a quality management system.[51]

But approaches to quality systems and concepts across the three ICH-regions are different. There are divergences in definition and interpretation of principles, applications and expectations. This means sub-optimal deployment of resources of industry and regulators. It could also result in potential delays regarding the implementation of innovations or improvement of pharmaceutical manufacturing. Moreover, different quality systems result in different approaches for inspections.[52]
Regional GMP requirements are quite different and a common approach for a pharmaceutical quality system within the ICH-regions was difficult. But as a quality system is considered as one of the key elements to achieve a science and risk-based approach it was necessary to develop a harmonized basis.
The harmonized guideline furthermore helps to promote a paradigm shift from a GMP compliance system at every stage of the product lifecycle (following a GMP checklist) to a global quality system over the entire product lifecycle.[53] GMP compliance alone will not get us to the post-approval regulatory flexibility.

6.1 History of ICH Q10

In order to achieve a harmonized approach of pharmaceutical quality systems in the three ICH-regions and driven by the ICH-Vision the Steering Committee approved a new topic "Quality Systems" (ICH Q10) at the meeting of the ICH Steering Committee and its expert working groups in Chicago, Illinois on November 9 -10, 2005.[45]
At this meeting the Final Concept Paper of ICH Q10[54] along with the Final Business Plan [52] has been endorsed by the ICH Steering Committee.
ICH Q10 reached Step 2 of the ICH Process on May 9, 2007. The guideline was approved by the Steering Committee and released for public consultation.[55] The guideline has currently reached the consultation phase (Step 3[xvii] of the ICH Process).
In the EU the guideline has been transmitted to the Committee for Medicinal Products for Human Use (CHMP) and to Interested Parties in May 2007. It is issued as *Note for Guidance on Pharmaceutical Quality System EMEA/CHMP/ICH/214732/2007*.[56] Deadline for comments is November 2007. It is considered to implement ICH Q10 as a new annex (Annex 21) of the EU GMP Guide.[57]
In the United States ICH Q10 was published in the Federal Register July 13, 2007, Volume 72, No. 134, pages 38604-38605. Deadline for comments is October 11, 2007. FDA's *Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations*[58] (in operation since September 2006) was developed to build a link between the cGMP guidelines and modern quality management elements.
In Japan ICH Q10 was released for consultation 13th July 2007, PFSB/ELD. The deadline for comments is October 1, 2007.[59]
Once ICH Q10 has been implemented into national law currently existing national guidelines/guidance will need to be modified or even replaced.

6.2 Scope of ICH Q10

ICH Q10 applies to pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle including pharmaceutical development, technology transfer, manufacturing and product discontinuation. The guideline applies for new but also for existing products.

[xvii] Step 3 of the ICH Process: Regulatory Consultation and Discussion

6.3 Objective of ICH Q10

The objective of ICH Q10 is to describe a model for an effective quality management system for pharmaceutical companies that:[50]

- ensures the realization of a product (to provide manufacturing processes capable of consistently producing a drug of the quality required to meet customer needs)
- establishes and maintains a state of control (development and use of effective monitoring and control systems for process performance and product quality)
- facilitates continual improvement over the product lifecycle

The guideline encourages a science and risk-based approach to quality decisions and it facilitates the realization of ICH Q8 and ICH Q9 (see section 7, page 27).

6.4 Concept of ICH Q10

The content of ICH Q10 not covered by current GMP requirements is optional. Those elements included in ICH Q10 and also required by GMP are mandatory.
The ICH guideline Q10 focuses on industry practice. It does not define a new regulatory framework but will complement existing GMP practices with modern quality system elements. Regional GMPs, ICH Guideline Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*[60] and International Standard Organization (ISO) Quality Management System guidelines are the basis for ICH Q10, with a strong focus on last-mentioned guidelines. The elements of ISO 9001: 2000 (Quality Management Systems – requirements)[61] and ISO 9004 (Quality Management Systems – guidelines for performance improvement)[62] serve as key elements for the foundation of a pharmaceutical quality system.
ICH Q10 bridges regional GMP requirements to a common approach for pharmaceutical quality systems throughout a product lifecycle.
A pharmaceutical company may choose to adopt certain or all elements of the guideline or can decide for an alternative approach. The extent to which the company will adopt a quality system probably depends on the already existing quality system at the company and the complexity of the processes.

The key elements of ICH Q10 are:[50]

- establishment of a robust pharmaceutical quality system including knowledge management and quality risk management
- management responsibilities
- continual improvement throughout the product lifecycle - four pharmaceutical quality system elements
- continual improvement of the pharmaceutical quality system itself

6.4.1 Knowledge Management and Quality Risk Management

Knowledge management and quality risk management are considered as the means to realize the science and risk-based approach concerning decisions related to product quality. Knowledge management is a "*systematic approach to collecting, analyzing, storing, and disseminating information related to products, processes and components*" (ICH Q10 EWG).[50]
Quality risk management facilitates the identification and control of potential risks during all stages of the product lifecycle.

6.4.2 Management Responsibilities

Another key element for an effective pharmaceutical quality system is a senior management being aware of their responsibility regarding the implementation of a quality system within their company.
The management should establish a quality policy and should take care for a good internal communication. The responsibility of the management additionally comprises quality planning, resource management, and review of the pharmaceutical quality system and the oversight of outsourced activities.

6.4.3 Continual Improvement throughout the Product Lifecycle - Four Pharmaceutical Quality System Elements

ICH Q10 defines four specific pharmaceutical quality system elements that shall augment the regional GMP requirements in order to achieve quality throughout all stages of a product lifecycle (pharmaceutical development, technology transfer, manufacturing, product discontinuation):[50]

- *process performance and product quality monitoring system* (to establish and maintain state of control, to continuously meet product quality, to facilitate continual improvement); quality risk management shall be used to establish the control strategy
- *corrective action and preventive action (CAPA) system* (to achieve product and process improvements)
- *change management system* (to evaluate all proposed changes by experts)
- *management review of process performance and product quality* (to assure management of process performance and product quality)

6.4.4 Continual Improvement of the Pharmaceutical Quality System

The pharmaceutical quality system itself should continually be improved. This can be achieved through periodically reviews of the pharmaceutical quality system as well as the monitoring of internal and external factors impacting the pharmaceutical quality system.

According to ICH Q10 the ultimate quality system begins with the development of active substances and excipients. Then it moves through product formulation, manufacturing process development, design of container closure and packaging, product release and storage. It ends with the discontinuation of the drug. The quality system shall be applied throughout the complete product lifecycle and not only during certain phases like e.g. the development or manufacturing phase. That is the basis to continuously produce high-quality products.
ICH Q10 assists manufacturers in establishing a robust pharmaceutical quality system and encourages them to improve manufacturing processes thus reducing undesired variability and leading to a more consistent product quality.
With a robust pharmaceutical quality system as suggested in ICH Q10 an applicant can prove that he can be responsible for self-management of changes. This results not only in less regulatory oversight but also in the reduction of batch failures and defect recalls.[52] According to the IBM Business Study of May 2005 a potential reduction of 3% of the cost of goods related to internal failures seems possible.[4]

ICH Q10 promotes the approach of a preventive action culture, which ensures that actions are taken before a problem arises. Quality monitoring and review, which form the basis for continuous improvement of processes, can be improved. Quality systems, that are effective not just to prevent errors, but also to be able to detect them, may help to give more confidence in quality systems. This can reduce regulatory oversight and promote regulatory flexibility.

7 Combination of ICH Q8, Q9 and Q10

“It is not a question of how well each process works, the question is how well they all work together.” (Lloyd Dobens and Clare Crawford, Thinking About Quality)[63]

The ICH guidelines Q8, Q9 and Q10 are closely inter-related and complement one another. Each guideline contains directly links to the other ones. ICH Q8 explicitly refers to ICH Q9 (e.g. that information from pharmaceutical development studies can be a basis for quality risk management) and vice versa (application of quality risk management to design a quality product and its manufacturing process).
Quality risk management is an important component of Quality by Design. A quality risk management supports the identification and assessment of critical attributes, necessary to establish appropriate specifications and the boundaries for the Design Space. Conducting a thorough risk assessment is an essential step in determining whether a developed Design Space is acceptable for its intended use or not.

ICH Q10 is necessary for the implementation of ICH Q8 and Q9 as it facilitates the realization of their potential benefits. ICH Q10 provides a pharmaceutical quality system not product specific while ICH Q8 focuses on products and requires product specific measures during the development. ICH Q8 provides the process understanding, which is the basis for continual improvement, one of the objectives of ICH Q10. And there is also a linkage between the processes for pharmaceutical development (ICH Q8) to a second objective of ICH Q10: to achieve product realization (to provide products quality that meets the requirements of customers). Furthermore, ICH Q10 should provide the ability to manage changes within the Design Space.
It is anticipated by the ICH-members that a pharmaceutical quality system (ICH Q10) facilitates the application of a quality risk management (ICH Q9) and vice versa should processes within a pharmaceutical quality system be based on appropriate principles of risk management.[64]

Annex 1 of ICH Q10 summarizes the potential benefit that can be achieved by the application of the three new ICH Quality guidelines. The most benefits and opportunities are expected when an effective pharmaceutical quality system is established in a company in combination with risk management principles and tools including the demonstration of enhanced product and process understanding.

8 Impact on Industry and Regulators

Industries as well as regulators are challenged to put the concepts of ICH Q8, Q9 and Q10 into practice. One common challenge might be to share the same understanding of the purposes and anticipated benefits through the adoption of the

three new ICH Quality guidelines. Therefore, it will be important to improve the communication between the pharmaceutical industry and regulators. Differing opinions of what should be shared with the authorities (patient compliance versus "critical" to business, "critical" to safety and efficacy) need to be solved.[65] But it will also be a challenge for the pharmaceutical companies to transfer their product knowledge and process understanding without increasing regulatory burden, manpower and costs.

8.1 Impact on Industry

Depending on the size of a company, the type of the products, the scientific knowledge of the products, the existing quality systems and the company's philosophy ICH Q8, Q9 and Q10 will have a more or less extensive impact on the pharmaceutical companies.
Some of the bigger pharmaceutical companies might already have implemented a pharmaceutical quality system as suggested in ICH Q10 and use quality risk management principles and tools as described in ICH Q9. They know the critical attributes of their products and processes very well. But for most of the pharmaceutical companies the adoption of ICH Q8, Q9 and Q10 will result in a change of their policies and their pharmaceutical manufacturing paradigm.
As all three guidelines are optional except of those elements that are already required through other guidelines (e.g. ICH M4(R1), ISO, national GMP guidelines) they need to decide which concepts (Quality by Design, Design Space, DoE, PAT, quality risk management etc.) and elements they want to implement. Before new systems, technologies or tools can be used they need to be established. The decision for and the implementation of new elements and concepts require prior evaluation. The companies will be faced with questions like: How to implement them in the existing systems? Are there enough resources to establish new systems and tools? Is the requested know-how available? What about costs? What will be the benefit for the company?

The implementation of a Design Space concept into a drug dossier is not mandatory. The company has to decide what would be the best for the future lifecycle of the product. In most cases the business point of view will be most crucial.
Some companies are too small and do not have the resources and the money needed for the development of a Design Space. Even if a company has enough manpower, knowledge and money they first have to evaluate for which product it would be worse to invest in a Design Space. If there is no benefit to be expected than the investment in a Design Space makes less sense.
Once decided to establish a Design Space the company has to decide when, how and to what extent starting the development of a such a concept.
Prior implementation of a Design Space in the dossier the manufacturer should carefully evaluate if it is the best one while considering factors like available technology, alternatives, associated risks or costs. It is recommended to discuss a planned Design Space concept with the authorities prior submission for approval.

As already mentioned-above enhanced knowledge of a product and the processes is the basis for the development of a Design Space. A better understanding of active substances, container material and excipients etc. is needed. It will e.g. not be enough regarding for excipients to rely solely on compendial standards. Detailed information on all components used for the drug is necessary.

ICH Q8 suggests conducting development studies to gain the required data. That means costs, manpower and time. The gained knowledge can be positive but also negative. Failures can be of importance from a scientific point of view but not from a business point of view.

Manufacturers are called to establish new and modern analytical and statistical methods to determine and define the critical parameters influencing the product quality. This will especially be important for new and complex products.
But if no or only less critical attributes can be identified having an impact on the quality of the product, what limits for the specification shall then be chosen? It will be difficult to determine the boundaries of a Design Space. Uncertainties often result in tighten specifications and in this case in a tight Design Space with less possibility for regulatory flexibility.
ICH Q8 suggests to perform DoE or to use PAT. DoE or/and PAT are rather new techniques. The challenge will be to implement DoE or PAT within the company. Furthermore, it is not yet clarified where and how to present these elements in the drug dossier.

Companies will furthermore have to face the problem that it is not a simple mechanism to apply Design Space to old nationally registered products.[65] For existing processes – already conducted on a commercial scale - it is more difficult to evaluate and implement with hindsight a broad Design Space. Usually DoE studies have not been conducted in the early phase of the development process. And later on it is difficult to determine the relationship between factors affecting a process and the output of that process.[66] Once a marketing authorization for a drug has been granted the implementation of a Design Space would mean a change to that marketing authorization. The applicant has to submit an application for variation. And that would mean an additional regulatory burden.
After a Design Space has been developed and implemented it should be maintained until the end of the product lifecycle. That means that the manufacturer has to undertake regular reviews and updates. It is recommended to evaluate all results including failures. The frequency of the reviews will depend on the robustness of the Design Space model.

The establishment of a Design Space can have an impact on the internal Change Control procedure of the company. Having implemented a Design Space it has to be differentiated between changes within the Design Space and changes outside the Design Space. Changes falling under the first category need prior review whereas the others do not. Therefore, the kind of changes shall be well documented. An internal Standard Operation Procedure (SOP) needs to be adapted accordingly.

Once a Design Space has been established, what are the submission criteria for it? Where and how shall it be presented in the dossier? It is also imaginable to describe the Design Space concept in a stand-alone document. Shall the applicant provide his own assessment conclusion? These are questions that still have to be clarified together with the regulators.

The applicant has to learn to present his knowledge in a way that enables the reviewer to “understand” the “story of the product”. As already mentioned-above there are many companies being reluctant to present their knowledge to the

regulators. But if they want to benefit the potential advantages of ICH Q8 they need to change this attitude.

It might also be a challenge to shift the focus from providing volumes of data in Section 3.2.P.2 Pharmaceutical Development to the presentation of significant and relevant scientific data and information on formulation attributes and process parameters. Especially the discussion of critical attributes and parameters influencing the product quality and how they relate to safety and efficacy need to be presented in the pharmaceutical development part of a dossier. As these data are basis for a scientific and risk-based approach.

Real-time testing instead of end-time testing is considered one of the potential benefits of a Design Space. Currently the pharmaceutical companies are testing their products according to the predefined release specification and shelf life specification.
The *Note for Guidance on Parametric Release (CPMP/QWP/3015/99)*[67] already claims that in-process tests and controls may be sufficient and may provide greater assurance of the defined quality of the finished product and that it is not necessary to repeat the test with the finished product. But the companies are faced now with the question if a third specification for the real-time testing will be necessary. Furthermore, it has to be clarified if it will be necessary to provide a validation for the association between in real-time quality control versus testing the finished product according to the specification.

Companies that want to establish a Design Space need to also consider the principles and tools of a quality risk management and the implementation of a robust pharmaceutical quality system.
Pharmaceutical companies need to be aware that risks always exist and that it is their challenge to identify, assess, reduce or mitigate them. It is important to understand the necessity of a quality risk management.
It can be assumed that most of the companies have already established quality risk management. In some companies however the principles are not completely considered or adequate tools (as suggested in ICH Q9) are missing. And sometimes quality risk management is not integrated into the existing quality system of the company.
The integration of quality risk management into existing systems will take time and needs to be co-ordinated. Quality risk management is not a process for a single department but for the whole company. That means that staffs from different departments need to be trained and educated. Adequate quality risk management tools need to be determined and adopted.

As the implementation of ICH Q10 is not mandatory the pharmaceutical companies can stick to their already established pharmaceutical quality system assuming that the current GMP requirements are met.
The company could be in the situation that it can already confirm the adequacy of its current quality system to ICH Q10. A company has the option to decide to enhance their quality system based on ICH Q10 or to establish a new quality system in accordance with ICH Q10.
Independent on the current state of the company's internal quality system the complete or partly adoption of ICH Q10 implicates costs and manpower. Furthermore, the involvement of contract manufacturers into the pharmaceutical quality systems needs to be taken into account. This might be an additional

challenge but the internal quality system is less valuable if external quality systems do not fit. A quality culture and policies need to be established by the management. The fundamentals of quality systems need to be communicated within the company. Appropriate training of quality staff will be necessary.

8.2 Impact on Regulators

The adoption of ICH Q8, Q9 and Q10 implicates a paradigm shift of review processes and inspection policies. The change to a more science and risk-based assessment and inspection strategy, rich in product knowledge and process understanding is still in its infancy.
Regulatory authorities maybe have to reconsider their responsibilities. An enhanced collaboration between assessors and inspectors at submission of a dossier and during the product lifecycle will become necessary to achieve the potential benefits anticipated with the implementation of the three new ICH Quality guidelines.[19]
A risk-based review means a comprehensive assessment of critical formulation attributes and critical manufacturing parameters. The regulators will need to establish the respective science branch. Therefore, pharmaceutical scientists, chemical engineers, industrial pharmacists need to be recruited to complement current review staff. The staffs need to be trained and educated to be able to carry out science and risk-based assessment and control.
Due to the different approaches provided by ICH Q8 for the presentation of pharmaceutical development in a dossier (baseline approach versus an enhanced approach) regulators need to be flexible. Different approaches of the industry will need different assessments by regulators. Different tools will need to be developed to satisfy the different approaches.
Regulatory flexibility - the potential benefit expected through the application of a Design Space - could also be a challenge for the assessors. They will be confronted with the question how broad regulatory flexibility can be defined. On the one side regulators are expected to grant regulatory flexibility but on the other side they have to assure product quality. That can be a conflict.
The regulators will have to deal with further open issues like e.g. how to deal with legacy products. How shall they be assessed in the future? How to deal with different regulatory processes (application for marketing authorization, variations, NDA, Abbreviated New Drug Application [ANDA] etc.)?

Some authorities of the ICH-regions could be faced with the situation that their current quality system is not suitable to challenge the new approaches. The FDA has already recognized this internal “problem”. In November 2005 the Office of New Drug Chemistry (ONDC) within Center for Drug Evaluation and Research (CDER) was reorganized to the Office of New Drug Quality Assessment (ONDQA) to implement a risk-based pharmaceutical quality assessment system (PQAS) and to replace the current CMC review system.[68] The new Vision could also prompt other authorities to think about the necessity of internal structural changes.

Inspectors especially need to get familiar with the principles and new tools of quality risk management to be able to adequately inspect the pharmaceutical companies. It is expected from the inspection staff to have qualifications to apply an appropriate degree of risk assessment.[69] They need e.g. to be able to judge if the industry has integrated an adequate quality risk management in its quality system.

Without knowing and understanding the tools inspectors will not be able to comprehend the decisions made by the industry. But this is absolutely necessary to achieve a common understanding.

9 Will the ICH guidelines Q8, Q9 and Q10 foster innovation?

The classic definitions of **innovation** include for example:

- the act of introducing something new: something newly introduced (The American Heritage Dictionary).
- a new idea, method or device. (Merriam-Webster Online)
- the successful exploitation of new ideas (Department of Trade and Industry, UK).
- the capability of continuously realizing a desired future state (John Kao, The Innovation Manifesto, 2005)

The ICH Q10 EWG defines innovation as: "*the introduction of new technologies or methodologies to pharmaceutical development and manufacturing*."[50]

Innovations in the pharmaceutical manufacturing are necessary to challenge the new discoveries (e.g. biotechnological products, complex drug delivery systems) and the overall goal to provide safe, effective and affordable medicines.
There are substantial unmet medical needs. Innovative advances are promised by new technologies such as robotics, miniaturization or information management. But innovations are a lengthy and costly business involving a great deal of risk.[70] And the regulatory framework of the past did not really encourage pharmaceutical companies to be open for innovations. Due to different regulatory environments within the ICH-regions there are a lot of concerns that innovation could result in regulatory impasse. What is required in one region is not necessarily relevant for the others. This is a difficult situation if the company aims to get Marketing Authorizations granted in all three ICH-regions.

With the application of a Design Space concept continual improvement of the product performance and the processes is expected but "innovation" is different to "continuous improvement". According to ISO 9000-2005 "*continual improvement" is defined as "recurring activity to increase the ability to fulfill requirements*".[49]
Continual improvement is an essential element in a modern pharmaceutical quality system. The aim is to reduce variability of attributes influencing product quality but not to change the fundamental design of a manufacturing process. Continuous improvement is a daily activity carried out by the quality staff.[3]
Developing innovations is a difficult and complex process. They may require changes in formulation and manufacturing design. Innovation is not part of routine manufacturing operations.[3]
Innovations will not take place inside a Design Space but outside of it. That means that the concept of the ICH guideline Q8 can provide the potential benefits (regulatory flexibility, fewer variations, less regulatory burden) for continuous improvement but not for innovations. But there is another aspect regarding ICH Q8 and innovations.
As innovation is based on researches, studies, enhanced knowledge and courage to follow new ways ICH Q8 could indirectly foster innovations.

The knowledge gained through conducting development studies to define a Design Space could also serve as basis for innovations. If a company follows the "enhanced (multi-dimensional) approach" (see section 4.5.3, page 16) as suggested in ICH Q8 the opportunity to "discover" innovations is increased.
Although the primary focus of ICH Q8 is not on the promotion of innovations it could indirectly foster innovations.

The purpose of ICH Q9 is to offer a systematic approach to quality risk management. The focus is on identification, reduction and mitigation of potential risks influencing product quality. The focus of ICH Q9 is not on innovations.
Through the concentration on the risks to quality recourses can efficiently be used. This could result in "free" recourses that can be used to work on innovations. But this is just a theoretical consideration. A convincing argument cannot really be found that would support the thesis that ICH Q9 alone does facilitate innovations.

ICH Q10 is the only guideline that explicitly mentions that the implementation of ICH Q10 should facilitate innovation. But it is not mentioned how a robust quality system can facilitate the introduction of new technologies or methodologies to pharmaceutical development and manufacturing.

Innovations require significant investment of resources. So what are the reasons for companies to meet the expenses? New technologies are developed as it is pushed by the general development and requirements in the pharmaceutical industry. The industry is pushed by business. Pharmaceutical companies invest in new innovative technologies and products where they can expect a potential financial benefit. Great economic benefits in return enable the industry to invest in new innovative technologies and products. But where are great economic benefits to be expected regarding ICH Q8, Q9 or Q10?
For the determination of a Design Space prior investment in development studies is more or less unavoidable. Afterwards due to regulatory flexibility costs for variations can be reduced. This could finally be an economic benefit and the saved money could be invested in innovations. But this is not a good argument as it is impossible to predict how much money can be saved through regulatory flexibility in relation to costs that have to be invested for the development studies.

The question if the ICH guidelines Q8, Q9 and Q10 will foster innovation premises that the pharmaceutical companies adopt these guidelines. But as already mentioned-above pharmaceutical companies are sometimes reluctant regarding the change of their systems and policies. Small and medium sized companies often do neither have the manpower nor the money to completely adopt ICH Q8, Q9 and Q10. The potentially advantages would not reimburse the prior necessary investments.

The ICH guidelines Q8, Q9 and Q10 do not provide any incentives for the development of innovative technologies and products providing a benefit for the patient. Regarding for example the new *Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use*:[71] For the presentation of results of studies in the paediatric population in accordance with an agreed paediatric investigation plan the holder of a patent or Supplementary Protection Certificate (SPC) shall be entitled to a six-months extension. ICH Q8, Q9 and Q10 do not provide incentives for innovations in that form.

ICH Q8, Q9, Q10 will neither provide any special incentive for innovations nor help to save costs that could be used to reinvest in innovations.
But what they provide is a harmonized regulatory environment for the ICH-regions. Harmonized guidelines reduce the regulatory burden of the pharmaceutical industry as the requirements in the European Union, the United States and Japan are the same. But just the availability of the guidelines alone cannot introduce new technologies or methodologies to pharmaceutical development and manufacturing. It is upon the industry and the regulators to implement them.

10 Conclusion and Outlook

The three ICH-regions European Union, United States and Japan agreed on a common Vision with the aim to change the current manufacturing paradigm of drug products. The areas where harmonization was necessary to achieve the Vision has been identified and brought on the way with the development of ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Pharmaceutical Quality Systems. It is the primary and overall objective to provide safe and effective medicines to patients. While establishing guidelines there is always the challenge to find the right balance between achieving the primary objective and not to be too restrictive to pharmaceutical industries.
The harmonization of processes and the development of harmonized guidelines is already a big challenge but to put them into practice will even be the bigger challenge for both, industry and regulators. Therefore, it will be important that they closely work together. Communication, understanding and trust between industry and regulators will play a key role especially at the beginning of the implementation phase.
A common understanding on the concepts of ICH Q8, Q9 and Q10 will be necessary. Speaking the same language and attaining the same goal facilitates the work in a team, this also applies to the collaboration between the ICH-parties, especially between industry and regulators.
All efforts of industry will be fruitless if regulators do not follow the commonly agreed approach and vice versa. If on the one side applicants implement a Design Space into the dossier than it is necessary that on the other side reviewers are able to assess such a dossier. If the pharmaceutical companies are not willing to share their scientific knowledge of product and processes with the regulators then they cannot expect a science and risk-based assessment.

Design Space can result in regulatory flexibility and can promote continual improvement. But even with an established and approved Design Space it will depend upon each company if they will really use the chance for continual improvement within the Design Space. Not to forget that a Design Space with very tight boundaries provides less space for continual improvement without prior approval. But nevertheless the concept of ICH Q8 provides at least the regulatory framework to reduce regulatory burden regarding changes.

Investments in further development studies do not automatically end up in a broad Design Space. So that the gained enhanced knowledge will finally not provide a benefit for the company but in any case for regulators and patients. But this presumes that the data even failures will be communicated to the authorities.

For a science and risk-based approach industry and regulators need to be able to identify what is critical to product quality. ICH Q9 provides different tools that can be adapted and implemented by every pharmaceutical company, independent e.g. on company size or product types. As we are talking about medicinal products for human use a suitable risk management as well as a robust quality system should be established in a pharmaceutical company anyway. But it is upon the company to decide to stick to their already established concepts or to come closer to the approach of ICH Q9 and Q10.
One important point of ICH Q10 is that it stresses the role of the senior management regarding the quality system of a company. An effective quality system demands a management being aware of its responsibility by establishing quality policies and supervising the quality system within and outside the company.
With a proper implementation of ICH Q9 and Q10 pharmaceutical companies can demonstrate that they have systems and tools in place that enables them to identify what is critical to product quality. That provides confidence and plays an important role regarding the relationship between industry and regulators.
For reviewers and regulators the application of risk management principles and tools provides furthermore the opportunity to concentrate on high-risk areas (product, process, company) and to a lesser extent to work on low-risk areas. That provides the opportunity to use their resources efficiently.
A closer co-operation of the pharmaceutical industry with other industries and universities would help to establish further standard processes based on their different experiences and knowledge with risk management.

ICH Q8, Q9 and Q10 provide a regulatory framework to come closer to the Vision but there are still a lot of questions that need to be answered. Further explanations and definitions of the principles and elements laid down in the three ICH guidelines will be necessary to achieve a common understanding. That is also demonstrated through the fact that the ICH guideline Q8 is currently being revised.
The definition of Quality by Design e.g. is not self-explaining, but needs further elaboration by industry and regulators before it can be implemented into daily practice.
As the guidelines describe “what to do” but do not provide information on “how” it shall be done, questions will not only have to be answered concerning “what to do” but in most cases “how to do it”. The concrete realization of the guidelines involves further discussions. It is for example defined what is meant with Design Space but authorities have not yet defined what data - amount and level – have to be provided. The same applies for the implementation of DoE and PAT.
After approval through the authorities the Design Space shall be mentioned in the marketing authorization. But it still has to be defined “where” and “how” it shall be mentioned in the marketing authorization.[19]
Prior realization of real-time control instead of end-product control as mentioned in ICH Q8 it has to be clarified if this would imply a third specification (besides release specification and shelf life specification). The relationship between real-time control and release specifications is a key issue in the submissions. There are already discussions on how they could fit together.[32]
So far there is no connection between the current variation regulation and Design Space. There is no problem expected regarding the implementation of principles of Design Space in the framework of the existing EU variation regulation.[19] But a harmonization is required for global approaches to post approval changes.

Quality by Design will be established in the ICH-regions but what about dossiers submitted outside ICH-regions. The regulatory landscape is not homogeneous. So far it is not known how non-ICH authorities will deal with science and risk-based submissions. Will they accept the new approaches of the ICH-countries or will it be necessary for the applicant to go a two-fold strategy: one science and risk-based approach and one traditional approach for all non-ICH regions. If they will not accept science and risk-based dossiers this could keep some companies from implementing the new concepts of ICH Q8, Q9 and Q10. Finally this can be a hurdle on the way to the new approach as defined by the Vision.

ICH Q8 Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality System can help to increase the pressure to make pharmaceutical manufacturing more efficient and to encourage regulators to focus on the most critical attributes influencing the product quality and patient safety.[8] But all three guidelines are not mandatory. It depends upon the companies if they want to implement the new proposed elements and concepts of ICH Q8, Q9 and Q10 or not.
In anyway the guidelines provide a good opportunity to think about the effectiveness of established internal processes and systems. If companies will change their policies and tools to be in line with the new guidelines will depend more or less on the “real” benefit they expect to get thereof.

Although there are some obscurities and hurdles, together ICH Q8, Q9, and Q10 provide the opportunity to realize a revised, optimized and less restrictive regulatory paradigm. It is based on scientific knowledge, greater transparency and efficiency, focusing on things that add value for patients. The basic regulatory framework to achieve the ICH-Vision is developed respectively en route. A lot of things are already brought on the way but there is still a lot of “fine tuning” necessary and not all pharmaceutical companies will be able to implement the new concepts. Having topics harmonized and fixed on paper is the one thing but the real life will finally show if they can be put into practice.
After the finalization of ICH Q8, Q9 and ICH Q10 some existing guidelines will need to be revised and new ones need to be established. Actually, Annex ICH Q8(R1) on specific dosage forms has been drafted to facilitate implementation of Quality by Design. The Annex provides examples for the application of Quality by Design concepts. An ICH working group is moving on to develop a further annex for parenterals.

Pharmaceutical industries as well as regulators are now in the position to decide to go a new way and follow the Vision or to go ahead on the old road. New ways are unfamiliar and often very bumpy at the beginning and a reason to avoid changes. Therefore it is important to be convinced from a new approach. It is important to recognize the benefit of the Vision. Currently, there are two distinct groups within the top 20 pharmaceutical companies, those who adopt the new concepts of the guidelines and others who follow a “wait and see” strategy.
It is now up to the regulators and the industry to bear the new challenge and to achieve the goals together. The implementation phase will need time, capacity and money prior pharmaceutical companies and regulators can get the benefit. It will be a step-by-step approach.

11 Summary

There are different factors that triggered the new ICH Quality guidelines ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Pharmaceutical Quality Systems.
The development of innovative manufacturing technology is far behind the development of new complex drugs. Most of the investments for research and development have been spent for the discovery and development of new molecules but less for innovative manufacturing technology.
The quality of the information on pharmaceutical development varies in the drug dossiers. Besides it had a different significance in the application for marketing authorization within the three ICH-regions European Union, United States and Japan.
And the testing of product quality is guidance-oriented. It is fixed on prior determined specifications.
At the ICH meeting in Brussels in July 2003 a five-year Vision was agreed which aims to develop a harmonized pharmaceutical quality system applicable throughout the product lifecycle emphasizing an integrated approach to risk management.
The goal is to shift from a data based approach to a science and risk-based approach. Traditional empirical approaches will need to be replaced with a much more fundamental scientific understanding. This common goal requires a harmonized regulatory environment.
The development of ICH Q8 was triggered by the adoption and implementation of the CTD in the ICH-regions. The key concept is Quality by Design. Quality cannot be tested into the product but has to be designed and built into it from initial point to all elements of the manufacturing.
The key elements provided in ICH Q8 are Design Space and PAT. A Design Space facilitates regulatory flexibility. Risk-based regulatory decisions, reduction of post-approval submissions and real-time quality control are the potential benefits for industry and regulators. More detailed scientific knowledge on product and processes is required for this concept.
A quality risk management supports the identification and assessment of critical parameters influencing the product quality. ICH Q9 provides adequate risk management tools and two risk management principles for a harmonized approach to risk management.
The implementation of ICH Q8 and ICH Q9 requires a robust quality system. ICH Q10 describes a model for an effective quality management that applies for drug substances and drug products throughout the product lifecycle. ICH Q10 defines specific pharmaceutical quality system elements that augment the different regional GMP requirements.
The new concepts are not mandatory. Thereof, the degree of the impact will depend on the decision of industry and regulators on what level they will adopt the guidelines. Factors like company size, type of product, already implemented systems but also the expected benefit influence this decision.
Several benefits are expected with the adoption of the guidelines amongst others innovation, especially of manufacturing technologies. It is discussed if the guidelines will foster innovation. They at least provide a harmonized regulatory environment that reduces the regulatory burden for pharmaceutical companies. But just the availability of the guidelines alone cannot introduce new technologies or methodologies to pharmaceutical development and manufacturing. It is upon the industry and the regulators to adopt these new guidelines.

ICH Q8 Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality System are inter-related and complement each other. Together they provide a regulatory framework to achieve the common Vision of the ICH-regions.
ICH Q8 is currently being updated and ICH Q10 has not been finalized yet. Already existing guidelines will need to be revised. It will be a step-by-step approach and the success will very much depend on the close co-operation between industry and regulators. There is still a lot of work ahead for both.

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