

The "Risk Based Approach" - an important tool for managing all the duties in Drug Regulatory Affairs

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List of Abbreviations

AE	Adverse Event
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
ASR	Annual Safety Reports
ATMP	Advanced Therapy Medicinal Products
BWP	Biologics Working Party
CAPA	Corrective Action & Preventive Action
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CMC	Chemistry, Manufacturing and Controls
CMS	Concerned Member State
cGMP	current Good Manufacturing Practices
CPP	Critical Process Parameter
CQA	Critical Quality Attributes
CTA	Clinical Trial Authorisation
CTD	Common Technical Document
DCP	Decentralised Procedure
DoE	Design of Experiments
DRA	Drug Regulatory Affairs
DRMP	Development Risk Management Plan
DSUR	Development Safety Update Report
EC	European Commission
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
ERMS	European Risk Management Strategy
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HMA	Heads of Medicines Agencies
IMP	Investigational Medicinal Product
IND	Investigational New Drug
ISO	International Standards Organisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency, UK
MP	Medicinal Product
MRP	Mutual Recognition Procedure
NCA	National Competent Authority
NCE	New Chemical Entity
ONR	ON-Regel
PDUFA	Prescription Drug User Fee Act
PQS	Pharmaceutical Quality System
QbD	Quality by Design
QbR	Question based Review
QTPP	Quality Target Product Profile
QM	Quality Management
QRM	Quality Risk Management

QWP	Quality Working Party
RIVM	National Institute for Public Health and the Environment, Netherlands
RM	Risk management
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of Toxicological Concern
VHP	Voluntary Harmonisation Procedure
WHO	World Health Organisation

1. Introduction

Current discussions on ways how to optimise the drug regulatory system frequently address the need to apply the "risk based approach". But the meaning of the phrase is unclear, and so is the estimation of the value of this tool: Is it just another buzzword, or is it a valuable tool with broad applicability?

Historically managing risk to health has always been in the focus of drug regulations: Issues of adulterated drugs potentially posing economic and health risks to consumers triggered the public interest in food and drug regulation in US resulting in the original food and drug act in 1906¹. The thalidomide disaster massively influenced the European drug regulations, and triggered the introduction of Directive 65/65/EEC (on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products) in 1965 (Rägo 2008).

Drug discovery and manufacturing is subject to change

(i) Increasing internationalisation in manufacturing and development of drugs significantly changed the sources and nature of public health risks. Even small and medium sized enterprises are able to provide global access to innovative products. Local events of international suppliers may trigger snowball effects with potentially global consequences.

(ii) Upcoming, entirely new technologies evolve at a rapid pace and provide a major opportunity for manufacturing and development of drugs, but may significantly alter the risk profile (e.g. Nanotechnology).

(iii) Patient's habits changed too: More and more patients

- try to get access to innovative drugs and investigational medicinal products.
- claim for reliable and comprehensible information („empowered patient”).

These changing conditions continuously challenges and matures the regulatory framework in US and Europe. New acts, regulations, directives and guidelines are set into force, demanding more specific expertise in the different technological fields.

“New governance”

In order to balance the increasing complexity – which has also been identified for completely different regulated fields (like the financial system) – “*new governance*” techniques have been developed: a principles (or standard) based regulation evolved and has been favoured over a cost-intensive rules-based system. This “*enhanced risk based regulation*” should for instance most effectively and efficiently regulate the financial sector, avoiding “*loophole*” behaviour and “*checklist*” style approaches (Ford 2008). By this means efforts and resources should focus on the risk relevant elements, and relieve the burden to elaborate on negligible points.

¹ <http://eh.net/encyclopedia/article/Law.Food.and.Drug.Regulation> 2010-12-31

The OECD recognised that regulatory systems are not able to remove all risks and has recommended **the governance of risk**: *"that regulatory action, when taken, should be proportionate, targeted and based on an assessment of the nature and magnitude of the risks and of the likelihood that regulation will be successful in achieving its aims"* (Black 2010).

Although different drug regulatory systems are applicable in US and Europe, both flagged that the application of risk based approaches might still help to advance the regulatory system.

The scope of this thesis is

- to describe to which extent the risk based approach is already implemented into the current legislation,
- to provide sources for definitions,
- to elaborate on the possibilities, opportunities and limitations given to apply this approach onto regulatory processes, and
- to discuss challenges to circumvent limitations of this approach

from the industrial and authorities perspective of drug developers, marketing authorisation holders and regulatory agencies.

Not within the scope of the master thesis is **clinical risk management in health care systems**: It is driven by the health service providers, addressing patient safety by providing standards, assessments and trainings with a broad view on organisational, clinical, and health & safety risks (Solvejg Kristensen & Paul Bartels 2010)². Clinical risk management is part of "**clinical governance**" focusing exclusively on the care of patients, and excluding any business considerations³.

² http://90plan.ovh.net/~extranetn/images/EUNetPaS_Publications/eunetpas-report-use-of-psci-and-recommandations-april-8-2010.pdf under <http://www.eunetpas.eu/> 2011-06-11

³ <http://www.clinicalgovernance.scot.nhs.uk/> 2011-06-11

2. Results

Aiming the most efficient promotion and protection of public health regulatory bodies need to focus their efforts on the risk relevant aspects. US and European standards, harmonised at the WHO and ICH level, addressing quality, safety and efficacy aspects of medicinal products are given in the first chapter. Crucial aspects concerning limitations in the applicability of risk management tools are presented in the second chapter. The third chapter presents ISO standards for risk management, because those are frequently part of a company's quality management (QM) system.

2.1. The risk based approach in drug regulation

Although differences in review styles between US and European authorities are evident, stepwise risk assessment and risk minimization are core elements of all drug regulatory systems⁴.

Why is risk the basis for measurement of drug quality?

In the traditional economic sense quality of products can be optimised on the basis of financial costs (Cogdill 2008): any investments in the quality of a product are not justified if the number of sold products is not increased. But for this purposes the consumer needs to have an idea about differences in the quality of products. The quality benefit is calculated on the basis of financial costs. This is applicable to products where pricing is based on efficient markets. But pricing of pharmaceuticals is not the product of an efficient market: the consumers (patients) can not differentiate the quality of drugs. Their expectations – based on the highly regulated market access and surveillance for drugs - is that the quality is uniform. Purchasing decisions are driven by physicians, insurance coverage, or lack of alternative treatments. Superior quality is only in the minority of cases a purchasing decision factor, and marketing driven. Consequently risk is a more appropriate basis for the measurement of drug product quality as the common denominator for all participants in the decision process (manufacturer, regulators, and patients) is *"their desire to minimize the sources of risk associated with drug therapy"* (Cogdill 2008).

One of the important initiatives highlighting the *"risk based approach"* has been the release of the **Pharmaceutical cGMP initiative** in August 2002 by the FDA (Department of Health and Human Services U.S Food and Drug Administration 2004a): *"Certain limitations in the definition of pharmaceutical quality were identified by a lack of observable connections between critical quality attributes and clinical performance, suggesting to recast pharmaceutical quality in terms of risk..."* and driven by the need to improve productivity (Woodcock 2004, 2007).

In May 2002 the European Agency for the Evaluation of Medicines Products (EMA) presented proposals for the establishment of a risk management strategy concentrating on centrally authorised products and referrals. This initiative focuses on efforts to improve the **European Pharmacovigilance system** (Heads of Agencies ad hoc Working Group 2003). The urgent need on reliable post-marketing

⁴ http://www.dgra.de/organisation/granzer_2006_09_07.pdf and <http://www.pharma.uni-bonn.de/www/dra/schnitzler> 2011-01-05

safety reporting systems has also been recognised by WHO (Kerr 2003). Continuous monitoring of medicinal products has been presented as one of the most challenging issues in the EMA Roadmap 2010 (European Medicines Agency 2005). The EMA Roadmap 2015 intends to progress the **European Risk Management Strategy (ERMS)** to investigate novel and better ways to monitor the safety and benefit/risk balance of medicines by introducing quantitative elements (European Medicines Agency 2011). The most recent **HMA strategy paper** discusses "*risk based proportionate regulation*" as one of the key themes which might make a real difference over the next five years. The considerations affect inspections as well as assessment procedures, without being too lax or too risk averse (Heads of Agencies 2010).

2.1.1. Pharmaceutical cGMPs for the 21st Century: A Risk Based Approach

The FDAs "*pharmaceutical cGMP initiative*" - issued in 2002 - had following objectives (Department of Health and Human Services U.S Food and Drug Administration 2004a):

- *"To encourage the early adoption of new technological advances by the pharmaceutical industry"*
- *To facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance*
- *To encourage implementation of risk based approaches that focus both industry and Agency attention on critical areas*
- *To ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science*
- *To enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities"*

FDA identified a number of different organisations with expertise in quality systems and / or risk management (RM) approaches to provide their experience to FDA staff. Besides training intentions – especially for members of the pharmaceutical inspectorate – several important changes to FDAs inspection program have been made and working groups under the oversight of the FDA cGMP Steering Committee have been realigned or established. Details on the achievements after finalisation of the initiative in 2004 have been published (Department of Health and Human Services U.S Food and Drug Administration 2004a).

Certain aspects of the Pharmaceutical cGMPs initiative focused primarily on implementing specific risk based approaches:

- Improving the public health impact for **choosing sites for inspection** by a **quantitative risk based site-selection model** to most effectively allocate FDA inspectional resources including risk factors (type of drugs, compliance history, level of process understanding...) (Department of Health and Human Services U.S Food and Drug Administration 2004b)
- Revision of different compliance programs towards a more risk based approach, including **preapproval inspection program** and **Active Pharmaceutical Ingredient (API) process inspection program**

- Initiating a study to **identify risk factors** leading to superior **manufacturing performance**

As a matter of consequence the risk based approach had been introduced to different guidelines, e.g.:

- Interpretation of the 21CFR Part 11 regulation with a Note for Guidance, which outlines the controls necessary for the regulated industry to utilize **electronic records** and electronic signatures (CBER 2003).
- Sterile Drug Products Produced by **Aseptic Processing**: Current Good Manufacturing Practices (draft guidance) (CDER 2004b)
- **PAT** - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance (draft guidance) (CDER 2004a)

A number of follow up action items have been triggered:

- + For instance in August 20, 2003 FDA released a "5-Part Strategic Action Plan to Protect and Advance America's Health" with **science based risk management** as one of its goals.
- + Supporting the international cooperation and development of guidelines at the level of **International Conference on Harmonisation** (ICH).
- + Comparison of the Chemistry, Manufacturing and Controls (CMC) review process used for **Abbreviated New Drug Application (ANDA)** review with the goals of the pharmaceutical cGMP initiative revealed that key scientific questions were not being addressed before (FDA 2009): "*All products are treated equally without regard to the risk to the consumer.*" Consequently a new review system for ANDA - had been developed:

Question based Review (QbR)

QbR is based on scientific and risk based assessment of product quality, including Quality by Design (QbD) elements and focussing on critical pharmaceutical quality attributes. FDA expected that the QbR enhances the current CMC evaluation of pharmaceutical quality in following respects:

1. it enables reviewers to recognise only those deficiencies in the CMC information, that affect product quality (emphasising quality by design).
2. it leads to more relevant specifications and manufacturing controls by encouraging sponsors to share their pharmaceutical development knowledge.
3. it contains a risk assessment section, which shall help to focus review efforts onto the most relevant questions.

2.1.2. The risk based approach in non-clinical drug evaluation (Module 4)

Unscrupulous behaviour in some early clinical trials triggered the establishment of regulatory standards also assuring ethical principles. It is in the interest of public health to foster innovation but to maintain protection of clinical trial subjects. Results of non-clinical (pharmaco-toxicological) studies are required to discover anticipated benefits justifying the potential risks of clinical studies.

The majority of **preclinical studies are conducted to carry out risk assessment** for a new compound before it is used in humans (Olejniczak).

Some of the preclinical studies overlap chronologically with each other, and with clinical studies. Because of the large heterogeneity of products it is not possible to fix a standard set of preclinical studies.

The most sensitive preclinical testing models need to be selected, until their limited – or irrelevant – biological meaning is convincingly shown. A “*bridge of interpretation*” is required to adequately transform preclinical knowledge into clinical safety and efficacy.

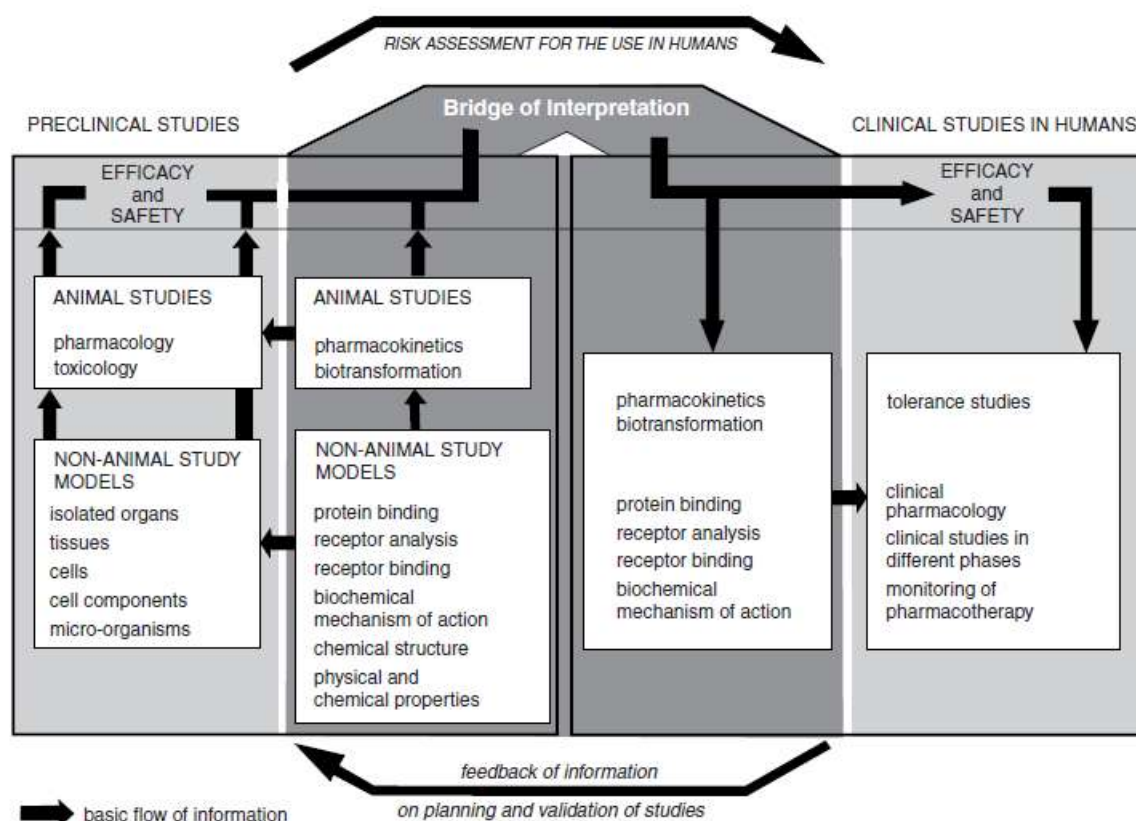


Figure 1: The intertwining of the most important biological fields of research of preclinical and clinical studies assess safety and efficacy (Olejniczak).

The nature of the product may limit the applicability and predictiveness of preclinical studies. For instance **biotechnology-derived products** frequently trigger immune responses in *in-vivo* studies. The limitations in analytical capabilities confirming the 3-dimensional structure of the comparatively high molecular weight active ingredients compared to small molecules demand a different approach in preclinical testing strategies. Accordingly, the **ICH S6** guidance document (Preclinical Safety Evaluation

of Biotechnology-Derived Pharmaceuticals) addresses **risk assessment for purposes on the decision of one or two (pharmacologically relevant) species** selected for toxicity testing.

Accordingly, **in-depth risk assessment** is also mentioned for evaluating carcinogenicity of **biotechnology-derived pharmaceuticals** and **nongenotoxic carcinogens of chemical origin**. These products elude a standard test battery because of their multiple mechanisms of action and the lack of sufficient understanding of the cellular and molecular events (Lima 2000).

Following this line of argumentation, any other clinical safety aspect (embryotoxicity, fertility,...) evaluated at the preclinical level needs to be estimated by appropriate risk assessment during the whole life cycle, accompanied by appropriate risk minimizing measures (e.g. exclusion of women of childbearing potential, co-medication, exclusion criteria, contraindication...) and discussed by appropriate risk communication (e.g. investigators brochure, labelling, SmPC).

Some examples of preclinical guidance documents incorporating or directly requesting risk management strategies:

An important risk based tool for carrying human risk assessment is the FDA issued **"Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers"**: based on allometric scaling an algorithm is applied to estimate the safe starting dose in clinical trials. A safety factor needs to be adjusted accordingly to mitigate identified harms or uncertainties. This guidance has been released in 2005 and is the only guidance concerning this subject in ICH region.

Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products CHMP/SWP/28367/07

This guideline especially deals with risk assessment and risk minimization ("risk identification and risk mitigation") strategies, by enlisting factors of risk from a quality, non-clinical and clinical perspective and emphasising the value of precautionary measures, stopping rules and risk communication in first-in-human clinical trials.

Environmental Risk Assessment of Medicinal Products for Human Use

CPMP/SWP/4447/00

This guideline describes the evaluation of potential risks of the medicinal product to the environment by a stepwise RA procedure, and outlines potential precautionary and safety measures.

Guideline on the Limits of Genotoxic Impurities CPMP/SWP/5199/02

EMA/CHMP/QWP/251344/2006

A threshold of toxicological concern (TTC) has been developed (1.5 µg/day intake of a genotoxic impurity), which is considered as an acceptable risk (excess cancer risk of <1 in 100,000 over a lifetime). The applicability is limited to compounds without sufficient evidence for a threshold-related mechanism because other compounds are established according to ICH Q3C (using permitted daily exposure, derived from NOEL, using uncertainty factors). This guidance is a pragmatic approach balancing appropriate safety against the need to develop innovative products (CHMP 2006; Müller).

The European Centre for the Validation of Alternative Methods (ECVAM) developed a software-based tool "**ToxRTool**" (**Toxicological data Reliability Assessment Tool**) (European Commission). It includes *in vivo* and *in vitro* data finally leading to the assignment of Klimisch categories. The **reliability categories** according to Klimisch reach from 1 (reliable without restrictions), 2 (reliable with restrictions), 3 (not reliable) to 4 (not assignable) (Klimisch 1997). The performance of the tool has been tested by experienced toxicologists and risk assessors in two independent experiments (Schneider 2009). This Microsoft Excel based approach should help to improve the transparency of the decision making process by integrating the totality of the toxicological data – and adjusted weighting according to the quality of the studies. In case the personal judgment differs from the calculated outcome, a change is possible based on documented reasoning.

2.1.3. The risk based approach and clinical evaluation of drugs (Module 5)

2.1.3.1. Clinical trials

Clinical trials are key elements required to evaluate the benefit risk profile of a drug candidate before any marketing authorisation can be granted. It is in the interest of public health to maintain public trust in clinical trials, required to promote drug development. Therefore authorisation and life-cycle management of clinical trials are under tight regulatory scrutiny.

Within different clinical trials there is a **large heterogeneity in the level and nature of risks**: First-in-man trials or pivotal, double blinded Phase 3 studies vss. non-interventional studies and Post Authorisation Safety Studies,... Therefore regulatory procedures are tailored to commensurate with the risk, i.e. by the obligation for registration or authorisation of clinical trials by competent authorities (e.g. interventional or non-interventional studies) or by the frequency and nature of inspection.

The design, management and assessment of clinical trials put a **special focus on risk assessment** (European Commission 2001): "*The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities,...*". Especially for minors and incapacitated adults not able to give informed legal consent a "*risk threshold...shall be specially defined and constantly monitored*".

In the FDA and EMA region different activities are ongoing where the risk based approach is considered to be an appropriate tool to **facilitate management and conductance of clinical trials**:

In Europe especially the Clinical Trials Directive (2001/20/EC) and the GMP directive (2003/94/EC) turned out to put some pressure on the financial feasibility of academic clinical research (European Commission 2001; European Commission 08.04.2005). The European commission identified the need to **support non-commercial trials** (Recital 11 of Directive 2005/28/EC foresees that it might be *unnecessary to apply certain of the details of Good Clinical Practice to studies conducted by public researchers...*). Later on, instead of separating commercial and non-commercial

trials, a differential application of the legislation, using a **risk based approach**, has been proposed (EMA 30.11.2007) to **account for the extent of the knowledge of the product** (e.g. novel or marketed). This should prevent to develop double standards in terms of GCP compliance and the quality and credibility of data. The regulations of clinical trials in Europe leaves sufficient flexibility to implement risk based approaches.

The MHRA risk stratification project

An Ad-hoc Working Group and the Risk-Stratification Sub-Group under the auspices of Department of Health (DH), Medicines and Healthcare products Regulatory Agency (MHRA) and Medical Research Council (MRC) developed a "**risk proportionate approach**" addressing key issues for clinical trials in the UK. Recently (28th March 2011) MHRA published a paper on the outcome of this joint project on its website⁵. A brief summary of this paper is given as follows:

A core set of risks inherent in a trial protocol, which impact on

- participant safety and
- participant rights, and
- the reliability of the results

has been proposed under the involvement of different stakeholders (academic researchers, clinical trial managers, research governance managers, MHRA assessors, GCP Inspectors).

Primarily the body of knowledge about the investigational medicinal product (IMP) is of relevance for **risk categorisation**, which is i.e. the **marketing status and standard of medical care**. Accordingly, simplification is possibly for some types of clinical trials, with consequences onto following aspects:

- the need for authorisation by the competent authority
- the content of the Clinical Trials Authorisation (CTA) application
- labelling
- IMP management
- safety surveillance
- trial documentation.
- GCP Inspection
- safety monitoring plan

The proposal includes that the IMP risk category and safety monitoring plan are submitted to the MHRA with the CTA application. This shall ensure that there is a shared understanding on this key aspect of the trial.

It has been decided not to go for a scoring system of individual risks associated with a study. This would describe a trial in relation to total risk, but facing the limited possibilities of risk adaptations, this would not add value. Therefore a core set of risks applicable to safety assessment of all clinical trials has been identified. Other factors, like funding, qualifications of the trial team, suitability of the host sites, are not addressed in this paper and should be covered by other measures.

(i) Concerning the **safety risks in relation to the IMP** it needs to be evaluated what is already known about the IMP. These potential risks need to be assessed relative to *"the standard of care for the relevant clinical condition and the level of clinical experience with the intervention, rather than the patients underlying illness or*

⁵ <http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf> 2011-05-13

the recognized adverse effects of the intervention". The clinical trial might present a safety risk that is "not", "somewhat" or "markedly" higher. For example studies with EU authorised medicinal products within the label present a risk that is not higher than standard of care (Type A trials).

(ii) Independent from IMP related risk categorisation **all other risks** need to be assessed. The assessment of these risks helps to setup mitigation activities in the conduct of the trial and collection of data.

The proposed risk assessment process and the associated documents (e.g. monitoring plan) should be generated by the chief investigator/protocol author together with key stakeholders. For all clinical trials an appropriate feedback loop remains essential, to appropriately adapt risk assessment by incoming data. As a matter of consequence, starting from 1st April 2011 the majority of Type A trials in the UK only require notification to the MHRA. Already after 14 days from receipt of notification the study may proceed, if no objections have been raised by the national competent authority (NCA)⁶.

In Europe CTA applications fall under the scope of the national legislation. Thus for multinational trials different clinical trial applications need to be managed and assessed individually by the different European NCAs. The **Voluntary Harmonisation Procedure** (VHP) provides the opportunity for a single application to the clinical trials facilitation group (CTFG) evaluating scientific questions on the protocol in a single procedure. In order to advance this approach a European harmonised view is essential to apply a risk based approach in the organisation of assessment of clinical trials⁷. Therefore, the Clinical Trials Facilitation group (CTFG – established by HMA to coordinate implementation of the EU clinical trials directive 2001/20 EC across the member states) action plan 2010-2011 enlists the development and implementation of processes for a risk based approach to CTA application and clinical trial safety information assessment⁸.

Further initiatives are on the way to implement QRM into GCP. For instance the work plan for GCP inspectors working group for 2011 enlists the finalisation of a **"Reflection paper on QRM in clinical trials"** as one of its tasks⁹.

The **Clinical Trials Transformation Initiative** (CTTI) conducts a project aiming to improve methods for efficient and effective monitoring of clinical trials. This public-private partnership comprising more than 60 organisations, including **US governmental agencies (FDA, NIH,...)** recommend the risk based approach to be used for creating quality systems identifying critical aspects of clinical trials. In fact, current guidelines do not ask for specific monitoring methods, rather go for adequate methods that need to be applied. Anyhow, sometimes sponsors might over-interpret regulatory provisions and apply the highest monitoring standard to all clinical trials. **"Risk based monitoring"** should help to clarify and prioritise the perceptions of risk

⁶ <http://www.ct-toolkit.ac.uk/> and http://www.ct-toolkit.ac.uk/route_maps/stations.cfm?current_station_id=319&view_type=map 2011-04-27

⁷ http://www.urpl.gov.pl/system/files/prezydencja/hmaAGENDA/66_HMA_H_5_2.ppt 2011-07-02

⁸ http://www.hma.eu/fileadmin/dateien/Human_Medicines/Working_Groups/CTFG/CTFG_ACTION_PLAN_2010-2011.pdf 2011-05-03

⁹ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/03/WC500103488.pdf 2011-05-10

aiming to generate essential and relevant data. More focus may be required on a systematic proactive risk assessment established and maintained by an interdisciplinary team¹⁰.

Actually FDA is drafting a guidance describing the agencies current thinking on risk based monitoring approaches¹¹. The **risk based source data verification approaches** instead of 100% source data verification rate should improve data quality and may reduce time to database lock, with significant cost efficiencies in large studies (Tantsyura 2010).

Similar to the European regulation of clinical trials, the FDA has tried to accommodate regulatory procedures to the level of anticipated risks: exclusively authorised drugs may be distributed in the US. Consequently for investigational medicinal products, an exemption from that legal requirement is necessary: the **IND (21 CFR part 312)**.

The primary objectives of the FDA in reviewing an IND are to assure the safety and rights of subjects in all phases of the investigation *"...and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety"* (21 CFR 312.22(a))

According to 21 CFR 312.22(b)) *"The amount of information ... that must be submitted in an IND to assure the accomplishment of the objectives ... depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the **known or suspected risks**, and the developmental phase of the drug."* A number of different guidance documents have been issued, to specify the expected amount of required information.

But FDA considers certain types of **studies to be exempt from IND regulation based on a risk assessment**: The Guidance for Industry "IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer"¹² clarifies the criteria which need to be met, because many INDs for cancer drugs were submitted containing studies that the Agency determined were exempted from IND regulation. Primarily new indications of already legally marketed drugs (but applying similar doses and schedules) or new combinations of drugs if these combinations have been described in the professional medical literature are addressed by this guidance.

2.1.3.2. Marketing authorisation

According to WHO *"assessing the safety, efficacy and quality of medicines, and issuing marketing authorization"* is one of the principle medicines regulatory functions (Kerr 2003).

The different legal types of Marketing Authorisation Applications (MAAs) reflect the **inherent risk based nature of the drug regulation**:

In the European region – according to Directive 2001/83/EC - **self-standing applications** require the submission of a full dossier containing common technical

¹⁰ <https://www.trialstransformation.org/projects/effective-and-efficient-monitoring/developing-effective-quality-systems-in-clinical-trials-an-enlightened-approach> 2011-05-13

¹¹ http://www.targetthehealth.com/NEWPDF/Centerwatch%20monthly_February2011_Article.pdf 2011-05-13

¹² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071717.pdf> 2011-04-09

document (CTD) Modules 1 - 5, independent on the source of data: primarily new data for Art. 8(3) procedures, published data for Art. 10a applications, new data on the combination of known active substances (without requesting data relating to each individual active substance) for Art. 10b applications, and for applications according to Art. 10c informed consent from the Marketing Authorisation Holder (MAH) for the content of modules 3 to 5 need to be shown.

The content of the dossier may be reduced for **applications based on a Reference Medicinal Product**, but is contingent on strict conditions – depending on the risk that identical clinical safety and efficacy can not be presumed:

According to Art. 10(1) of Directive 2001/83/EC – **generic applications** - the *“applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic.....”*

A generic medicinal product (as defined in Art. 10(2)(b) of Directive 2001/83/EC) has:

- *the same qualitative and quantitative composition in active substances as the reference product,*
- *the same pharmaceutical form as the reference medicinal product,*
- *and whose **bioequivalence** with the reference medicinal product has been demonstrated by appropriate **bioavailability studies**...*

Based on the **Biopharmaceutics Classification System (BCS)** - classifying solubility and permeability of a drug substance - criteria are applied to setup conditions waiving the need of ***in vivo* bioequivalence** studies for immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. The risk of inappropriate biowaiver decisions is minimized by considering relevant risk factors:

Such as BCS classification, *in vitro* dissolution characteristics, excipients affecting bioavailability...

The BCS-based biowaiver is not applicable for products with a narrow therapeutic index. Different salts of test and reference products are possible if both belong to BCS class I.

The CHMP **“Guideline on the Investigation of bioequivalence”**

(CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) – specifies in detail the requirements for the design, conduct, and evaluation of bioequivalence studies for immediate release dosage forms with systemic action¹³. In principle the FDA applies a similar BCS-based biowaiver system, which are also applicable to above mentioned ANDAs¹⁴.

If bioequivalence cannot be shown – either because of the results of bioavailability studies or because bioavailability studies are not appropriate (for Example for locally applied and locally acting drugs) - **Article 10(3)** of Directive 2001/83/EC requires that the results of appropriate pre-clinical tests or clinical trials shall be provided.

Similarly to Art 10(3), **biological medicinal products** are excluded from the generic approach (**Art 10(4)**). Their specific nature and strong process dependence of

¹³ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf
2011-04-16

¹⁴ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf>
2011-04-16

product quality request for results of appropriate pre-clinical and clinical studies and need to comply with the relevant criteria stated in Annex 1. However, the extent of additional pre-clinical and clinical studies depends on the analytical capabilities and the results of the quality comparability exercise.

Especially the provisions for **biosimilar applications** ask for **risk based development programs**, focusing on the control and mitigation of relevant risks. The high molecular weight together with restricted analytical possibilities to examine three dimensional structures, the limited predictivity of preclinical studies due to species specific immune reactions and further characteristics stipulate specific, distinct consideration in drug regulation. Art. 10(4) provides sufficient flexibility for addressing product specific risks, which need to be covered by scientifically justified studies at the level of quality, safety and efficacy.

A considerable number of product specific guidelines for biosimilar development have been issued by CHMP. One of the most recently drafted biosimilar guidelines is the "**Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies**" (EMA/CHMP/BMWP/403543/2010)¹⁵. It emphasises the need for a risk based approach for the non-clinical development program on a case by case basis: The outcome of *in vitro* studies shall help to decide on the need, focus and extent of *in vivo* studies.

One of the additional requirements of biological medicinal products according to Annex I of Directive 2001/83/EC is the need *"to demonstrate that the medicinal product is manufactured in accordance with the **Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products** and its updates, published by the EC in the Official Journal of the European Union"*.

Thus the Note for Guidance is legally binding for MAHs for Medicinal Products (MPs) in the EU. In 2004 - with Revision 2 – it **introduced risk assessment into the regulatory compliance process** in order to justify in exceptional circumstances the use of specified risk materials for the manufacturing of active substances. The development of the Transmissible Spongiform Encephalopathy (TSE) regulation in Europe is another example how regulatory guidance implemented a risk based approach to balance the risks against the public health needs.

The issue of **unwanted immunogenicity** has an important impact on benefit risk evaluation of biological medicinal products: different risk factors contribute, but likelihood, severity and occurrence of clinical consequences vary on a case by case basis. The limited predictivity of immunogenicity in pre-clinical studies and the fact that exclusively the humoral arm of immunogenicity is analytically ascertainable on a routine basis additionally complicates the development program. Aiming guidance for this complex situation the "**Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins**" CHMP/BMWP/14327/06 had been issued: besides enlisting of risk factors, risk analysis is recommended to decide on the extent and duration of immunogenicity studies, and the Risk Management Plan (RMP) shall include immunogenicity specific aspects concerning risk identification & characterisation (e.g. antibody assays), risk monitoring, risk minimisation & mitigation strategies and risk communication. Accordingly, the bioanalytical strategy for

¹⁵ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf
2011-04-16

assessment of humoral immune responses should be designed to commensurate with the level of risk (Shankar G 2007).

The recently drafted guideline on "**Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use**"¹⁶EMA/CHMP/BMWP/86289/2010 is another example emphasising the risk based approach¹⁶.

ATMPs and the concept of the risk based approach

Many of the molecular peculiarities attributed to biological medicinal products are also applicable to medicinal products developed by gene therapy, somatic cell therapy and tissue engineering, summarised as advanced therapy medicinal products (ATMPs). However, their novelty, complexity and technical specificity called for a *lex specialis* in the European drug regulation and introduced additional provisions to those laid down in Directive 2001/83/EC (ATMP Regulation (EC) No 1394/2007 and Directive 2009/120/EC (European Union 2009)). The risk based approach shall be outlined in CTD Module 2, specific requirements regarding CTD Module 3, 4 and 5 are enlisted, and additional requirements are set:

*"Due to the specific nature of advanced therapy medicinal products, a **risk based approach may be applied to determine the extent of quality, non-clinical and clinical data** to be included in the marketing authorisation application,..." (European Union 2001).*

The risk based approach as defined in Annex I, part IV of Directive 2001/83/EC should not be mixed-up with Risk Management and benefit – risk assessment of marketing authorisation applications. Details regarding the practical application are drafted in the Concept Paper – "**Development of a guideline on the risk based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products**" CHMP/CPWP/708420/09¹⁷.

A request to draw up detailed guidelines addressing the post authorisation follow-up of efficacy and adverse reaction, and risk management has already been raised in Art. 14 (4) of Regulation (EC) 1394/2007: The "**Guideline on Safety and Efficacy follow-up Risk Management of Advanced Therapy Medicinal Products**" (EMA/149995/2008) emphasises the need for adequate data at the time of marketing authorisation to enable proper benefit-risk assessment¹⁸. But due to the limited experience and fast evolving knowledge with ATMPs the need for generation of long-term data in post-authorisation phase is given. Therefore besides routine pharmacovigilance measures, specific monitoring activities as detailed in the EU-RMP have been integrated.

FDA regulates these very heterogeneous products on a case-by-case basis by similar means with different guidance documents. For instance the Guidance for Industry "**Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events**" recommends a decision tree in order to estimate the risk level for

¹⁶http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c 2011-04-16

¹⁷http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500069264.pdf 2011-04-15

¹⁸http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf 2011-04-15

gene therapy clinical trials required to decide on the long-term follow up observations¹⁹.

Benefit Risk Assessment

The final decision on granting or refusing marketing authorisation in US or EU is the evaluation of the risk benefit balance. Limitations in the definition of risk have been identified in the EU legislation of medicinal products:

The governing Community code Directive 2001/83 defines the "*Risks related to use of the medicinal product*" as "*any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;*" and "*any risk of undesirable effects on the environment*" (European Union 2001). Consequently, a risk is defined as a risk – a circular reasoning. This lack of clear definition of risk might lead to a lack of consensus on the term, which is of crucial importance when assessing benefit-risk balance (Phillips et al. 2009) (Cone et al. 2006).

Similarly, the "**Guideline on the definition of a potential serious risk to public health**" in the context of Article 29(1) and (2) of Directive 2001/83/EC (June 2006) – established to guide on referral/arbitration grounds – provides a definition:

"it is defined as a situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health. It may relate to efficacy, safety, quality, overall risk benefit, and product information issues."

However, it only enlists issues which normally would not be considered as grounds for a 'Potential Serious Risk to Public Health' (European Commission 2006).

A lack of consensus in the meaning of "benefit" and "risk" has also been observed for the FDA region (Coplan et al. 2010).

Consequently EMA started a **benefit-risk methodology project** with a clear definition for these terms as one of the objectives (EMA/213482/2010): it started in 2009 in collaboration with the London School of Economics and the University of Groningen^{20 21}. The objective of this project – under participation of the NCAs of France, The Netherlands, Spain, Sweden and UK - is "*to explore methodologies that can improve the current practice of benefit-risk assessment for medicinal products, with an aim to increase the consistency and transparency of the regulatory process.*" The project consists of 5 work packages, with two of them at a finalised stage, the third is actually ongoing. It is still scheduled to run until end of 2011.

For the evaluation of marketing authorisation applications (MRP/DCP) the risk based approach is repeatedly discussed as a prerequisite for a functioning work sharing within the **European Medicines Regulatory Network (EMRN)**²²: In exceptional cases a member state can refuse to recognise a marketing authorisation (MRP) draft assessment report, but needs to provide a detailed explanation²³. The decision on

¹⁹<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078719.pdf> 2011-04-15

²⁰http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/04/WC500089603.pdf 2011-01-29

²¹http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/10/news_detail_001129.jsp&url=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jenabled=true 2011-01-29

²²http://www.hma.eu/uploads/media/Strategic_Day_II_stakeholders_information_230109_final.pdf 2011-01-29

²³http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Application_for_MAA/Guideline_AR_MPR_DCP_2006_09_Rev3.pdf 2011-01-29

the time and effort undertaken for assessment rests with each member state. The baseline is to meet the obligations of a RMS (or Rapp/Co-Rapporteur for centralised procedure). Member states acting as CMS need to find a decision how much resources are assigned to support the assessment. The implementation of risk based approaches for targeted assessment is actually the most promising and valid consideration. For this purposes only experienced and/or accredited assessors should be allocated²⁴.

HMA supports **the risk based approach** for **selection of MRP/DCP products for testing** and the "*need for high level requirements for tools for sharing of risk data*" aiming to further improve the EMRN²⁵. The Working Group on Product Testing considers this as one of the key components of a collaborative approach to the sampling and testing of MPs between EEA regulatory authorities²⁶.

2.1.3.3. Drug safety and surveillance

Collection, verification and presentation of adverse reaction reports is of utmost importance to safeguard public health. Before authorisation - at the stage of clinical trials - characterisation of rare adverse events is not possible because inadequately big clinical studies would need to be finalised before access to innovative products is given. Thus post marketing surveillance of medicinal products is key to complete the safety profile of a medicinal product.

As indicated under 2.1 the ERMS initiative identified the need to optimise clinical safety reporting in Europe. The Eudravigilance Database (an EMA centralised safety data processing network and management system) suffers on the validity (i.e. double reporting) and population (i.e. underreporting) with individual case safety reports (ICSRs) received from MAHs via member states. The efforts are legally based on Article 8 (3)(ia) of Directive 2001/83/EC requiring - for MAAs - to submit "*a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce.*" The "**Guideline on Risk Management Systems for Medicinal Products for Human Use**" (integrated in Volume 9) has been published in 2005 and provides a definition of a RMS as "... a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of the effectiveness of those interventions" (European Commission 12.09.2008). The guideline has been followed by the publication of the companion template Annex C in 2006²⁷.

While a **Pharmacovigilance System** is company specific, the **RM system** is product specific. Consequently the submission of an EU-RMP is necessary to fulfil the requirement for a RM System. Part I of the EU-RMP consists of a safety specification and a pharmacovigilance plan (essentially as outlined in ICH E2E). Part II evaluates the need for risk minimization activities. In case, a RMP is required (including the assessment of the effectiveness). One important step in risk management and risk minimisation activity is risk communication – across different functions and

²⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500015431.pdf 2011-02-01

²⁵ <http://www.hma.eu/uploads/media/28.Oct.2009.pdf> 2011-02-01

²⁶ <http://www.hma.eu/63.html> and http://www.hma.eu/uploads/media/2010_07_LaHulpe_BE.pdf 2011-02-01

²⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Templates_and_Form/2009/10/WC500006317.pdf 2011-02-01

development stages. Details on the legal background and guidelines for marketing authorisation holders, competent authorities and agency in Europe are outlined in "VOLUME 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use" (European Commission 12.09.2008).

Recently, a **new EU Pharmacovigilance Legislation** aiming to promote and protect public health has been published on 31st Dec 2010 (being effective with national implementation of community law in 2012): Regulation (EU) No 1235/2010 (amending Regulation (EC) No 726/2004) and Directive 2010/84/EU amending Directive 2001/83/EC). It strengthens EMAs role in collection, management and evaluation of safety data (with the Eudravigilance database becoming the single point of receipt of pharmacovigilance information for all MPs authorised in the EU - including nationally authorised products).

It establishes a **Pharmacovigilance Risk Assessment Committee (PRAC)** thereby strengthening the focus of risk management on MPs within EMA region. According to Regulation 1235/2010 the Regulation (EC) No 726/2004 will be amended as follows: Article 61a

"6. The mandate of the Pharmacovigilance Risk Assessment Committee shall cover all aspects of the risk management of the use of medicinal products for human use including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit."

Definitions for RMS, RMP, PHV System, PHV System Master file are now provided in Directive 2010/84, and amending, as regards pharmacovigilance, Directive 2001/83/EC:

'28b. Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.

28c. Risk management plan: a detailed description of the risk management system.

28d. Pharmacovigilance system: a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk benefit balance.

28e. Pharmacovigilance system master file: A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products.'

Henceforth definitions for RM are given in the European legislation, providing a harmonised approach covering all MPs irrelevant which route of application (national, MRP/DCP or centralised) has been taken²⁸.

The computerised information database for **post-marketing safety surveillance** in **US** makes use of the **Adverse Event Reporting System (AERS)**. Manufacturers are obligated to report adverse events, whereas reporting is voluntary for consumers and health care professionals²⁹.

²⁸<http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/08/782&format=HTML&aged=0&language=en&guiLanguage=en> and <http://www.forum-institut.de/de/reg-affairs-newsletter/dezember-2010/> 2011-02-12

²⁹<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> and <http://www.fda.gov/Safety/MedWatch/default.htm> 2011-02-12

In 2002 one of the PDUFA III goals has been to produce **Guidance for Industry on Risk Management activities for Drugs and Biological Products**. After issuing concept papers and public consultation final guidance documents for Premarketing³⁰, RiskMAP³¹ and Pharmacovigilance³² were provided to the public in 2005.

The focus on a drug safety program has been re-initiated under PDUFA IV. In 2006 the Institute of Medicine (IOM) released a report with recommendations to improve FDA's risk assessment, surveillance, and the safe use of drugs (drug safety program). The FDA's response to this report – issued in 2007 and aligning above mentioned recommendations with ongoing and new FDA actions – put a commitment to improve the drug safety system, focussing on *“new methods of signal detection, data mining and analysis that are enabling researchers to generate hypothesis about and confirm the existence and cause of safety problems, as well as about the unique genetic and biologic features of the person...”* With this **“science of safety”** approach a new balance between enabling innovative products and improving drug safety should be found. And *“A more modern, efficient, and risk based drug development process will improve FDA's ability to detect safety related problems earlier.”*

An upgrade of the web-accessible adverse event (AE) reporting system has been initiated and a quality assurance system ensuring efficient risk management. Importantly, a *“much more formalized, semi-quantitative approach to benefit and risk analyses and continuing reorganization of regulatory processes”* has been requested. The **Risk Minimization Action Plans** (RiskMAP) – as defined by FDA – is a *“strategic safety program designed to meet specific goals and objectives in minimizing known risks of a medication while preserving its benefits”*. In a relatively small number of cases a RiskMAP has been required, based on the Agency's own interpretation of risk information. The FDA Amendments Act of 2007 significantly expanded FDA authority, with the possibility to dictate specific tools to be used to mitigate safety risks for new products and already approved products by requesting **Risk Evaluation and Mitigation Strategies (REMS)**³³.

The initial focus of Pharmacovigilance activities on detection and evaluation of signals in the post-approval environment expanded efforts to early and late stages of pre-approval development. A **Development Risk Management Plan (DRMP)** has been outlined as part of a systematic approach to manage safety during clinical development by the Council for International Organizations of Medical Sciences (CIOMS) **“Report of CIOMS Working Group VI”**³⁴. First examples underlining the successful generation of DRMPs by empowering multidisciplinary teams achieving a

³⁰ http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4136b1_01_Premarket%20Risk%20Assessment.pdf 2011-02-12

³¹ http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4136b1_03_Risk%20Minimization%20Action%20Plans.pdf 2011-02-12

³² <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf> 2011-02-12

³³ http://www.painedu.org/articles_timely.asp?ArticleNumber=28

http://www.ppd.com/services/post_approval/faq.htm#

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm094886.htm>

<http://www.fda.gov/downloads/safety/safetyofspecificproducts/ucm184049.pdf>

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM171627.pdf> all 2011-02-13

³⁴ http://www.cioms.ch/publications/blurbs/management_of_safety_information.htm 2011-02-13

robust understanding of the benefit risk profile of a medicinal product are published (Heaton S. 2009).

In summary, with the ongoing European and US initiatives further advancements for the early detection of drug safety issues are expected. In any case the safety RMP is legally binding³⁵.

2.1.4. The risk based approach and quality of medicinal products (Module 3)

According to WHO "**Controlling and monitoring the quality of medicines on the market**" is one of the principle medicines regulatory functions to protect and promote public health (Kerr 2003). Assuring consistent and sufficient quality of medicinal products is a prerequisite for reliable results of preclinical and clinical studies and ensures safety and efficacy of authorised medicinal products.

The WHO justifies the existence of drug regulatory systems on the "**information asymmetry**": patients and consumers do not have the equipment and knowledge required for independent assessment, which is especially true for the assessment of drug quality.

Thus repeated GMP inspections, besides assessment of quality of investigational medicinal products, in the frame of marketing authorisations or variations, are important tools to safeguard public health.

Every quality aspect has to be evaluated for its influence on clinical safety and efficacy addressing the special needs of the targeted patient population. A strong emphasis of science in regulation limits regulatory burden and puts a focus on critical quality aspects, being of relevance for assuring safety and efficacy.

This aspect is well implemented in the different quality guidelines for medicinal products, and is finally a risk based approach:

Risk assessment is an important part of **viral safety evaluation**, either for products derived from cell lines or for products derived from human or animal source material³⁶. The potential serious clinical consequences (especially for parenteral products) together with the limitations in analytical methods of virus detection require the application of complementary approaches instead of single elements: selection of donors, viral testing in starting materials and products as well as virus validation studies showing the capability of the purification process to remove or inactivate viruses are expected.

ICH Q5A presents different cases (A-E) for viral safety of cell lines considering different factors like presence of viruses or virus-like particles, evidence of infecting humans, identified or non-identified viruses. These cases represent a **risk based classification** with examples for the design of the virus validation program.

³⁵ [http://www.ich.org/fileadmin/Public_Web_Site/Training/GCG - Endorsed Training Events/Advanced workshop Rev of Drug Dev in CT/Day 4/10-Risk_Management.pdf](http://www.ich.org/fileadmin/Public_Web_Site/Training/GCG_-_Endorsed_Training_Events/Advanced_workshop_Rev_of_Drug_Dev_in_CT/Day_4/10-Risk_Management.pdf) 2010-12-29

³⁶ http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5A_R1/Step4/Q5A_R1_Guideline.pdf,
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003633.pdf (CPMP/BWP/269/95 Rev. 4) and <http://www.who.int/bloodproducts/publications/EMEA-animal%20sera.pdf> (CPMP/BWP/3354/99) 2010-12-29

Risk assessment for virus transmission by plasma-derived medicinal products is required to substantiate any statement on virus safety and any remaining potential risk in the product information for these products (as outlined in the **"Note for Guidance on the Warning on Transmissible Agents in SPCs and Package Leaflets for Plasma-derived Medicinal Products"** (CPMP/BPWG/BWP/561/03)), including a quantitative estimation of the probability of virus contamination and estimation of virus particles in the finished product³⁷.

For instance with **ICH Q3A and B (Impurities in new Drug Substances and in new Drug Products)** a classification is provided, with defined thresholds for reporting, identification and qualification for impurities³⁸. The chemistry and safety aspects of impurities are addressed demanding on the one hand a reasonable expectation for the occurrence of certain impurities but also requiring the reduction of the content of those impurities, which are of known human relevant risk.

ICH Q3C – Impurities: Guideline for Residual Solvents - provides a Classification of Residual Solvents by Risk Assessment³⁹: Production processes might lead to the presence of residual solvents. Although aiming complete absence of these organic volatile chemicals, the possibilities to completely remove them by practical manufacturing techniques are sometimes limited. Depending on their possible risk to human health solvents have been categorised into three different classes, requiring avoiding (class I) or limiting their presence (class II) or accepting solvents with low toxic potential (class III). Even class I solvents might be acceptable for certain patient populations, if the decision is based on a strong justification in a risk benefit assessment.

Another example of already implemented, science and risk based approaches focussing on quality of drug development is the possibility of **reduced designs in stability testing programs**: i.e. bracketing and/or matrixing going for a reduced testing frequency, or certain factor combinations are not tested at all. The bracketing design assumes that stability of intermediate levels is represented by the stability of the extremes tested. Thus only samples on the extremes of certain design factors (like strength, package size) are tested at all time points as in a full design. With matrixing only selected subsets of the total number of possible samples for all factor combinations are tested at a specified time point. Both aspects are risk based approaches of saving resources by limitation to those samples in a stability program, which are of critical value. The possibility of a reduced stability testing is already stated in **ICH Q1A(R2) (Stability Testing of New Drug Substances and Products)**, more detailed information is provided in ICH Q1D – Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products, issued in 2002.

The **development and setting of specifications** in drug development is finally also a risk based approach:

³⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003753.pdf and

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/CompliancePrograms/ucm095419.pdf> 2010-12-29

³⁸ <http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html> 2010-12-30

³⁹ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002674.pdf 2010-12-30

According to ICH Q6A: "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval."

Likewise ICH Q7 (GMP for APIs) elaborate on "critical parameters/attributes".

"12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

- Defining the API in terms of its critical product attributes;*
- Identifying process parameters that could affect the critical quality attributes of the API;*
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.*

*12.12 Validation should extend to those operations determined to be **critical to the quality and purity** of the API."*

Thus in the development of specifications and of the manufacturing process a **stepwise limitation to the meaningful (critical) parameters** affecting quality of medicines is required. The robustness of the process depends on the successful efforts undertaken to get the process under control targeting the relevant product attributes. I.e. those characteristics which form (relevant) risk regarding clinical safety and efficacy shall be part of the specifications or shall be included to control the manufacturing process.

In the early 2000s FDA identified a **cost pressure in manufacturing** because of equipment utilisation rates in the range of 15-20%. Studies revealed that the total cost of the manufacturing infrastructure exceeded that of research and development (R&D) by two- or threefold (Kenny 2005). The regulatory burden to implement changes required to improve manufacturing has been identified as one of the major hurdles in fostering innovation (Krause 2008). Marketing authorisation holders were reluctant to provide detailed information on manufacturing to the authorities in order to prevent the need for type II variations if future manufacturing changes might occur. In case of insufficient quantitative understanding concerning variability of product attributes on consequences to safety and efficacy more frequently specifications are tightened in order to mitigate the unknown level of risk (Woodcock 2004). This comprehensible attitude might lead to unrealistically restrictive design tolerances, with consequences on affordability or availability (Cogdill 2008).

With the "cGMPs for the 21st Century Initiative" FDA issued the PAT guideline and promoted a "Quality by Design" model of regulatory approval compared with a "quality by test results" orientation.

The objective of the **PAT initiative** (launched in 2003) has been to promote a more thorough understanding of the manufacturing process in order to achieve more predictable and efficient manufacturing (Clark 2011). QbD expands the PAT objective upstream in the lifecycle from manufacturing authorised medicinal products to the development of investigational medicinal products – science based and – coevally – based on profound knowledge on the basic principles, conditions and parameters of the process.

Frequently the possibilities to establish or expand a design space are limited to the CMC part of the dossier: proofing that certain process parameters vary in a specific range and match the pre-fixed product specifications. In case of strong process

dependence of the quality attributes of a product (i.e. when quality attributes can not be controlled exclusively on the basis of meeting predefined specifications, like for instance biological medicinal products) additional preclinical or clinical data might need to be filed to assure safety and efficacy of the product.

With the implementation of ICH Q8-9-10 a **"New Paradigm"** concerning quality of drugs has been introduced: Quality must be built in by design, it will not only improve by additional testing and inspection. It has been promoted by FDA's pharmaceutical cGMP initiative, recognising the value of designed experiments for determining the quality of drugs.

QbD - Old wine in new skins?

The key concept of Quality by Design is based on application of Process analytical Technologies (PAT) and the determination of Design Space. So the initial process development strategy of stopping process development after consistency runs performed once the process is locked has been expanded by the possibility that "comprehensive understanding" is given to model the functional relationship between quality attributes and their impact onto safety and efficacy.

The earliest professional work on QbD goes back to Dr. Genichi Taguchi (Cogdill 2008): Already in 1947 he started to use designed experiments based on orthogonal arrays aiming to improve the quality and yield of industrially produced penicillin. He recognised that statistical process control is able to bring existing processes into control. But quality improvement is most efficiently achieved already at the earliest phase in the lifecycle – during design. Taguchi grouped process development into the phases of system design, parameter design and tolerance design. Concerning pharmaceutical development system design corresponds to the content of ICH Q8 and tolerance design addresses the development of specifications.

Parameter design is the engineering of the system by offline experiments aiming to *"minimize performance variation in the presence of uncontrollable variance factors or noise"*. The identified problem is that the usual pass/fail testing strategy does not distinguish between actual pieces exactly meeting the target and those which just meet the specifications. The less the deviation from the target design, the less is the loss, and the higher is the quality. But noise minimization is not a primary goal, as he stated that *"it's just as unethical to add tremendous cost to ensure products are of good quality as it is to ship defective goods"* (Ealey 1994): no investment without meaningful risk reduction. Taguchi developed the so called **"Continuous Quality Loss Function"**, which is a calculation of the mean squared deviation of error. He integrated direct and indirect costs, providing the basis to estimate *"the actual loss related to one or more levels of deviation"*.

As already pointed out, for drugs "risk" is a more appropriate basis for measurement of drug quality, because of the inelastic demand sensitivity to quality variation. The least common denominator for evaluating drugs from the perspective of manufacturers, patients and regulators is to minimize risk. Thus a risk based quality measurement system is able to transform product attributes (like API content) to estimates of risk (e.g. because of toxicity or inefficacy).

ICH Q8-9-10 guidelines – a “new paradigm”?

ICH Q8-9-10 guidelines are closely connected with each other, the application of their principles is optional (ICH secretariat 2005). These guidelines introduced the “new paradigm” by shifting the traditional, empirical “trial and error” approach of quality data submissions and regulatory evaluations to a science and risk based approach (Robert 2010):

Regional GMPs are usually not applicable across the lifecycle. With the application of ICH Q8-9-10 principles an integrated approach is given, including the results generated in the R&D phase. The importance of considering these principles already during clinical research stages is mentioned, but the guidelines are not directly applicable to the content of clinical trial submissions.

The idea behind the “new paradigm” is to offer a framework where on the top of baseline expectations additional data are presented, providing a **higher degree of regulatory freedom** in operating the manufacturing process. Enhanced knowledge can be achieved by different means (experimental design, process analytical technology) and is required to establish a design space based on scientific understanding. Working within the design space – as defined in ICH Q8 - is not considered a change (ICH secretariat 2009). The scope of ICH Q8 (Pharmaceutical Development) is an advancement to the basic GMP requirements on quality as set out in ICH Q7 (GMP Guide for Active Pharmaceutical Ingredients) (ICH secretariat 2000).

Quality Risk Management

Application of “quality risk management” (ICH Q9) shall help to achieve a science based knowledge transfer in CTD section 3.2.P.2 (Pharmaceutical Development) of a marketing authorisation application and should be updated accordingly during the whole life cycle (ICH secretariat 2008).

ICH Q9 is probably the most relevant guidance concerning risk based approaches in drug regulatory affairs (ICH secretariat 2005). It addresses the lack of structured risk management for quality of pharmaceuticals and gives a **definition for risk**: “*the combination of the probability of occurrence of harm and the severity of that harm*”.

QRM is guided by two primary principles:

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

Thus ICH Q9 recognises the appropriate use of QRM: **formal** (recognised tools and/or SOP) and **informal risk management processes** (empirical tools and/or internal procedures) might be acceptable.

QRM essentially focuses on quality, and does not primarily target preclinical and clinical evaluation. But it is in close relationship to these fields, as the primary goal is to achieve effective and safe drugs. Consequently it **clarifies management responsibilities** (“decision makers”), i.e. to coordinate QRM across various functions and to provide adequate resources.

ICH Q9 provides an overview of a typical QRM process, outlining methods of risk assessment, risk control, risk communication and risk review.

ICH Q9 Annex I: Risk Management Methods and Tools	ICH Q9 Annex II: Potential Applications for Quality Risk Management
Basic RM Facilitation Methods	QRM as part of integrated QM
Failure Mode Effects Analysis (FMEA)	QRM as Part of Regulatory Operations
Failure Mode, Effects and Criticality Analysis (FMECA)	QRM as part of development
Fault Tree Analysis (FTA)	QRM for Facilities, Equipment and Utilities
Hazard Analysis and Critical Control Points (HACCP)	QRM as Part of Materials Management
Hazard Operability Analysis (HAZOP)	QRM as Part of Production
Preliminary Hazard Analysis (PHA)	QRM as Part of Laboratory Control and Stability Studies
Risk Ranking and Filtering	QRM as Part of Packaging and Labelling
Supporting Statistical Tools: like Design of experiments (DoE), Histograms, Pareto Charts, Process Capability Analysis.	

Table 1: ICH Q9 Annex I and II

ICH Q10 - **Pharmaceutical quality system (PQS)** - complements ICH Q8 and Q9, including GMP regulations and is based on **ISO quality concepts** (ICH secretariat 2008). PQS is based upon **ISO 9000:2005**, international standards related to quality management systems. It gives guidance on a global harmonisation of quality management systems.

PQS should help **to link pharmaceutical development and manufacturing activities**, facilitating innovation and continual improvement driven by science- and risk based approaches.

The three objectives of applying PQS are to achieve **product realisation**, to **establish and maintain a state of control** and to **facilitate continual improvement**.

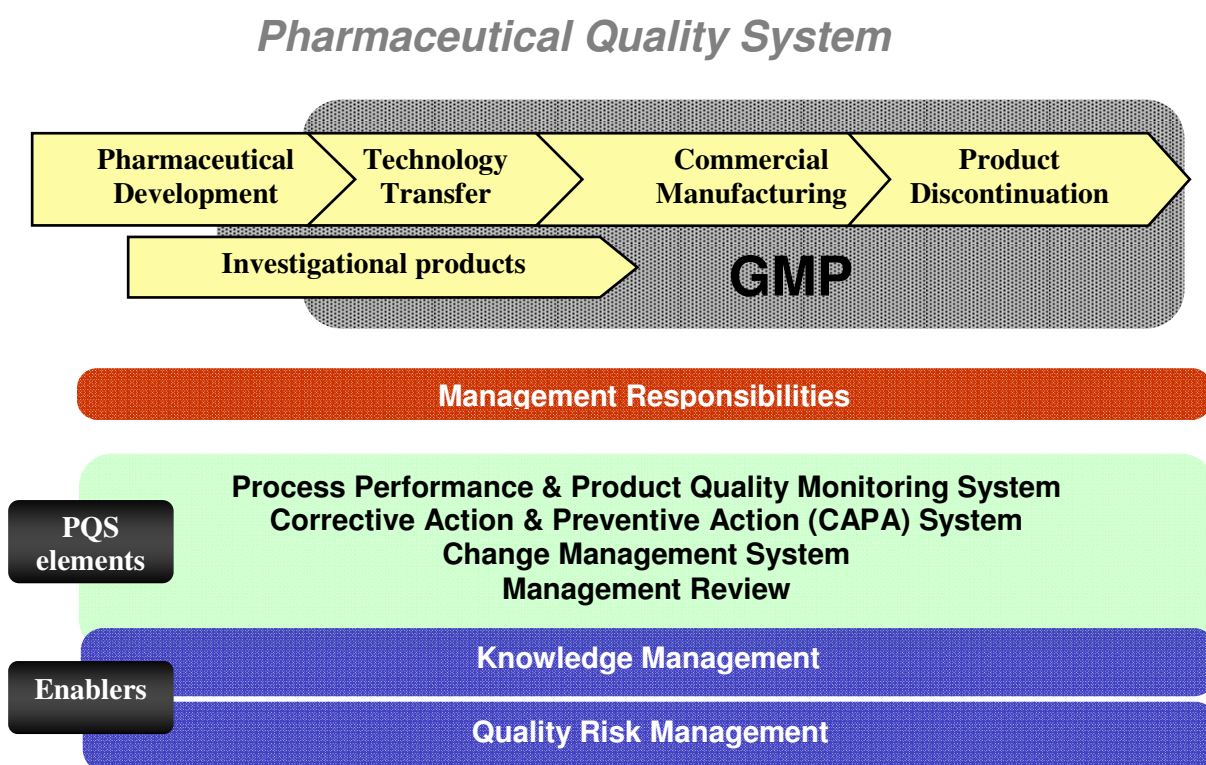


Figure 2: Diagram of the ICH Q10 Pharmaceutical Quality System Model (ICH secretariat 2008)

PQS covers the **whole life cycle** of a medicinal product: pharmaceutical development, technology transfer, commercial manufacturing and product discontinuation.

The four PQS elements are applicable to all stages of the pharmaceutical lifecycle:

- Process performance and product quality monitoring
- CAPA system
- Change management system
- Management review of process performance and product quality

Especially in change management systems risk based approaches should help to evaluate, approve and implement changes properly, preventing unintended consequences but being flexible enough to allow **continual process improvement**.

The **enablers** of key importance for applying PQS models are **knowledge management (KM) and QRM**:

KM is systematic approach of information management related to products and manufacturing processes, applicable throughout the pharmaceutical lifecycle emphasising scientific approaches.

QRM as an integral part of a pharmaceutical quality system shall help to identify, evaluate and control potential risks to quality in a proactive way.

It needs to be mentioned that marketing authorisation holders are already now obliged to "*take account of scientific and technical progress*", as expected by Article 23 of Directive 2001/83/EC (European Union 2001).

Annex I provides potential opportunities to enhance regulatory approaches, but does not represent the actual regulatory process, which is determined by region. It roughly describes scenarios and links them with potential opportunities: e.g.

- increased use of **risk based approaches for regulatory inspections**;
- facilitate science based pharmaceutical quality assessment;
- optimise science **and risk based post-approval change processes** to maximise benefits from innovation and continual improvement;
- enable innovative approaches to process validation;
- establish real-time release mechanisms.

The ICH Q11 guidance – currently at the level of a concept paper – intends to apply ICH Q8-9-10 principles to APIs. It deals with CTD sections S 2.2. - S 2.6 of Drug Substances including both **chemical entities and biotechnological/biological entities**. It harmonises the scientific and technical principles relating to the description and justification of the development **and manufacturing process at the DS level**.

In the regulatory field the determination of the first GMP relevant process step (and required documentation for API starting materials) is an ongoing discussion: Although outlined with ICH Q7 but enforced due to the increasing globalisation of suppliers in manufacturing. The development of the ICH Q11 guidance document is an appropriate platform to internationally align a definition and approach for API starting materials. Again, one strategy is to go for a science and risk based approach instead of a "one size fits all" policy⁴⁰.

In summary, the principles introduced with ICH Q8-9-10 (QTPP, CPP, DoE, CQA,...) are not really that new (Hoefler 2005). The "**Guideline on General Principles of Process Validation**" published in 1987 by FDA states:

*"Assurance of product quality is derived from ... **adequate product and process design, control of the process, and in-process and end-product testing**. Due to the complexity of today's medical products, **routine end-product testing alone often is not sufficient to assure product quality** for several reasons. Some end-product tests have limited sensitivity."*

This statement is equivalent to the ICH Q8 statement: *"It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design."* Further ICH Q8 terms are enlisted and compared with statements of the above mentioned, 23 year old FDA guideline.

Obviously important aspects of the "new paradigm" introduced with ICH Q8-9-10 have already been part of earlier guidelines.

⁴⁰ <http://www.egagenerics.com/doc/ega-20101207-pos-pap-starting-materials-rev00-FINAL.pdf>

ICH Q8 Terms and Definitions	Guideline on General Principles of Process Validation, FDA 1987
Quality Target Product Profile (QTPP) <i>A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.</i>	<i>During the research and development (R&D) phase, the desired product should be carefully defined in terms of its characteristics, such as physical, chemical, electrical and performance characteristics. It is important to translate the product characteristics into specifications as a basis for description and control of the product.</i>
Critical Quality Attributes (CQA) <i>A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.</i>	<i>A manufacturer should evaluate all factors that affect product quality when designing and undertaking a process validation study.</i>
Critical Process Parameter (CPP) <i>A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.</i>	<i>Key process variables should be monitored and documented.</i>
Design space <i>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.</i>	<i>As with prospective validation, it may be insufficient to assess the process solely on the basis of lot by lot conformance to specifications if test results are merely expressed in terms of pass/fail. Specific results, on the other hand, can be statistically analyzed and a determination can be made of what variance in data can be expected.</i> <i>The test conditions for these runs should encompass upper and lower processing limits and circumstances, including those within standard operating procedures,..</i> <i>Acceptable ranges or limits should be established for each characteristic to set up allowable variations.</i>

Table 2: Comparison of ICH Q8 Terms and Definitions with the content of the FDA Guideline on General Principles of Process Validation, as published in May 1987; adapted from (Dietrich 2011)

New paradigm challenges monographic standards

Currently used design space models frequently use quality surrogates (e.g. dissolution, moisture content), which might not always fix the clinical performance. A recent publication challenged the univariate specifications utilized in the USP tests for extended-release theophylline tablets by a risk simulation platform used to generate quantitative estimates of inefficacy and toxicity (Short 2010): it turned out that the USP specifications were too lenient for content uniformity in terms of inefficacy and toxicity, and the criteria for dissolution testing were too strict for inefficacy and inaccurate for toxicity. The USP tests failed to fix the clinical interaction between content uniformity and dissolution variability.

Falsified medicines

ICH Q9 principles are also useful with regards to prevention of falsified medicines. The European Parliament adopted an EC proposal amending Directive 2001/83/EC aiming to identify false representations of medicinal products. The measures impose many different aspects such as inspections of API manufacturers, importers or distributors within the EU at a risk-based frequency⁴¹. It calls for the adoption of a *"list of certain categories of excipients identified on a **risk-based approach** taking into account their source and their intended use. ...shall apply the appropriate GMP on the basis of a formalised risk assessment in accordance with the applicable guidelines referred to in the second paragraph of Article 47,..."*⁴². Similar approaches are followed in the US region. FDA ranked more than 1000 APIs in order to identify drugs and APIs that *"could be targeted for adulteration"* based on a **multifactorial risk based model**⁴³. New anticounterfeiting technologies and risk-based frequency of inspections shall help to prevent counterfeiting.

2.1.5. Risk based approach and GMP

Risk management is already now one of the most important GMP topics for medicinal products. First steps towards RM of medicinal products were taken in Europe in 2001 with Annex 15 of the EU-GMP guidance addressing **"risk assessment"** for validation purposes (GMP News: ICH Q 9).

For authorised medicinal products in EU Eudralex Volume 4 is fully applicable, describing Quality risk management as a *"systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.... the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk"* (European Commission 15.02.2008). Examples of the processes and applications of QRM are provided in Annex 20 of Volume 4, on the basis of a revision (effective since 01 July 2008) including the concept of Product quality review (European Commission 15.02.2008).

Part II (Basic Requirements for Active Substances used as Starting Materials) of **Volume 4** has been revised accordingly to **incorporate principles of QRM** in line with the ICH Q9 guideline on QRM and is in operation since 31 July 2010: "To

⁴¹ <http://pharmtech.findpharma.com/pharmtech/Drug+Delivery/Risk-Assessment-for-Excipients-for-Enhanced-Patient/ArticleStandard/Article/detail/714491>

⁴² <http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2010-0148&language=EN>

⁴³ <http://blog.pharmtech.com/2010/10/15/fda-commissioner-hamburg-discusses-counterfeit-drugs-at-conference/>

achieve the quality objective reliably there must be a comprehensively designed and correctly implemented quality system incorporating Good Manufacturing Practice, Quality Control and QRM" (section 2.19).

So the principles of risk management are in place and integrated in the regulatory guidance documents concerning quality. However, Annex 20 clearly states that *"QRM becomes an integral part of a manufacturer's quality system."* But *"Annex 20 itself is not intended, however, to create any new regulatory expectations; it provides an inventory of **internationally acknowledged risk management methods and tools** together with a list of potential applications at the discretion of manufacturers."* By this means in the European regulatory field the risk management concept has been strengthened with regards to quality of medicinal products, and now provides clearer guidance on the applicability of methods and tools.

A **"Concept paper on Revising Chapter 8 of the EC guide to GMP to introduce risk-based concepts and to provide for more effective investigations and CAPA actions"** has been issued recently addressing QRM principles to be applied when investigating quality defect/complaint issues and when making decisions in relation to product recalls ⁴⁴.

Additionally, further documents guiding the activities of inspectorates of European national competent authorities have been revised: The **"Compilation of Community Procedures on Inspections and Exchange of Information"** is a collection of GMP inspection-related procedures and forms which is used as the basis for standard operating procedures of the quality systems established within the inspectorates themselves.

As outlined in one of the two general documents - **"Quality systems framework for GMP inspectorates"** – *which is effective since 1 April 2008* - risk management should be implemented *"for assigning resources, prioritizing tasks and activities to carry out its obligations"*. The risk based approach should also be **implemented in conducting of inspection**. Consequently European inspectorates have to apply risk management as a part of the quality systems framework since April 2008 (European Commission 04.03.2011).

With the pharmaceutical cGMP initiative **FDA** enforced the risk based approaches (see 2.1.1), explicitly **expanding the RM activities beyond the validation efforts** to all business activities – inline with QRM aiming improved patient safety (GMP News: ICH Q 9). By this means FDA more and more focuses on process knowledge and understanding, but less on pure process data. This is underlined by FDA's New Process Validation Guidance (FDA 21.01.2011): It emphasises the risk based approach based on scientific sound rationale with process validation as three-staged life cycle approach (Pharmaceutical Guidelines: FDA's New Process Validation Guidance 2011).

⁴⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105200.pdf

2.2. Uncertainty Matrix

Regulatory science has a strong focus on reaching consensus: *"When preparing the opinion, each committee shall use its best endeavours to reach a scientific consensus..."* (Article 61 point 7 of Regulation 726/2004) (European Union 2004). But consensus is more a single "definitive" interpretation of evidence reducing the intrinsically plural, conditional nature of knowledge (Stirling 2010): *"Absence of evidence of harm is not the same as evidence of absence of harm"*. The higher the pressure on **consensus building** the higher is the need to ignore divergent views. But it is crucial not to rely solely on aggregated data, but also to identify the incomplete areas of knowledge. Therefore tools like the "uncertainty matrix" are available.

The quality of risk management depends on the quality of the input ("Quality in – Quality out"). Simple application of risk management, disregarding differences between risks, ambiguity, ignorance and uncertainty, is not valid.

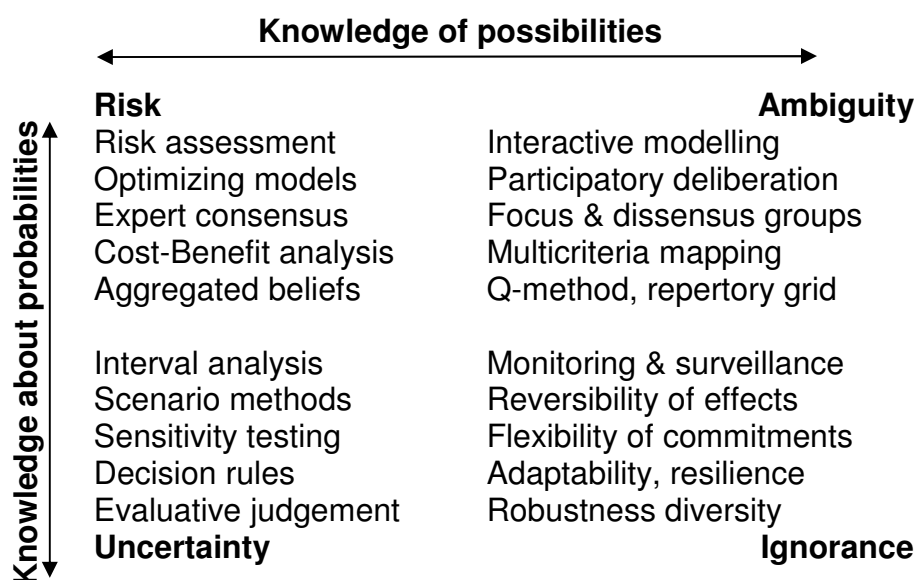


Figure 3: Uncertainty Matrix: different quantitative and qualitative Methods to deal with Risk, Ambiguity, Uncertainty and Ignorance need to be managed (Stirling 2010)

The National Institute for Public Health and the Environment working for the Dutch government (RIVM) recommended the application of the uncertainty matrix to professionalise the communication between different stakeholders by accepting the divergent interpretations of evidence and focus on documenting the reasons rather than selecting one favoured option in absence of knowledge (van der Sluijs 2003).

2.3. Definitions of risks based on ISO Standards

The sense of the term ranges from the occasional use of risk management methods to the more holistic view of regulating risks to society (risks to health, safety, the environment or financial well-being). It might be implemented in the frame of (quality-, project-, process-) management or designed according to the specific needs of the field of activity or line of business (e.g. by firms' own internal risk models like for insurance companies and banking). Anyhow, the degree of implementation shall be commensurate with the level of risk (Hutter 2005).

A relevant definition for the "risk based approach" being applicable to governmental activities is provided by OECD: ***"the development of decision-making frameworks and procedures to prioritise regulatory activities and deploy resources, principally relating to inspection and enforcement, based on an assessment of the risks that regulated firms pose to the regulator's objectives"*** (OECD Reviews of Regulatory Reform: Risk and Regulatory Policy).

From a general perspective risk based concepts are a combination of different interpretations concerning risks (probabilities, distributions, extent of loss) and concepts (sample allocation, data evaluation, risk modelling). A well defined setting for the purpose and the objective of the process is required, and clarity on limitations (Stüger 2009).

The ISO 31000 standard series ("Risk management – Principles and guidelines") provides a generic basis and guidance for the application of risk management (RM). It defines terms and deals with principles, the organisational framework and the RM process. It is a top level document, giving guidance for organisations from a general perspective. On the basis of ISO 31000 the ONR series 4900x **"Risk Management for Organisations and Systems"** has been generated. The ONR 49000 describes detailed specifications for risk management and has a high relevance for practical applicability (Österreichisches Normungsinstitut Wien / Komitee Risikomanagement 2010).

A broadly applicable definition of **risk** is *"the combination of the probability of an event and its consequences"*.

Risk = Probability x Consequence

Certain scenarios, triggered by threats, opportunities, change of circumstances or hazards can lead to risks.

Usually we think that the consequence of risk is negative – with something going wrong. But from a generalized perspective the consequences could be positive as well – with new upcoming opportunities. Thus deviation from the expected result is positive or negative (*"effect"*).

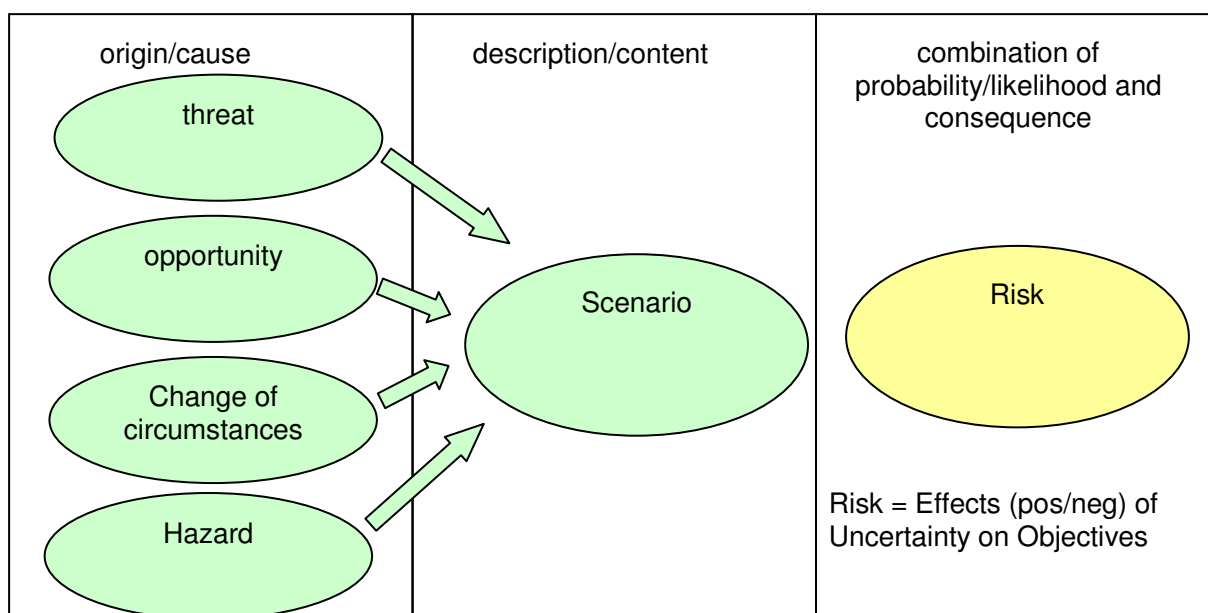


Figure 4: Definitions of Risk (Österreichisches Normungsinstitut Wien 2010a)

Risk is something unexpected, an “effect of uncertainty on objectives”.

Uncertainty needs to be estimated or determined by means of probabilities. The **objectives** depend on the organisation or system. They might address strategic, operational or financial aspects, safety and security of people, objects and the environment.

Risk is a consequence of events or changes of circumstances.

With “**consequences**” being the outcome of an event or change of circumstances (development) that affects the objectives. Consequences might be attributed/characterized by different categories: (i) (un)certainty, (ii) positive or negative influence on objectives (profits-loss, advantage-disadvantage, and benefit-damage), (iii) qualitative or quantitative nature, (iv) personal injury or material damage.

Probability has an objective (statistical) and subjective meaning by measuring or estimating uncertainty:

In its objective meaning it is a relative frequency of future events or changes of circumstances.

In full or partial lack of background information and/or causal relationships the objective meaning is replaced by scientific opinion or personal conviction, described as uncertainty of statements.

Probability of a risk may be counted over time (e.g. annual probability) or related to a number of cases (incident, probability).

All elements of an organisation’s management system concerned with managing risk form the **risk management system**.

Initially the processes and routines of virtually every organisation restrict RM to sub-fields within an organisation. Now this bottom-up approach is completed by a top-down approach to highlight the obligation of upper management.



Figure 5: RM covers the top-down and the bottom-up approach (Winkler 2010)

Corporate governance is executed by **top management** to align the activities of all employees to common objectives. RM interacts with integrated management systems and management information systems to ensure compliance with legal requirements and normative guidelines.

Definition of elements of the RMS required to check for effectiveness is described in ONR 49001. Crucial elements are the determination of the organisational framework, the action taken by management the handling of risks, traceability, verifiability and target-orientation. Consequently the RMS might vary with size, complexity, risks exposure and organisational structure. A strong commitment of senior management is required to integrate RM in the decision-process of organisations and to improve the RMS by the "**plan-do-check-act**" model.

The RM process describes activities required to direct and control an organisation with regard to risks: **context, risk identification, risk analysis, risk evaluation and risk treatment**. Depending on the varying needs in diverse applications, especially the method of risk evaluation might differ.



Figure 6: Risk Management Systems (Winkler 2010)

ONR 49002-1 embeds RM in the management system, either to integrate it into the existing management system or established as a separate sub-system.

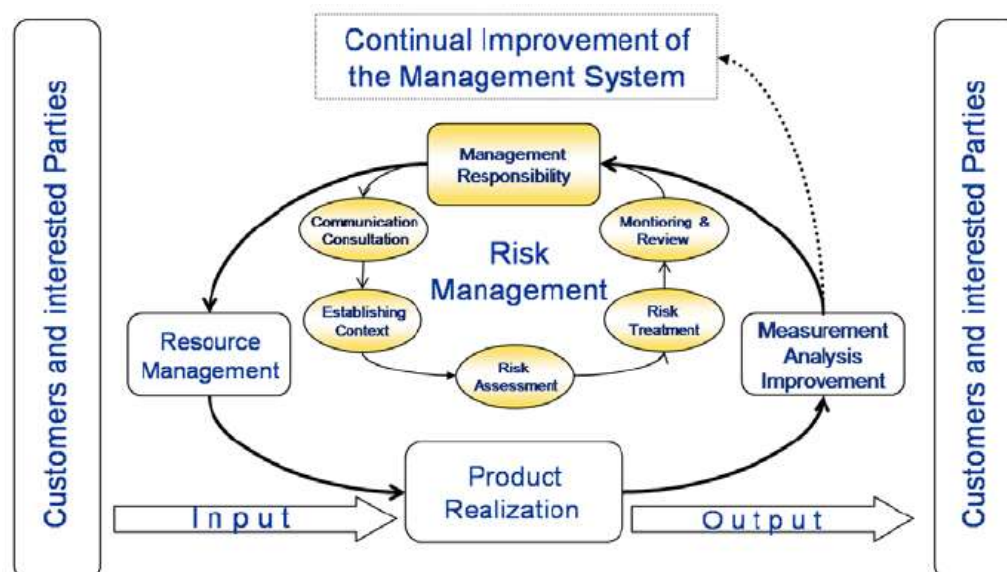


Figure 7: RM as a management responsibility in the process model of ISO 9000(Winkler 2010)

ONR 49002-2 briefly describes which methodologies in risk assessment can be applied in practice.

Method	Risk management process					
	Identification	Conse- quences	Proba- bility	Level of risk	Treatment	
Brainstorming	+++	+	+		+	creativity techniques
Delphi method		++	++		++	
Root cause analysis	++	+	+		++	
Fault tree & event tree analysis		++	+++	+	+	scenario analysis
Scenario Analysis	+++	+++	++	++	++	
CIRS ¹⁾	+++		+		+	indicator analyses
CBRM ²⁾	+++	+				
FMEA ³⁾	+++	++	++	+	++	
Hazard analysis	++	+++	++	++	++	functional analyses
HAZOP ⁴⁾	+++	+++	++	+	++	
HACCP ⁵⁾	++	++			++	
Standard deviation		++	+++	++		statistical methods
Confidence interval		++	+++	++		
Monte Carlo simulation	+	++	+++	++		

- 1) Critical incident reporting system (CIRS)
- 2) Change-based risk management (CBRM)
- 3) Failure mode and effects analysis (FMEA)
- 4) Hazard and operability study (HAZOP)
- 5) Hazard analysis and critical control points (HACCP)

Figure 8: Methodologies in risk assessment, slightly changed from (Winkler 2010)

ONR 49002-3 deals with emergency, crisis and business continuity management. Essentially unexpected and severe risks may strike an organisation, demanding an adequate and quick response to emergency and crisis. Besides that, restoring operational functions by **business continuity management** is required. It may start in planning with the "business impact analysis", deals with assignment of responsibilities to top management, emergency operation leader or a crisis management team and (internal and external) crisis communication.

3. Discussion and Outlook

The development of new drug candidates, the application of innovative technologies and the increasing globalisation in development, manufacturing and distribution of medicinal products challenges the regulatory systems to continuously adapt their processes to meet the patients' needs.

FDA ("Pharmaceutical cGMPs for the 21st Century"), EMA ("European Risk Management Strategy") and HMA ("risk based proportionate regulation") identified the risk based approach as an adequate tools to improve regulatory efficiency:

- increasing regulatory performance by more targeted allocation of resources to activities with the greatest public health gain.
- structured decision making on predefined criteria by handing-over individual responsibility to upper management for undertaken, deferred or omitted action.
- enhanced internal and external credibility by cross-functional development and advancement of a common understanding of risks.

The term "risk based approach" in the regulatory field is unevenly used. But it has been an essential element of legislation and guidance documents since the introduction of medicines regulation promoting and protecting public health.

Risk assessment is one of the ultimate goals of preclinical studies

The cardinal logic of the development methodology is that emerging data derived in a series of preclinical and clinical studies modify the development strategy and individual component studies (see ICH E8: General Considerations for Clinical trials)⁴⁵. Before entering any clinical trial risk assessment on the basis of toxicological and other preclinical studies is required.

The management and organisation of clinical trials matured with time to more multinational trials, increasing numbers of professional clinical study centers and with different responsibilities contracted out to CROs. The currently applied ICH harmonised GCP standard (ICH E6(R1): Good Clinical Practice) remains valid and applicable, but has been finalised in 1996⁴⁵. Critical areas of maintaining data integrity may have shifted meanwhile. Therefore further activities try to advance the currently applied standards and processes accordingly to take into account the diversity of clinical trials, like:

risk based quality management of clinical trials specifying critical aspects of clinical trials driven by the Clinical Trials Transformation Initiative and a **risk stratification project** for adequately targeting key issues for clinical trial applications by the MHRA.

Clinical Phase I to IV studies are not necessarily aligned to the level and nature of potential risks. Currently a revision of the European clinical trials Directive 2001/20/EC is discussed. The concept paper addresses "*more precise and risk adapted rules for the **content of the application dossier** and for safety reporting*"⁴⁶. According to Marimbert the revision of the Directive 2001/20/EC should give a robust

⁴⁵ <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

⁴⁶ http://ec.europa.eu/health/files/clinicaltrials/concept_paper_02-2011.pdf 2011-06-29

legal ground to the “coordinated DCP like approach of the VHP and provide a firm basis for a risk based approach”⁴⁷.

Rationalise Risk

Virtually any organisation is also exposed to financial, market, operational and legal risks (Tworek 2010). Thus it is essential to clarify which risk has to be addressed, achieving a harmonised view on that subject.

But not every “risk” is linked to harm. Risk as the “*deviation from the unexpected*” could also have positive consequences. Perceptions of risk vary because of cultural or psychological connotations, leading sometimes to strong public concerns against some relatively minor risks and vice versa (Kasperson). This might also be true for manufactured risks (a risk produced by human activity), with divergence between reality and relative risk perception (Beck). Aiming to safeguard public health it is a core responsibility of regulatory bodies to rationalise risk and select an appropriate mode of **risk communication**.

Managerial approaches

DRA units hold responsibility for a broad variety of duties and need to maintain the interface to various departments within an organisation but also to regulatory bodies, public health organisations and various patient groups. They are organised by different managerial approaches and usually confronted in parallel with Quality Management, Project Management and Risk Management. These different managerial approaches have a lot in common (Meier 2010). Thus from an organisational wide perspective pragmatic approaches are required to merge or apply these different perspectives to a functional unit. In the context of project management risk based approaches are most frequently designed as “Risk Management Planning Process” in order to identify, analyse and respond to risks. Depending on the project objectives, a Risk Management Plan needs to be developed integrating qualitative and quantitative elements⁴⁸. Generic and innovative pharmaceutical industries have frequently integrated Project Management into their matrix organisation guided by the Pareto-Principle to increase efficacy and efficiency.

Quality risk management

With the introduction of the ICH Q8-10 series the pharmaceutical industry is encouraged to generate more process understanding and - by submitting these data - achieving more regulatory flexibility. In any case the “minimal approach” (i.e. the current or traditional regulatory standard) is still common and implementation of ICH Q8-10 principles is the exception. From a regulatory perspective, the door to a risk based approach by application of QRM is open, but not obligatory.

The Variation Regulation Nr. 1234/2008 (Annex II, classification of variations) classifies “*variations related to the introduction of a **new design space** or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines*” as major variations of type II⁴⁹. By this means ICH Q8-9-10 is introduced into the European Variations Regulation.

⁴⁷ http://www.afssaps.fr/content/download/27077/359733/version/1/file/cftg_program100610.pdf 2011-05-10

⁴⁸ <http://project-management-knowledge.com/definitions/q/quantitative-risk-analysis/> 2011-06-12

⁴⁹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0007:EN:PDF>

The more complex the manufacturing process, the more adequate is the application of a risk based approach. Therefore the European ATMP Regulation (EC) No. 1394/2007 introduced the concept of the risk based approach into the Community code. FDA (CBER) follows the same approach concerning this very heterogenic product class, but did not role out a specific legislation and relies on guidelines applying a case-by-case concept⁵⁰.

For regulatory agencies the implementation of risk based approaches by application of QRM as outlined with ICH E9 is advisable. The "Work Plan for the Joint CHMP/CVMP Quality Working Party 2011" mentions the work on the development of an EU harmonised approach to application of QRM to the assessment of applications⁵¹. The first fundamental question will be if those principles are advantageous with regards to efficiency and maintain or even increase the quality of the assessment.

Risks of risk based approaches

There is a lack of experience with risk assessment methodologies in the pharmaceutical field. Inadequately implemented risk based approaches can lead to over-, under- or misregulation. Following aspects should be considered:

Workload: Much needs to be done upfront, and risk based approaches do not necessarily pay off financially.

Statistics: From a manufacturing point of view in the pre-approval phase statistics is merely helpful, because limited number of batches is available.

Losing the focus: Risk based approaches provide tools, but still the subject matters. Thus qualified, experienced experts shall be selected aiming to reach the relevant objectives, preventing the application of oversophisticated tools.

Interdisciplinary action: Lack of experience with cross-functional teams in development and assessment might impede successful implementation. Regulators and scientists as well as scientific experts and inspectors need to work effectively together.

Science: Access to independent experts needs to be ensured allowing critical scientific assessment. Pragmatic solutions need to be applied to ensure a balance between early access to innovative drugs and safeguarding public health. In case comprehensive clinical data are not yet available conditional marketing authorisation may be granted with the obligation to substantiate the initial expectations by follow up measures (EMA) or post marketing commitments (FDA).

Ignorance of gaps in knowledge and divergent views: Risk based approaches are no substitutes for a lack of knowledge. Tools like the "uncertainty matrix" may help to professionalise communication by enforcing a comprehensive discussion for the development of mitigation strategies.

⁵⁰ http://www.taylorwessing.com/uploads/tx_siruplawyermanagement/The_Regulation_of_Advanced_Therapies.pdf 2011-06-12

⁵¹ http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2009/11/WC500014314.pdf 2011-06-12

4. Executive Summary

European and US initiatives promote the application of “risk based approaches” in drug regulatory affairs to meet today’s patients needs. Risk based approaches have always been core elements of drug regulation and are frequently addressed in existing guidelines at the level of Quality, Safety and Efficacy. Importantly, it has the effect of focusing on critical aspects and not placing too much time on low-risk products.

Re-emphasising “risk based approaches” is also key to foster innovation and expand regulatory flexibility. It promotes a shift from “guideline thinking” to “public health thinking” aiming to meet the changing conditions of a globalised industry and provide early access to innovative products and technologies.

With the adoption of ICH Q8-9-10 the added value of scientific approaches and multidisciplinary perspectives has been emphasised. A link between ISO standards of risk management, pharmaceutical quality and patient safety has been generated. It can be applied optionally to different regulatory operations, development and manufacturing activities.

As any other tool “risk based approaches” have their limitations and may trigger new risks. Consequently, the performance of risk based approaches should be evaluated to decide on its effectiveness and to maintain target orientation.

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

Mank, den _____
Günter Waxenecker