Federal Institute
for Drugs
and Medical Devices

# Status Quo – Regulation im Bereich der Nanomedizin

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12. Internationaler Behördendialog – Berlin

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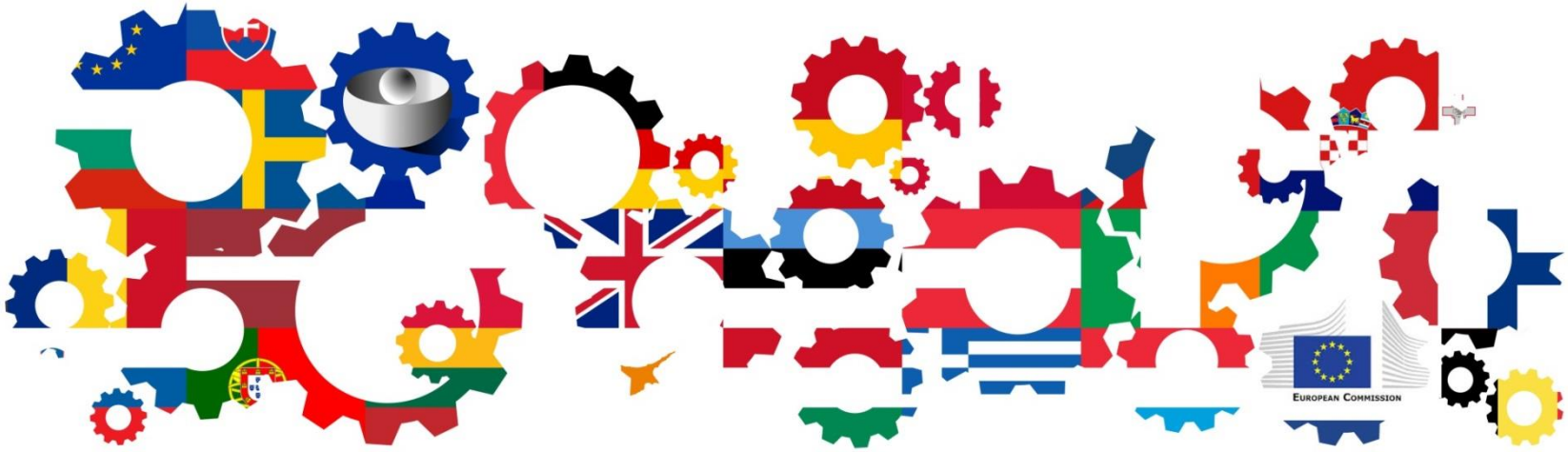
# The European medicines regulatory network




~ 50 national regulatory authorities | European Commission | European Medicines Agency

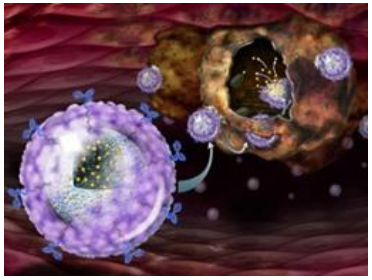
Network of more than European 4,500 experts

BfArM - National Competent Authority in Germany

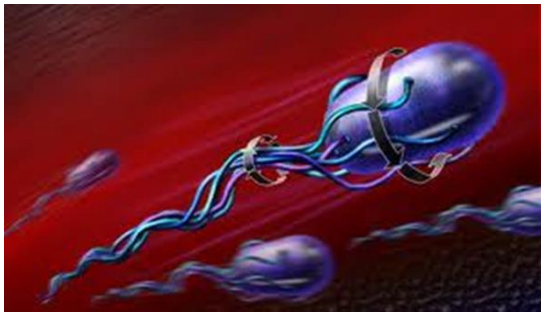
- Licensing and improving the safety of medicinal products (pharmaceuticals)
- Evaluating the risks of medical devices

Paul Ehrlich Institute (PEI) in Germany responsible for e.g. vaccines, blood products, ATMP etc.

# Potential Benefits of Nanomedicines



- Better efficacy
- Improved safety profile
- Reduced dose
- Patient friendly (frequency/route of administration) – improved compliance and quality of life
- Improved targeting / control and site specific release
- Exploit multiple mechanisms of action
- Improved transport across biological barriers
- Formulation opportunities
- Re-development of known active substances



# Abgrenzung Arzneimittel / Medizinprodukte

**Medizinprodukte**

Produkte aller Art zur Anwendung für Menschen; Hauptwirkungsweise nicht pharmakologisch, immunologisch oder metabolisch

medizinische Zweckbestimmung

**Arzneimittel**

Stoffe oder Zubereitungen aus Stoffen zur Anwendung im/am Menschen oder Tier; Unterteilung in
- Präsentationsarzneimittel
- Funktionsarzneimittel

**gesetzliche Grundlagen**

**Medizinproduktegesetz (MPG) und EU-Verordnungen**

National (BMG)

Europäisch (EU-Kommission)

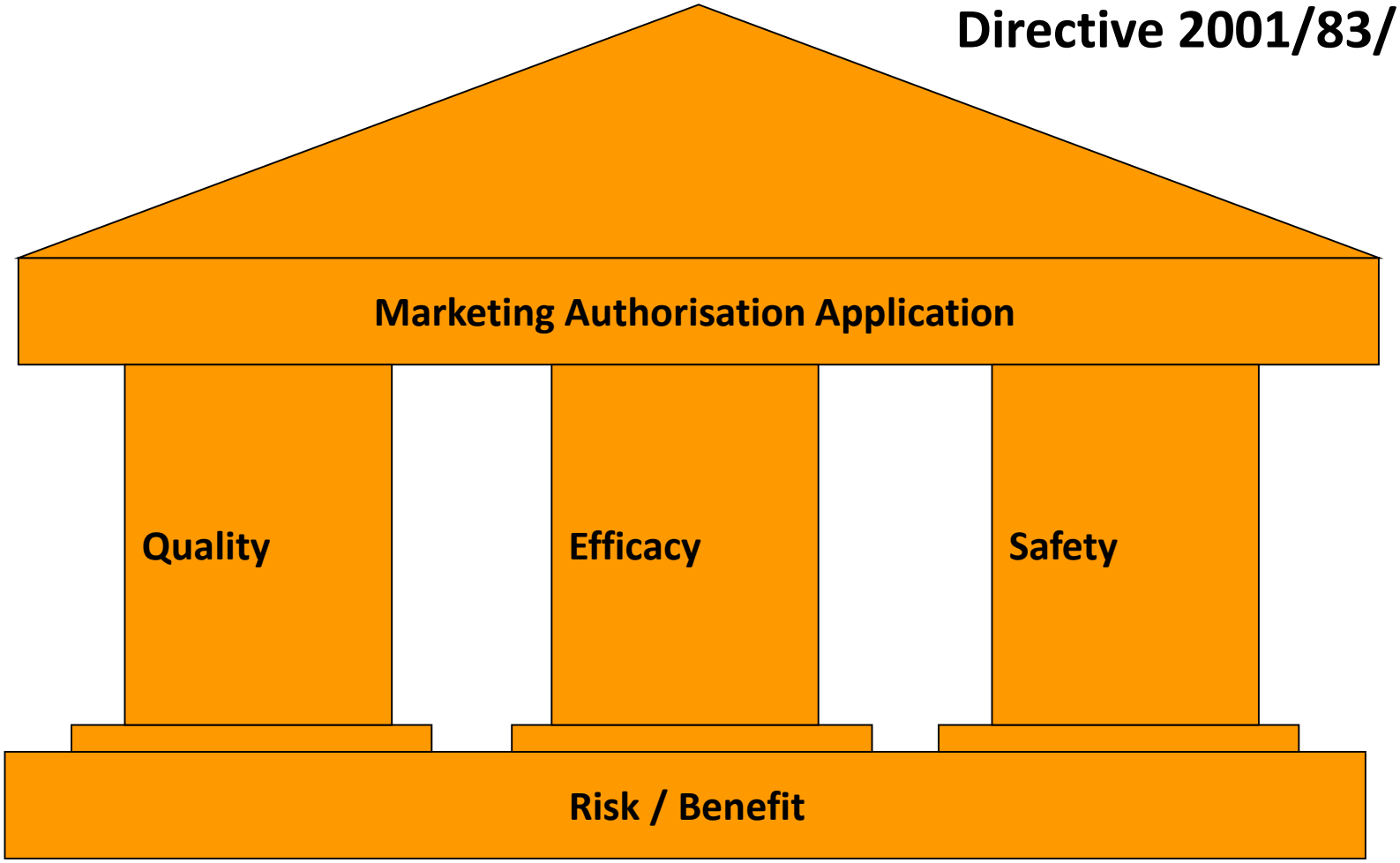
**Arzneimittelgesetz (AMG) + Richtlinien/Verordnung**

**Verordnung über Medizinprodukte (MDR) - (EU) 2017/745**
**Verordnung über In-vitro-Diagnostika (IVDR) - (EU) 2017/746**

RL 2001/83/EG Humanarzneimittel
RL 2001/82/EG Tier-Arzneimittel
VO(EG)726/2004 Festlegung von Gemeinschaftsverf.
RL 2001/20/EG klin.Prüfungen

**EU 536/2014 Verordnung über klinische Prüfungen**

# Directive 2001/83/EC




+ Pharmacovigilance: Risk Management System / Risk Management Plan

ICH
harmonisation for better health

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

About ICH | Work Products | Meetings | Training | Newsroom

# ICH Guidelines / Work Products /

The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories.

## Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

## Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

## Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

## Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

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- Overview
- Research and development
  - Adaptive pathways
  - Advanced therapies
  - Clinical trials
  - Compassionate use
  - Compliance
  - Data on medicines (ISO IDMP standards)
  - Ethical use of animals

Home > Human regulatory > Research and development > Scientific guidelines

# Scientific guidelines

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**The European Medicines Agency's Committee for Medicinal Products for Human Use prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing authorisation applicat elines reflect a harmonised approach of the EU M how to interpret and apply the requirements for fety and efficacy set out in the Community direct**

The Agency strongly enc authorisation holders to follow these guidelines. Applica n guidelines fully in their applications at the time ould seek scientific advice, to discuss any proposed de ent.

- Scientific guidelines
  - Search guidelines
  - Biologicals
  - Clinical efficacy and safety
  - Clinical pharmacology and pharmacokinetics
  - ICH
  - Multidisciplinary
  - Non-clinical
  - Q&A on quality
  - Quality

**Related content**

- Search for scientific guidelines
- Committee for Medicinal Products for Human Use (CHMP)

**Related EU legislation**

- Directive 2001/83/EC
- The rules governing medicinal products in the European Union

**Related documents**

# Pharmaceutical Quality
# Good Manufacturing Practice (GMP)

Information on Drug Substance and Drug Product

- Composition
- Pharmaceutical Development
- Manufacturing Process
- Excipients (for novel excipients specific safety studies are required)
- Control (specification, analytical methods, method validation)
- Container Closure System
- Stability

# Non-clincial Tests
# Good Laboratory Practice (GLP)

- Toxicity (single dose, repeated dose)
- Examination of reproductive function
- Embryo/foetal and perinatal toxicity
- Mutagenic potential
- Carcinogenic potential
- Pharmacodynamics
- Pharmacokinetics
- Local tolerance

# Clincial Trials
# Good Clinical Practice (GCP)

Required studies strongly depend on indication and type of product to demonstrate acceptable efficacy and safety

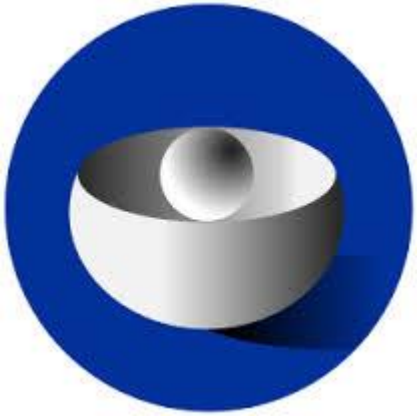
- Bio-pharmaceutics and Associated Analytical Methods
- Clinical Pharmacology Studies
- Clinical Efficacy Studies
- Clinical Safety Studies
- Synopses and Results of Individual Studies

- Special regulations for rare diseases (orphans)

# European Commission Definition of Nanomaterial

- In 2011 the EC published a recommendation on the definition of nanomaterial predisposing size as the critical factor (1-100 nm)
- Acknowledged that an upper limit of 100 nm is not scientifically justified across the whole range of nanomaterials.
- Noted the 'special circumstances prevailing in the pharmaceutical sector' and stated that the Recommendation should 'not prejudice the use of the term "nano" when defining certain pharmaceuticals and medical devices'.
- Review of definition is on-going. The main elements (definition only related to size and particle number size distribution) are planned to remain the same.

# EMA Working Definition of Nanomedicines



- Purposely designed systems for clinical applications
- At least one component at nano-scale size
- Resulting in definable specific properties and characteristics
  - related to the specific nanotechnology application and characteristics for the intended use (route of administration, dose)
  - associated with the expected clinical advantages of the nano-engineering (e.g. preferential organ/tissue distribution)
- And needs to meet definition as a **medicinal product** according to European legislation.

# Nanomedicines authorised in Europe (Examples)

| Tradename/ active substance | Platform/technology | Indication | MAH | Approval |
|---|---|---|---|---|
| **Liposomes** | | | | |
| Caelyx® doxorubicin hydrochloride | API in sterically stabilised (Stealth®) pegylated liposomes | multiple myeloma, ovarian neoplasms, breast neoplasms, Kaposi sarcoma | Janssen-Cilag International N.V. | 21/06/1996 |
| Myocet® doxorubicin | liposome-encapsulated doxorubicin-citrate complex | breast neoplasms | Cephalon Europe | 13/07/2000 |
| Visudyne® verteporfin | liposomal formulation of semisynthetic mixture of porphyrins | degenerative myopia, age-related macular degeneration | Novartis Europharm Ltd. | 27/07/2000 |
| DepoCyte® cytarabine | multivesicular liposomes with unique structure of multiple non-concentric aqueous chambers (DepoFoam®) | meningeal neoplasms | Pacira Limited | 11/07/2001 |
| Mepact® mifamurtide | fully synthetic analogue of a component of *Mycobacterium sp.* cell wall encapsulated in multilamellar liposomes | high-grade resectable non-metastatic osteosarcoma | IDM PHARMA SAS | 06/03/2009 |
| **Nanoparticles** | | | | |
| Rapamune® sirolimus | API particles in nanocrystal colloidal nanodispersion stabilised with poloxamer | prophylaxis of organ rejection in renal transplant | Wyeth Europa Ltd | 13/03/2001 |
| Emend® aprepitant | colloidal dispersion of nanocrystals | nausea and vomiting | Merck Sharp & Dohme Ltd. | 11/11/2003 |
| Abraxane® paclitaxel | solvent-free colloidal suspension of albumin-bound spherical nanoparticles | metastatic breast cancer | Abraxis BioSciences Ltd. | 11/01/2008 |
| Cholib® fenofibrate / simvastatin | nanocrystal colloidal dispersion | dyslipidemias | Abbott Healthcare Products Ltd | 26/08/2013 |
| **Polymer-conjugates** | | | | |
| Macugen® pegaptanib | pegylated modified oligonucleotide | wet macular degeneration | Pfizer Limited | 31/01/2006 |
| **Gas dispersions** | | | | |
| SonoVue® sulphur hexafluoride | sulphur hexafluoride gas as 'microbubbles' dispersion | contrast agent for echocardiography and ultrasonography | Bracco International BV | 26/03/2001 |

National bzw. DCP/MRP:
Eisen-Kohlenhydrat-Komplexe

nature nanotechnology

ANALYSIS

PUBLISHED ONLINE: 24 APRIL 2017 | DOI: 10.1038/NNANO.2017.67

# The evolving landscape of drug products containing nanomaterials in the United States

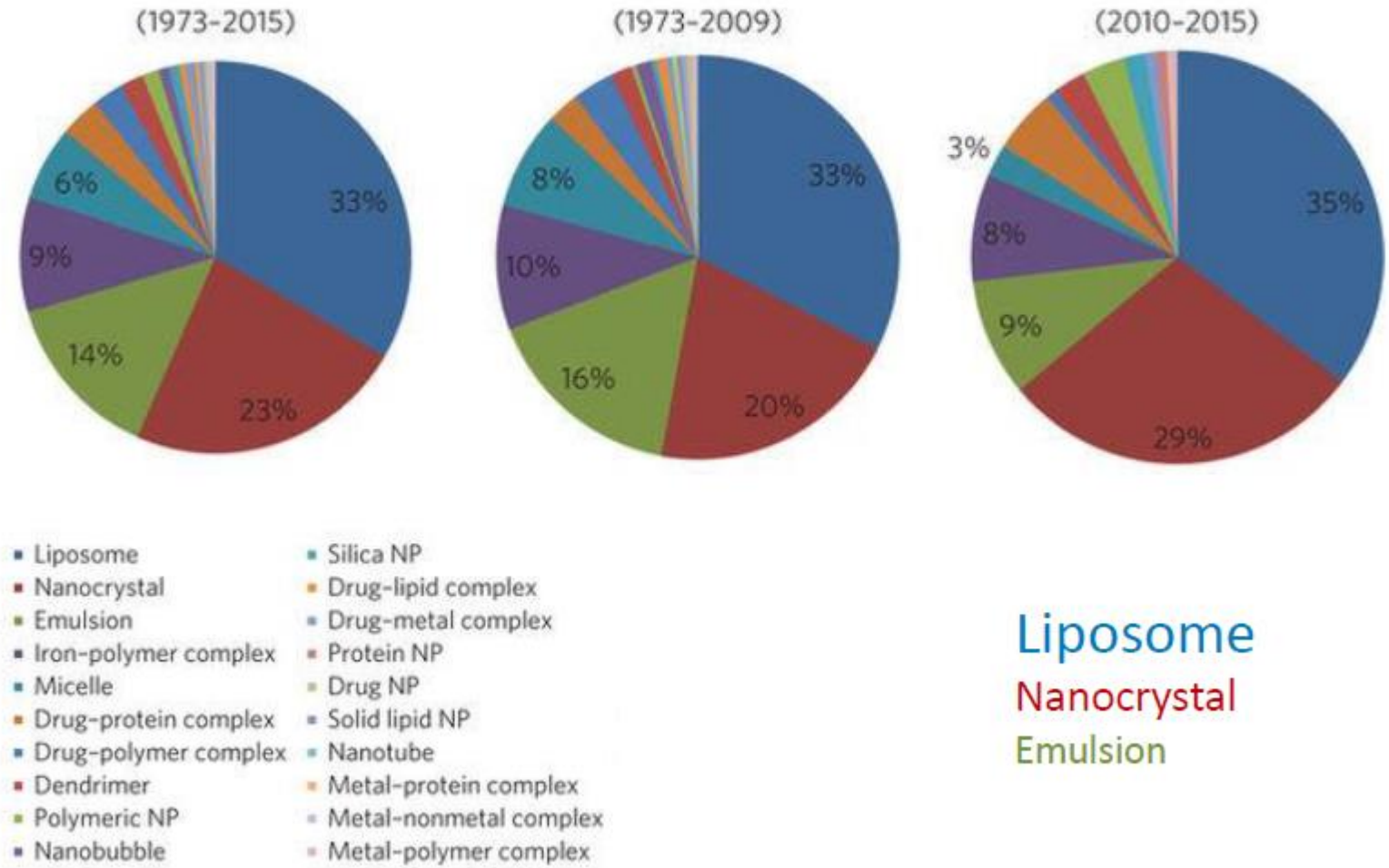
Sheetal R. D'Mello, Celia N. Cruz, Mei-Ling Chen, Mamta Kapoor, Sau L. Lee and Katherine M. Tyner*

**The Center for Drug Evaluation and Research (CDER) within the US Food and Drug Administration (FDA) is tracking the use of nanotechnology in drug products by building and interrogating a technical profile of products containing nanomaterials submitted to CDER. In this Analysis, data from more than 350 products show an increase in the submissions of drug products containing nanomaterials over the last two decades. Of these, 65% are investigational new drugs, 17% are new drug applications and 18% are abbreviated new drug applications, with the largest class of products being liposomal formulations intended for cancer treatments. Approximately 80% of products have average particle sizes of 300 nm or lower. This analysis identifies several trends in the development of drug products containing nanomaterials, including the relative rate of approvals of these products, and provides a comprehensive overview on the landscape of nanotechnology application in medicine.**

# Evolution of Drug Products Containing Nanomaterials

FDA

## Type of Formulation




Liposome
Nanocrystal
Emulsion

S. D'Mello, C.N. Cruz, M. Chen, M. Kapoor, S. Lee, K.M. Tyner. The evolving landscape of drug products containing nanomaterials in the United

# Multidisciplinary Reflection Papers on Nanomedicines Published by EMA

- Data requirements for intravenous **iron-based nano-colloidal products** developed with reference to an innovator medicinal product
- Data requirements for intravenous **liposomal** products developed with reference to an innovator liposomal product
- Development of **block-copolymer-micelle** medicinal products - *Joint MHLW/EMA*
- **Surface coatings**: general issues for consideration regarding parenteral administration of coated nanomedicine products

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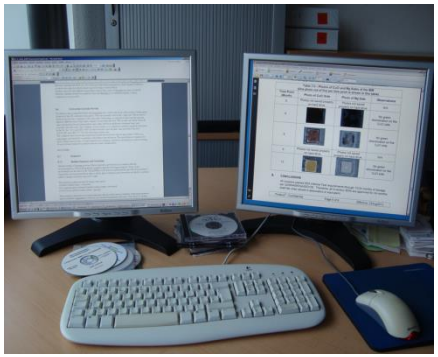
# Regulatory Challenges

- Diversity of products
- Limited experience
- New technologies
- Classification issues between medicinal products and medical devices, food and cosmetics including regulatory implications
- Regulation of products which combine and integrate diagnostic and therapeutic properties
- Advances in nanoscience leading to creation of more complex, hybrid structures

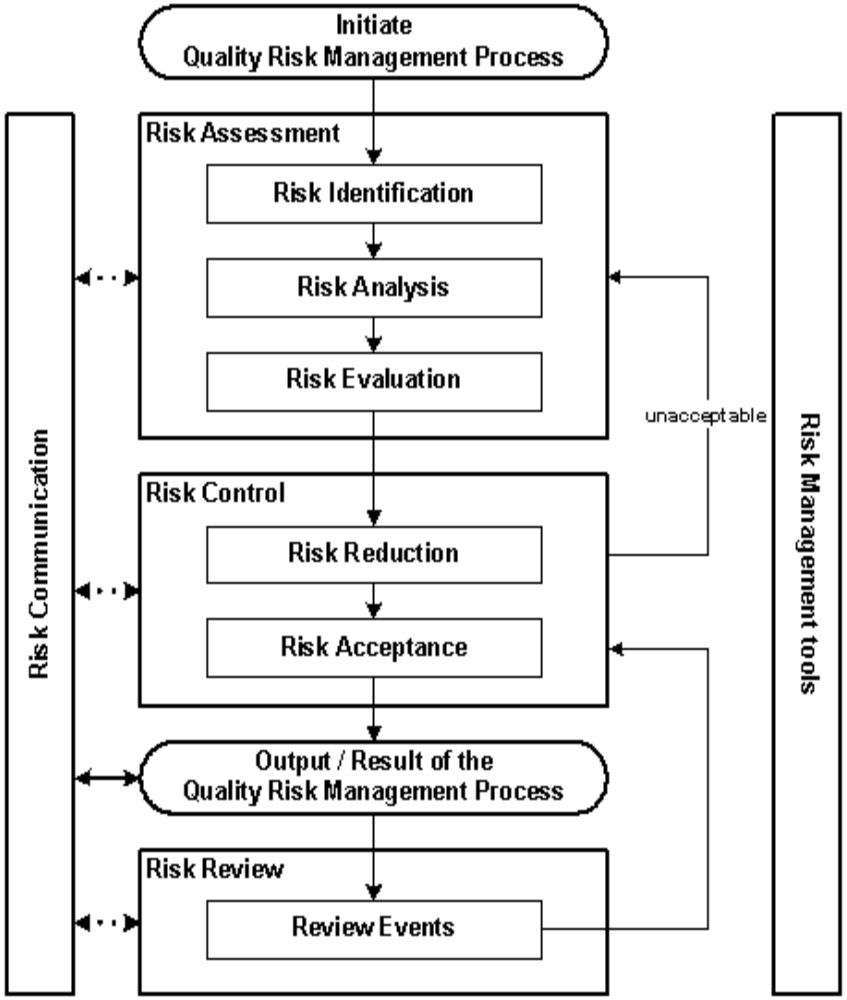


# Risikobewertung - ICH Q9

ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT

Q9



# Kontrollstrategie

- Bewertung des vorhanden Wissens
- Planung von Risikoanalysen und Prozesscharakterisierung
- Durchführung von Prozesscharakterisierungsstudien zur Behebung von Wissenslücken mit hohem Risiko
- Entwicklung einer kommerziellen Kontrollstrategie
- Bewertung und Anpassung der kommerziellen Kontrollstrategie

- Prozessverständnis ist von entscheidender Bedeutung (anstelle von Prozesserfahrung)
- Bewertung von Prozessänderungen in der Entwicklung und Einfluss auf Ergebnisse von Präklinik und Klinik

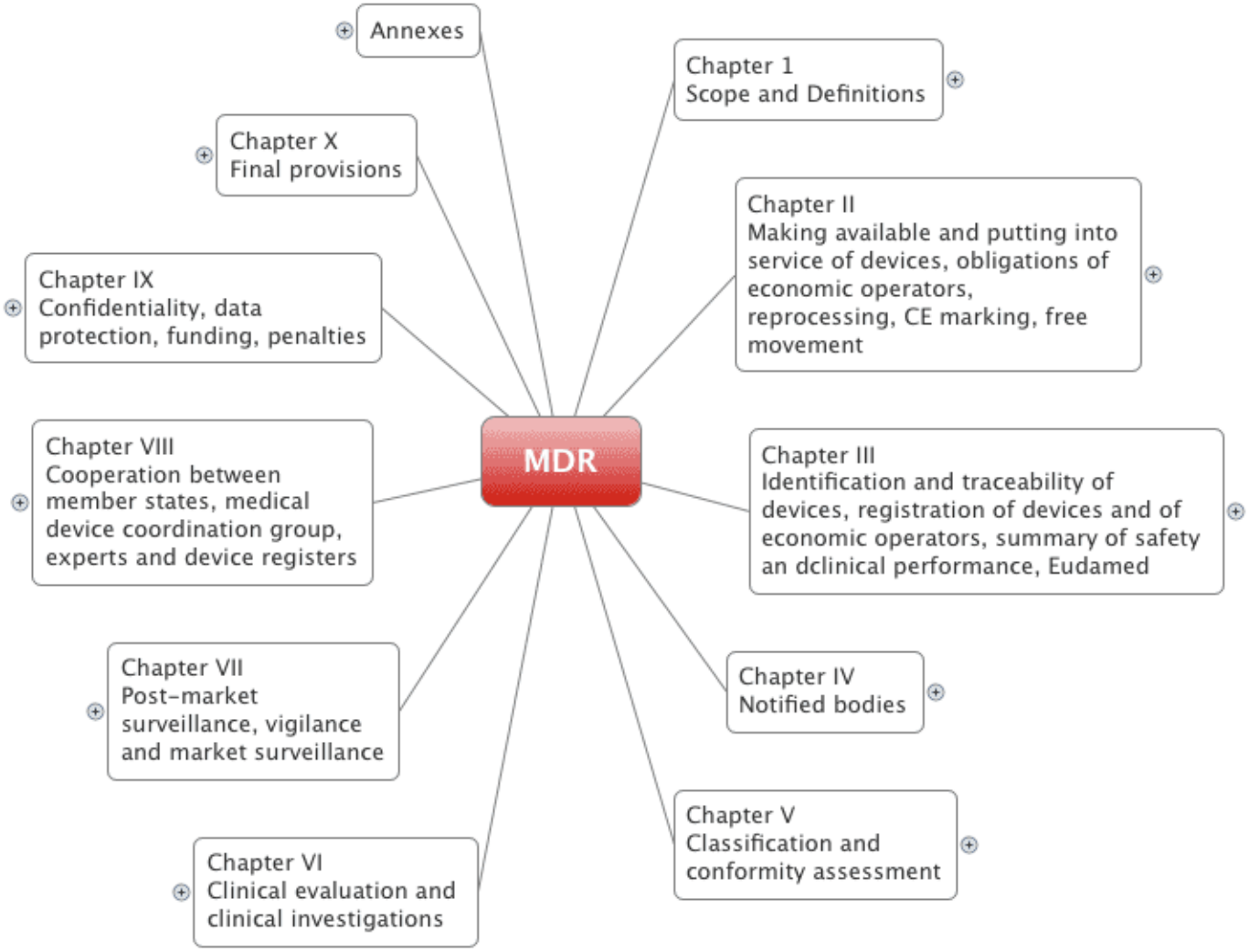
# Medizinprodukte

- Seit 25. Mai 2017 neue europäische Gesetzgebung für Medizinprodukte
  - Übergangsfrist von 3 Jahren
- Medical Device Regulation (MDR, Medizinprodukte-Verordnung)
  - EU 2017/745
- EU-Verordnung über In-Vitro-Diagnostika (IVDR)
  - EU 2017/746

- Frühere Medizinprodukte-Richtlinien:
  - Directive 90/385/EECG (Active implantable medical devices)
  - Directive 98/79/EC (In-vitro diagnostic medical devices)
  - Directive 93/42/EEC (Other medical devices)

- Einteilung in Risikoklassen

# Overview Medical Devices Regulation (MDR)



# Medical Devices – New EU Regulation - Nano

- Risiken und Nutzen der Verwendung von Nanomaterialien in Produkten sind nicht wissenschaftlich geklärt.
- Verwenden Hersteller Nanopartikel, bei denen ein hohes oder mittleres Potenzial für interne Exposition besteht, so sollten sie bei Auslegung und Herstellung der betreffenden Produkte besondere Vorsicht walten lassen.
- Diese Produkte sollten den strengstmöglichen Konformitätsbewertungsverfahren unterzogen werden.
- Sofern sie nicht nur mit unversehrter Haut in Berührung kommen, werden die Produkte so ausgelegt und hergestellt, dass die Risiken in Verbindung mit der Größe und den Eigenschaften der Partikel, die in den Körper des Patienten oder des Anwenders eindringen oder eindringen können, so weit wie möglich verringert werden. Besondere Aufmerksamkeit ist bei Nanomaterialien geboten.

# Medical Devices – New EU Regulation - Nano

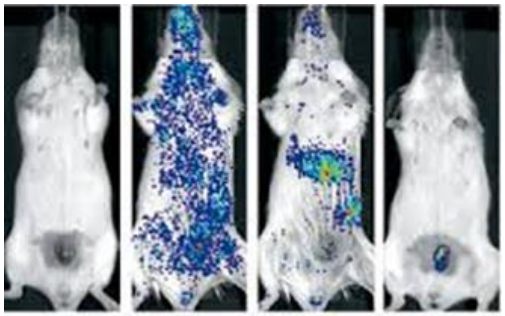
Regel 19

Alle Produkte, die Nanomaterial enthalten oder daraus bestehen, werden wie folgt zugeordnet:

- der Klasse III, wenn sie ein hohes oder mittleres Potenzial für interne Exposition haben;
- der Klasse IIb, wenn sie ein niedriges Potenzial für interne Exposition haben, und
- der Klasse IIa, wenn sie ein unbedeutendes Potenzial für interne Exposition haben.

# Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices

- Veröffentlichung der Europäischen Kommission (SCENIHR) im Januar 2015
- Betrachtung von nanospezifischen Risiken von Medizinprodukten im Rahmen des Konformitätsbewertungsverfahrens
- Abgestuftes Konzept zur Risikobewertung mit 4 verschiedenen Phasen
  - Bewertung des Potentials des Medizinprodukts zur Freisetzung von Nanopartikeln
  - Bestimmung der Verteilung sowie das Persistenzpotential der Teilchen
  - Toxikologische Bewertung
  - Finale Risikobeschreibung
- Potentielles Risiko von Nanomaterialien in Medizinprodukten ist im wesentlichen durch die Freisetzung freier Nanopartikel und die Dauer der Anwendung bestimmt

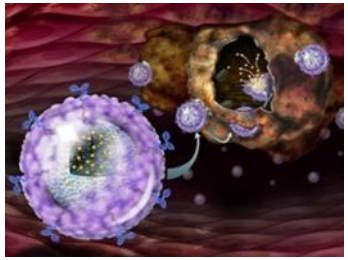


# Wissenschaftliche Beratung - Scientific Advice

- Nationaler Scientific Advice durch BfArM und PEI
- Zentraler Scientific Advice durch die EMA
- Optimierte Entwicklungsprogramme durch fortgesetzten Dialog
- Verkürzt durchschnittliche Zeit zur Zulassung
- Höhere Chancen für positive Entscheidungen
- Neuartige Therapien und KMUs erhalten speziellen Support
- Umfassende Information auf der BfArM-Homepage
- Beratung in der Entwicklungsphase oder vor Antragsstellung
- 2017: 292 abgeschlossene Verfahren
- Relativ geringe Kosten für nationale Beratung

# European Regulatory Agencies Position on Nanomedicinal Products

- Die Zulassung von „nanomedizinischen“ Arzneimitteln und das Vigilanzsystem für „nanomedizinische“ Arzneimittel und Medizinprodukte stellt besondere Anforderungen
- Die Risikobewertung umfasst die wirksame In-Vivo-Form (Darreichungsform, biologische Umwandlung, freie Partikel)
- Im Vordergrund der Bewertungen stehen die spezifischen Eigenschaften sowie die Art der Anwendung
- Die vorhandenen Werkzeuge der Bewertung der Qualität, Pharmakologie-Toxikologie und Klinik kommen zum Einsatz und werden derzeit als ausreichend erachtet
- Generierung von Expertise bei Zulassungsbehörden
- Identifikation von Bedarf für neue Guidelines / Reflection Papers
- Frühzeitige Beratung / Scientific Advice
- Internationale Zusammenarbeit der Behörden



# Thank you for your attention !

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The views expressed in this presentation are those of the speaker and do not necessarily represent those of the BfArM and other European Regulatory Agencies