General requirements for the approval of nanomedical products

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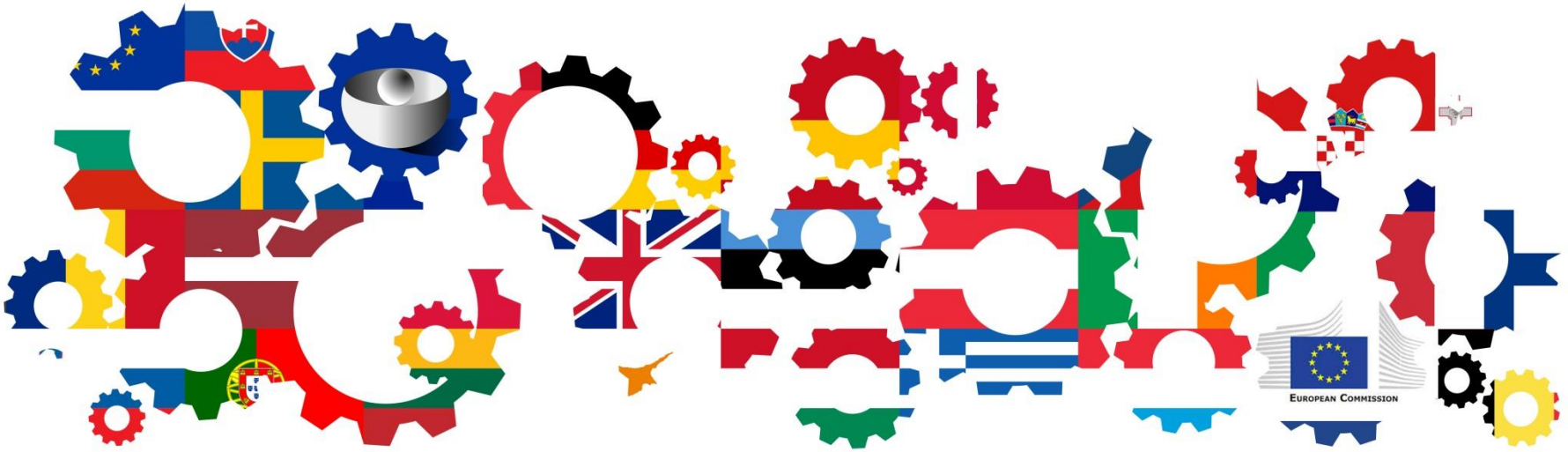
The European medicines regulatory network



~ 50 national regulatory authorities European Commission European Medicines Agency

Classification Issues

Primary intended purpose achieved by one of the following means:

PHARMACOLOGICAL
METABOLIC
IMMUNOLOGICAL
(and All ATMPs)
(and All *in vivo* diagnostics)

↓

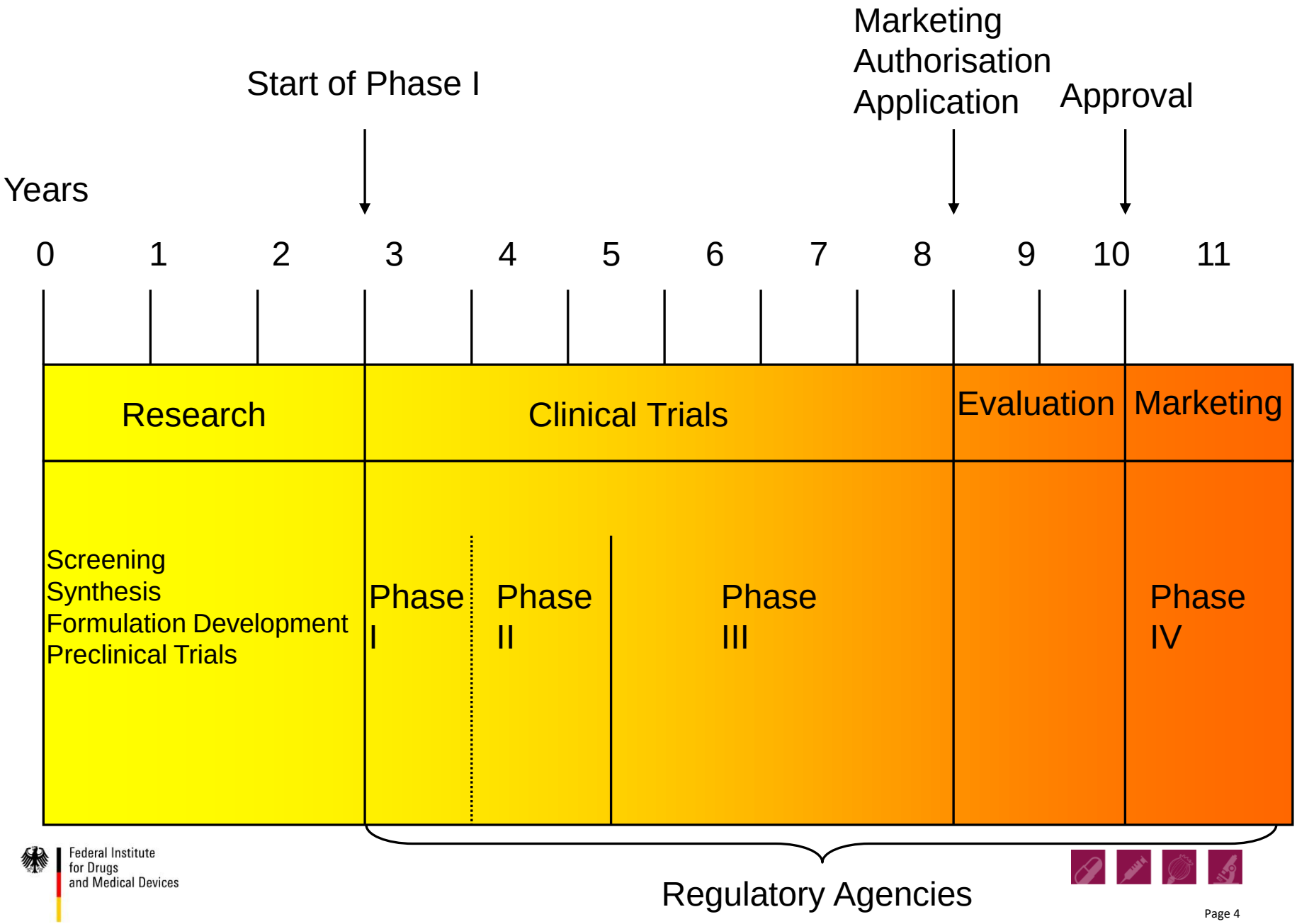
Medicinal Product

Primary intended purpose achieved by other means:

PHYSICAL
SIMPLE CHEMICAL
MECHANICAL
DIGITAL

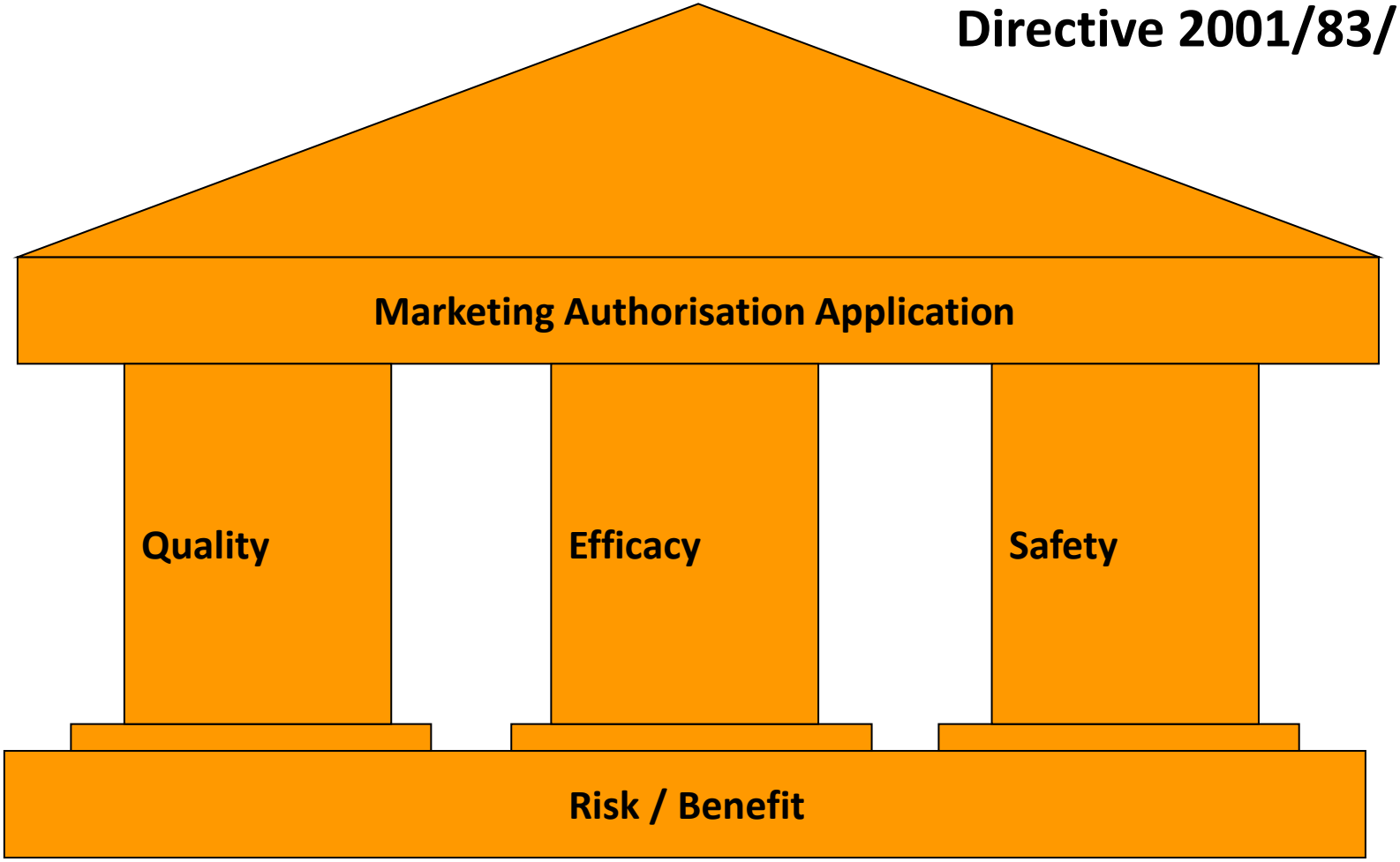
↓

Medical Device
Or Active Implantable Medical Device



Federal Institute for Drugs and Medical Devices

Directive 2001/83/EC



+ Pharmacovigilance: Risk Management System / Risk Management Plan

National Rules of Pricing and Reimbursement

Pharmaceutical Quality
Good Manufacturing Practice (GMP)

- Information on Drug Substance (active ingredient / API) and Drug Product
  - Composition
  - Pharmaceutical Developement
  - Manufacturing Process
  - Excipients (for novel excipients specific safety studies are required)
  - Control (specification, analytical methods, method validation)
  - Container Closure System
  - Stability
- Special requirements for biologics

Non-clincial Tests
Good Laboratory Practice (GLP)

The toxicological and pharmacological tests must show:

- the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings
- the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings

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

Clinical 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
- Clinical Safety
- Synopses and Results of Individual Studies

Special regulations for orphan diseases

Clinical Trials – Phase I to Phase III

When an acceptable safety profile has been established for a new drug in pre-clinical or non-clinical studies in animals development moves to the clinical phase.

- **In Phase I trials usually in healthy volunteers the safety and dosing is determined.**
  - 20 – 80 subjects
  - Patients e.g. for oncological indications
- **Phase II trials are used to establish the efficacy of the drug in a small patient cohort usually against a placebo.**
  - 50 – few hundred subjects
  - Proof of concept
  - Dose finding
  - Defining patient population
- **In Phase III trials, the treatment is given to large groups of patients to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.**
  - 1000 to million patients

CTA – Clinical Trial Application

- Application Form
- Protocol
- Investigators Brochure
- Investigational Medicinal Product Dossier (IMPD)
- Labelling
- GMP Certificates / Importing Licences
- Insurance for Patients / Volunteers
- Involvement of Ethic Committee

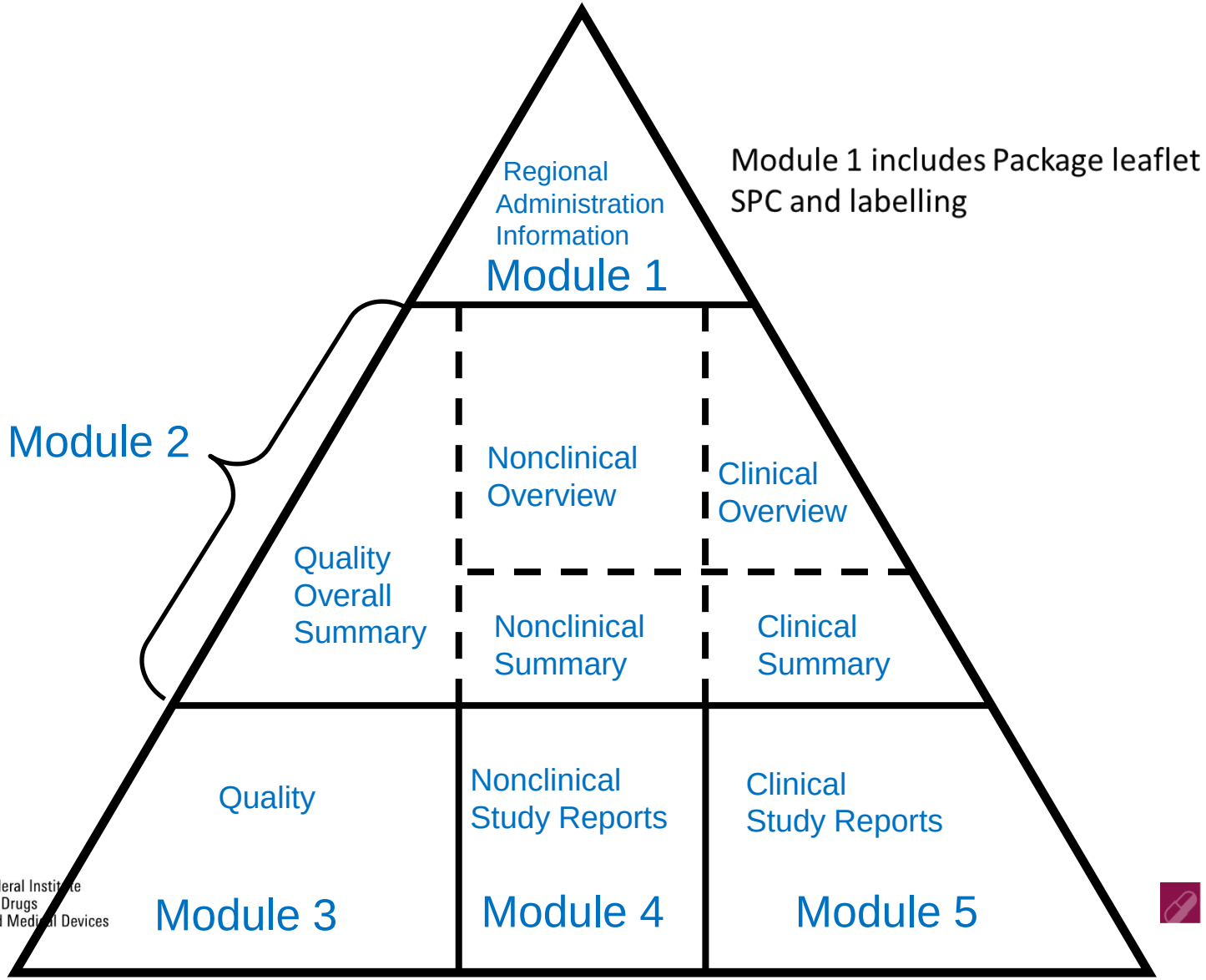
Phase I / First in man

TeGenero Case – March 2006

First in man study
Same dose given to 6 volunteers simultaneously
Multiple organ failure
No intensive care at study site
Three weeks coma for one volunteer
Up to 12 weeks hospitalisation

Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07 Rev. 1)

Registration Dossier
CTD – Common Technical Document



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).

Multidisciplinary: nanomedicines

Share

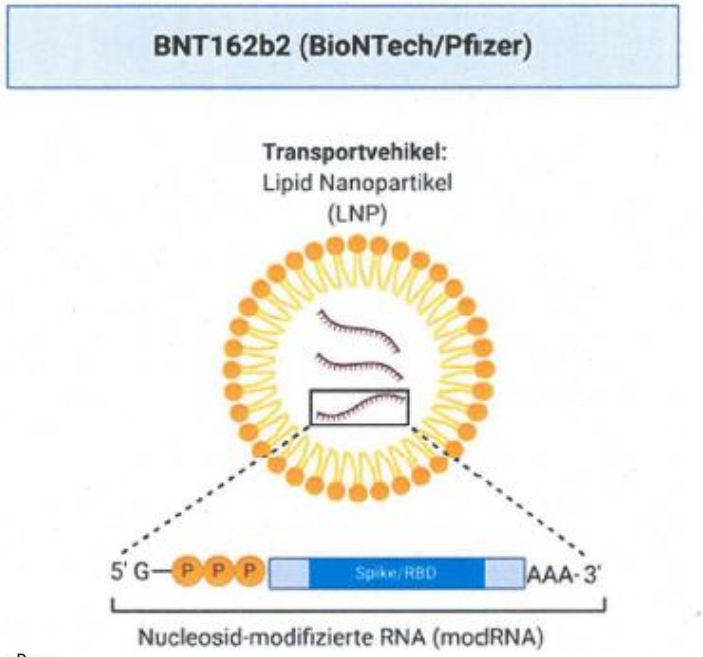
The European Medicines Agency's scientific guidelines on nanomedicines help medicine developers prepare marketing authorisation applications for human medicines.

For a complete list of scientific guidelines currently open for consultation, see Public consultations.

- 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
- Surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products

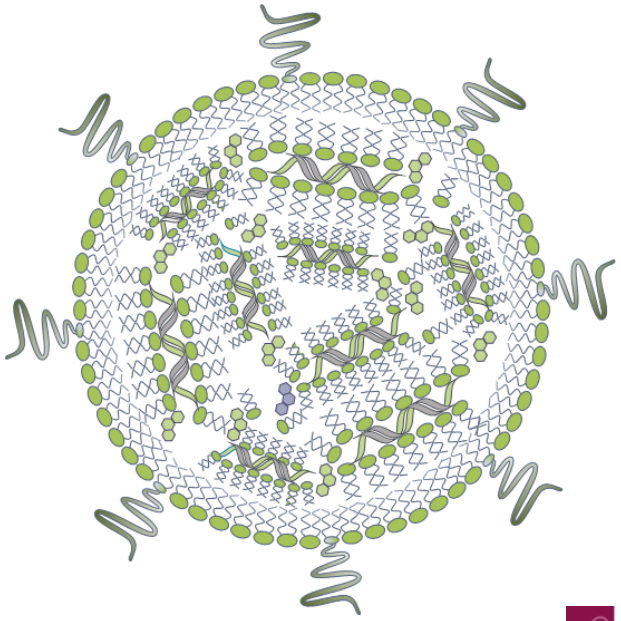
Nanomedicine

With the recent release of highly effective vaccines for the SARS-CoV2 virus based on lipid nanoparticle/mRNA technology, the spotlight shines once again on the nanomedicine field. Slow but continuous progress has been achieved over the past two decades in this still emerging biomedical area, with occasional high-profile break-throughs.



Quelle: Gelbe Liste

Onpattro (siRNA)



Quelle: Sanofi-Genzyme

Patient – Product - Process

Patient

Medicinal Product

Formulation and Process

Efficacy
Safety

Critical Quality Attributes (CQAs)

Material Attributes
Critical Process Parameters (CPP)

Defining the Control Strategy

- Existing knowledge evaluation
- Risk assessments and process characterisation planning
- Execution of process characterisation studies to address high risk knowledge gaps
- Development of commercial control strategy
- Evaluation of commercial control strategy

- Quality attribute assessment is based on information obtained from analytical testing, non-clinical and clinical studies, and requirements for the drug product manufacturing process

- Analytical testing is crucial in defining the control strategy

Critical Quality Attributes

- Some attributes are relevant irrespective of whether the formulation is a nanomedicinal product or not and have to be addressed in pharmaceutical development studies
  - Appearance, assay, purity, particulate matter, sterility, bacterial endotoxines, deliverable volume, pH, osmolality etc.
- Nano-related attributes
  - Case by case (depends on nanosystem and dosage form)
  - Different for e.g. liposomes, pegylated liposomes, lipid nano particles, iron sucrose complexes, nano-emulsions, nano-crystals etc.
- Control strategy also addresses testing of materials (raw materials, excipients and active ingredient)
- Supplier qualification
- Changes during development → comparability approach according to basic principles described in ICH Q5E

Scientific Challenges

- Characterisation and stability
- Applicability and relevance of current methods to assess characterisation and biodistribution
- Functionalities of the nanosystems, bio-interface and reactivity of the final product including coating and “excipients”
- Link between quality attributes and potential toxicity
    - Increased reactivity, surface issues, crossing biological barriers, specific degradation products and unanticipated toxic effects
- Risk characterisation
- Subtle changes in composition and/or physicochemical characteristics of nanomedicines could result in substantial changes in the pharmacology and toxicity
- Upscaling and transition to GMP processes
    - Manufacturing
    - Analytical routine release methods

Critical Quality Attributes

- Size
- Size distribution or polydispersity index
- Shape / morphology
- Surface charge
- Surface composition
- Encapsulation efficiency
- Non-encapsulated active pharmaceutical ingredient
- Release (in-vitro dissolution test)
- Polymer molecular weight
- Polymer biodegradability
- Interaction with biological medium
- Conjugation chemistry
- Aggregation / Agglomeration
- In-use stability / compatiblity with e.g. devices

Scientific Advice in Europe by EMA and National Authorities

- Optimise medicine development programmes through ongoing dialogue
- Reduce time for approval of marketing authorisation applications
- Increase chances for positive outcome
- Emerging therapies and SMEs will benefit from specific support
- Follow-up advice is appreciated to ensure continuity and bridging the gap between clincal phases and marketing authorisation
- EMA:
  - 2005: 194
  - 2010: 400
  - 2015: 510
  - 2019: 674

Scientific Advice in Europe by EMA and National Authorities

National Agencies (BfArM: 345 procedures in 2019)

- Open interactive discussion for efficacy, safety, quality and regulatory issues
- Gives you a national opinion
- You see your assessors
- Costs (e.g. BfArM 200 – 10,000 Euro)

http://www.bfarm.de (Advice procedures)

Sometimes helpful to visit more agencies in Europe

EMA Support for SMEs

- SME-Office
- Direct assistance by phone, email, teleconference or through briefing meetings on regulatory aspects of the pharmaceutical legislation
- SMEs receive help on how to navigate the array of services available, support in identifying the most relevant guidance, or advice on regulatory strategy for a product development or authorisation
- SME User Guide
- Workshops and Training Sessions (Presentations available on www.ema.europa.eu)
- Newsletter
- Fee Incentives (e.g. for Scientific Advice (up 90% !)

  Standard rate from €44,400 to €89,000

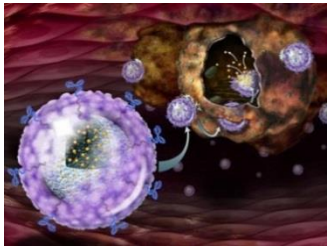
- 1912 registered companies (End of 2020)

EMA's Innovation Task Force (ITF)

- Multidisciplinary group that includes scientific, regulatory and legal competences
- Forum for early dialogue with applicants on innovative aspects in medicines development
- Identify the need for specialised expertise at an early stage with the Agency's committees and their working parties
- ITF briefing meetings are intended to be much earlier than when one would normally seek scientific advice
- ITF briefing meetings facilitate informal exchange of information and guidance in the development process
- To help ensure EMA awareness and preparedness for assessment of the most recent developments in innovative medicine

Conclusion - European Regulatory Agencies Position on Nanomedicinal Products

- Evaluation of any nanomedicine based on established principles of benefit/risk analysis, rather than solely on the basis of the technology per se (including Risk Management Plans and Environmental Risk Assessment)
- The current regulatory framework is sufficiently robust to evaluate and authorize nanomedicinal pharmaceuticals as specific scientific expertise is involved and experts are consulted
- Specific properties of new nanomedicinal products will be reviewed
- Route of administration is essential
- Additional studies not yet described in current guidelines may be required on a case-by-case basis
- Continued evaluation on the need for additional guidance
- Interaction with regulatory agencies and scientific advice at an early stage



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