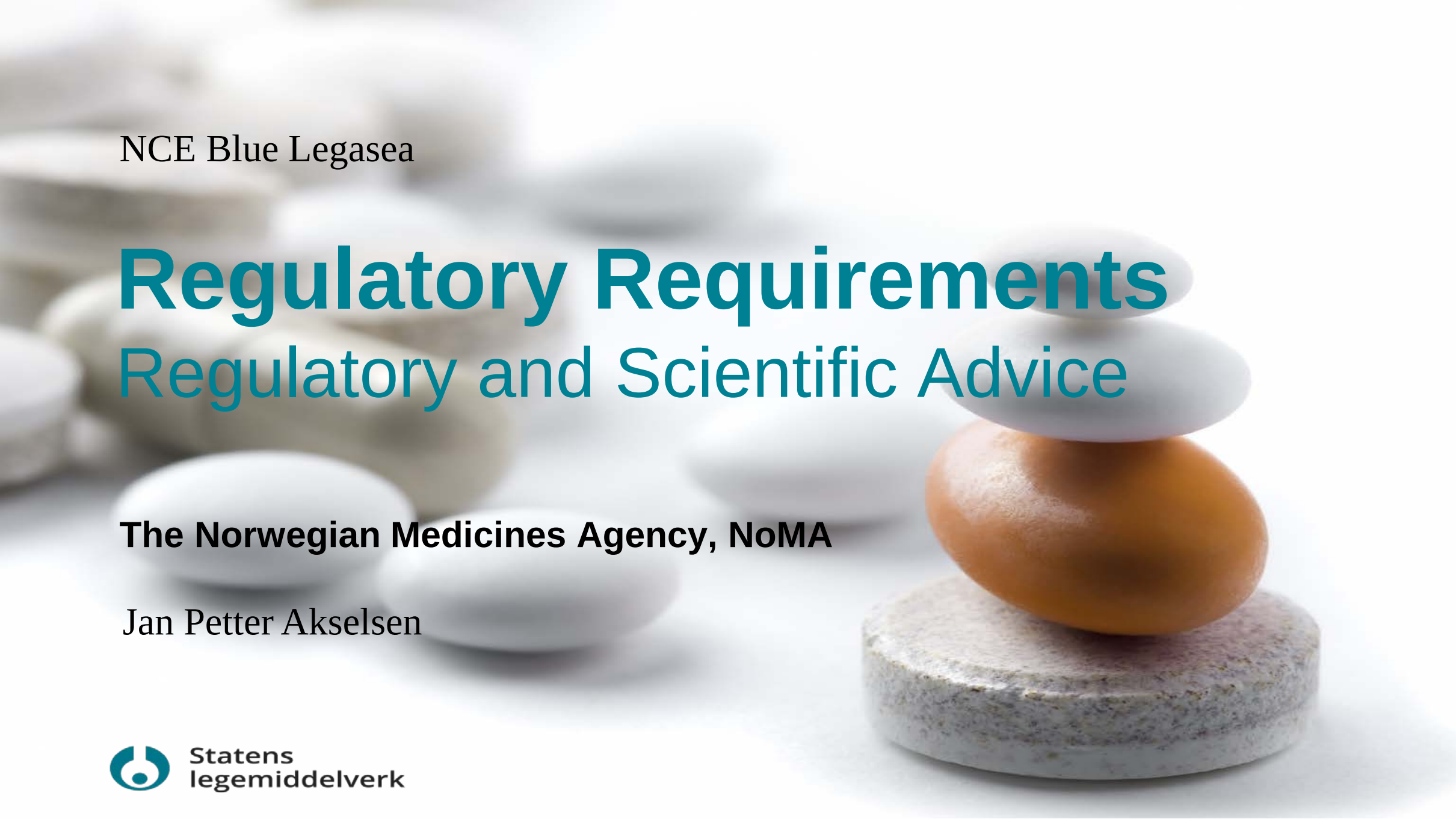
NCE Blue Legasea

Regulatory Requirements

Regulatory and Scientific Advice



The Norwegian Medicines Agency, NoMA

Jan Petter Akselsen

Statens legemiddelverk

Content

- Medicines Authorities; Structure and Roles. Politics
- Regulations, Marketing Authorisation
- Drug Development
  - Classification, quality, pre-clinical and clinical trials
- Medical Devices
- Scientific Advice and Innovation Support
- Questions and Discussion

Regulation of Medicinal Products

From Research to Patients…..

Research and Development
Q, Non-clin., Clin I,II,III

SA and dialog

B/R MA

C/B
Start using

Continued evaluation during use

Methods, data, required evidence vs. medical need, R/R and B/R FIH, f II, III GMP

SPC with documented indication, contraindications, dose, precautions

High cost Prioritization!

Patients and Public Health

The Norwegian Medicines Agency (NoMA)

- ✓ 320 Employees
- ✓ Covering all aspects in regulation of Medicinal Products
- ✓ Partner in EU-network
- ✓ Cost/benefit and HTA
- ✓ Medical Device
- ✓ Advice and Support

Regulates based on;
-National law and regulation
-EU directives and regulations
-EU guidelines
-Scientific experience and knowledge

New political priorities

- Secure optimal quality in drug therapies
- Equal and fast access to new medicinal products
- Low prices on pharmaceuticals

- Create good environments for research and innovation

- Help business development and creation of new jobs !!

Who takes decisions in Norway?

Stortinget

European Commission

Ministry of health and care

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Decision Forum
-Directors from all Health Enterprises

Statens legemiddelverk
Norwegian Medicines Agency

Use and Pay

Prescriber
Patient

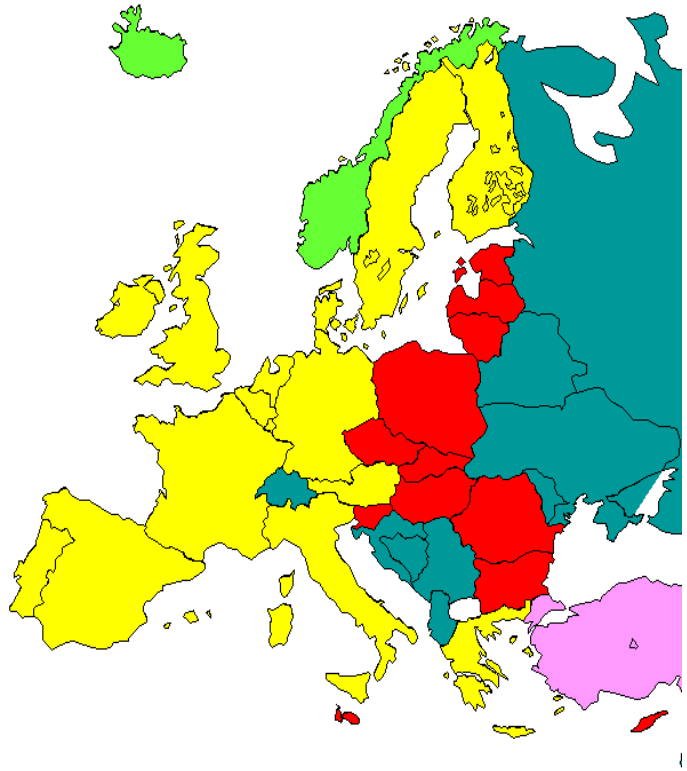
MA and Reimbursement

European work sharing

- ✓ **National Authorities working in EU-network**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

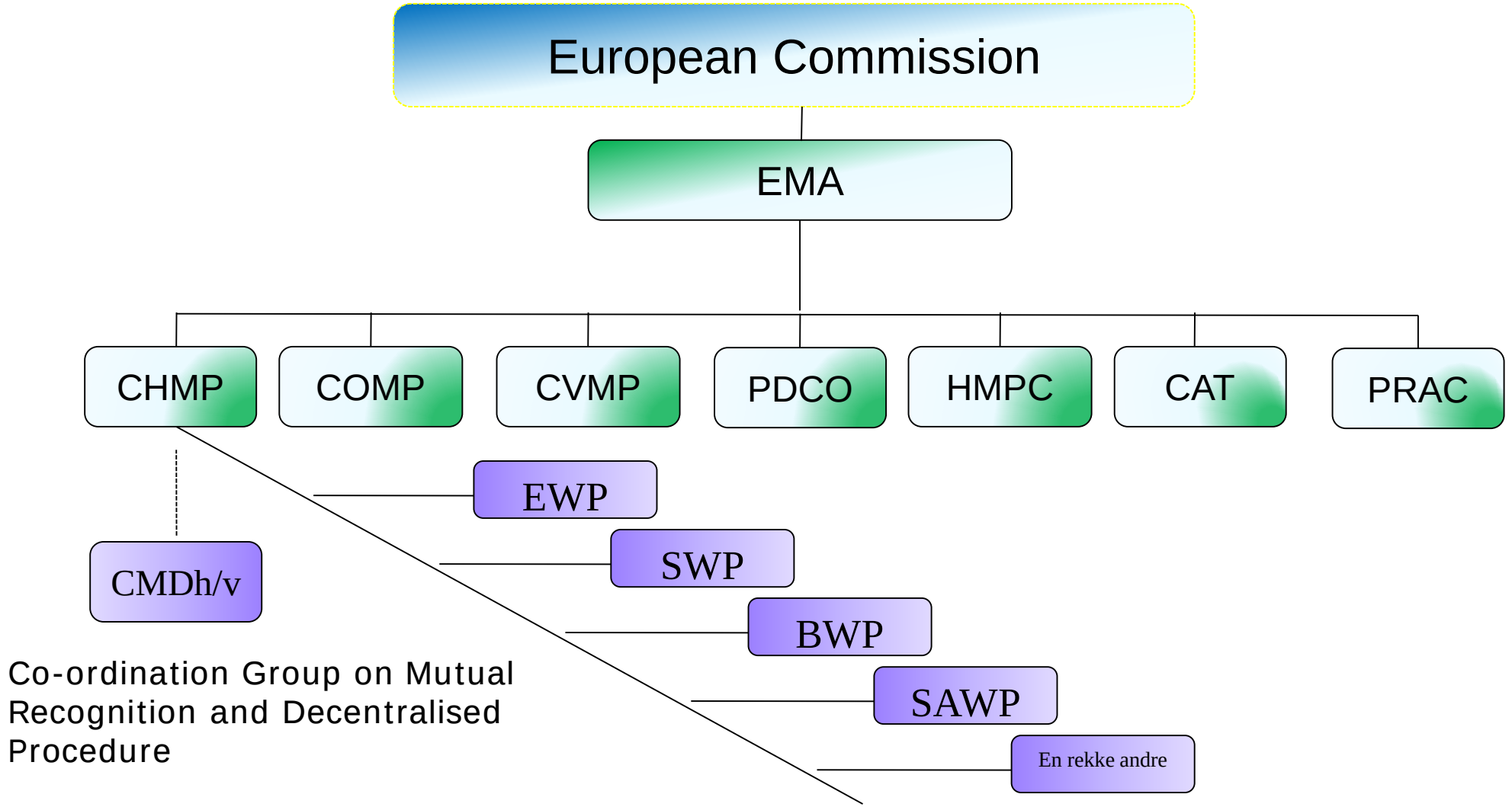
CHMP/CVMP/CAT
Committee for Medicinal Products for Human Use/Veterinary Use/ATMP



- ✓ **EEA-agreement 2000;**
  Norway fully participate in the «drug-democracy»

- ✓ **Brexit !**

European Network



European Medicines Agency

Mission statement

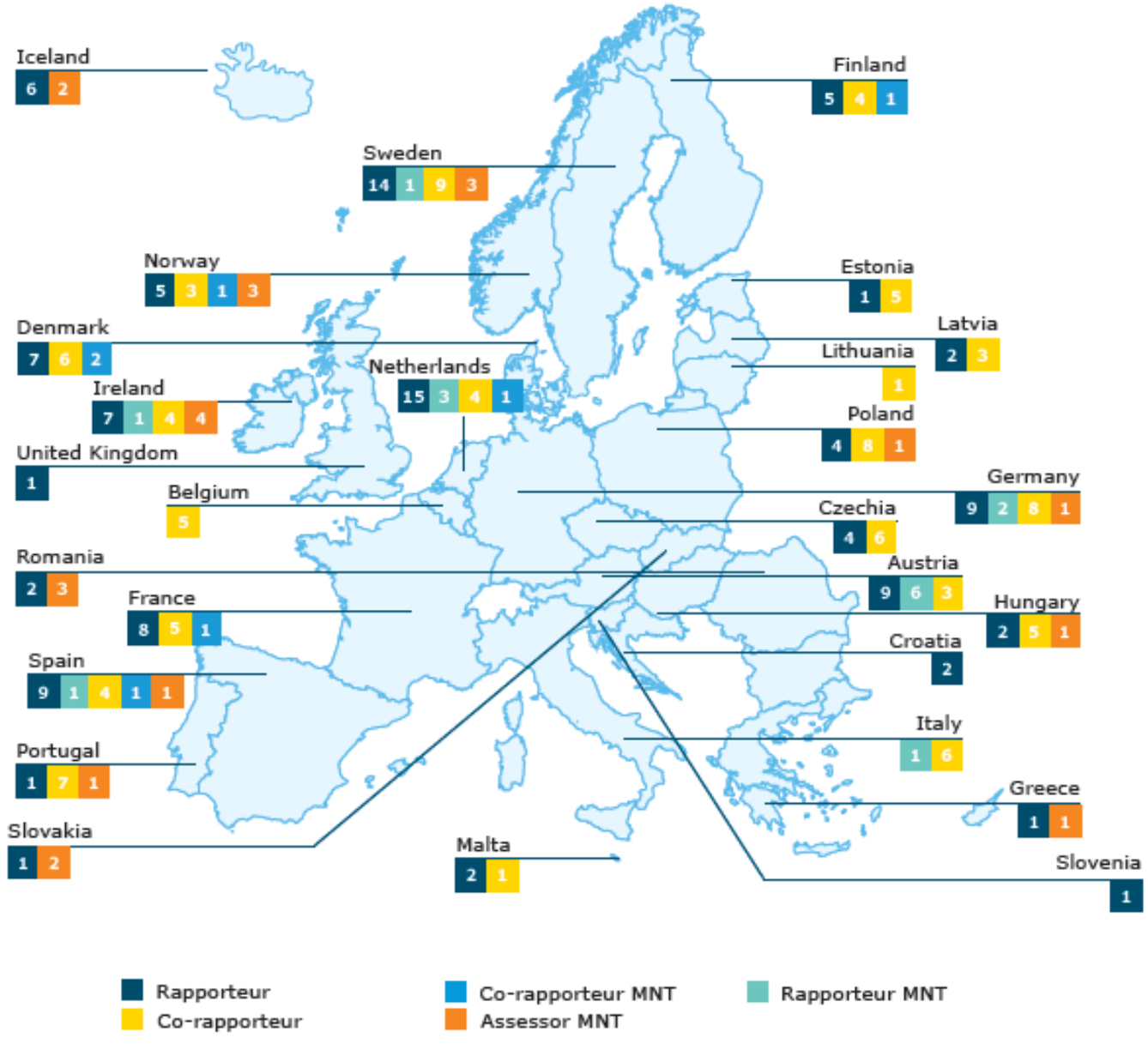
- The mission of the European Medicines Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

NoMA fully engaged in the EU-network

- Marketing Authorisation Applications (incl. Variations)
- Central Scientific Advice
- Pharmaco Vigilance
- Development of Guidelines and Regulations

- Soon: Common Procedure for Clinical Trials

CP i 2018


Iceland
6 2
Finland
5 4 1
Sweden
14 1 9 3
Norway
5 3 1 3
Estonia
1 5
Latvia
2 3
Lithuania
1
Denmark
7 6 2
Netherlands
15 3 4 1
Ireland
7 1 4 4
Poland
4 8 1
United Kingdom
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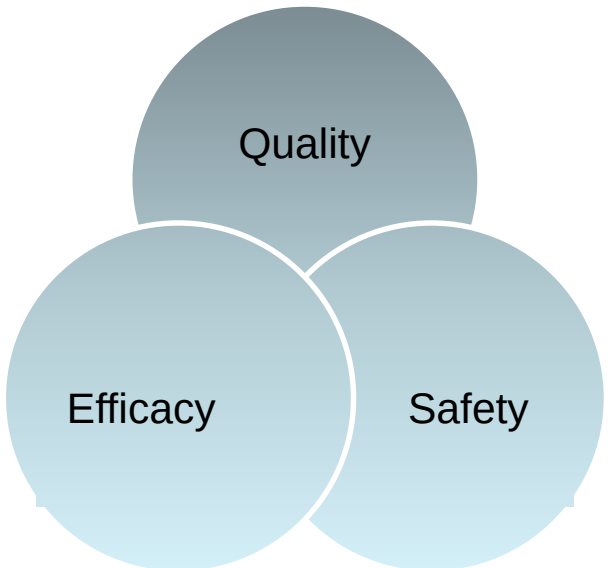
Germany
9 2 8 1
Belgium
5
Czechia
4 6
Romania
2 3
Austria
9 6 3
France
8 5 1
Hungary
2 5 1
Croatia
2
Spain
9 1 4 1 1
Italy
1 6
Portugal
1 7 1
Greece
1 1
Slovakia
1 2
Malta
2 1
Slovenia
1
Rapporteur
Co-rapporteur
Co-rapporteur MNT
Assessor MNT
Rapporteur MNT

Marketing Authorisation (MA)

- Medicinal products need marketing authorisation before launch in the market
- Robust; quality, safety and efficacy documentation required



Evaluation for MA

Continues in the whole life cycle

Different Procedures for Marketing Authorisation

- National Procedure- NP
  - *Mutual Recognition Procedure- MRP*
- Decentralised Procedure - DCP
- Centralised Procedure - CP

- New Indications
- Changes to the SPC*

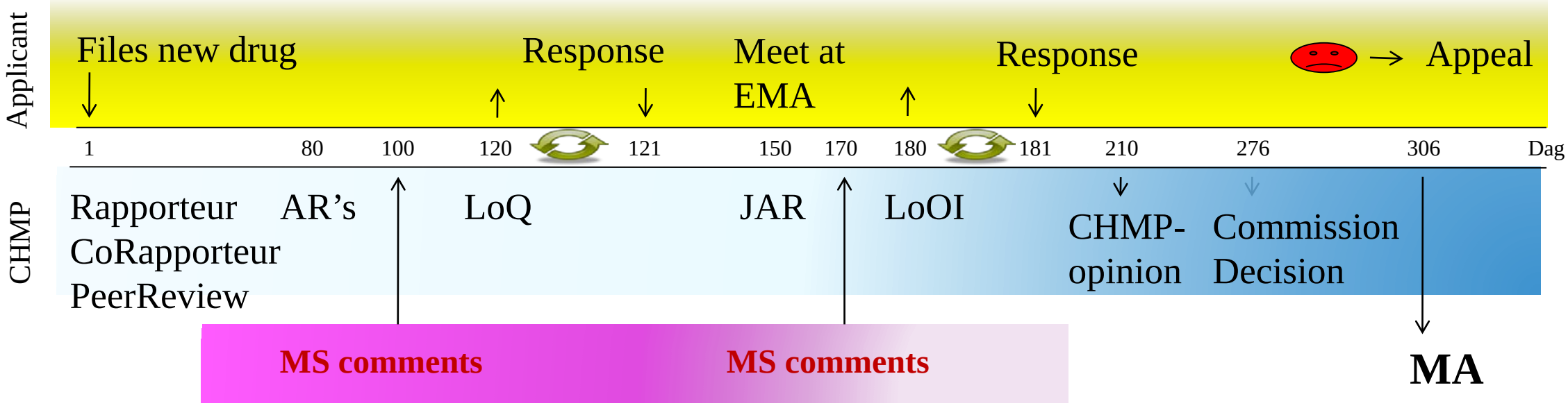
European and National Law and Regulations

*Summary of Product Characteristics

European Marketing Authorisation

✓ Central Procedure (CP), 1995 in EU, 2000 in Norway

- Mandatory for several therapeutic areas and classes of medicinal products
- For most new innovative drugs
- Application filed to EMA
- Decision valid for whole EEA



Approvals in 2018

All New Approvals in CP

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Human medicines highlights 2018

Authorisation of new medicines

Key figures on the European Medicines Agency's (EMA) recommendations for the authorisation of new medicines in 2018:

84 Positive opinions

42 New active substances

5 Negative opinions

10 Withdrawn applications

3 Advanced therapy medicinal products

21 Orphan medicines

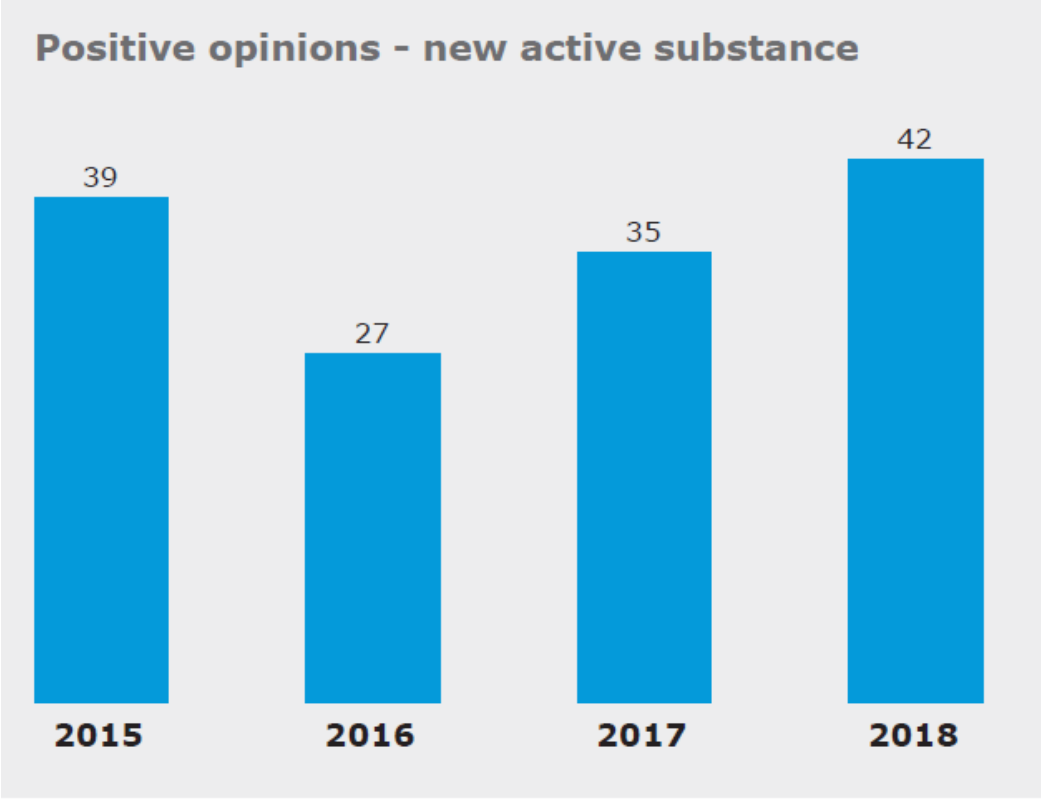
4 Accelerated assessments

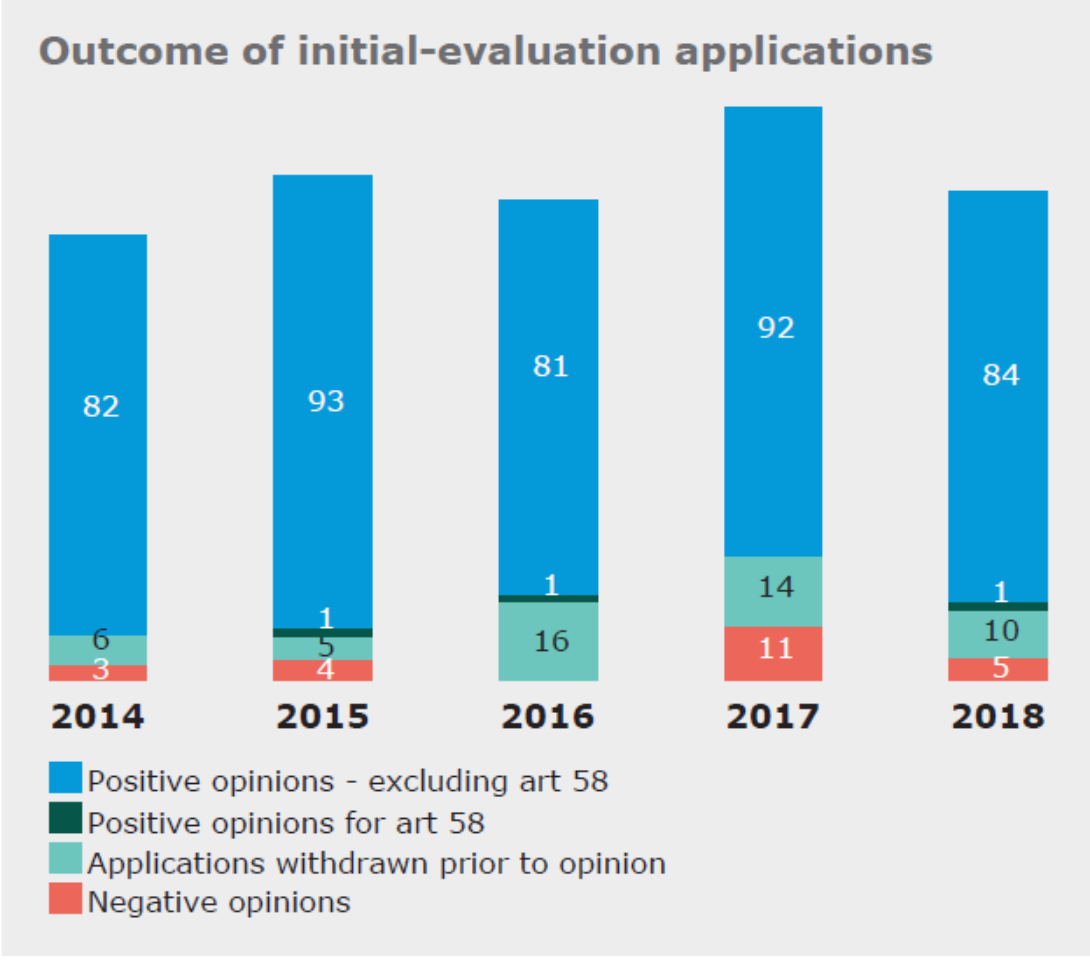
1 Conditional marketing authorisations

3 Approval under exceptional circumstances

See more on the new recommendations from page 2.

Approvals in 2018

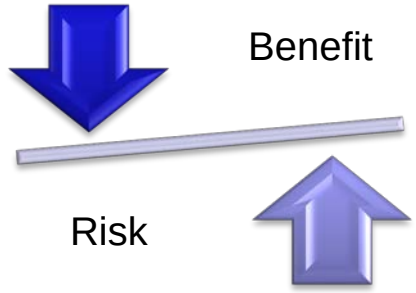




+ 67 variations in indication

Assessment of benefit / risk

- ✓ Risk risk trade-off ?
  - ✓ how much risk is acceptable for a given or anticipated benefit?
  - ✓ how much uncertainty is acceptable at the time of marketing authorization?



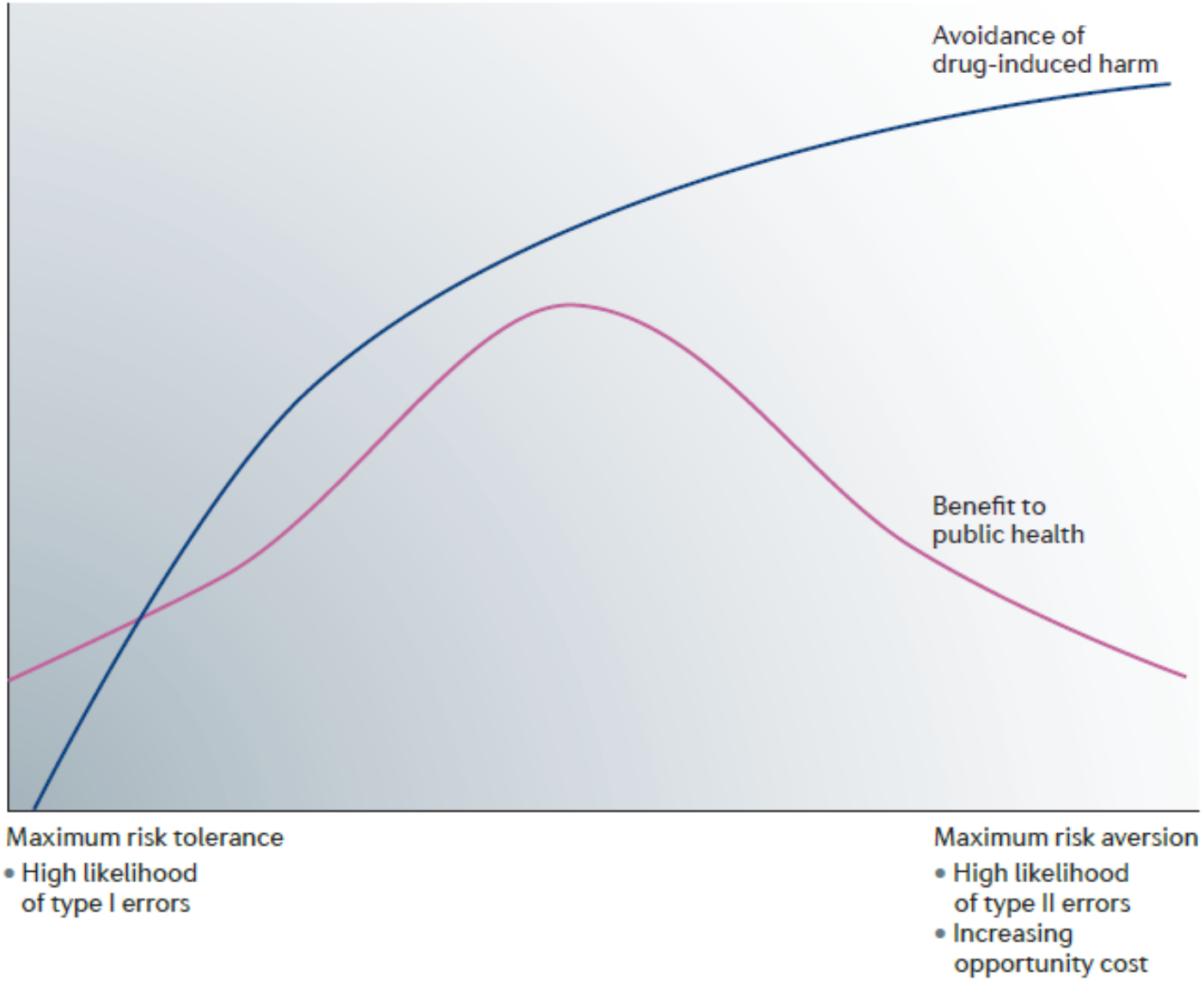
Can the benefit/risk documentation be trusted ?

-Pharmaceutical quality
-Preclinical and mode of action
-Clinical trial design, selection of patients, dose used, comparator, endpoints (are the endpoint clinically relevant ?)
-Are trials conducted according to GCP and outcome from inspections?
-Safety system and documentation

OPINION

The risks of risk aversion in drug regulation

Hans-Georg Eichler, Brigitte Bloechl-Daum, Daniel Brasseur, Alasdair Breckenridge, Hubert Leufkens, June Raine, Tomas Salmonson, Christian K. Schneider and Guido Rasi



Decisions for Marketing Authorisation

- Based on;

✓ Scientific assessment in EU-network
Quality, efficacy and safety. RMP

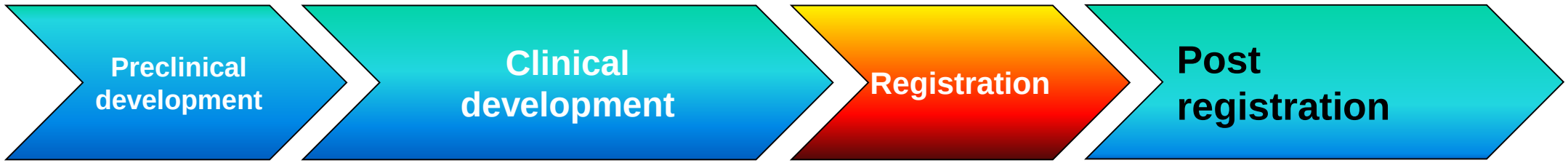
✓ The basis for decision
Benefit vs. risk

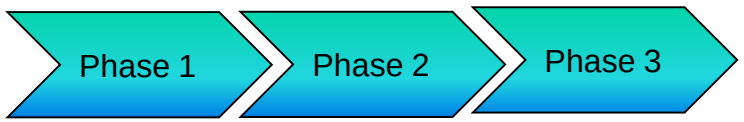
✓ MA includes….
SPC, PV and labelling

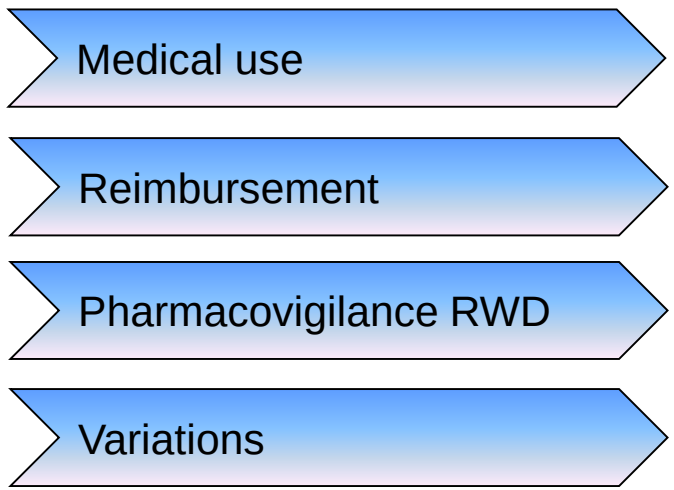
Key to legal marketing!

✓ Reason for refusal
”Potential serious risk for human health”

Drug Development

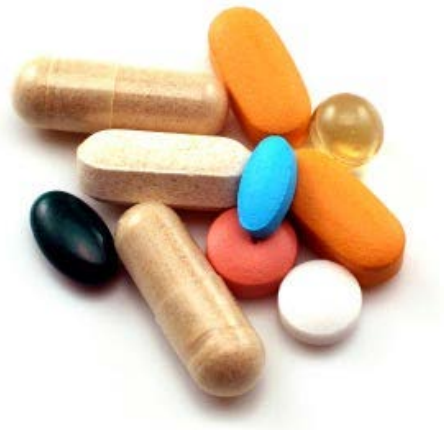






..a structured process!

Is my product a medicinal product?

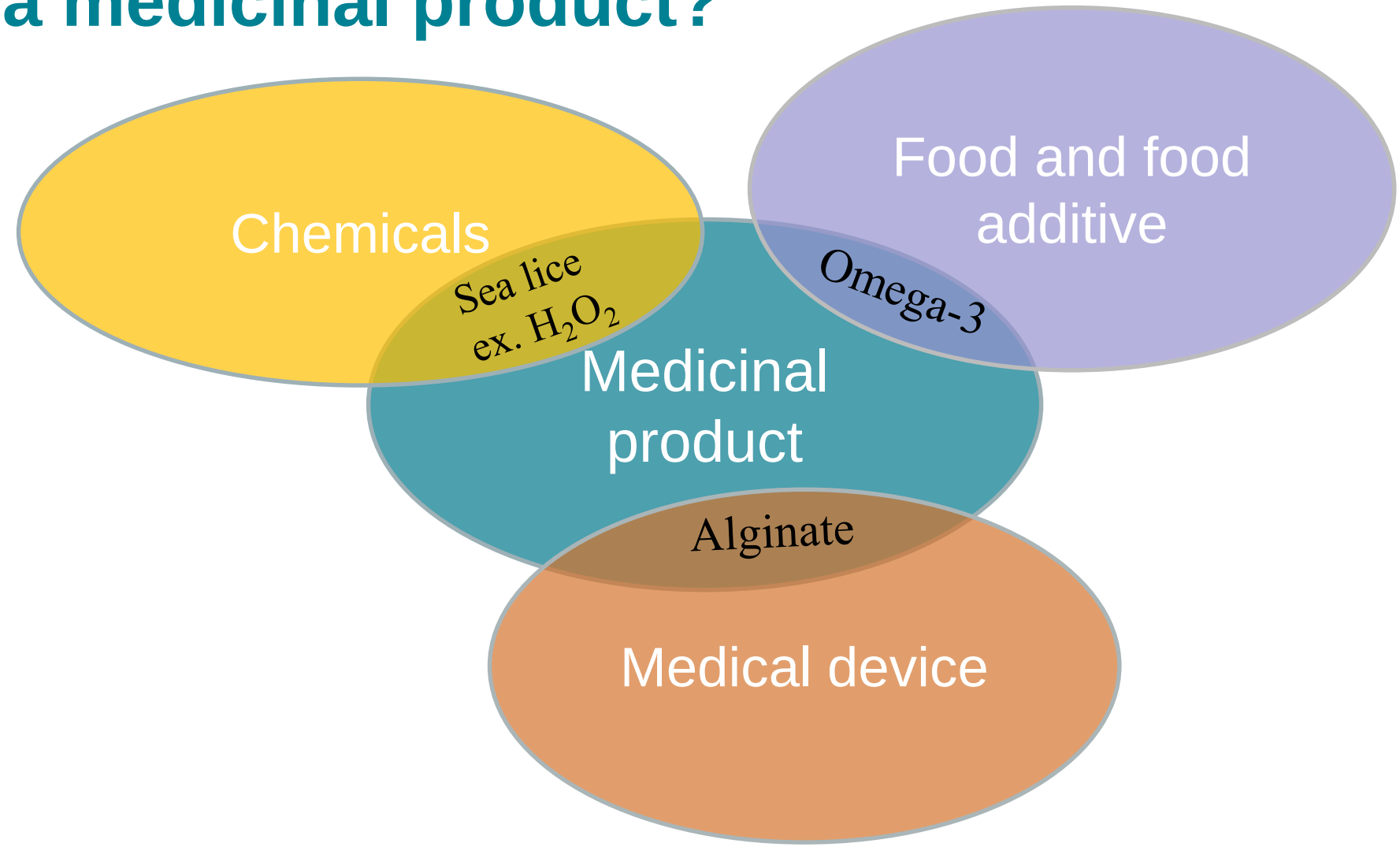


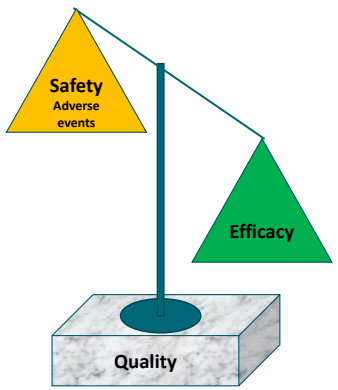


CLASSIFICATION

Medicinal or non-medicinal product?

What is a medicinal product?





Pre-approval:
Marketing Authorisation

Definition of a medicinal product

Medicines Act § 2 :

«Med legemidler forstås i denne lov stoffer, droger og preparater som er bestemt til eller utgis for å brukes til å forebygge, lege eller lindre sykdom, sykdomssymptomer eller smerter, påvirke fysiologiske funksjoner hos mennesker eller dyr, eller til ved innvortes eller utvortes bruk å påvise sykdom.»

Directive 2001/83/EC:

Medicinal product :

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Why classify products?

- Determine whether or not the Medicines Act is applicable for the product in question

- Ensure that patients have access to medicinal products that are assessed with regard to quality, safety and efficacy

Current handling of classification

Decisions are based on an overall evaluation of a specific product

- Function:
  - Content (effect at the specific dose) – pharmacologic, immunologic or metabolic
  - Health risk
- Presentation:
  - Form of administration (ex. FMT. iv. injection…)
  - Purpose, claims, indication
  - Marketing (text, images)
  - How is the product perceived (historical data)

Product quality

- Pharmaceutical Quality
  - API* and all Excipients
- You must document the whole Supply Chain
- Production:

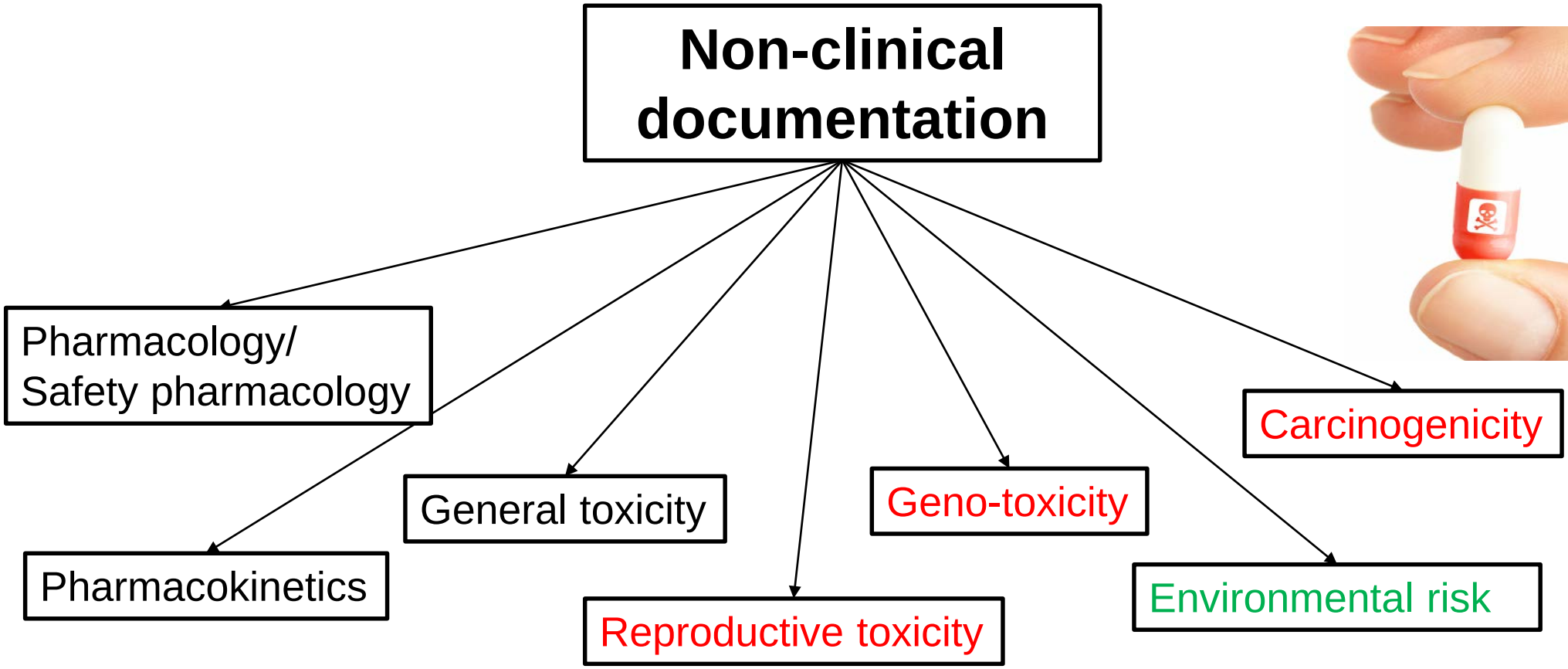
  -GMP

  --environment and ethics

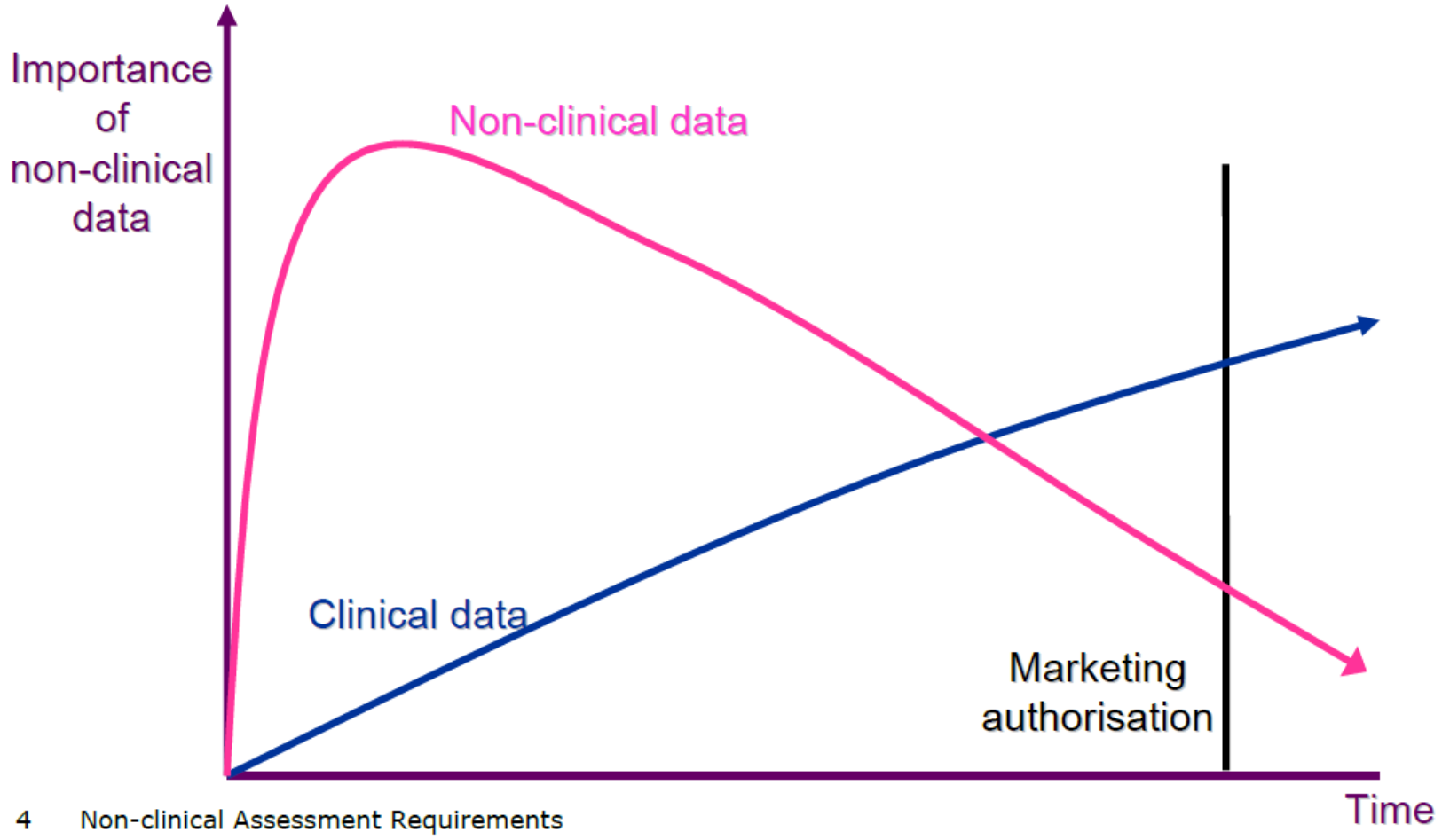
Globalisation

*Active Pharmaceutical Ingredients, ICH Q7

Non-clinical data



Relevance of non-clinical studies in drug development



Nieto-Guiterrez, M. (2011) European Medicines Agency.

Why do we need non-clinical data?

- Knowledge about the pharmacological and toxicological profile
- Used to establish a safe first dose in humans
- Basis for risk assessment and potential safety measures
- Continuous benefit/risk-assessment

Regulatory requirements throughout development

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

December 2009
EMA/CPMP/ICH/286/1995

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

Step 5

Transmission to CHMP	July 2008
Adoption by CHMP for release for consultation	July 2008
End of consultation (deadline for comments)	October 2008
Final adoption by CHMP	June 2009
Date for coming into effect	December 2009

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	01 February 2018

Clinical Trials

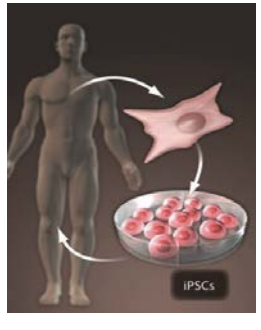
- Should be planned and conducted according to high scientific standards and existing guidelines!

- It’s not about believing, it’s about evidence!!

Definition of a clinical trial

- Any systematic study on medicinal products with the intention to provide new knowledge or verify existing knowledge regarding the effect or influence of the medicinal product on:
  - Physiological function, interaction, side effects
  - Uptake, distribution, metabolism and excretion
  - therapeutic value/benefit of the medicinal product
- Applies to medicinal products with and without market authorization
- OBS: Advanced therapy is defined as medicinal products in EU

Gene therapy



Cell therapy

Tissue therapy

=

Medicinal products

Assessment of the application

- Clinical trials must be approved (pre-approval)
- The application (protocol) will be assessed with respect to scientific validity
  - Hypothesis, endpoint, population, dosage, safety/monitoring, statistics
- Factors to be considered in the assessment
  - Trials in early vs late phase (FIH/phase I vs phase IV)
  - Authorized medicinal products vs medicinal products in development
  - Approved indication vs new indication

Medical Device

- NoMA is the Competent Authority for medical devices

What is a Medical Device?

…any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

(definition § 1-5, Norwegian regulation on medical devices)

What is a medical device?

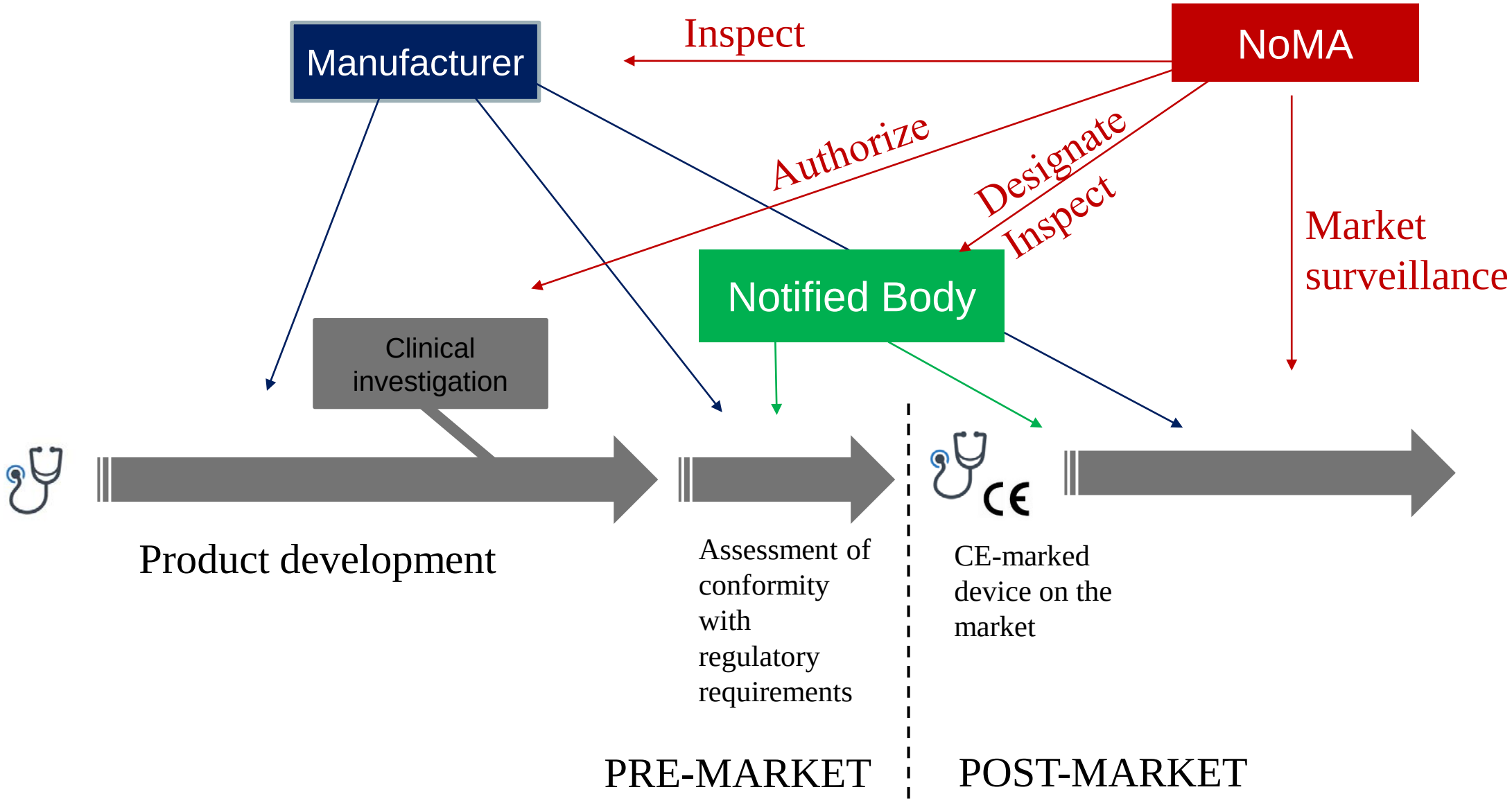
…any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosi
- diagnosi or handicap
- investiga al process,
- control c

any device intended by its manufacturer to be used for a medical purpose

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

Roles and actors



Get Advice and Help

- National Regulatory and Scientific Advice
- Central Scientific Advice
  - Coordinated by EMA SAWP
  - Work done by NCA

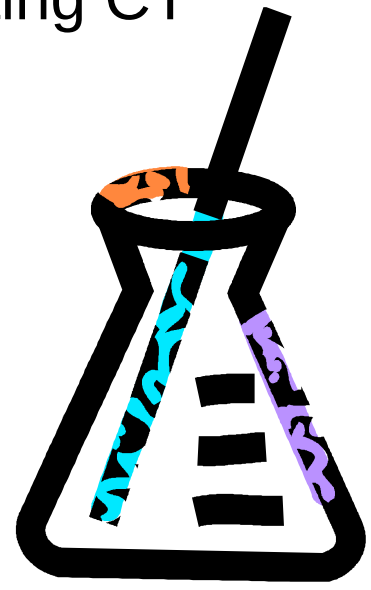
- Use CRO`s

https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

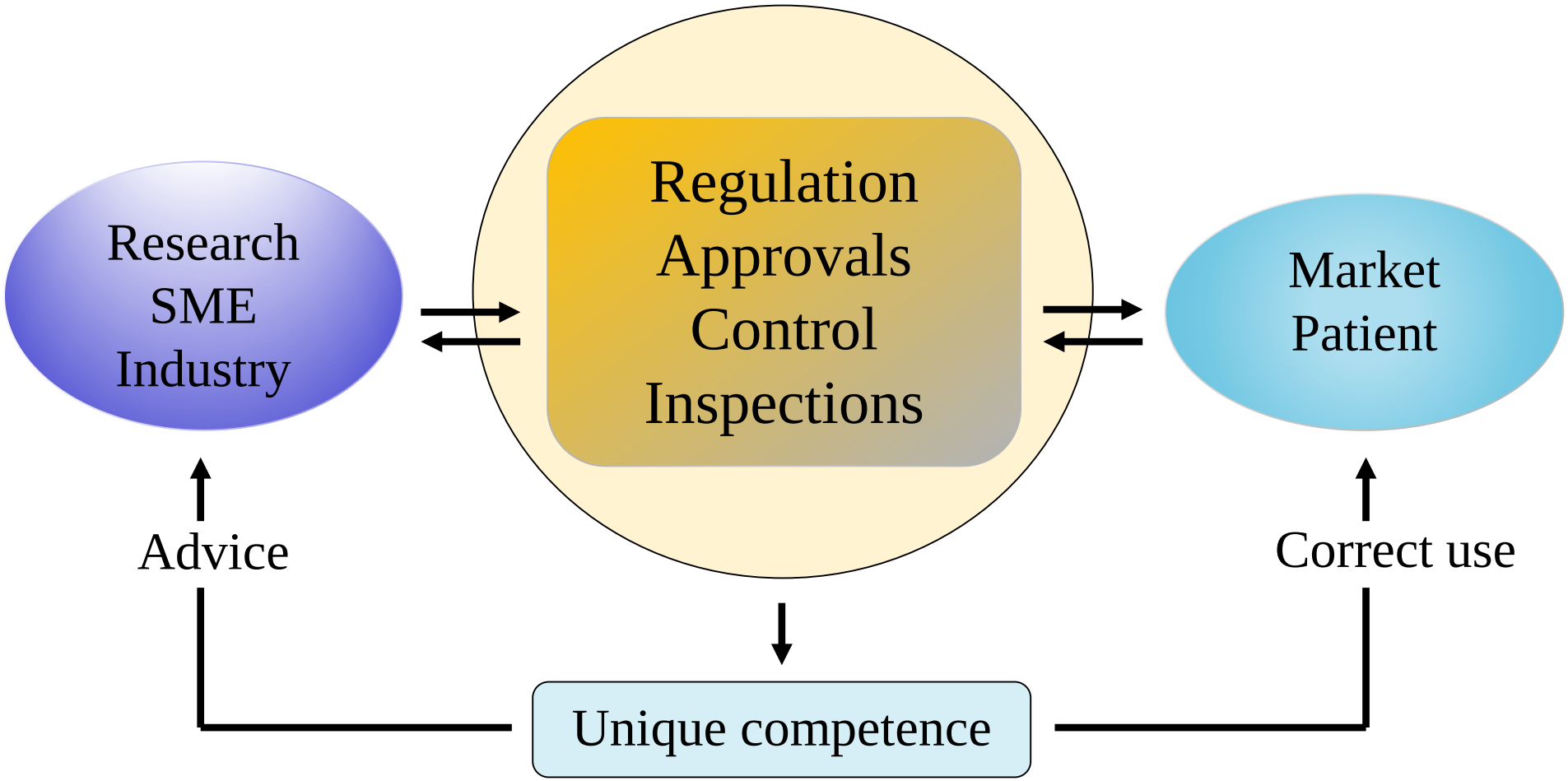
“Innovation Office” at NoMA

Mission;

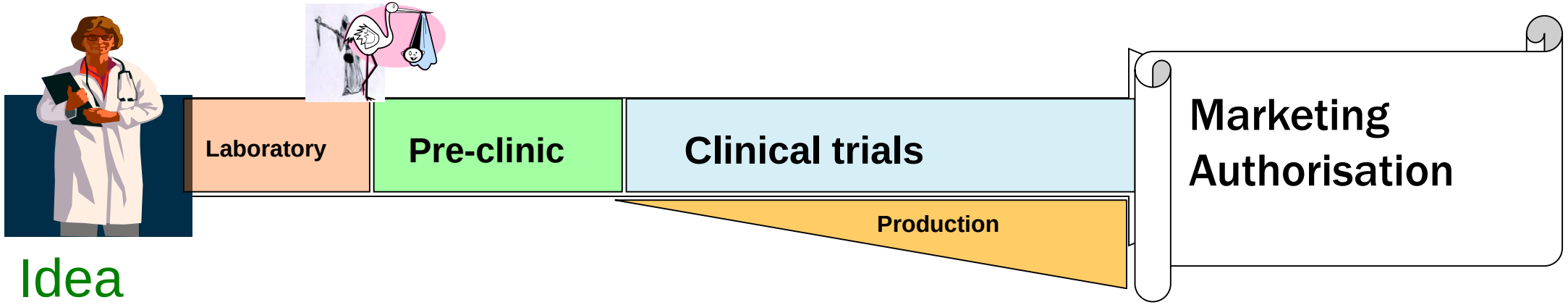
- ✓ Give help and contribute to; «get it right the first time»
  - Advice academia and investigators planning and conducting CT
  - Offers regulatory and scientific advice to companies
    - Start-ups, SME and Big Pharma
- ✓ Easy accessible and pro-active
- ✓ Without partnering!



Concept; reuse of regulatory competence



Stepwise dialogue with authorities !



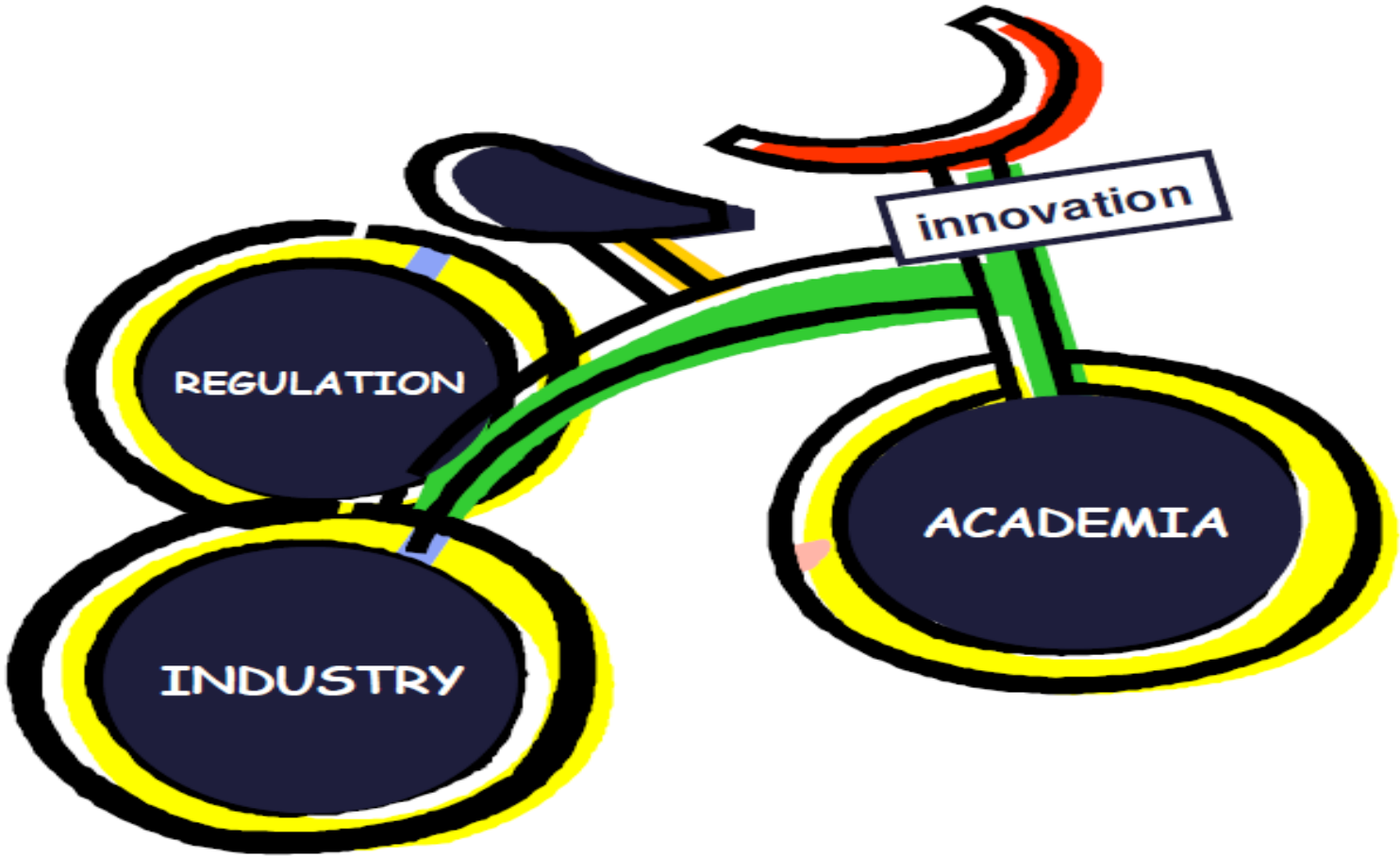
Idea

Low threshold national advice
Regulatory strategy

National regulatory and scientific advice

EMA/CXMP scientific advice

You need to have a Regulatory Strategy!



Questions ?

www.legemiddelverket.no

ask-us@legemiddelverket.no

www.ema.europa.eu

Statens legemiddelverk

EU-Regulatory Tools….

Current tools

- Conditional Approval
- Accelerated Assessment
- Exceptional Approval
- Orphan Regulation
- ATMP classification
- Compassionate use
- Scientific Advice. HTA
- SME-office

New; Supporting development

- **PRIME**
- Innovation Task Force and EU-IN
- STARS
- Modelling and simulating

New; Development concept **AP**

- Incremental development
- Involving all stakeholders. HTA
- Alternative phase III- Registries and RWD

Vitenskapelig og regulatorisk veiledning i forbindelse med legemiddelutvikling

Legemiddelverket tilbyr veiledning og råd om utvikling av humane og veterinære legemidler.

Dette skal gi brukerne

- forståelse av veien fra idé til godkjent produkt.
- tilgang på ekspertise med erfaring fra utredning av søknader.
- mulighet til å diskutere en søknad før den sendes inn, slik at dokumentasjonen er i henhold til regulatoriske krav.
- råd om hvordan gjennomføre studier for at de skal kunne gi tolkbare resultater første gang studiene gjennomføres. På den måten sparer bedrifter og samfunnet tid og ressurser.

Hva kan Legemiddelverket tilby?

Vi tilbyr råd og veiledning i alle faser av legemiddelets livsløp på bakgrunn av vår generelle vitenskapelig/regulatorisk ekspertise innen alle faser av legemiddelutvikling. Denne ekspertisen tilegnes og utvikles gjennom utredning av søknader i både nasjonale og europeiske prosedyrer. I det europeiske legemiddelsamarbeidet har Norge de samme rettighetene og pliktene som de

Legemidler til mennesker

Ingvild Aaløkken
Område rask tilgang
Tlf. +47 472 70 572
E-post

Legemidler til dyr

Tonje Høy
Fagdirektør
Veterinærmedisinsk faggruppe

Forespørsel om vitenskapelig og/eller regulatorisk rådgivning ved legemiddelutvikling

Statens legemiddelverk

Skjema sendes via e-post til: Ask-us@legemiddelverket.no
Innsendt dato:
Deres referansenummer:

Opplysninger om firma/organisasjon

Navn på firma/organisasjon:	
Kontaktperson:	
Telefonnummer:	E-post:

Opplysninger om preparatet

Forespørselen gjelder: ☐ Legemiddel til mennesker ☐ Legemiddel til dyr

Virkestoffnavn og eventuelt preparatnavn:

ATC-kode dersom kjent:	Legemiddelform:

Indikasjon *(inkludert målart for legemiddel til dyr)*:

Har legemidlet tidligere vært gjennom vitenskapelig rådgivning? ☐ Ja ☐ Nei
Hvis ja, spesifiser hos hvilken legemiddelmyndighet:
☐ EMA ☐ Legemiddelverket, oppgi saksnummer:
☐ Andre myndigheter, spesifiser:

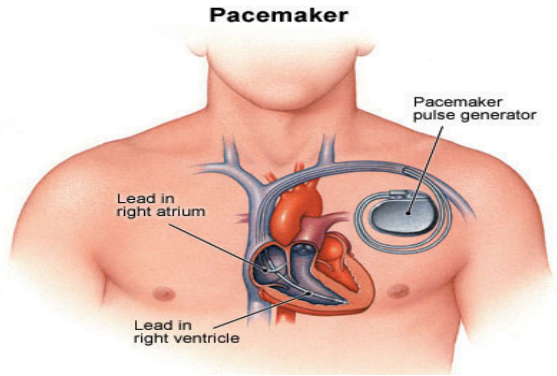
Tenkt godkjenningsprosedyre*: ☐ Nasjonal ☐ MRP/DCP ☐ CP	Tenkt søkegrunnlag*: ☐ Fullstendig ☐ Generisk ☐ Hybrid ☐ Biosimilar ☐ Annet:

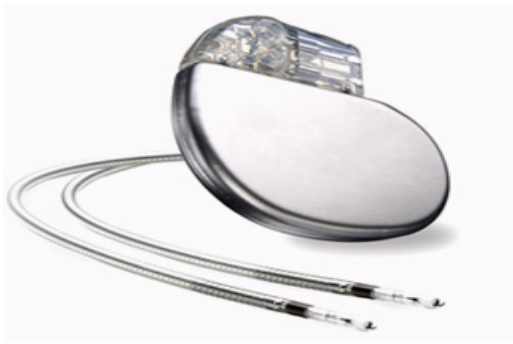
** Dersom relevant*

Opplysninger om ønsket rådgiving

Rådgivning gjelder: ☐ Tilvirkning	**Ønsket ekspertise:** ☐ Preklinikk ☐ Klinikk

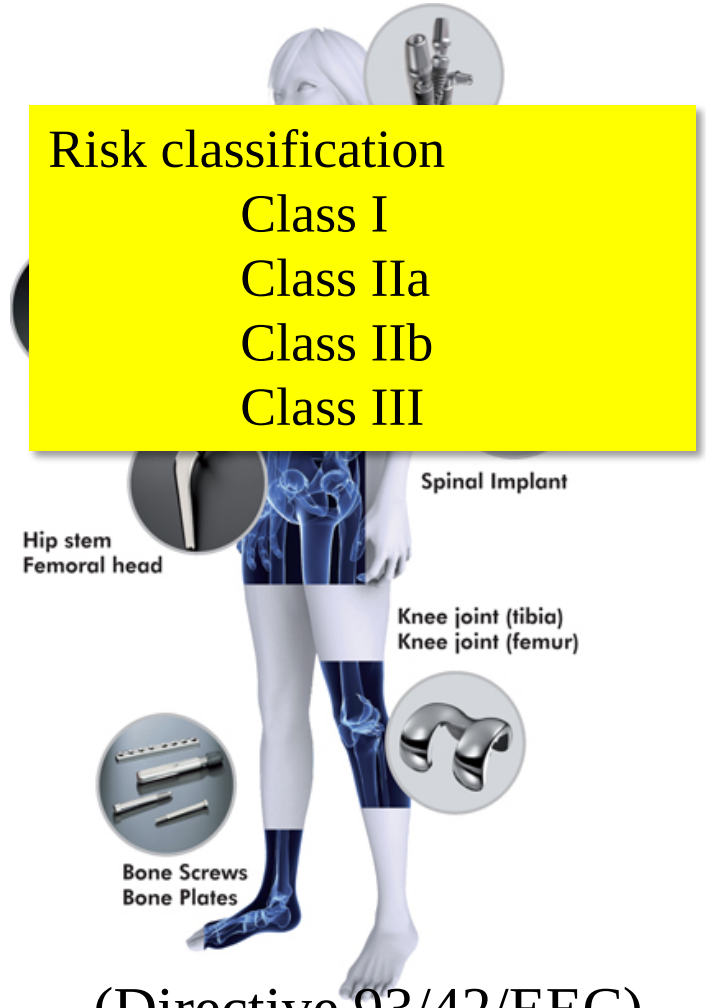
Active implantable medical devices





(Directive 90/385/EC)

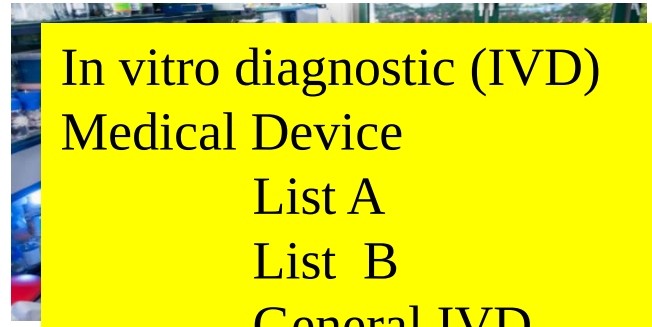
Medical Devices



Risk classification
- Class I
- Class IIa
- Class IIb
- Class III

(Directive 93/42/EEC)

In vitro diagnostic medical devices



In vitro diagnostic (IVD) Medical Device
- List A
- List B
- General IVD

(Directive 98/79/EEC)