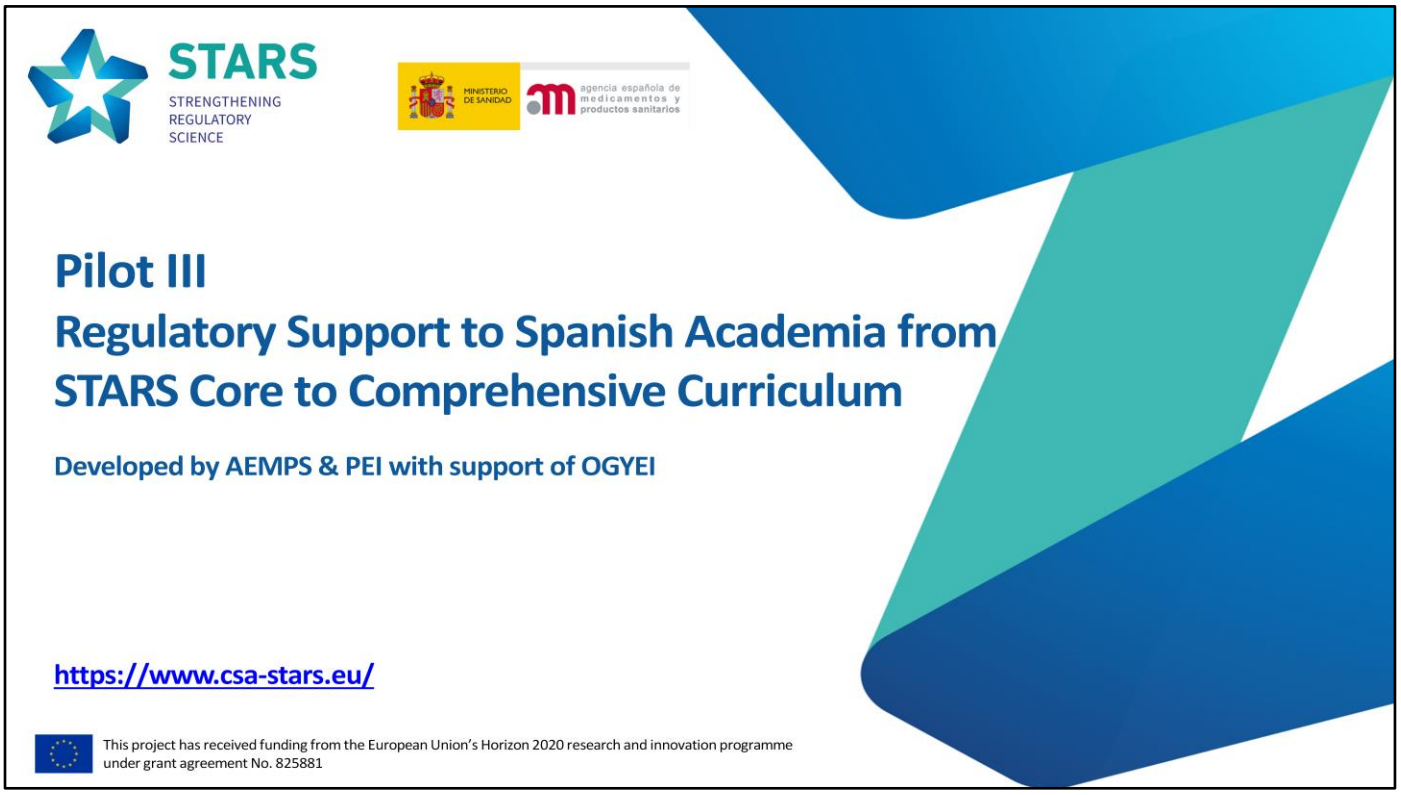


We are happy to welcome you, also in the name of the STARS consortium, to the first free online Curriculum teaching regulatory science to academia. This course is part of an EU Commission project, which aims to strengthen regulatory knowledge in academia to improve the translation from basic research into clinical practice. For more information please check the website through the link in the slide.

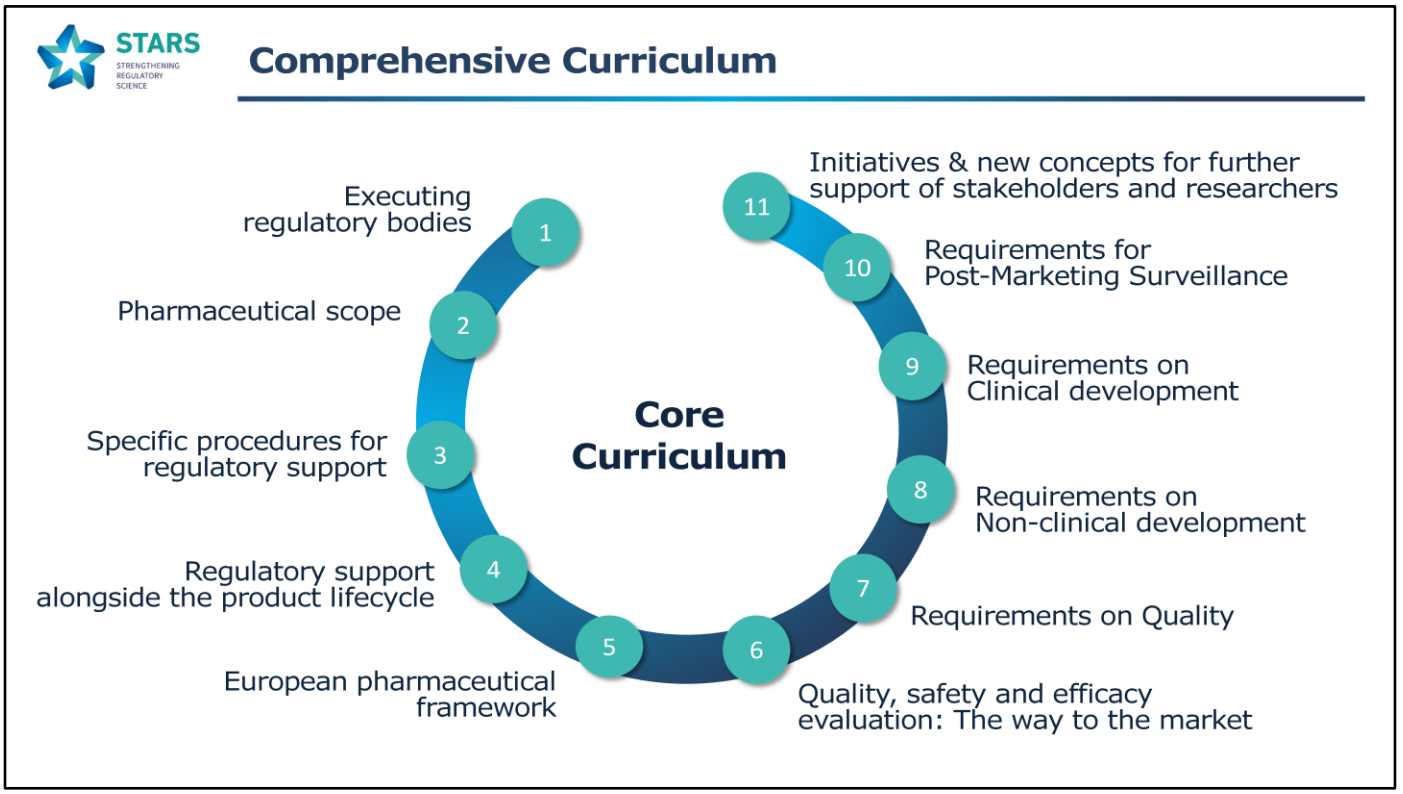
Pilot III was implemented by the Spanish Agency AEMPS with the support of the German Agency PEI. The aim of this course is to train or give to the academia researchers an overview of the basic regulatory knowledge, which covers the topics detailed in slide 4 (Comprehensive Curriculum-Core Curriculum).

Abbreviations

ADR	Adverse Drug Reaction
AEMPS	Spanish Agency of Medicines and Medical Devices
ATMP	Advanced Therapy Medicinal Product
BWP	Biologics Working Party
CAT	Committee for Advanced Therapies
CHMP	Committee for Human Medicinal Products
CMA	Conditional Marketing Authorisation
CMC	Chemistry, Manufacturing & Controls
CMS	Concerned Member State
CMDh	Co-ordination Group for Mutual Recognition & Decentralised procedures - Human
COMP	Committee for Orphan Medicinal Product
CTA	Clinical Trial Application
CTCG	Clinical Trials Coordination Group
CTD	Common Technical Document
DCP	Decentralized Procedure
EC	European Commission
ED	Early Dialogues
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETF	EMA pandemic Task Force
EU	European Union
EU-IN	EU-Innovation Network
EUnet(HTA)	European Network of (Health Technology Assessment)
EU-NTC	EU Network Training Centre
FDA	U.S. Food and Drug Administration
HCPWP	Healthcare Professionals' Working Party
HIV	Human Immunodeficiency Virus
HMA	Heads of Medicines Agencies

Abbreviations

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMPD	Investigational Medicinal Product Dossier
ITF	Innovation Task Force
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MRP	Mutual Recognition Procedure
MS	Member State
NCA	National Competent Authority
NP	National Procedure
NFPO	Not-for-Profit Organization
PAES	Post-Authorisation Efficacy Studies
PASS	Post-Authorisation Safety Studies
PCWP	Patients' & Consumers' Working Party
PDCO	Paediatric Committee
PRAC	Pharmacoviligance Risk Assesment Committee
PRIME	Priority Medicine
QWP	Quality Working Party
RMP	Risk Management Plan
RMS	Reference Member State
SA	Scientific Advice
SAG	Scientific Advisory Group
SAWP	Scientific Advice Working Party
SME	Small & medium-sized enterprises
SNSA	Simultaneous National Scientific Advice
STAMP	Expert Group of the European Commission on the Safe & Timely Access to Medicines for Patients
SWP	Safety Working Party
TF AAM	HMA/EMA Task Force on Availability of authorised medicines for human and veterinary use

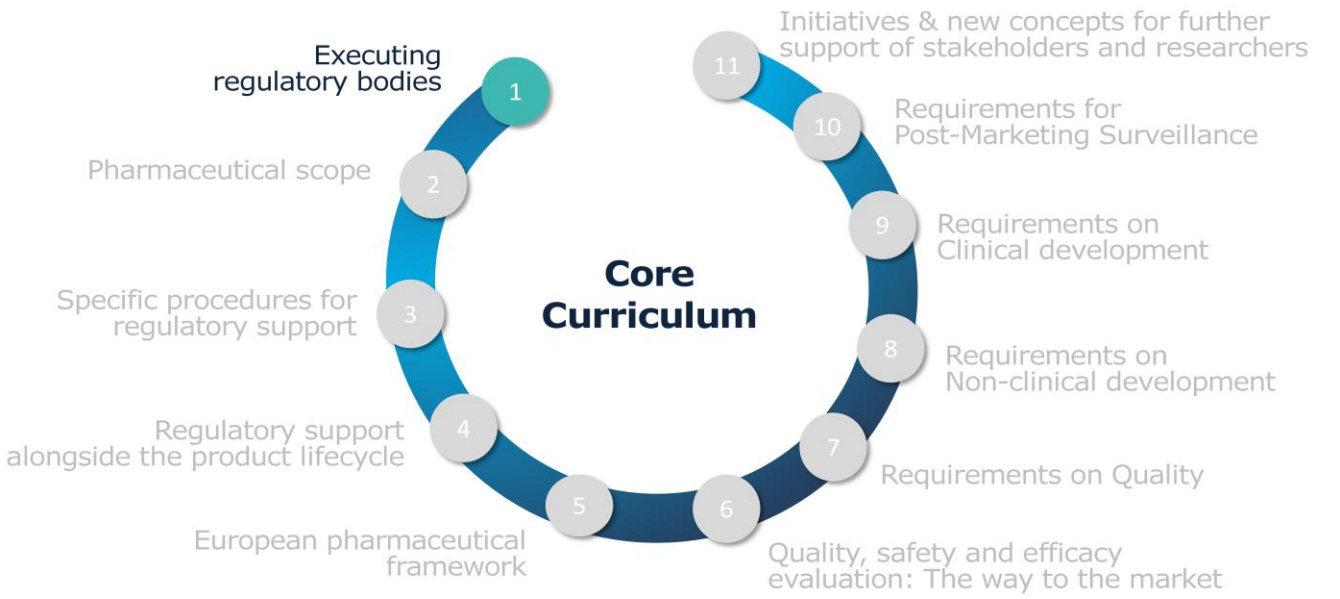


The aim of Pilot III is to give support for academia from the STARS Core to Comprehensive Curriculum. Therefore, the information included is based on the Core Module from the Comprehensive Curriculum with the purpose of extending this information in the future and cover the information included within the rest of the modules. This module covers the following topics:

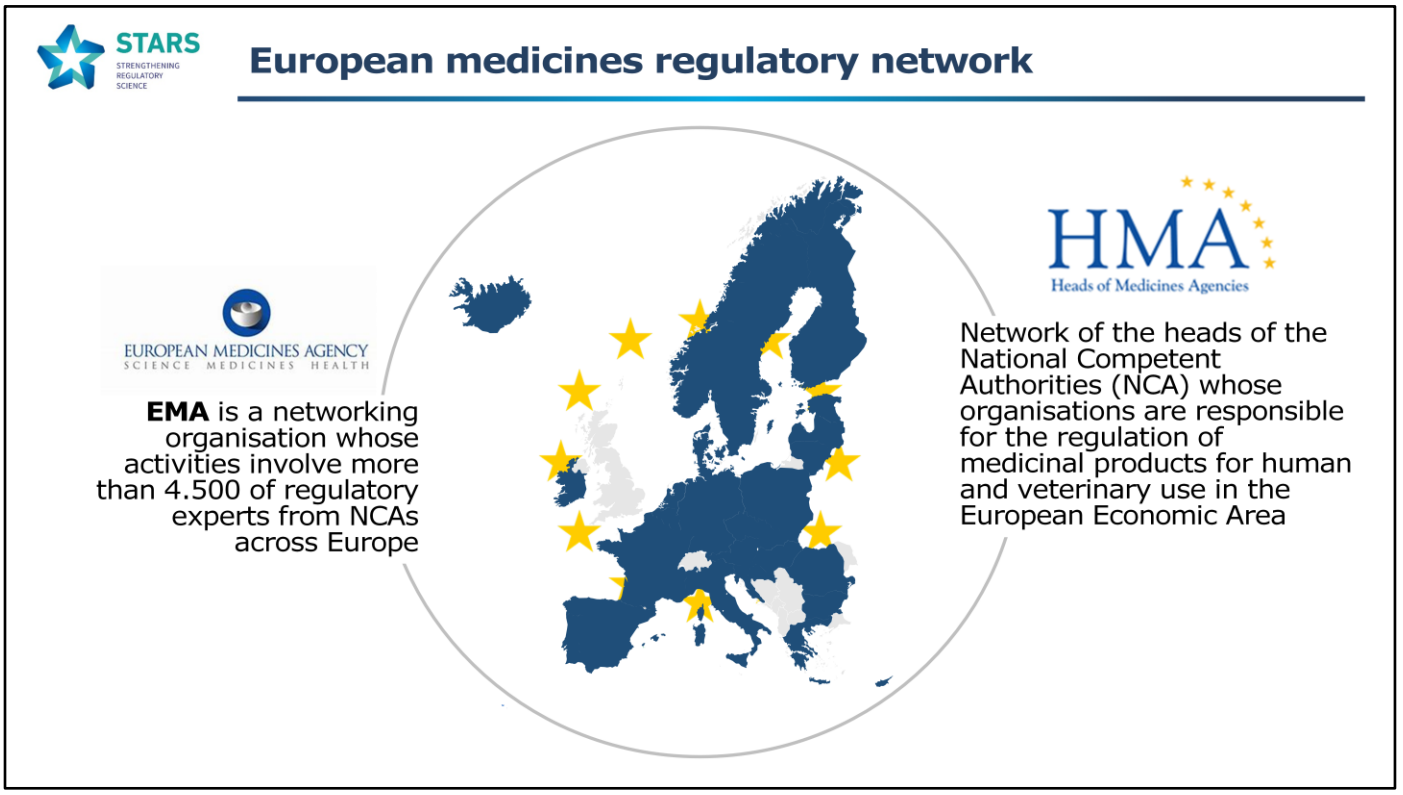
- Executing regulatory bodies
- European and national pharmaceutical scope
- Specific rocedures for regulatory support
- Also regulatory support alonside the product lifecycle
- The European pharmaceutical framework
- Requirements for quality, non-clinical, and clinical development and the post-marketing surveillance.

It is also included some hints about some initiatives and new concepts for further support of stakeholders and researchers.

Comprehensive Curriculum



The Executing regulatory bodies.

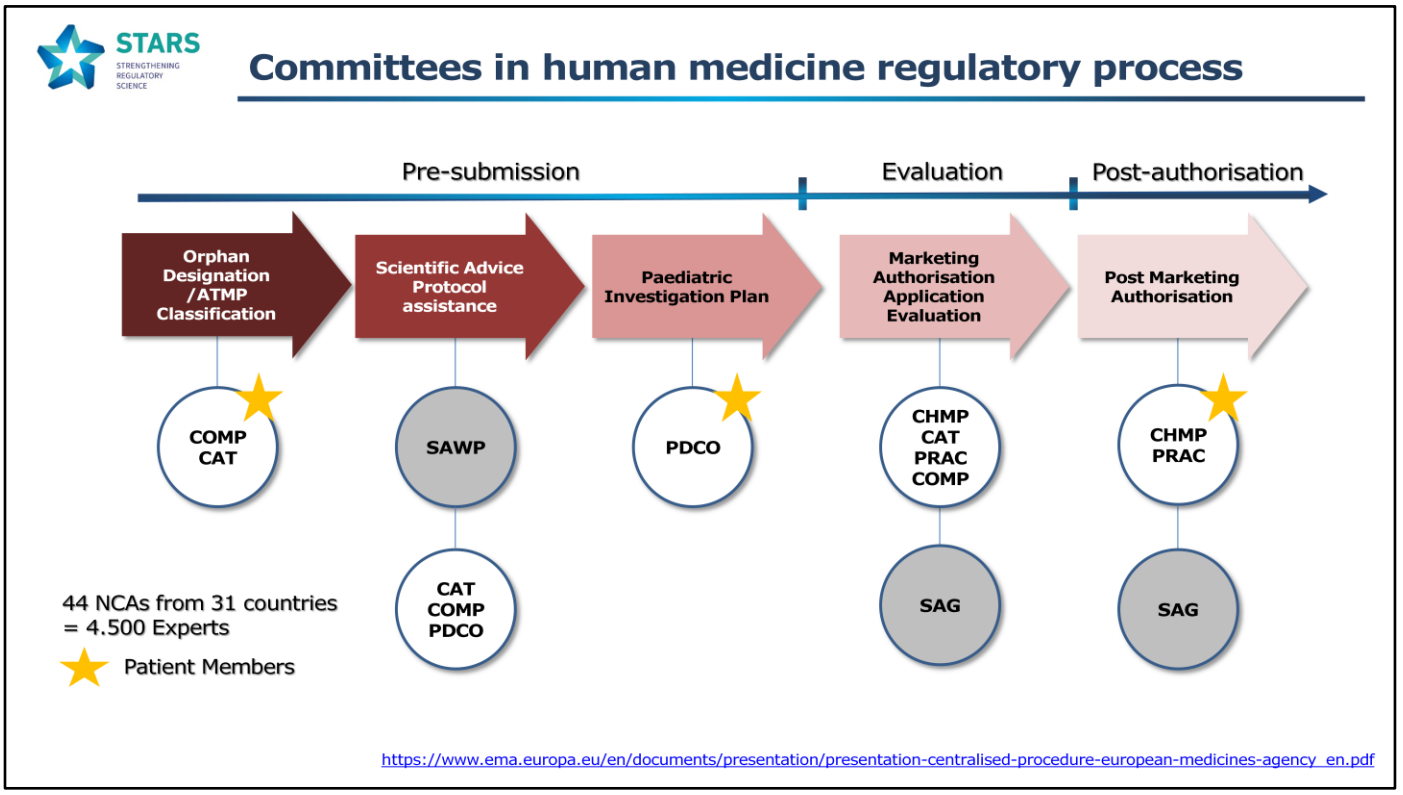


The European medicines regulatory network is composed of the European Medicines Agency (**EMA**) and the Heads of Medicines Agencies (**HMA**). Both networks work in a close collaboration to successfully regulate the medicinal products for human and veterinary use in Europe.

The EMA is a networking organisation whose activities involve more than 4.500 of regulatory experts from NCAs among 27 EU Member States across Europe, as well as Iceland, Norway and Lichtenstein, by being part of different working groups. This collaborative model is the basis of the EMAs success as it gives the EMA access to a pool of experts (including regulators, academics, patients and healthcare professionals) from across the EU, obtaining the best available scientific expertise.

The HMA co-operates with the European Medicines Agency and the European Commission in the operation of the European medicines regulatory network and it is a unique model for cooperation and work-sharing on statutory, as well as voluntary regulatory activities.

The HMA is coordinated and supervised by a **Management Group** and it is supported by several **Working Groups**, covering specific areas of responsibility, and by a **Permanent Secretariat**.



This slide shows an overview of the medicines regulatory pathway and the different procedures where the committees interact.
There are **7 committees** that evaluate medicines at the European Medicines Agency:

- **CAT** Committee for Advanced Therapies
- **CHMP** Committee for Human Medicinal Products
- **COMP** Committee for Orphan Medicinal Product
- **HMPC** Committee on Herbal Medicinal Product
- **PDCO** Paediatric Committee
- **PRAC** Pharmacovigilance Risk Assessment Committee
- **CVMP** Committee for Veterinary Medicinal Products

The EMA **secretariat** supports the work of these committees in a **scientific and logistic capacity**.
It is important to underline that four of these committees have members representing **patients' organisations**, what provides important opportunities for patients as it contributes to the expertise and experience of the EMA with their diseases' area of interest.

The **Scientific Advice Working Party (SAWP)** and the **Scientific Advisory Group (SAG)** are mentioned in this slide because they are essential on the above-mentioned procedures.

Working Groups at EMA & HMA

Standing working parties (EMA)

- Healthcare Professionals' Working Party (HCPWP)
- Biologics Working Party (BWP)
- Patients' and Consumers' Working Party (PCWP)
- Quality Working Party (QWP)
- Safety Working Party (SWP)
- Scientific Advice Working Party (SAWP)

1. Working Groups HMA Joint

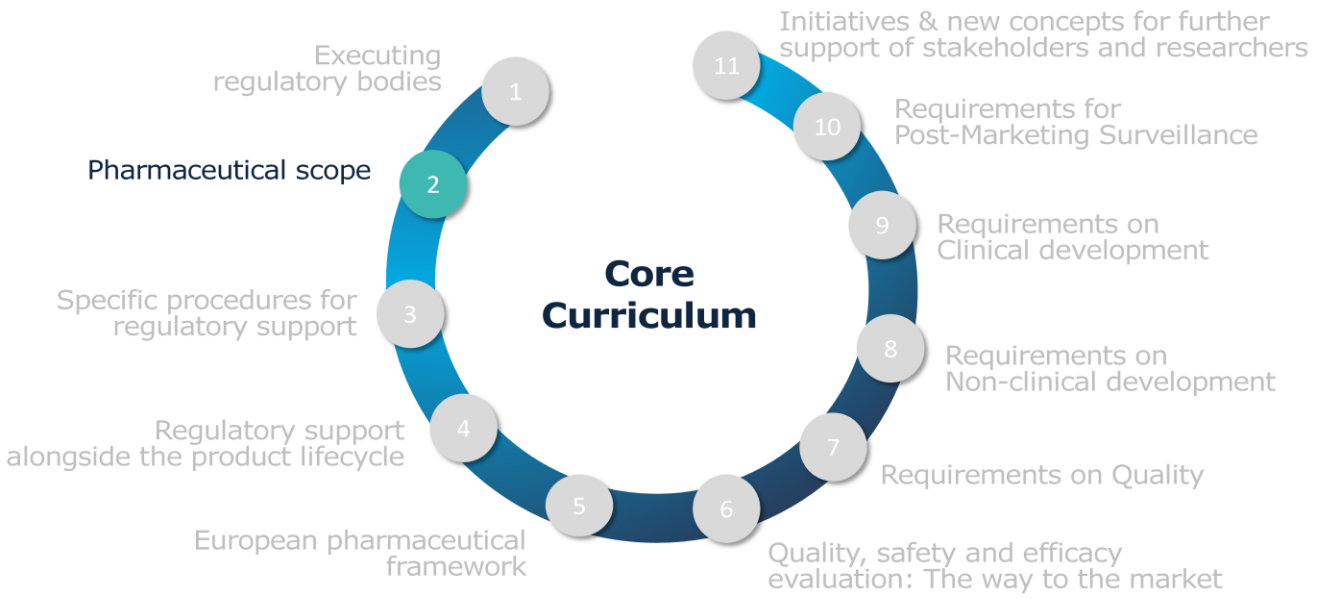
- EU Network Training Centre (EU NTC)
- EU-Innovation Network (EU-IN)
- HMA/EMA Task Force on Availability of authorised medicines for human and veterinary use (TF AAM)

2. Working Groups HMA Human

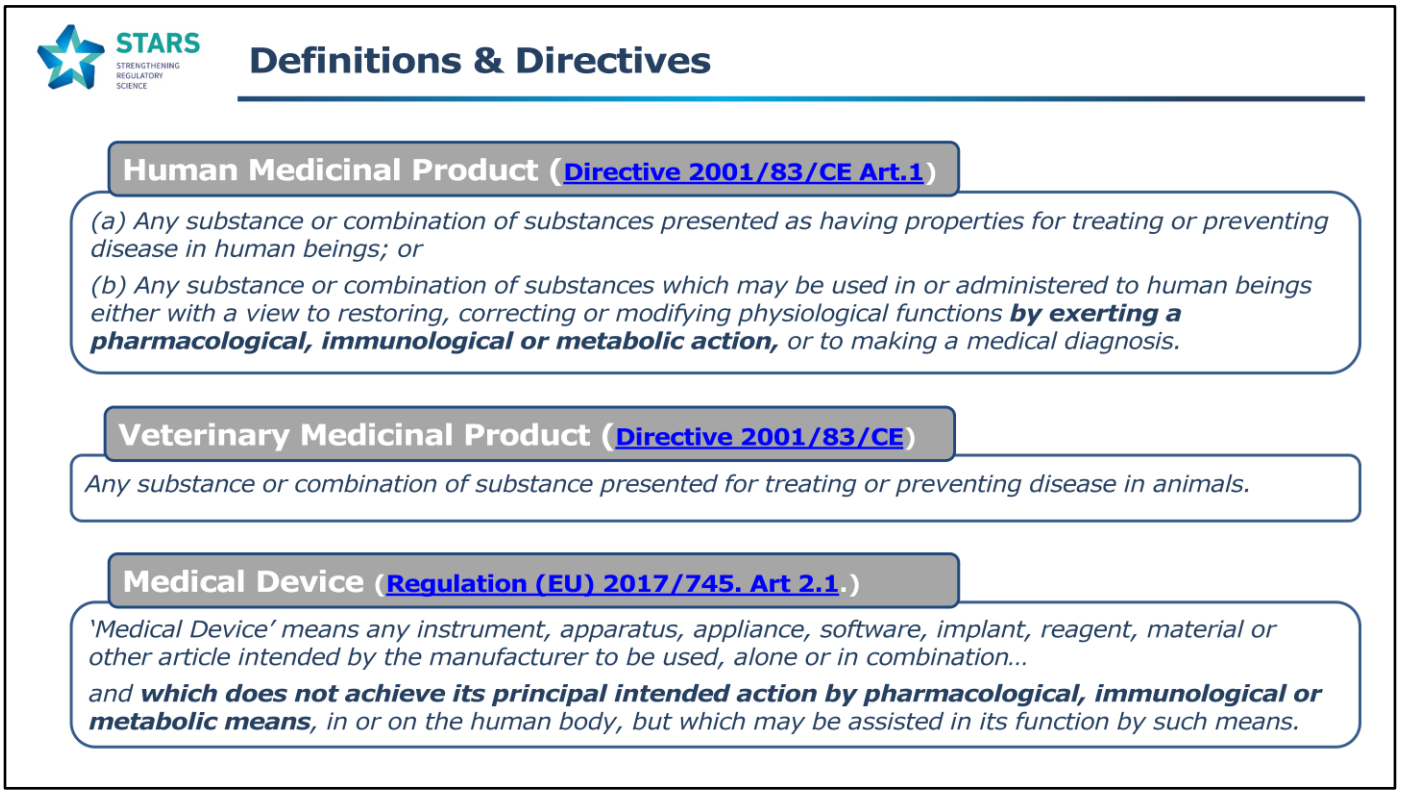
- Clinical Trials Coordination Group (CTCG)
- Timely Access Subgroup

EMA's **committees**, **working parties** and related groups are composed of European experts from the NCAs of the EU and European Member States. The HMA also has its own working parties, shown in this slide. For further information please click to the links in blue.

Comprehensive Curriculum



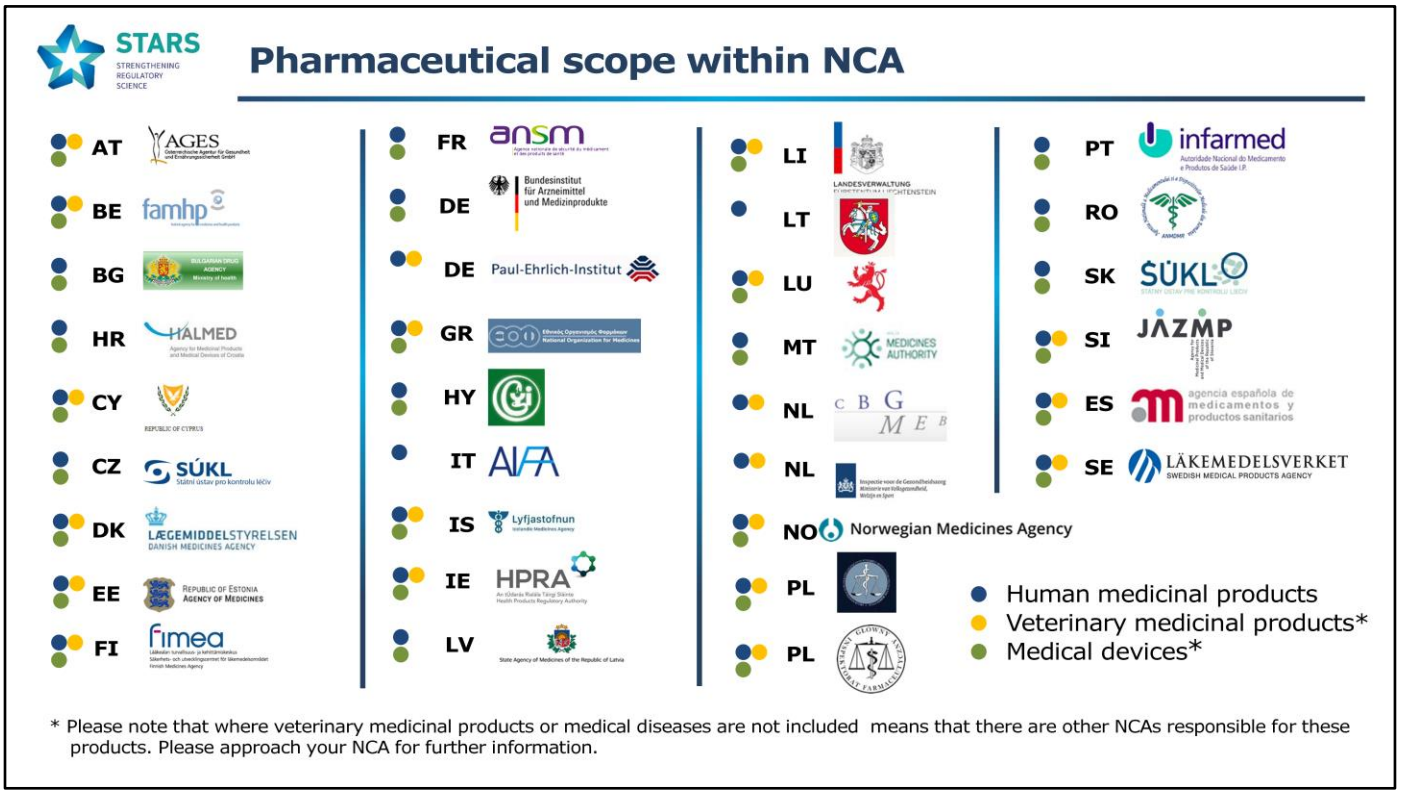
Pharmaceutical Scope.



The European Union (EU) legal framework for pharmaceuticals is aimed at ensuring a high level of **protection of public health**. It is based on the principle that the placing of a medicine on the market is subject to the granting of a marketing authorisation by the competent authorities.

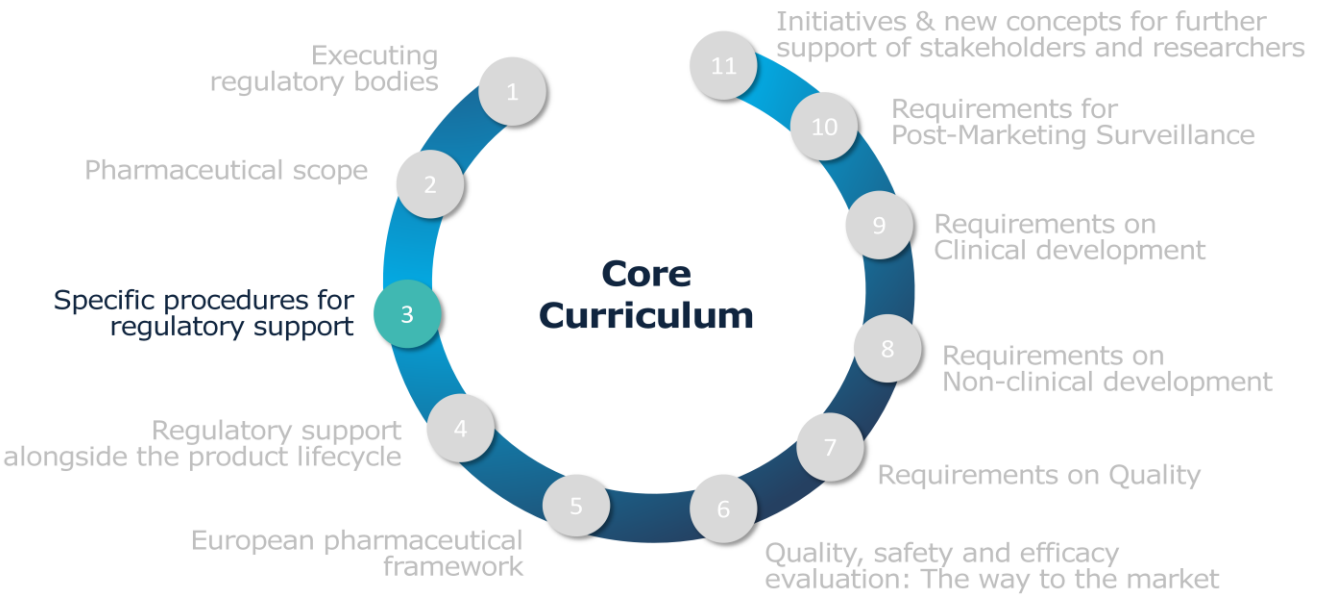
The Community codes for veterinary and human medicines are set out in **Directive 2001/82/EC** and **Directive 2001/83/EC**, respectively. They provide the legal framework for the authorisation, manufacturing and distribution of medicines in the EU.

This legal framework has been amended and enhanced over time by further legal acts that cover specific areas of pharmaceutical law.

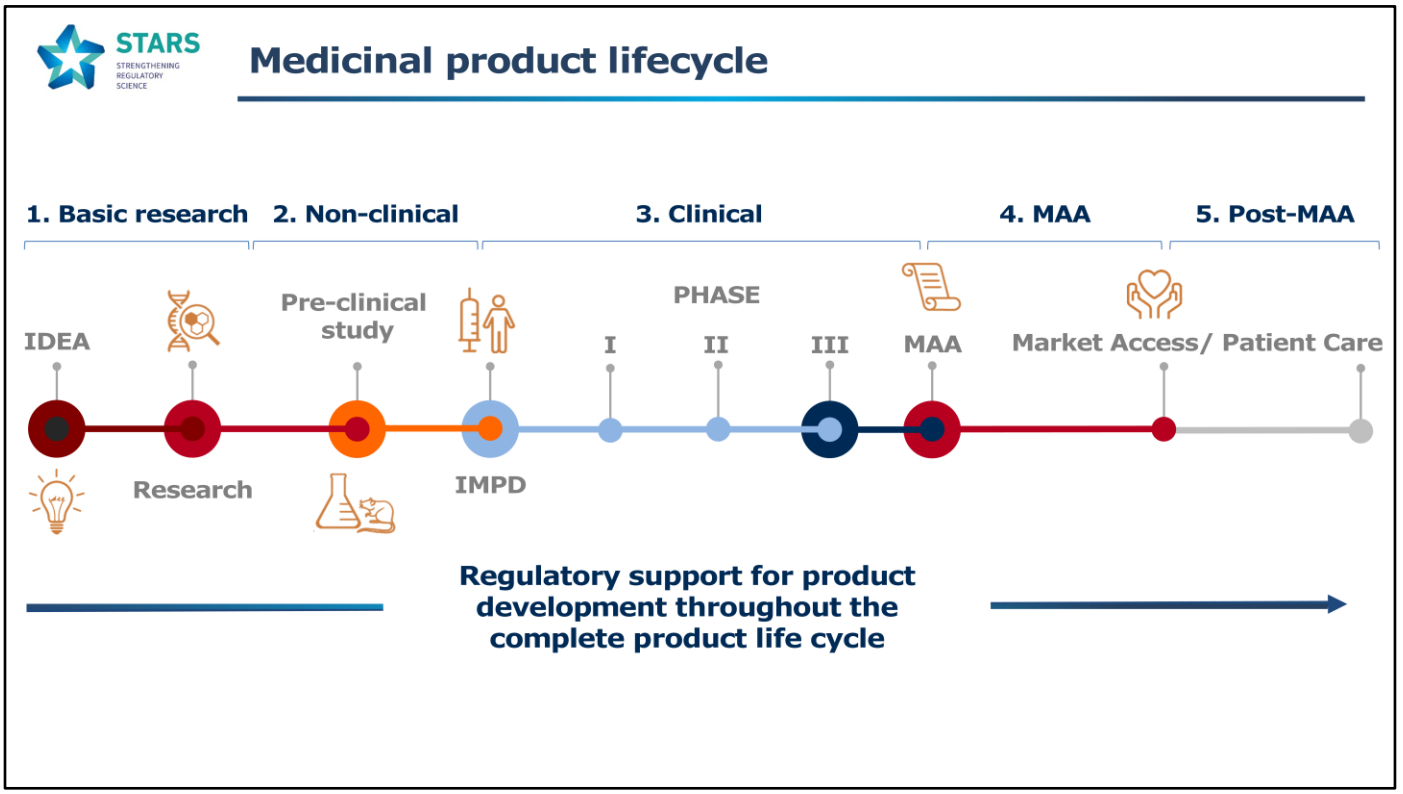


The pharmaceutical scope within each NCA of the 27 EU Member States as well as Iceland, Norway and Lichtenstein, is shown in this slide, which plays a key part in the European regulatory system for medicines. Please, note that this presentation only includes detailed information of the regulatory system for **human medicinal products**. For detailed information on medical devices or veterinary medicinal products, approach your NCA(s).

Comprehensive Curriculum

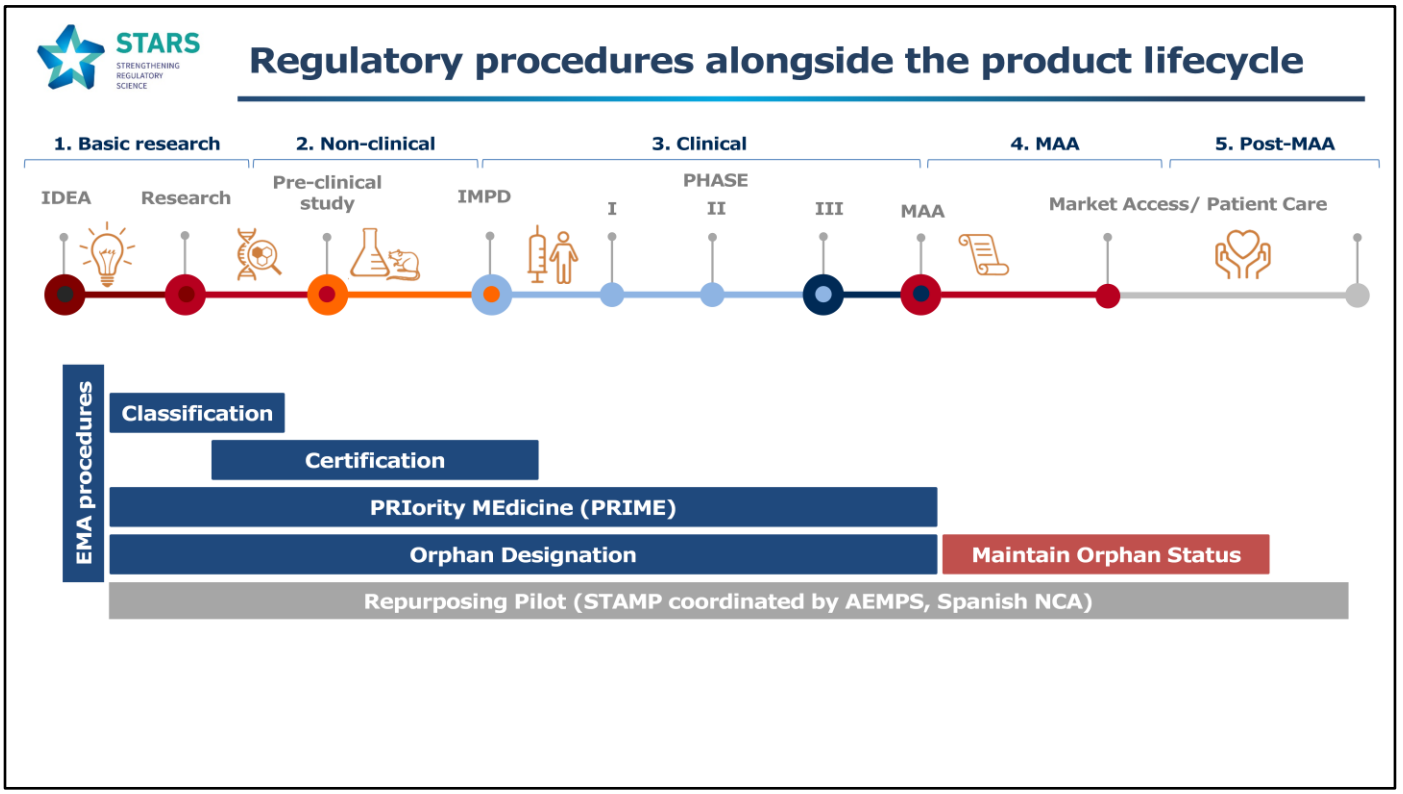


Specific procedures for regulatory support.



The **medicinal product lifecycle** is shown in this slide in order to give a short overview of the different regulatory steps from basic research to marketing authorisation and post-marketing surveillance.

The following slides show the regulatory support throughout the complete product life cycle.



This part of the presentation will focus on the **regulatory procedures alongside the product lifecycle** given by EMA with the exception of the Repurposing Pilot which is a STAMP project coordinated by AEMPS.

Procedures for regulatory support by EMA

ATMP Classification

- Scientific recommendation of the CAT if ATMP, i.e. borderline products
- Facilitation of regulatory procedure
- Orientation for national agencies
- Free of charge
- Evaluation max. 60 days
- Not legally binding
- EMA publishes the outcome of the assessment
- Criteria for ATMPs: Regulation (EC) No 1394/2007
- advancedtherapies@ema.europa.eu

ATMP Certification

- Certification of quality and non-clinical data by the CAT
- Identify potential issues prior to MAA
- Only pre-assessment procedure
- Evaluation max. 90 days
- Not (yet) open to «academia»
- Criteria for ATMPs: Regulation (EC) No 1394/2007
- advancedtherapies@ema.europa.eu

PRIME

- Foster and facilitate early interaction
- Raise awareness of requirements earlier in development
- Focus efficient development
- Promote generation of robust and high quality data
- Promote generation of high quality data
- Facilitated by knowledge gained throughout development
- prime@ema.europa.eu

The procedures for regulatory support from EMA are summarised in this slide with a detailed overview of the **ATMP Classification and Certification** as well as the **PRIME** procedure. For further information, please click the links facilitated in blue in the slide.

STAMP - Repurposing Pilot

- Objective of the Pilot is to connect academic researchers with regulatory authorities on **repurposing projects**
- Facilitate the regulatory recognition of **new indications** for well-established authorised medicines
- These medicines should be past their term of **patent protection**

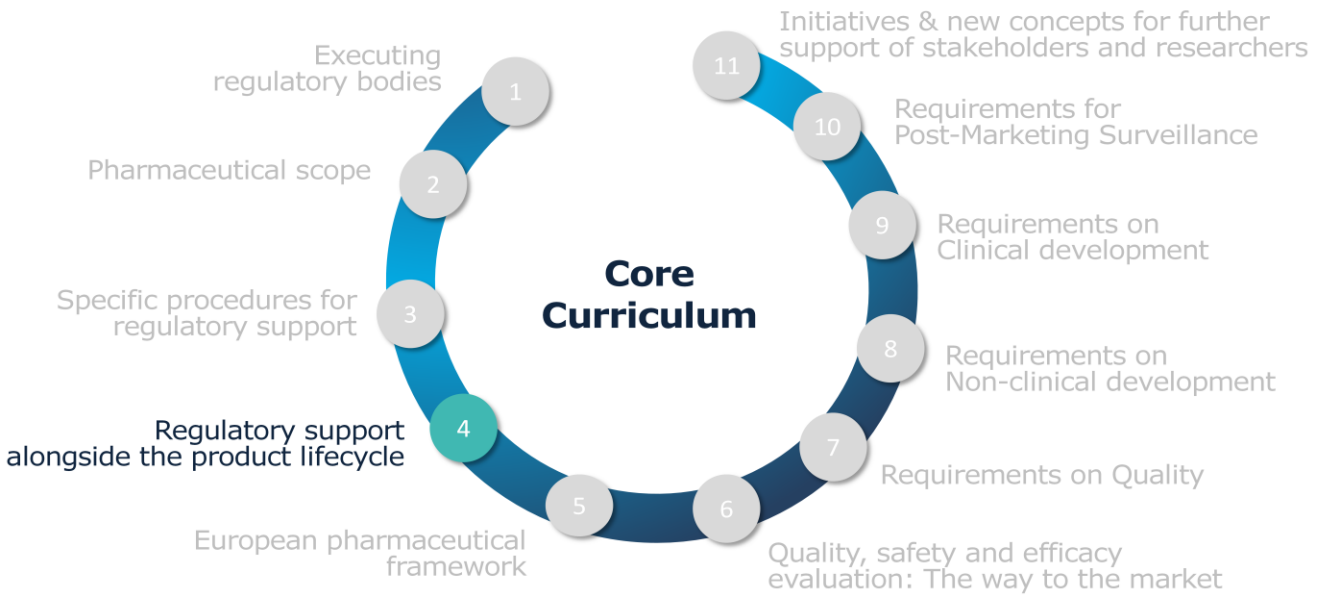
- Framework to support not-for-profit organisations (**NFPOs**) & **academia** (institutions & individuals) in repurposing authorised medicines
- STAMP consists of **representatives** of the member states, the EMA, & stakeholders from NFPOs, patients, healthcare professionals, industry, health technology assessment bodies & payers

For additional information contact
innov_spain@aemps.es

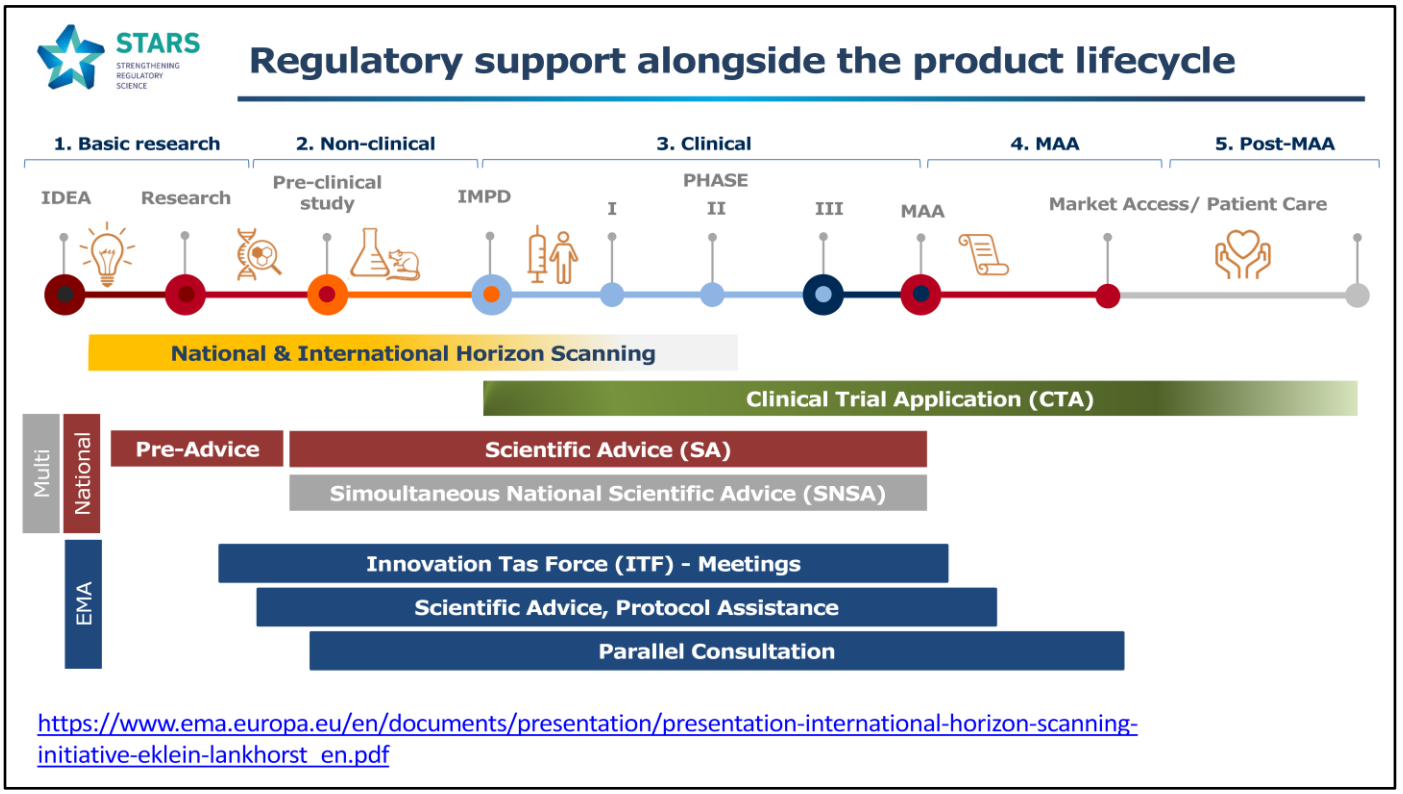
The Pilot project was designed to support the repurposing of medicines as a follow-up to the European Comission´s Expert Group on Safe and Timely Access to Medicines for Patients (**STAMP**). The aim of this innitiative is to **support not-for-profit organisations and academia** to gather or generate sufficient evidence on the use of an established medicine in a **new indication** with the view to have this use formally authorised by a regulatory authority. Therefore, is a way of making **new treatment** options available to patients.

As a part of the pilot, the NCA and EMA will provide regulatory support, primary scientific advice, to help these stakeholders generate a sufficiently robust data package to support a future application by a pharmaceutical company.

Comprehensive Curriculum



Regulatory support alogside the product lifecycle.



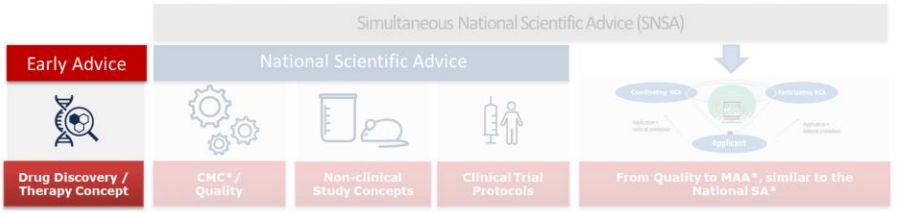
https://www.ema.europa.eu/en/documents/presentation/presentation-international-horizon-scanning-initiative-eklein-lankhorst_en.pdf

This slide shows a brief overview of all the regulatory support alongside the product lifecycle given by NCAs or EMA.
Starting by the yellow bar: the **International Horizon Scanning Initiative** (IHSI) coordinated by EMA and the **national Horizon scanning initiatives** have the aims to:

- Inform decision-makers on emerging and new pharmaceuticals for reimbursement decisions and policy development on issues that are relevant for the managed entry and monitoring of new products.
- Enhance collaboration between member states by identifying relevant issues for collaboration.
- Enable prioritisation according to potential impact.
- Allow early dialogue between relevant stakeholders.
- Understand the future regulatory challenges to come and how start dealing with them now.

The other support tools are explained in more detailed later on.

Early Advice



- **Early** stage of development
- **Informal** discussion with experts
- **Regulatory** basic orientation of product development
- **Exchange** to prepare a national scientific advice meeting
- **Free** of charge (depending on national regulations)

Contact point: Innovation Offices from each NCAs
AEMPS: innov_spain@aemps.es

An **early advice format**, e.g. kick-off meetings, pre-advice meetings, innovation meetings/innovation office advice, are usually offered by the innovation offices of each NCA. Particularly in Spain this support is given through the email detailed in the slide and it is given to researchers from academia or clinical researchers.

This advice offers a very early support tool for the researchers at an stage of the product development which can be used as a **preparatory meeting** before seeking a National Scientific Advice or getting a basic orientation on regulatory aspects of the development. It is normally **free** of charge (it differs between each NCA) and **not legally binding** and it is an informal exchange with experts on general issues.

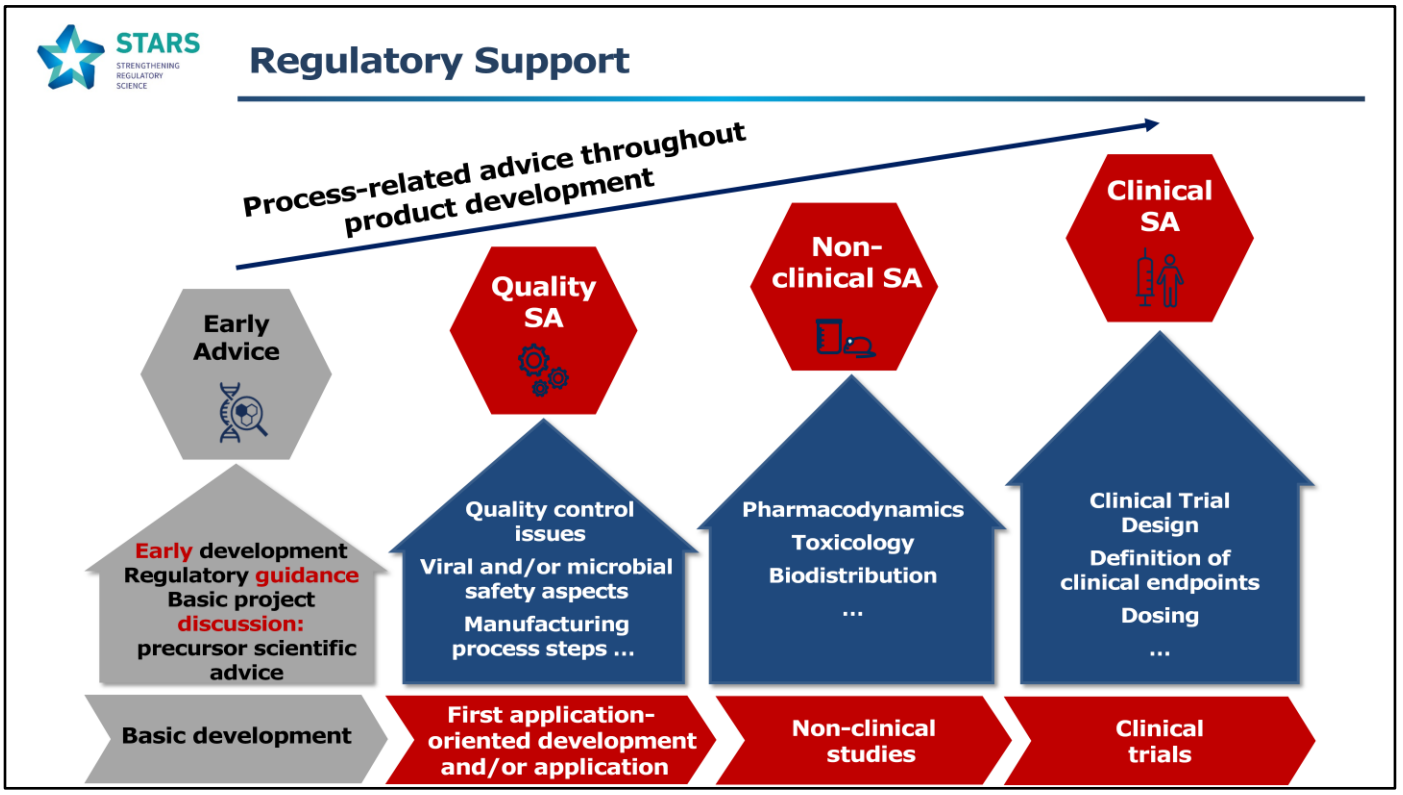
National Scientific Advice

- **Advice** on procedural and regulatory aspects
- **Life cycle** of product development
- **Focus** on product related aspects
- **Quality, non-clinical & clinical** issues
- **Stepwise** advice (several meetings parallel to product development stages)

Contact point: NCA at each Member State
AEMPS: ascina@aemps.es

The **National Scientific Advice** is given in a more structural way on procedural and regulatory aspects throughout the different stages (life cycle) of the product development. Particularly in Spain this support is given through the email detailed in the slide.

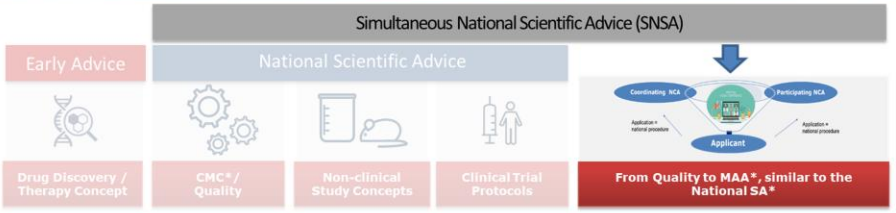
The focus of this advice format is on **product related aspects**, for example discussion of quality, non-clinical and clinical issues in one advice or as a stepwise concept in parallel to process developmental stages, which means a subsequent advice at each stage of the product development (shown in more detail later on this presentation).



As mentioned above, the regulatory support can also be helpful as an stepwise approach. The applicants have the opportunity to **address their questions process-related**. For example, a first approach would be to receive an early advice to get support on the project development, followed by a scientific advice once the product is further in the developmental process and the questions get more specific.

If it comes to the first application-oriented development and/or application the SA is of help by addressing specific questions on quality, non-clinical and clinical issues in different meetings, to get more input to improve the studies before applying to MA.

Simultaneous National Scientific Advice (SNSA)

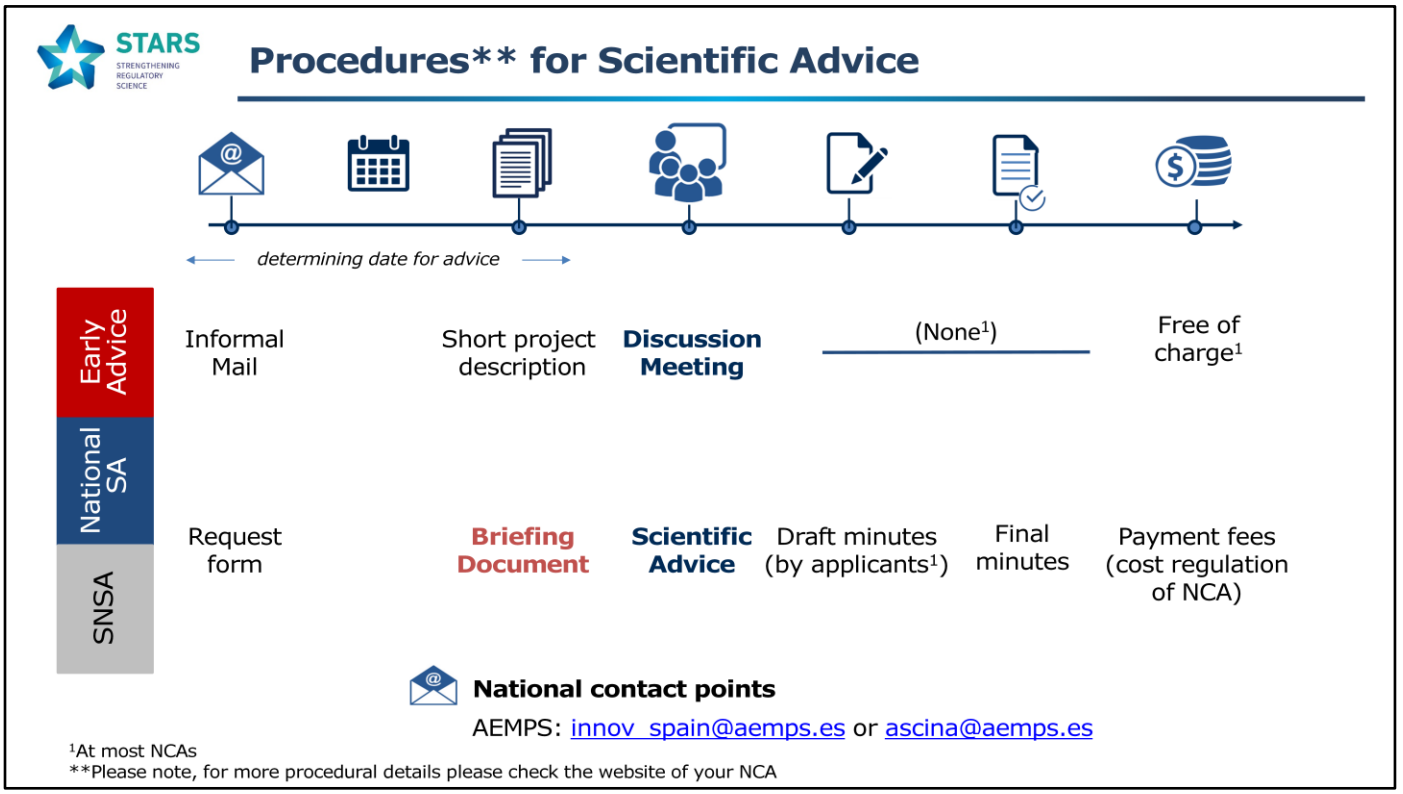


- **Multinational** support (at early stage of development)
- Avoiding significant different positions and maximise **consistency** of advice
- Early identification of **consolidated views** & divergent opinions
- **Paving way** to scientific advice at EMA, e.g. SAWP, ETF etc.
- **Supporting tool** for timelines of the new clinical trial regulation

Contact: SNSA@pei.de

Simultaneous national scientific advice (**SNSA**) gives the applicant the opportunity to get opinions from more than one NCA on the early stage of product development. The aim is to early identify consolidated or divergent views or opinions, especially with the view to align positions for multinational clinical trials. Furthermore, the SNSA can prepare the applicant for a SA at EMA, e.g. SAWP, ETF.

Such interactions are expected to **increase dialogue** between the involved agencies and sponsors from the beginning of the life cycle of a new product, provide a deeper understanding of the bases of regulatory decisions, optimise product development, and avoid unnecessary testing replication or unnecessary diverse testing methodologies.

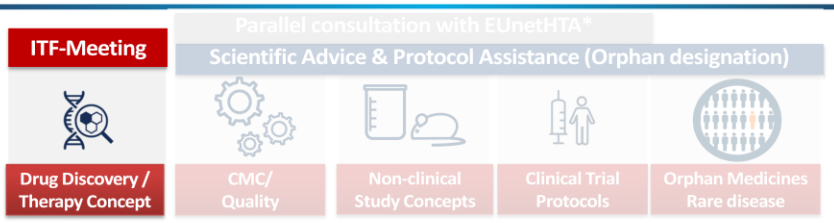


This slide shows a short overview of the procedures for applying to an early, national or SNSA advice. Note: for more procedural details please check the website of your NCA or contact your agency via email, because the timelines and documents needed to apply for an advice differ from one NCA to another.

In summary, to apply for an **early advice** an informal email is sufficient, including a short project/product description and the questions to seek advice on. In general, at many NCAs the advice is free of charge and no minutes will be drafted.

The National SA and SNSA need to be applied by a formal request form offered by the NCAs. In addition, the applicant should include a briefing document containing all the information about the product and questions with their proposed answers. The applicant will draft the minutes and they will be sent to the NCAs for revision. This advice is normally not free of charge and the cost is regulated by each NCA.

Innovation Task Force (ITF) - Meeting



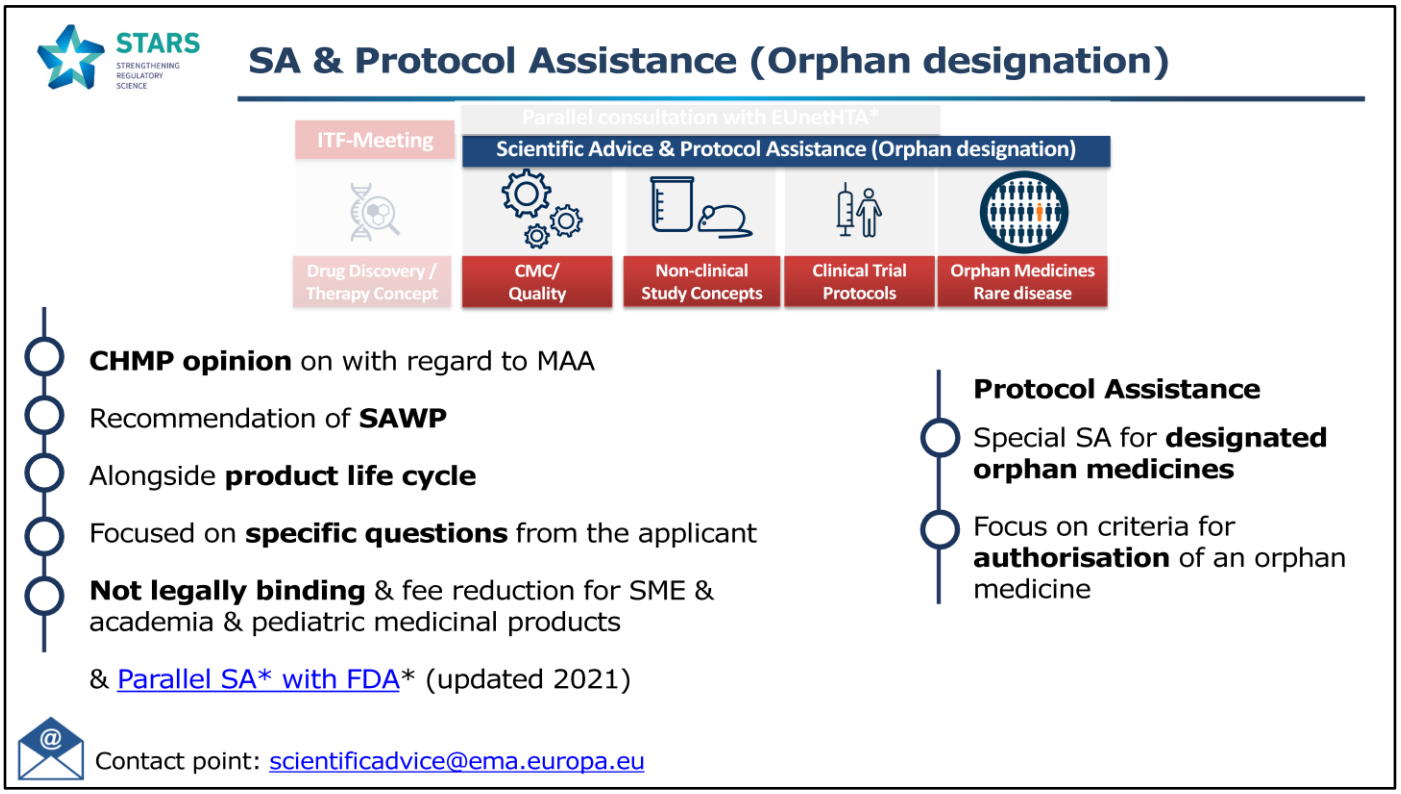
- Forum for early dialogue of medicines **innovation**
- **Emerging** therapies & technologies
- **Broad** scope: scientific, regulatory & legal
- **Advice** on specialized expertise (procedures) at an early stage
- **Multidisciplinary** expertise, involving EMA committees & working parties
- **Informal** exchange; not legally binding & free of charge

itfsecretariat@ema.europa.eu for human medicines, or
tfvet@ema.europa.eu for veterinary medicines

The **Innovation Task Force** (ITF) is a multidisciplinary group that includes scientific, regulatory and legal competences. It was set up to ensure **coordination** across the EMA and to provide a forum for early dialogue with applicants.

Objectives of the ITF:

- Establish a platform for **early dialogue** with applicants, to identify scientific, legal and regulatory issues relating to the emerging therapies and technologies.
- Provide regulatory advice on the eligibility of medicines for Agency procedures.
- Increase awareness and learning in emerging therapies and technologies at the Agency.
- Identify the need for specialised expertise at an early stage.
- Address the impact of emerging therapies and technologies on current scientific, legal and regulatory requirements with the EMA's committees and their working parties.



The **Scientific advice given by EMA** is another possibility which also helps to ensure that developers perform the appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during the evaluation of the marketing authorisation application.

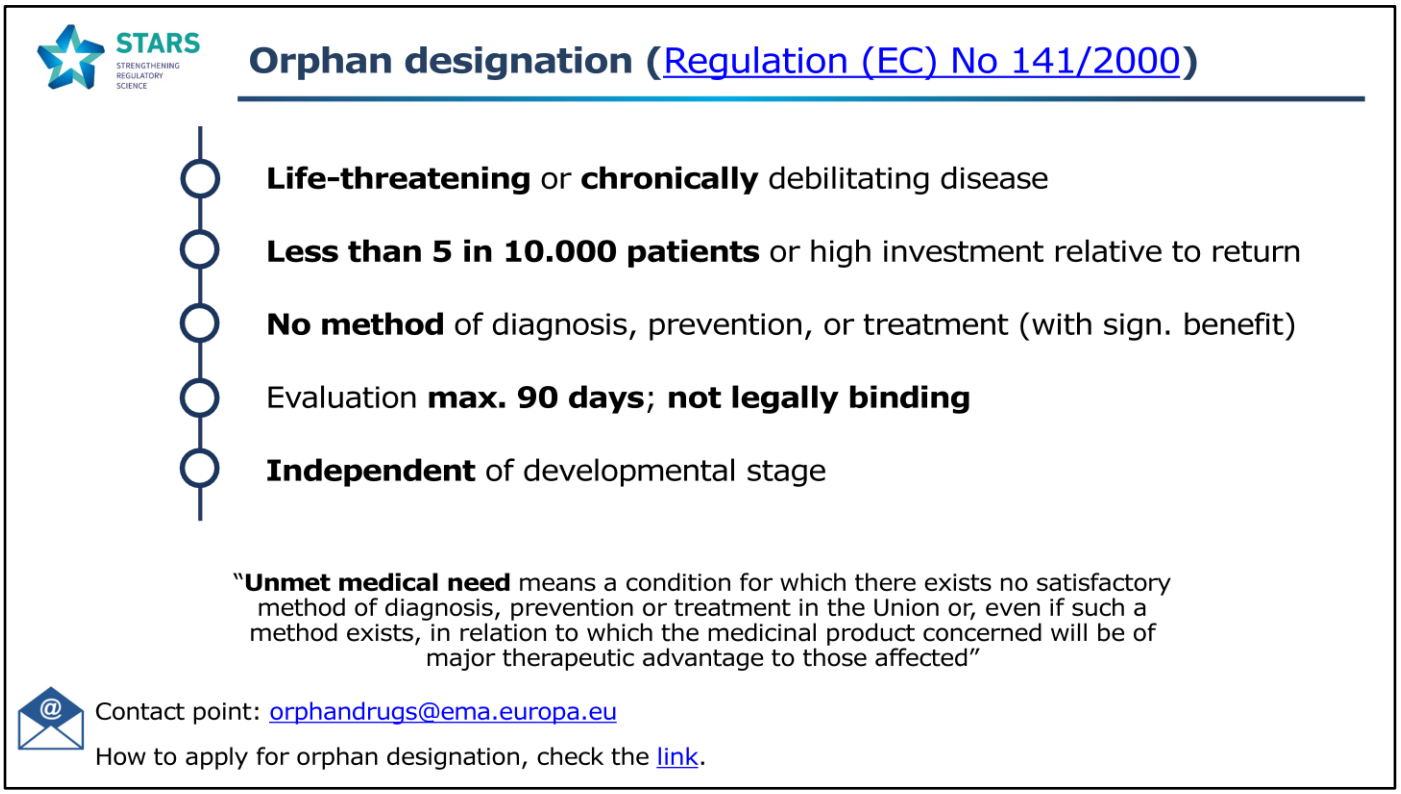
For human medicines, Scientific Advice/protocol assistance are given by the **CHMP** on the recommendation of the Scientific Advice Working Party (**SAWP**).

Scientific advice is **prospective** in nature. EMA does not pre-evaluate the results of the studies and in no way concludes on whether the benefits of the medicine outweigh the risks. Is **not legally binding**, neither for the EMA nor for the medicine developer with regard to any future marketing authorisation application for the medicine concerned.

EMA is responsible for reviewing applications from sponsors for orphan designation which is mainly focused on evaluating if the medicinal product meet the criteria to be considered an orphan medicinal product.

The **parallel SA** with the FDA of the United States has a long history and was updated in 2021. For more information please check the link on this slide.

The next slide will focus on orphan medicines in more detail.



About 30 million people living in the European Union (EU) suffer from a **rare disease**. The European Medicines Agency (EMA) plays a central role in facilitating the development and authorisation of medicines for rare diseases, which are termed **'orphan medicines'** in the medical world.

The EMA is responsible for reviewing applications from sponsors for orphan designation. To qualify for orphan designation, a medicine must meet a number of **criteria**:

- it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Applications for orphan designation are examined by the EMA's Committee for Orphan Medicinal Products (**COMP**), using the network of experts that the Committee has built up. The evaluation process takes a maximum of 90 days from validation.

For information on how to apply, see how to apply for orphan designation.

Parallel consultation with EUnetHTA

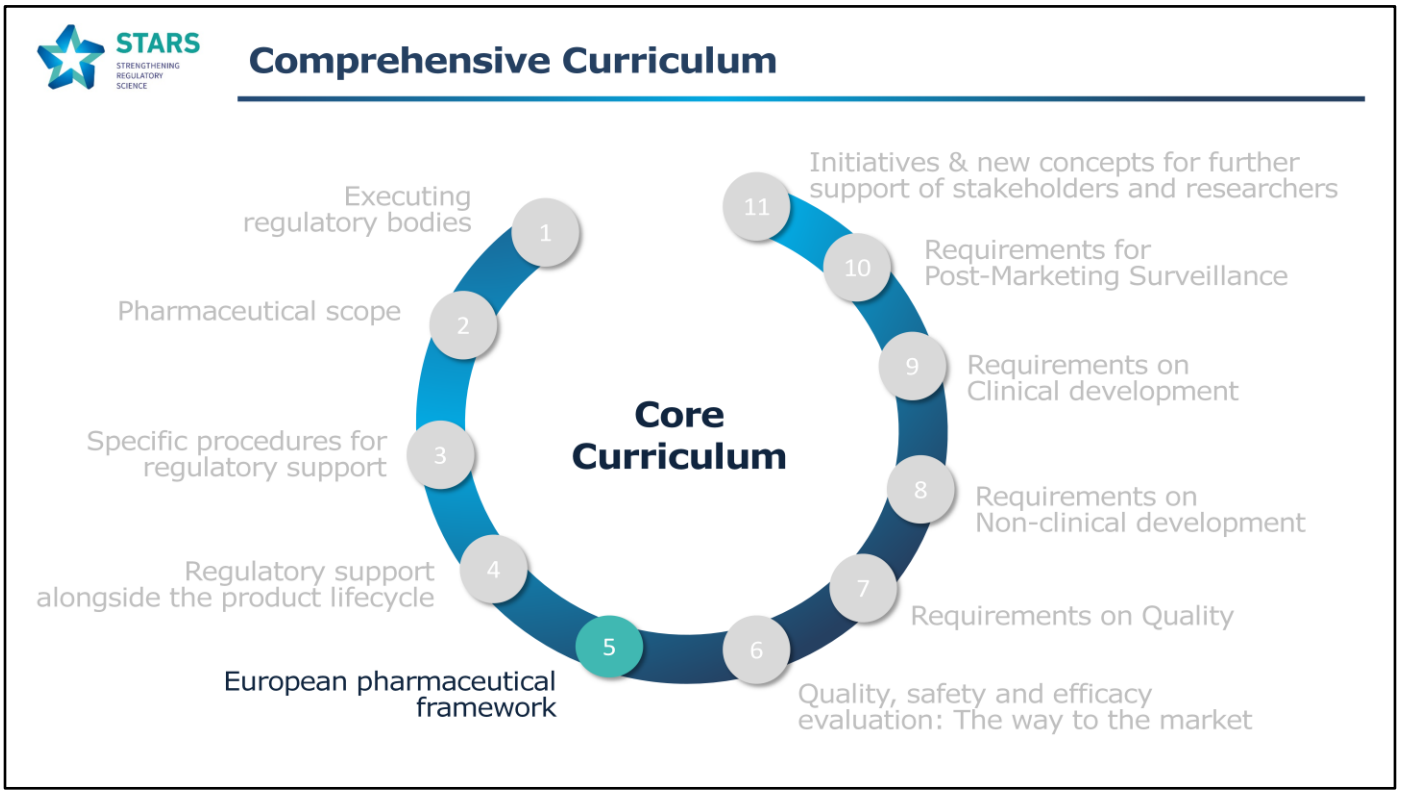
- Single gateway for **parallel consultations**
- Medicine developers can obtain feedback from **regulators and HTA bodies** in European Member States
- States on the **evidence-generation** plans to support decision-making on MA & reimbursement of new medicines at the same time
- Regulators and HTA bodies or other stakeholders to early discuss the **development plan**

Contact EUnetHTA ED secretariat:
eunethta-has@has-sante.fr

EMA parallel consultation with EUnetHTA is a initiative that replaces the former procedure by EMA and HTA bodies, whereby medicine developers had to contact Member State HTA bodies individually.

Consultations can take place **before or after** the product is placed on the EU market. The objective is to help to generate optimal and robust evidence that satisfies the needs of both regulators and HTA bodies.

Interactions between medicine developers, regulators and HTA bodies or other stakeholders to discuss the development plan enable to **generate evidence** to meet the needs of respective decision-makers as efficiently as possible. This procedure facilitates to the **patients access** to important new medicines and benefits overall public health.



European pharmaceutical framework.

Authorisation procedures within the Europe

Marketing Authorisation = allowance for market access

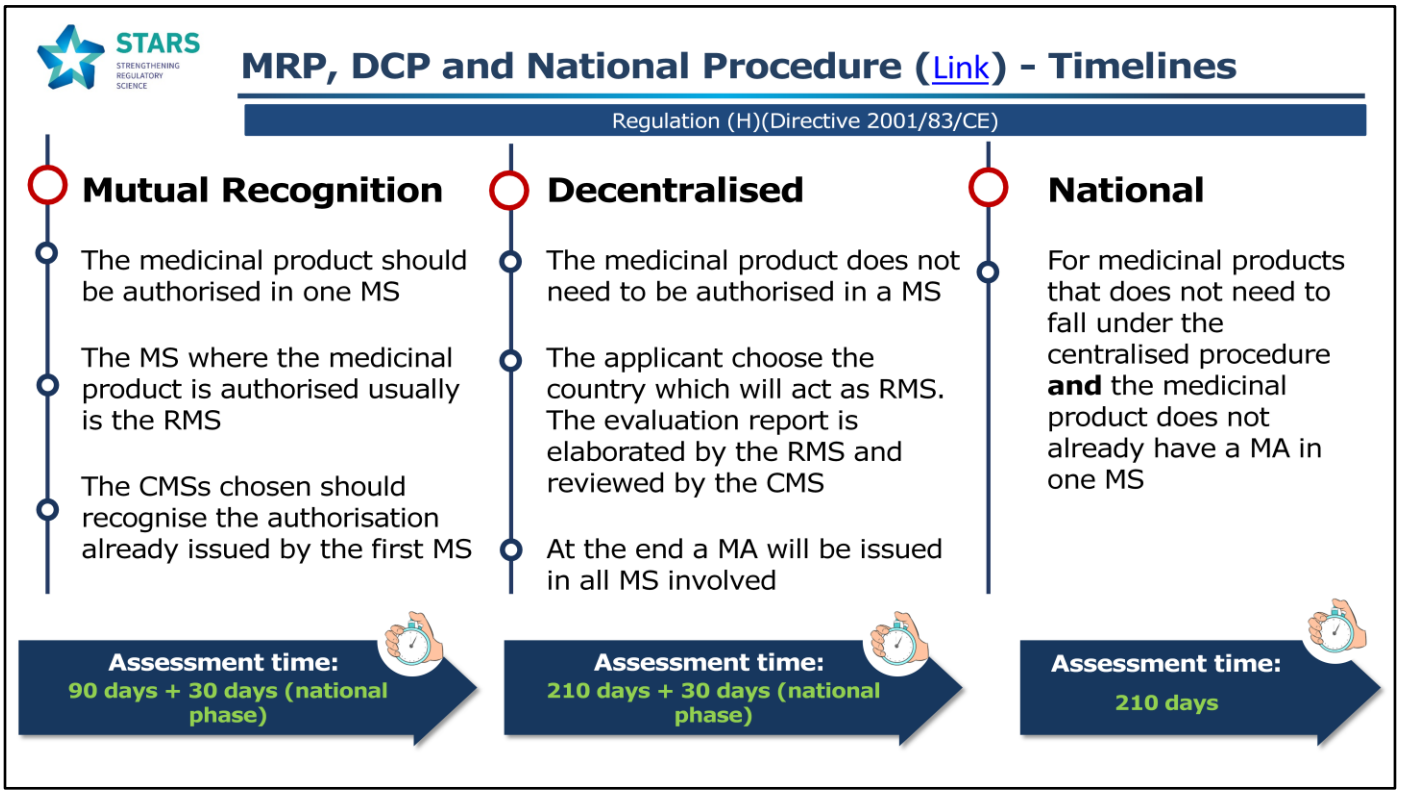
Centralised procedure ⟺ National authorisation procedure via NCAs

Authorised by the European Commision	Evaluated and Authorised by the National Competent Authority		
Centralised procedure (Evaluated by EMA)	**Mutual Recognition Procedure (MRP)** (CMDh/v)	**Decentralised Procedure (DCP)**	**National Procedure (NP)**
The applicant submits the application for obtaining a MA to the EMA in order to obtain a MA in all MS at the same time.	The medicinal product is already authorised in one MS and the applicant submits the application for obtaining a MA in other MS (CMS).	The applicant submits the application for obtaining a MA simultaneously to various MS within the EU. One acts as RMS.	The applicant submits an application for obtaining a MA in one MS.

In Europe, all medicines must have a marketing authorisation before they can be used by patients.

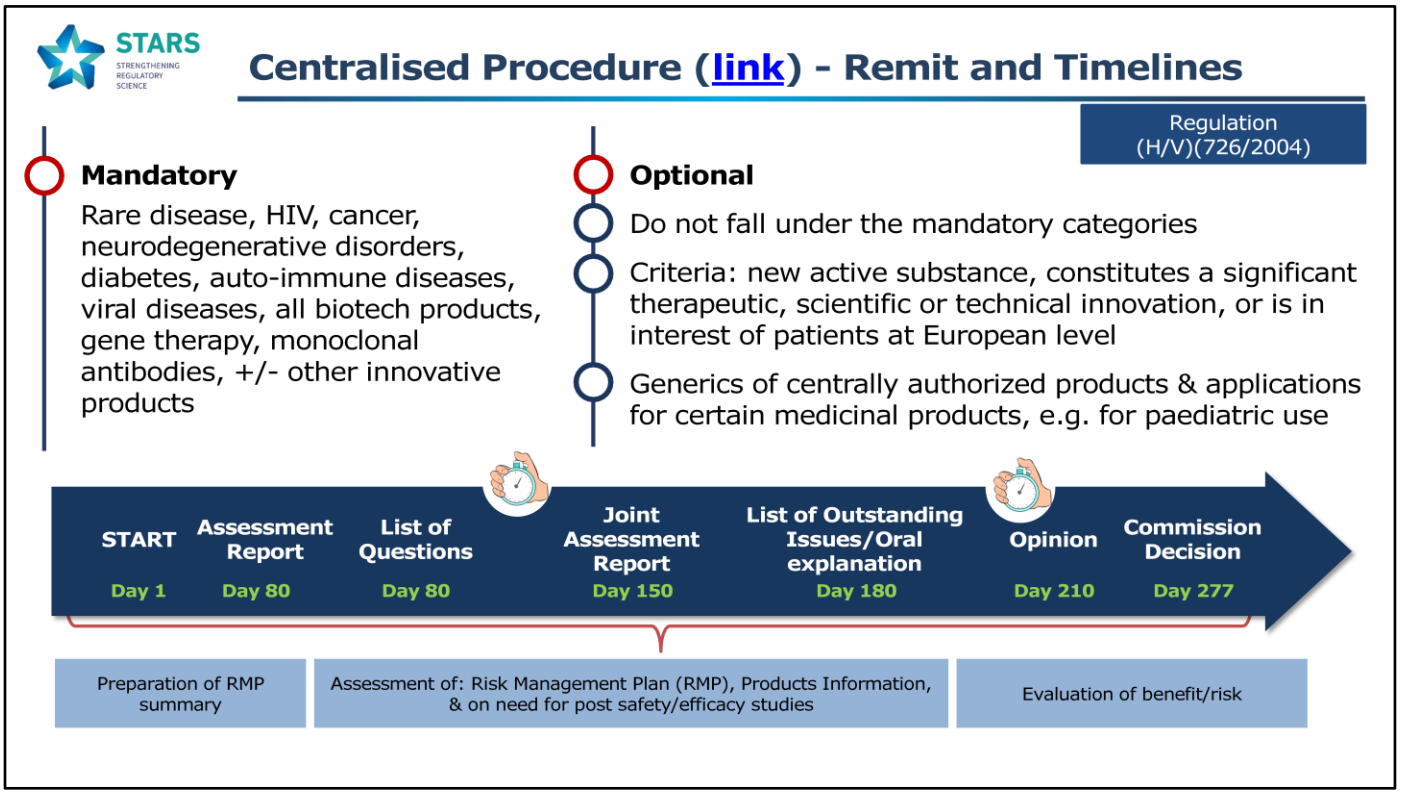
The marketing authorisation could be granted by the European Commission when the dossier has been submitted as **Centralised Procedure** (CP) after being evaluated by EMA or evaluated and authorised by the NCAs when the MA application has been submitted as **Mutual Recognition** (MRP), **Decentralised** (DCP) or **National** (NP) Procedure.

Through the **Centralised Procedure**, EMA gives an opinion and it results in a single marketing authorisation for all MS. Using the **National Procedure**, the medicinal product is authorized at national level. Using the **Decentralized Procedure** and **Mutual Recognition Procedure** the MA will be given in several MS.



The difference of choosing the MRP or DCP is that for using the former the medicinal product has to be **previously authorised in one MS**. In the MRP the MS where the medicinal product is authorised usually acts as **RMS** and the **CMSs** chosen should **recognise** the authorisation already issued by the first MS. In the DCP the medicinal product does not need to be previously authorised. The applicant chooses the country which will act as RMS and the evaluation report is elaborated by the RMS and reviewed by the CMS involved in the procedure.

This slide also show the assessment timelines among the above-mentioned procedures.



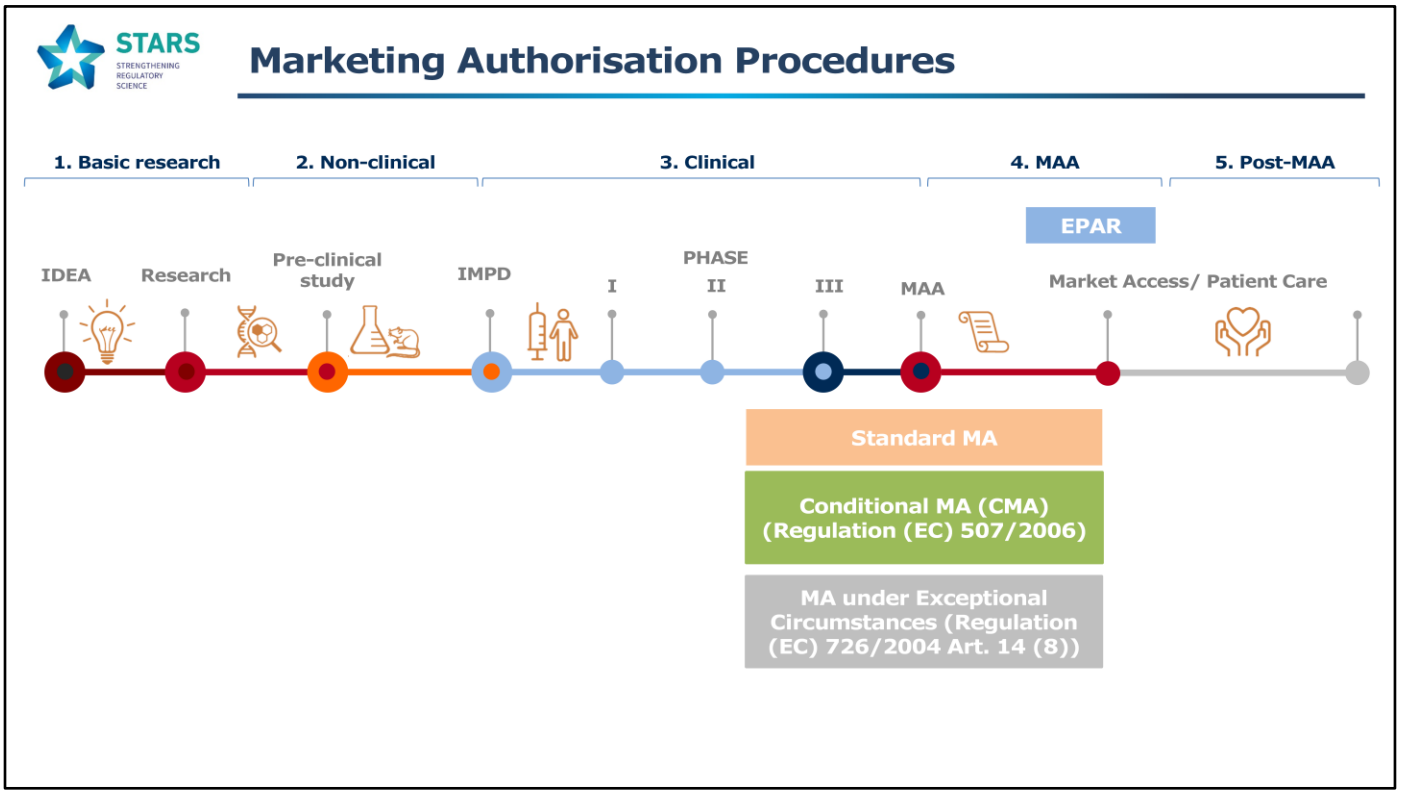
This slide shows the medicines which have to be submitted using the **CP** such as medicines for rare diseases (sometimes called orphan drugs), and for some **disease areas** like HIV/AIDS, cancer, neurodegenerative disorders and diabetes. The biotechnological products, gene therapy products, and all innovative products have also to be submitted using this procedure to the EMA. There are other medicinal products that can apply for a CP even if they do not fall under the mandatory categories just mentioned.

The EMA has specific committees and working parties (mainly constituted by assessors from the NCAs) that are specialised in the evaluation of these products and disease areas.

The assessment of an application for a new medicine can take up to 210 working days. This active evaluation time is interrupted by at least one 'clock-stop' during which the applicant prepares the answers to the questions conducted by the **CHMP**. The clock stop happens after day 120 and may also happen after day 180, when the CHMP has adopted a list of questions or outstanding issues that need to be addressed by the applicant.

The assessment leads to an opinion from the CHMP by **day 210**.

Following a CHMP opinion the European Commission takes usually its decision, a **legally binding** authorisation, after 67 days. With prior agreement, these timelines can, under some circumstances, be accelerated. For further information about this, please check EMA's Website.



Once the quality, safety and efficacy of the medicinal product has been approved a standard MA will be granted. In special cases medicinal products can also be authorised under **conditional** MA or MA under **exceptional circumstances,** which are explained in detail in the following slide.

The **EPAR** is a published information on the medicine assessed for the public and it will be explained in detail subsequently.

CMA versus Exceptional Circumstances

Regulation (EC) No 726/2004 & Regulation (EC) No 507/2006

Conditional Marketing Authorisation (CMA)	Exceptional Circumstances
Comprehensive data# not available at MAA	
• To be provided after approval	• Cannot be provided at all
• Scope: orphan drugs, emergency threats, serious and life-threatening diseases	• Criteria: rarity, state of scientific knowledge
• Approval = 1 year	• Authorisation = 5 years (renewable)
• Benefit/risk balance= annual renewal based • (review of specific obligations & reconfirmation)	• Benefit/risk balance: annual reassessment
• Provision of comprehensive data → full MA	• Full MA= provision of «full dossier» (rare cases)

#Comprehensive data: *"...it might be acceptable that studies are smaller in size and/or with a shorter duration and/or different endpoints than those normally expected for confirmatory studies in the particular indication for respective type of the medicinal product..."*

In addition to a **Standard Authorization,** where comprehensive data has been provided to enable full evaluation of quality, safety and efficacy, **Conditional Marketing Authorization** (CMA) is a pragmatic tool for the "fast-track" approval of a medicine that fulfills an unmet medical need. Despite the early approval under conditions, it guarantees that the medicine meets rigorous EU standards for safety, efficacy and quality and that comprehensive data are required to be generated post-approval.
These authorisation is valid for **one year** and can be renewed annually. Once a conditional marketing authorisation has been granted, the marketing authorisation holder must fulfill specific obligations within defined timelines. Only by the time when full data are generated by the applicant, the CMA will be converted into a standard (full) marketing authorisation.

Some medicines are approved under **Exceptional Circumstances** when the applicant is unable to provide data on the efficacy and safety of the medicine. This usually occurs when the indication is so rare that the applicant cannot reasonably be expected to provide comprehensive evidence or it is contrary to medical ethics to collect such information. It should be reviewed annually to reassess the risk-benefit balance, in an annual re-assessment procedure. It will normally not lead to the completion of a full dossier and become a standard marketing authorisation.

European Public Assessment Reports – EPAR

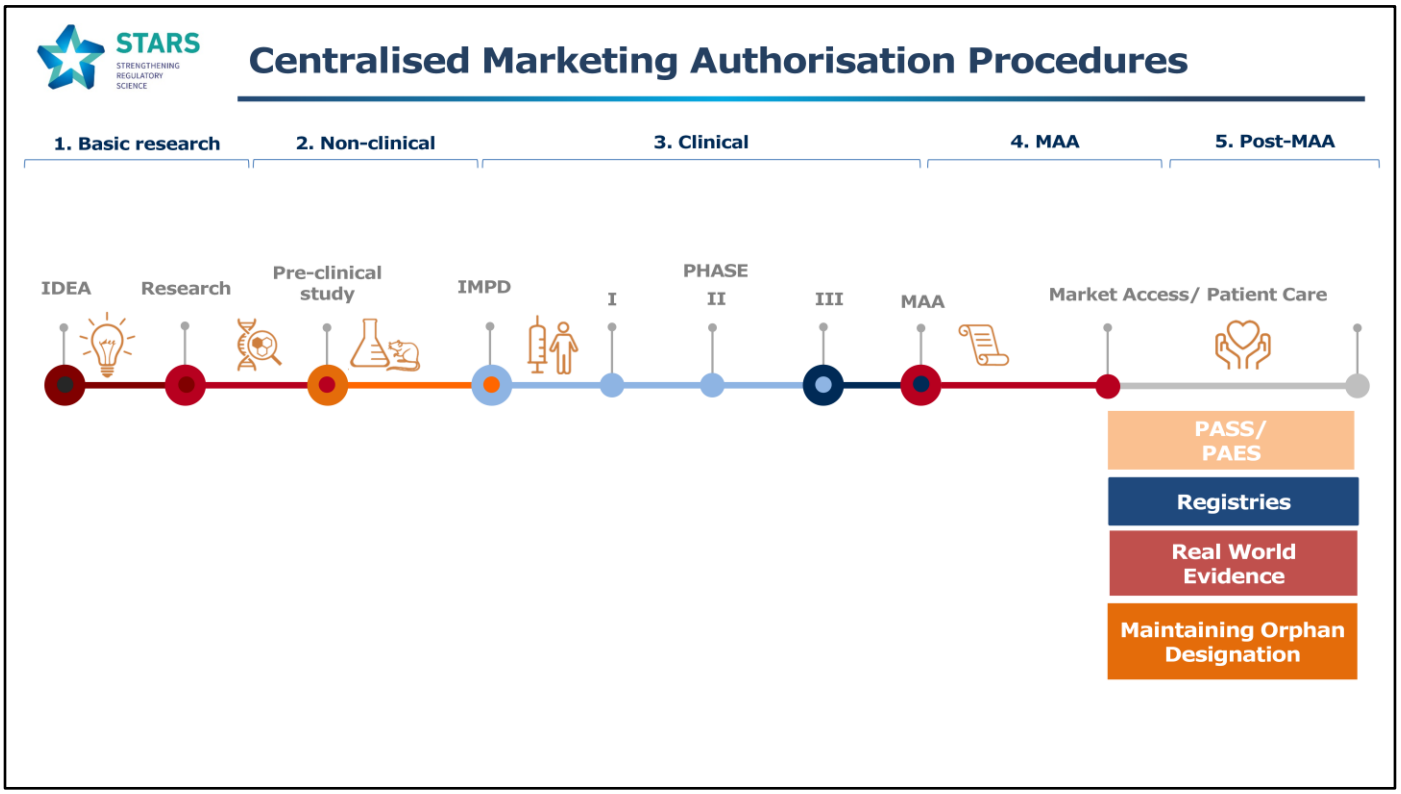
Article 13(3) of Regulation (EC) No 726/2004

- **EPAR** = public assessment report for **each centrally authorised medicine**
- Transparent and appropriately detailed body of information
- Confidential scientific assessment is removed before publishing
- EPARs periodically updated & reflect the latest regulatory information on medicines
- Some components, e.g. public-friendly overview, labelling, etc., are always published in all official EU languages

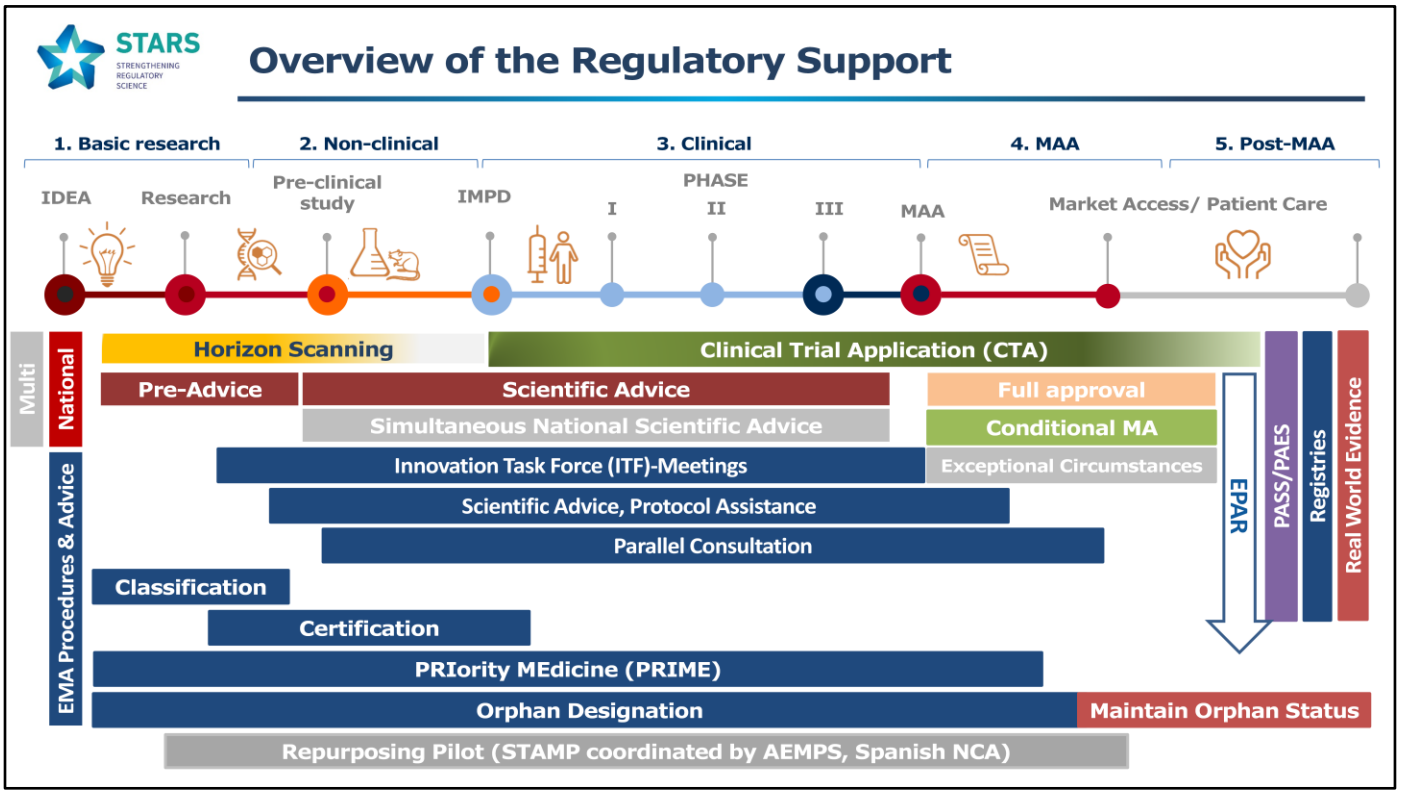
- EPAR(s) has(ve) the following structure:
  - **Overview:** public-friendly in Q&A format
  - **Authorisation details** about product & MA holder
  - **Product information:** package leaflet & summary of product characteristics; labelling; list of all authorised presentations; pharmacotherapeutic group; therapeutic indications
  - **Assessment history**, e.g. EPAR(s) for initial authorization & for any variation concerning major changes to the marketing authorisation; orphan maintenance assessment report or withdrawal assessment report…

The EMA publishes the European Public Assessment Report (more often known as **EPAR**) for all medicines granted by a marketing authorisation by the European Commission and it can be found at EMA's website.

The EPAR includes a short document written in the form of a **question and answer document** for the public that gives an overview of the process. All these documents are reviewed by patients to make sure they are understandable. Many of these documents are available in all the languages of the European Union. The EPAR summary and all package leaflets are available in all official languages of the European Union.

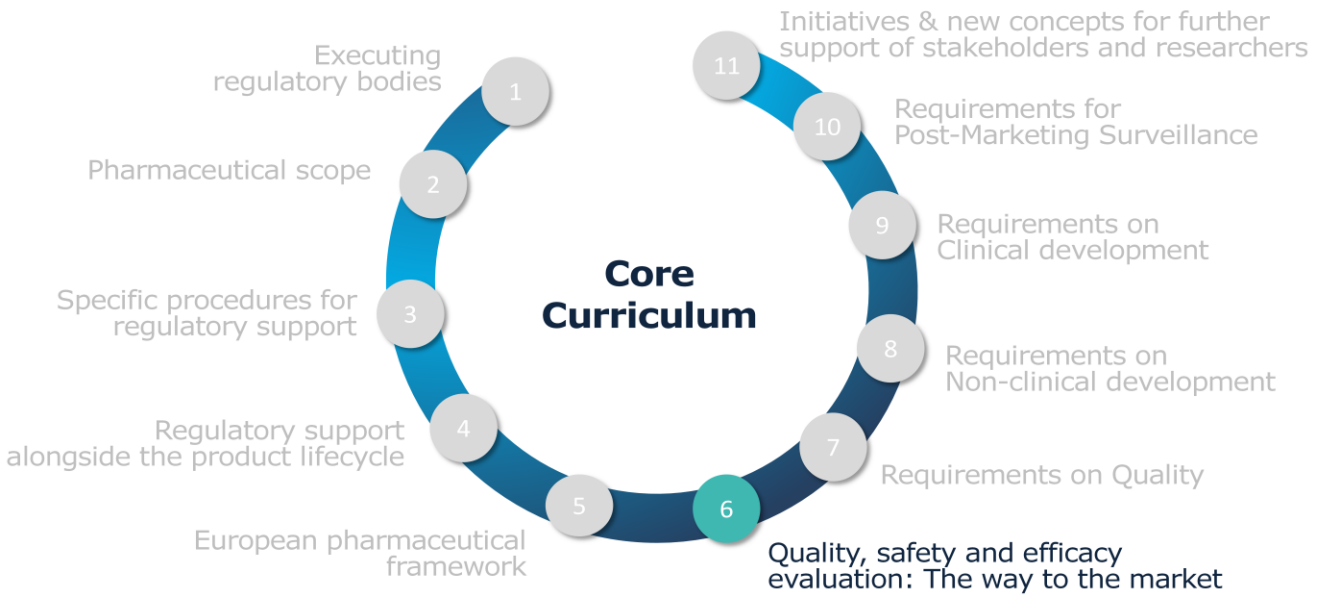


After obtaining the marketing authorisation the applicant will need to complete data using registries, gather **real world evidence** and maintain the orphan drug designation, if this case is given. For more detials please refer to the clinicial part of this presentation.



Overview of the regulatory procedural and supporting landscape throughout Europe.

Comprehensive Curriculum

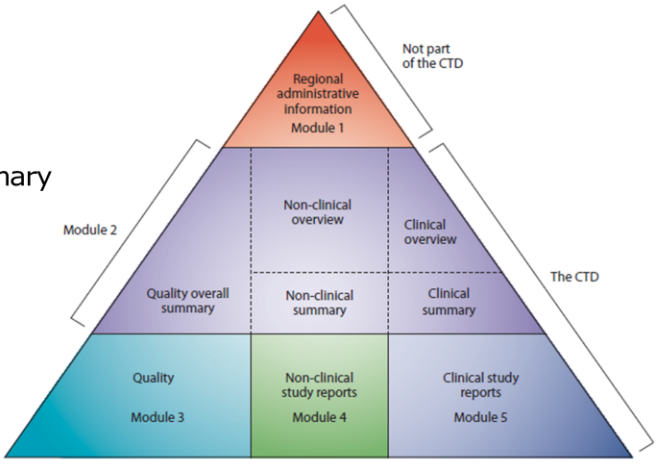


Quality, safety and efficacy evaluation: The way to the market.

Common Technical Document (CTD)

Common Technical Document

Module 1	Administrative information
Module 2	Quality overall summary
	Non-clinical overview & summary
	Clinical overview & summary
Module 3	Quality data (specifications, stability studies, process validation, etc.)
Module 4	Non-clinical study reports
Module 5	Clinical studies reports



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

The application for obtaining a MA has to follow the format of the Common Technical Document (**CTD**). It is an internationally agreed format which was developed by EMA, FDA and Japanese ministry of Health. Its overall structure is detailed in the ICH website.

The CTD is organised into five modules.

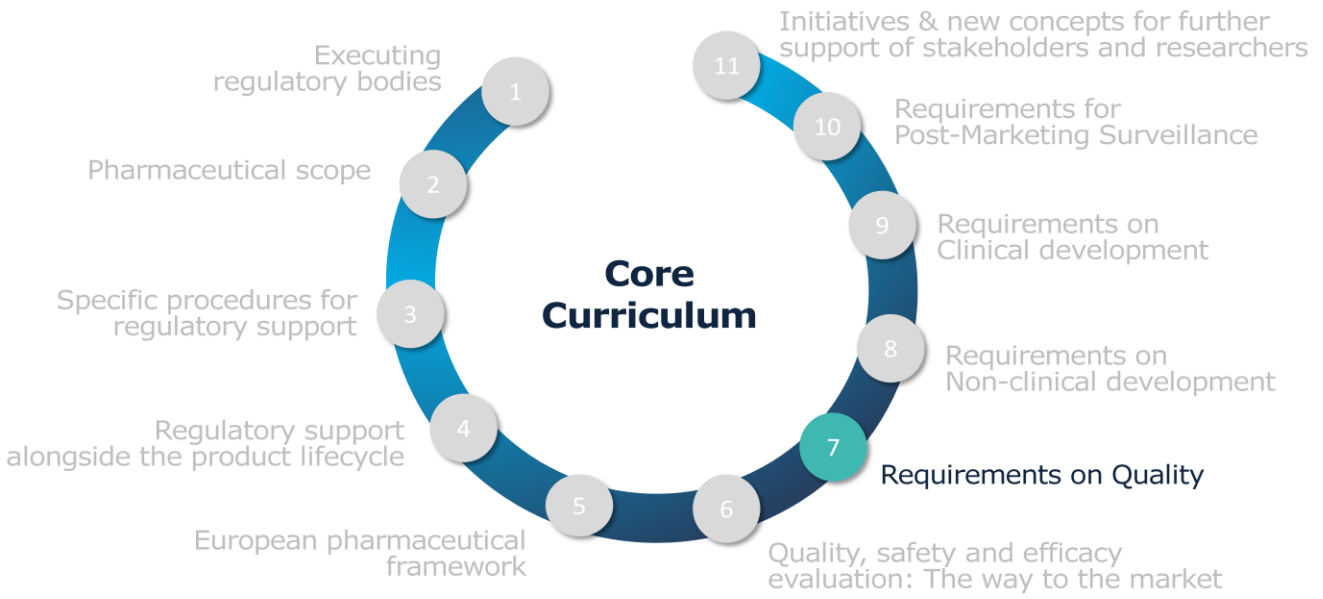
- **Module 1** is the administrative information
- **Module 2** contains the overall summaries for quality, non clinical and clinical
- **Module 3** is dedicated to quality
- **Module 4** contains the non-clinical reports
- **Module 5** contains the clinical reports

Links to EMA Scientific Guidelines & ICH Guidelines

- Search for scientific guidelines
- Quality guidelines
- Quality of medicines: questions and answers
- Biological guidelines
- Non-clinical guidelines
- Clinical efficacy and safety guidelines
- Multidisciplinary guidelines
- International Conference for Harmonisation (ICH) guidelines

The Guidelines are not mandatory but reflect a **harmonised approach** of the EU Member States and the EMA on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives. For further details please click on the links given in the slides (blue).

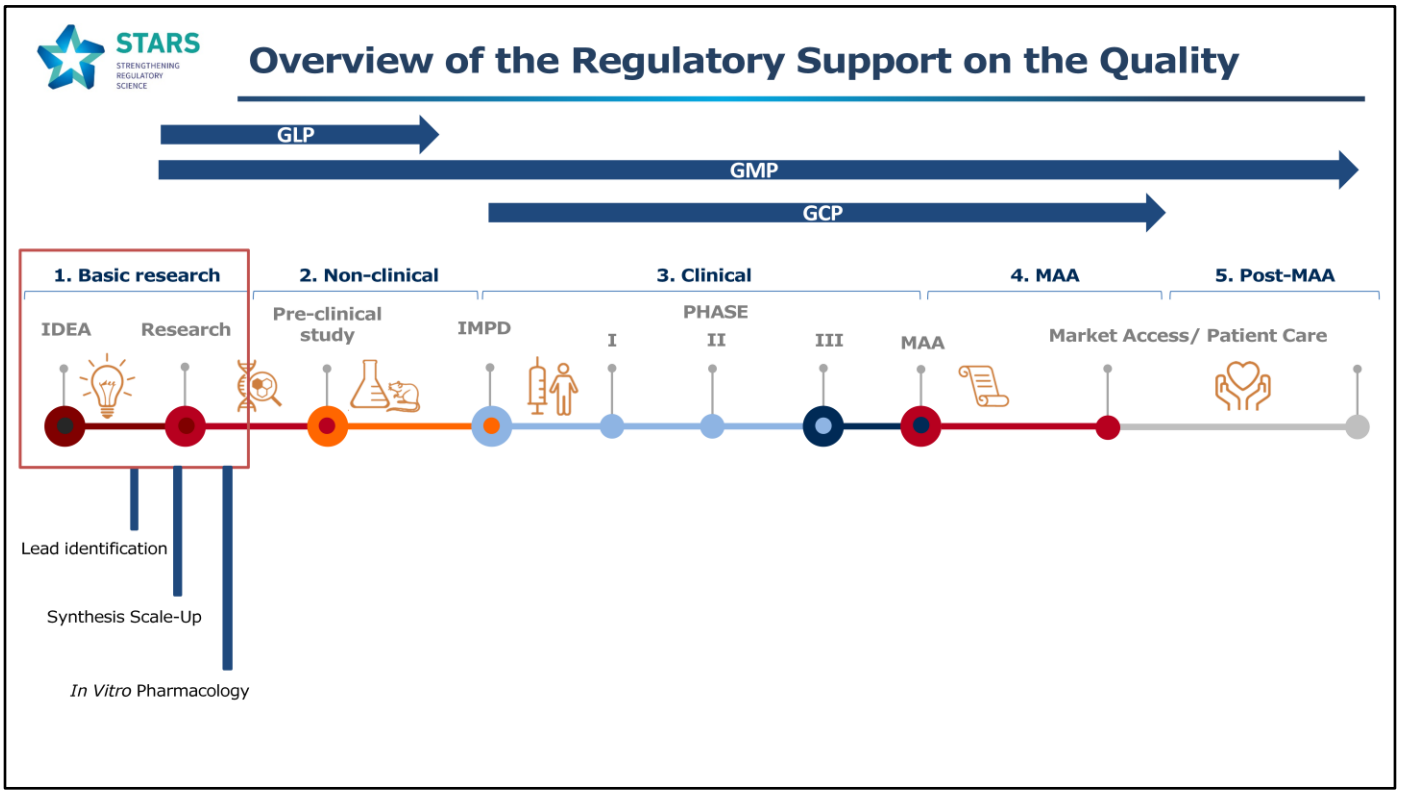
Comprehensive Curriculum



Requirements on Quality.

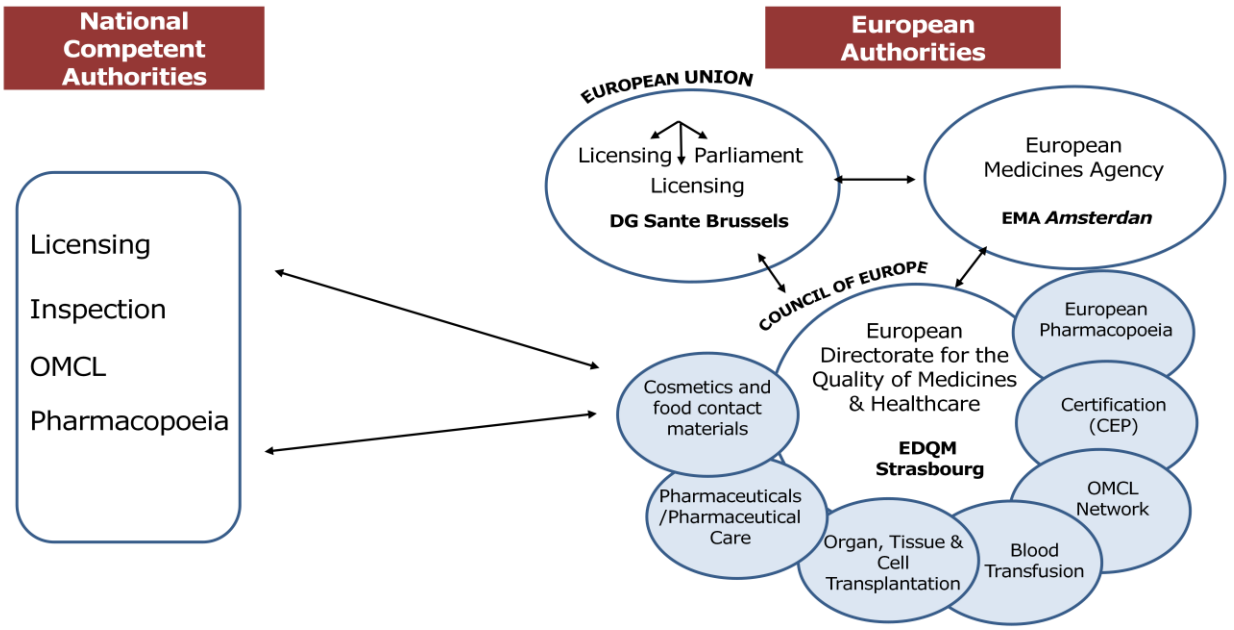
Abbreviations

API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
ATMP	Advanced Therapy Medicinal Product
BWP	Biologics Working Party
CAT	Committee for Advanced Therapies
CEP	Certificate of Suitability
CHMP	Committee for Human Medicinal Products
CMDh	Co-ordination Group for Mutual Recognition & Decentralised procedures - Human
DP	Drug Product
DS	Drug Substance
EC	European Commission
EDQM	European Directorate for the Quality of Medicines and healthcare
EMA	European Medicines Agency
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMPD	Investigational Medicinal Product Dossier
ITF	Innovation Task Force
MAA	Marketing Authorisation Application
NCA	National Competent Authority
OMCL	Official Medicines Control Laboratories
Ph.Eur.	European Pharmacopoeia
QWP	Quality Working Party
TSE	Transmissible Spongiform Encephalopathies



This part will be focused on the quality that the product should have in order to apply for a MA.

Interrelations between National & European Authorities



This slide shows the **interrelations** between National and European Authorities and the activities carried out by them.

European Directorate for the Quality of Medicines & HealthCare - EDQM

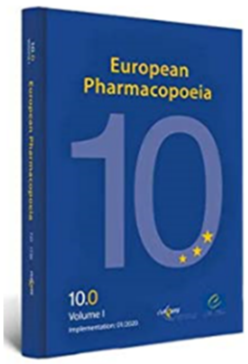
- **EDQM** contributes to basic human right of access to good quality medicines & healthcare, & promotes & protects human and animal health by:
- Establishing & providing **official standards** for the manufacture & quality control of medicines
- Granting Certificates of suitability (**CEP**)
- Coordinating a network of Official Medicines Control Laboratories (**OMCL**)
- Proposing ethical, safety & quality standards for **blood transfusions**, **organ**, **tissue & cell transplantation**
- Working with national, European & international organisations in efforts to combat **counterfeiting/falsification** of medical products
- Providing policies & model approaches for the **safe use** of medicines
- Establishing standards for **cosmetics & food contact materials**

Among the authorities shown on the previous slide we would like to emphasise the role of the EDQM. The government body is the **European Pharmacopoeia Commission** which is responsible for the maintenance of its content, but is the EDQM which provides the **scientific and administrative support** and issues the **certificates of suitability**, which verify the compliance of pharmaceutical substances with European pharmacopoeia standards.

Their main activities are described in this slide.

Pharmacopoeia

(European Pharmacopoeia, United States Pharmacopoeia – National Formulary, Pharmacopoeia of each member state)



- General notices
- General chapters
- General monographs
- Individual monographs

- Provide **common quality standards** throughout the pharmaceutical industry
- Collection of **monographs** describing both the individual & general quality standards for substances, dosage forms, medicines & analytical methods
- **Legally binding** & apply throughout the entire lifecycle of a product
- Certificates of suitability (**CEPs**)– quality of a given substance can be suitably controlled by the PhEur. monograph – not for biological
- **TSE**

For products under development, which are products in clinical trials, reference to either the European Pharmacopoeia, or the Pharmacopoeia of each member state, or the United States Pharmacopoeia, or the Japanese Pharmacopoeia are acceptable within the regulatory framework.

The European Pharmacopoeia is a single reference publication providing **common quality standards** throughout the pharmaceutical industry in the European Union. The Ph. Eur. is a **collection of monographs**, which describe both the individual and general quality standards for pharmaceutical preparations, their constituents, dosage forms, and analytical methods.
Some requirements may apply simultaneously to **all classes of substances** and are covered by several general monographs and some other requirements are **specific** for a single substance. Monographs including the general monographs and chapters are **legally binding** unless the scope of the particular monograph clearly states that the text is not mandatory.

The quality standards of the European Pharmacopoeia should apply throughout the entire **life-cycle** of the product.
The quality of a given substance can be suitable controlled by corresponding Ph. Eur. monographs issuing a **CEP**. The certification is not limited to controlling just the **chemical** quality of the pharmaceutical substances, but it is also extended to products with risk of Transmissible Spongiform Encephalopathy (**TSE**).

CEP does **not** apply **for biologicals**.

Legislative framework

EudraLex Volume 4: Principles and detailed guidelines of GMP for medicinal products

ICH Guidelines for Quality

Q1A–Q1F	Stability
Q2	Analytical validation
Q3A–Q3D	Impurities
Q4–Q4B	Pharmacopoeias
Q5a–Q5E	Quality and biological products
Q6A–Q6B	Specification
Q7	Good manufacturing Practice
Q8	Pharmaceutical development
Q9	Quality risk management
Q10	Pharmaceutical quality system
Q11	Development and manufacture of drug substance
Q12	Lifecycle management

Quality EMA Quality

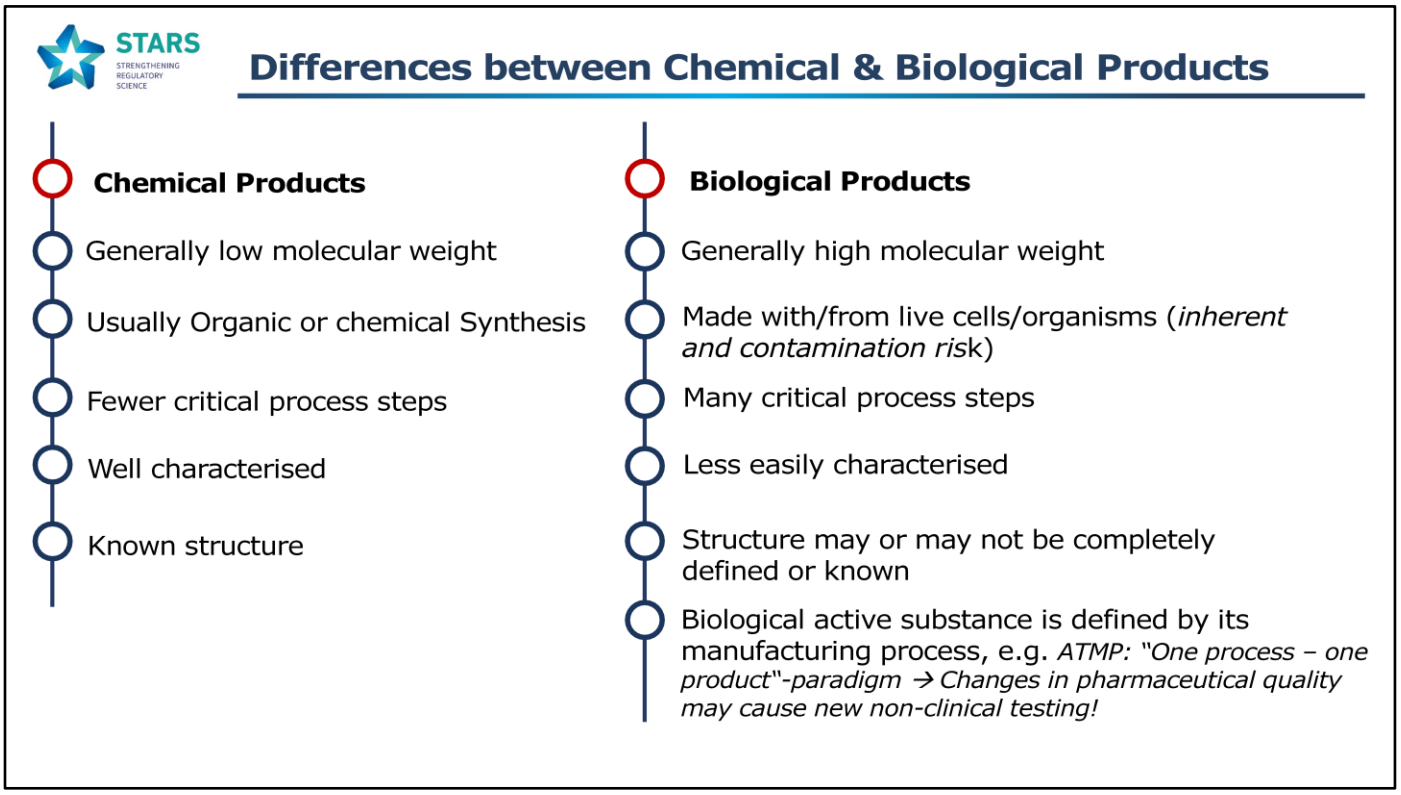
- Active substance
- Manufacturing
- Impurities
- Specifications, analytical procedures and analytical validation
- Excipients
- Packaging
- Stability
- Pharmaceutical development

This slide summarises the legislative framework, which set standards to ensure the quality that will affect on the safety and efficacy for the investigation of medicinal products.

EudraLex Volume 4 contains guidance for interpretation of the principles and guidelines of **Good manufacturing practice** for medical product.

Other important guidelines can be found on the ICH website and on the EMA website. These are scientific guidelines prepared via a process of **scientific consensus** with industry experts and regulatory authorities working side-by-side. These guidelines are **not legally binding**; however, they should be considered as harmonised community position on how to demonstrate the quality, safety and efficacy of medicinal products. The Agencies strongly encourage the manufacturers and sponsors to follow these guidelines. Any **deviation** from these guidelines should be appropriated justified. These guidelines also **complement** the European Pharmacopoeia monographs. Besides, on EMA and ICH websites sections dedicated to quality guidelines and guidelines for biological medicines can be found.

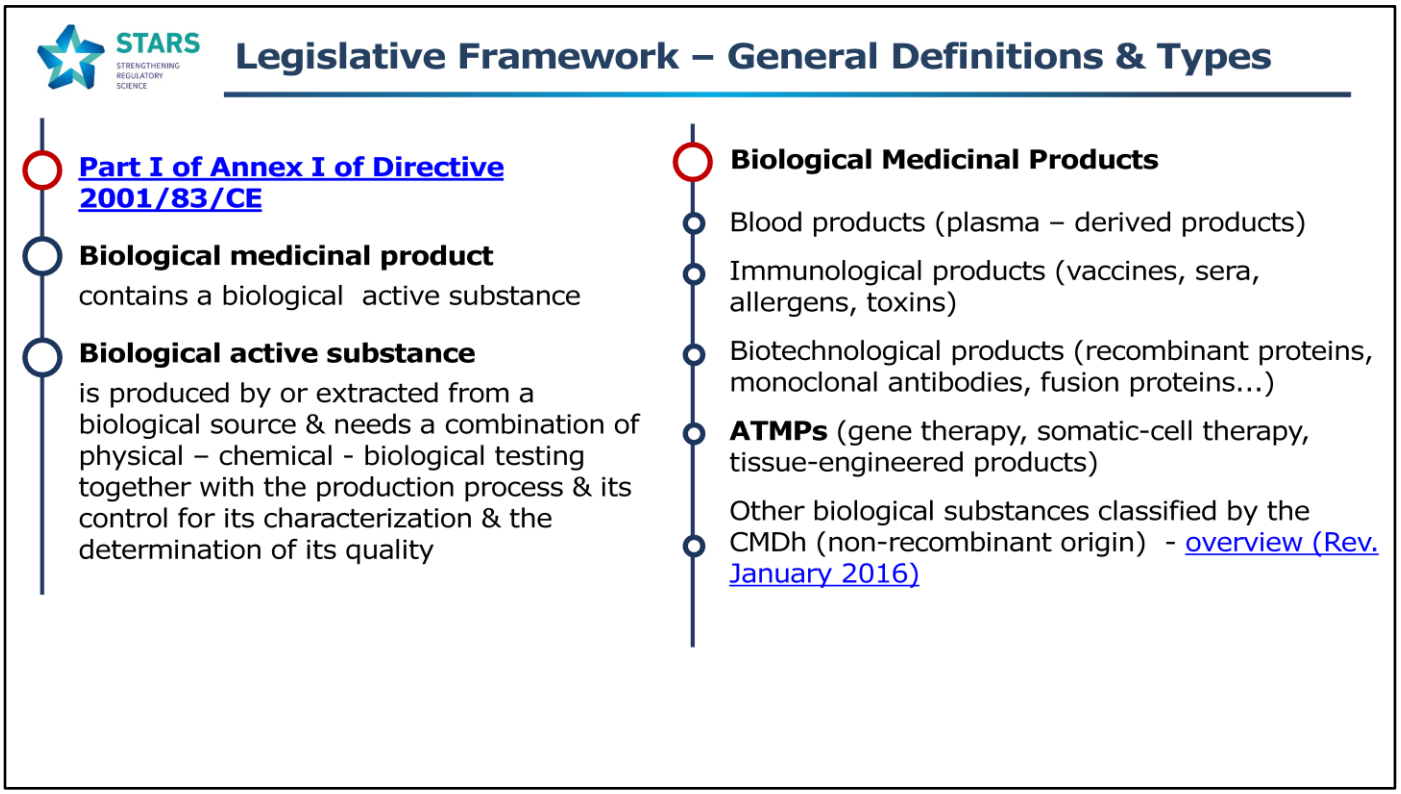
Harmonisation achievements in the Quality area include **pivotal milestones** such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.



This slide summarises the main differences between the chemical and biological products. Requirements for chemical and biological products are different; therefore, different guidelines and different requirements have to be applied.

The **chemical products** are well-characterised products with known structure, with generally low molecular weight, and are usually synthesised by a organic or chemical way with fewer critical process steps.

The **biological products** have generally less easily characterised high molecular weight, whose structure may or may not be completely defined or known, and they are made with or from live cells or organisms with many critical process steps.



Some parts of the IMPD (detailed information will be in a following slide) are required only for biological products. The legislation framework, the general definition for the biological products and active substance can be found in **Part I of Annex I of the EU Directive 2001/83/EC**.

A **biological medicinal product** is a product which contains a biological active substance. A **biological active substance** is a substance that is produced by or extracted from a biological source and that needs a combination of physical – chemical - biological testing together with the production process and its control for its characterisation and the determination of its quality.

On the right side of the slide, it can be seen the summary of biological products according to the legislation in EU. These are **blood** products, **immunological** products, **biotechnological** products, **advanced therapy** medicinal products and **other** biological substances which are classified by CMDh.

Relevant EMA guidelines for Biological Medicinal Products

EMA Guidelines

CHMP/BWP/534898/2008 rev.1

Requirements for quality documentation concerning biological investigational medicinal products in clinical trials

EMA/CAT/852602/2018 DRAFT

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

CHMP/BWP/398498

Virus safety evaluation of biotechnological investigational medicinal products

ICH Guidelines

ICH Q5D

Derivation & characterisation of cell substrates used for production of biotechnological/biological products

ICH Q6B

Specifications: test procedures & acceptance criteria for biotechnological/biological products

This slide shows **relevant EMA guidelines**. For conducting a **clinical trial** the most important guidelines for biological products are the **CHMP guidelines**:

- "Requirements for quality documentation concerning biological investigational medicinal products in clinical trials"
- "Virus safety evaluation of biotechnological investigational medicinal products".

The **ATMPs** are excluded from the scope of this guideline. There is a draft guideline regarding this type of products: "EMA/Committee for Advanced Therapy guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials".

It is also possible and highly recommended to use **specific ICH guidelines** for the development and the requirements of dossier for biological products:

- **ICH Q5D** "Derivation and characterisation of cell substrates used for production of biotechnological/biological products"
- **ICHQ6B** "Specifications: test procedures and acceptance criteria for biotechnological/biological products".

IMPD (Investigational Medicinal Product Dossier)

- It is a key document related to the Drug Product required for approval of the clinical trial applications (**CHMP/QWP/545525/2017 guideline**)
- It is divided into 4 distinct sections:
  A. Quality (Chemistry, Manufacturing & Controls data)
  B. Non-clinical pharmacology & toxicology data
  C. Previous clinical trial & human experience data
  D. Overall risk & benefit assessment
- Information on quality, manufacture & control of IMPs
  - ✓ Adapted to the existing level of knowledge & phase of development
  - ✓ Most up-to-date information
  - ✓ Different amount of information for each product (limited data should be justified)
- Full IMPD vs. Simplified IMPD

From the quality point of view, the **Investigational Medicinal Product Dossier** is a key document related to the drug product required for approval of the **clinical trial application**. The IMPD not only forms the basis for clinical trial approval through subsequent modifications and amendments, but also forms the basis for the **dossier to support a future marketing authorisation application**. So the informative value of the IMPD is significant for the overall success of the drug development programs.

The IMPD contains information on the **quality**, **manufacture** and **control** of all investigational medicinal product used in each clinical trial. Its content should be adapted to the existing level of knowledge and product phase of development which means that is should contain the most up-to-date information relevant to the clinical trial available at the time of submission of the application. The IMPD does not need to be a large document, the amount of information contained in the dossier is dependent of various factors, such as the nature of the product, indication, patient population or phase of development. If there is limited, or not available data it must be properly justified.

Full IMPD is required if there is no marketing authorisation in the community, meanwhile **simplified IMPD** will be sufficient if the information has already been assessed. There are situations in which the summary of product characteristic of commercial product (SmPC) will substitute the IMPD.

For biological product there are some differences in the requirements of the dossier.

Classification of active substances

Guideline on summary of requirements for active substances in the quality part of the dossier (**CHMP QWP/297/97 rev. 1 corr**)

Certificate of suitability to the monographs of the European Pharmacopoeia (CEP)

- Used for existing substances described in the Ph. Eur.

Active Substance Master File (ASMF)

- Applicable to all active substances (new and existing active substances)

Full details of manufacture in Marketing Authorisation Application

- It can be used for all active substances (new and existing active substances)

The **drug substance** section of the dossier is acceptable to be referred by the active substance master file (**ASMF**), the certificate of suitability (**CEP**) or **full details** of the manufacture in the Marketing Autorisation Application.

The CEP can be used for existing substances described in the Ph. Eur., while the ASMF is applicable to all active substances (new and existing active substances), so as the submission of full details for the manufacture in Marketing Authorisation Application.

Drug Substance & Drug Product section

Drug Substance section

Reference to ASMF or CEP

Full data

2.1.S Drug substance

- 2.1.S.1 General information
- 2.1.S.2 Manufacture
- 2.1.S.3 Characterisation
- 2.1.S.4 Control of the drug substance
- 2.1.S.5 Reference standards or materials
- 2.1.S.6 Container closure system
- 2.1.S.7 Stability

2.1.S.4 Control of DS	Phase I	Phase 2	Phase 3
2.1.S.4.1 Specification	Batch results may be acceptable	Preliminary specification	Specification
2.1.S.4.3 Validation of analytical procedures	Table of acceptance criteria for validation	Tabulated summary of validation results	
2.1.S.4.4 Batch analyses	All batches used so far	Current batches	

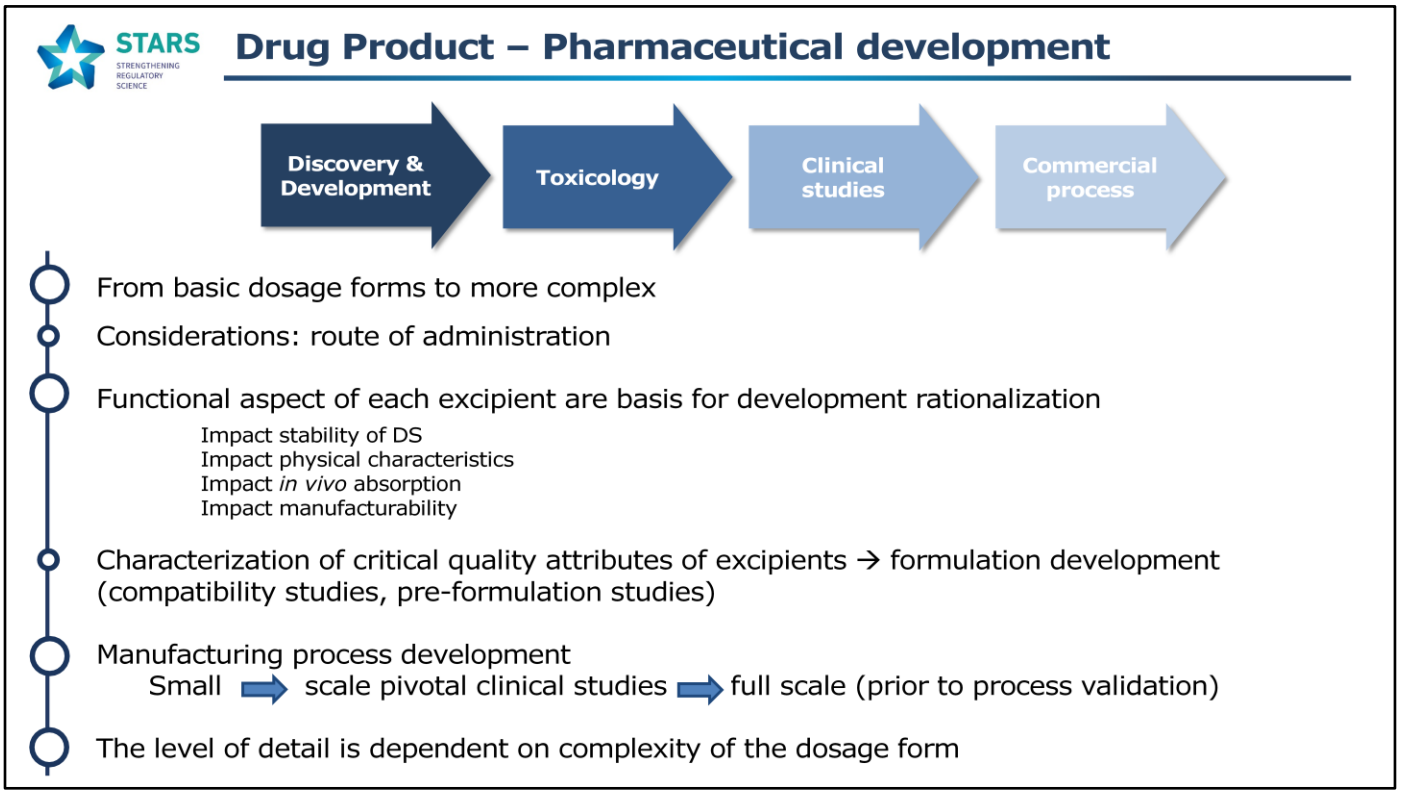
Drug Product section

2.1.P Drug product

- 2.1.P.1 Description and composition
- 2.1.P.2 Pharmaceutical development
- 2.1.P.3 Manufacture
- 2.1.P.4 Control of excipients
- 2.1.P.5 Control of the IMP
- 2.1.P.6 Reference standards or materials
- 2.1.P.7 Container closure system
- 2.1.P.8 Stability

2.1.P Drug product	Phase I	Phase 2	Phase 3
2.1.P.2 Pharmaceutical development	Short description where applicable	Brief summary (changes of clinical relevance)	Summary (changes of clinical relevance)
2.1.P.3.4 Control of critical steps and intermediates	Data for non-standard processes and sterile products		Control of critical steps and intermediates
2.1.P.5.1 Specification	Batch results may be acceptable	Preliminary specification	Specification
2.1.P.5.3 Validation of analytical procedures	Table of acceptance criteria for validation	Tabulated summary of validation results	

The sections on the CTD are similar for the **drug substance** and for the **drug product**. It can be noticed that, additionally to the specification and validation of analytical methods, the pharmaceutical development of the drug product should also be discussed regarding the phase of the development.



Once the main compound has been identified, its efficacy and toxicity should be evaluated in pre-clinical trials. Whether those results are promising it can be further evaluated in clinical studies and subsequently the product could be authorised (that is the basic concept of pharmaceutical development).

In general, more basic dosage forms should be selected at the beginning of the development, taking into account that the route of administration is determined by the characteristics of the active substance, the intended use and site of action. The functional aspects of each excipient should be also considered at the development of the product formulation, as they may have an impact on the stability of the API, the physical characteristics, *in vivo* absorption and the manufacturability. Additionally, identification of critical physico-chemical characteristics of the drug substance and excipients through compatibility and pre-formulation studies is crucial for the formulation development. Commonly, parameters to be evaluated during pre-formulation studies include particle size, solubility or dissolution behaviour.

After the characterisation of the drug substance (the excipients and their potential interaction), the manufacturing process development can proceed. It begins at the small scale and then continues to a minimum of 10% of full production scale for pivotal clinical studies for ultimately arrive to the full scale production, meaning batches production, which are made before the validation of the process.

The level of detail which should be provided for pharmaceutical development is dependent on the complexity of the dosage form and on the stage of development.

For biologicals, the manufacturing process differs from the manufacturing process of the

chemical APIs. Its process is split into downstream and upstream and it is a complex process. Indeed, any variation on the process could have an impact on the quality, safety and efficacy of the drug substance and drug product.

Drug Product – Dosage forms

- Designed for easy and accurate administration
- Classification:
  - Based on route of administration
  - Based on the physical form
- Requirements for different dosage forms are specified in the European Pharmacopoeia
- Additional requirements for dosage forms that need to be reconstituted prior to administration (e.g. powder for solution for infusion)
  - Diluents (sometimes separate IMPD for diluent may be necessary)
  - Compatibility with diluent and material used for administration
  - In-use stability studies

The term “dosage forms” refers to the pharmaceutical preparation or formulation in which specific mixture of drug substance and excipients are presented in a particular configuration to enable easy and accurate administration and delivery of the drug substance.

The dosage forms are classified by both, the route of administration (e.g. oral, topical or parenteral dosage forms) and the physical form (e.g. solid or liquid dosage forms). The European Pharmacopoeia defines general quality requirements for different dosage forms that have to be considered during the development.

For dosage forms that need to be reconstituted before administration, some additional information may be required. If there are no authorised diluents used in the clinical trial, a separate IMPD for that diluent may be necessary. Additionally, compatibility of the drug product with the diluent and the material used for administration has to be demonstrated so as in-use stability studies conducted.

Stability studies

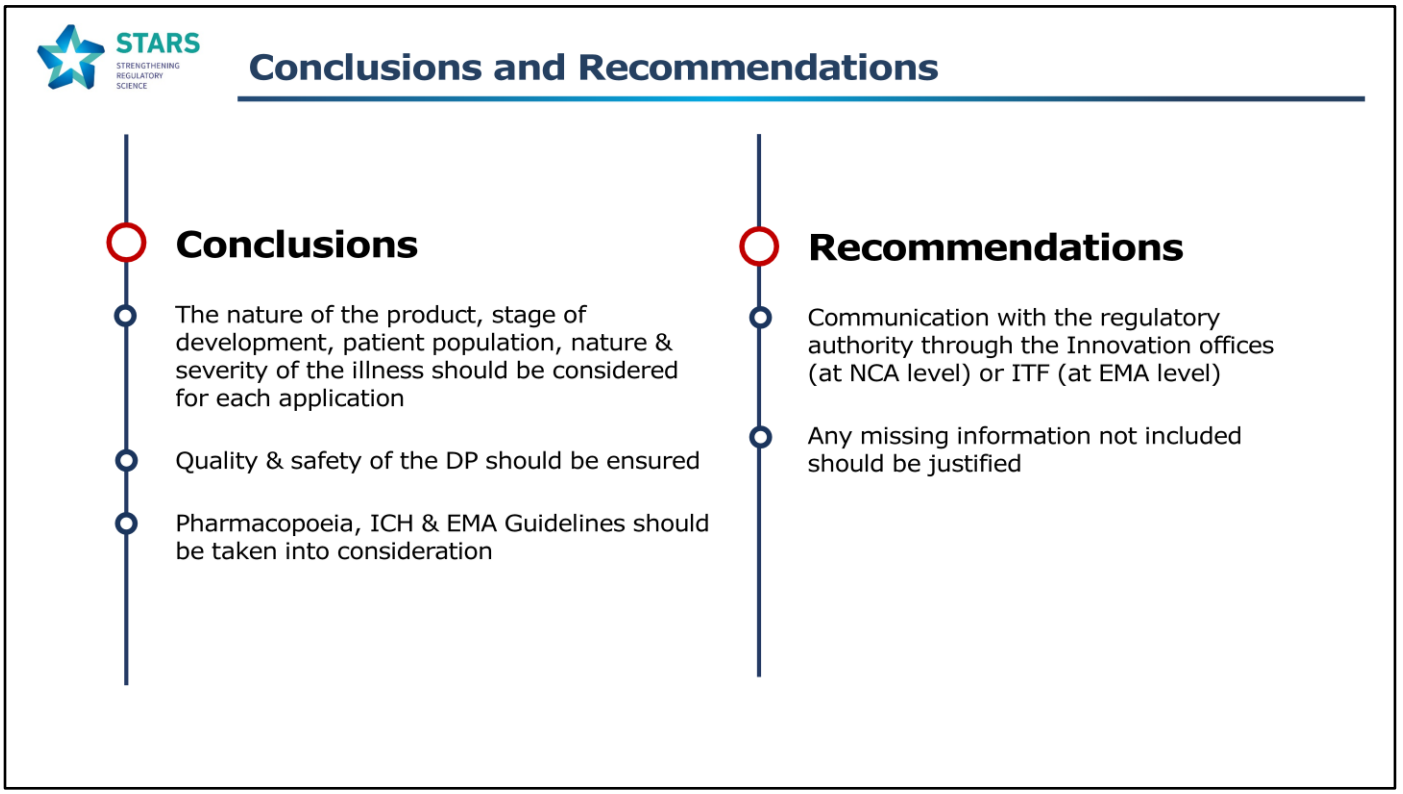
- Provide evidence of how the quality of DS or DP varies with time under the influence of variety of environmental factors
  - Long-term testing
  - Accelerated testing
  - Stress testing
- Representative for the storage conditions, formulation, batch size, manufacturer, & container closure system
- Retest period vs. Shelf-life
- Common mistakes
  - Insufficient discussion of results & trends
  - Not all stability indicating parameters are included
  - Missing stability protocol
  - Data is provided in such a way that assessment of trends is impossible

Stability studies provide evidence on how the quality of drug substance or drug product varies with time under the influence of different environmental factors such as temperature, humidity and light. The drug substance and the drug product should be, in general, evaluated under storage conditions that are representative for its storage. This are called **long-term conditions** and the length of the long-term stability studies should cover the proposed retest period or shelf life.

Stability studies under **accelerated conditions** can help to predict the degradation rate at long-term storage conditions and to set the retest period of the shelf life. **Stress testing** can help to identify the degradation products and to validate the stability indicators of the analytical methods which are used during stability studies.

A very important thing is that the batches placed on the stability studies have to be representative of the manufacturing process or synthesis and the batch size. Moreover, they have to be stored in a container closure system used for clinical storage.
It should be emphasised that there is a difference in the meaning of term retest period and shelf life. The **shelf live** means the expiry date and applies to the drug product only. The **retest period** is the period up to which the drug substance can be used for the manufacturer and after that it has to be retested before using it to ensure that it still complies with the specification. This term is used just for drug substance. Retest period is not possible for biological DS.

The **most common mistakes** when presenting the stability data are: insufficient discussion of results and trends, omission of some stability indicating parameters during the testing, missing stability protocol or the fact that the data are presented in such a way that the assessment of the trends is impossible.

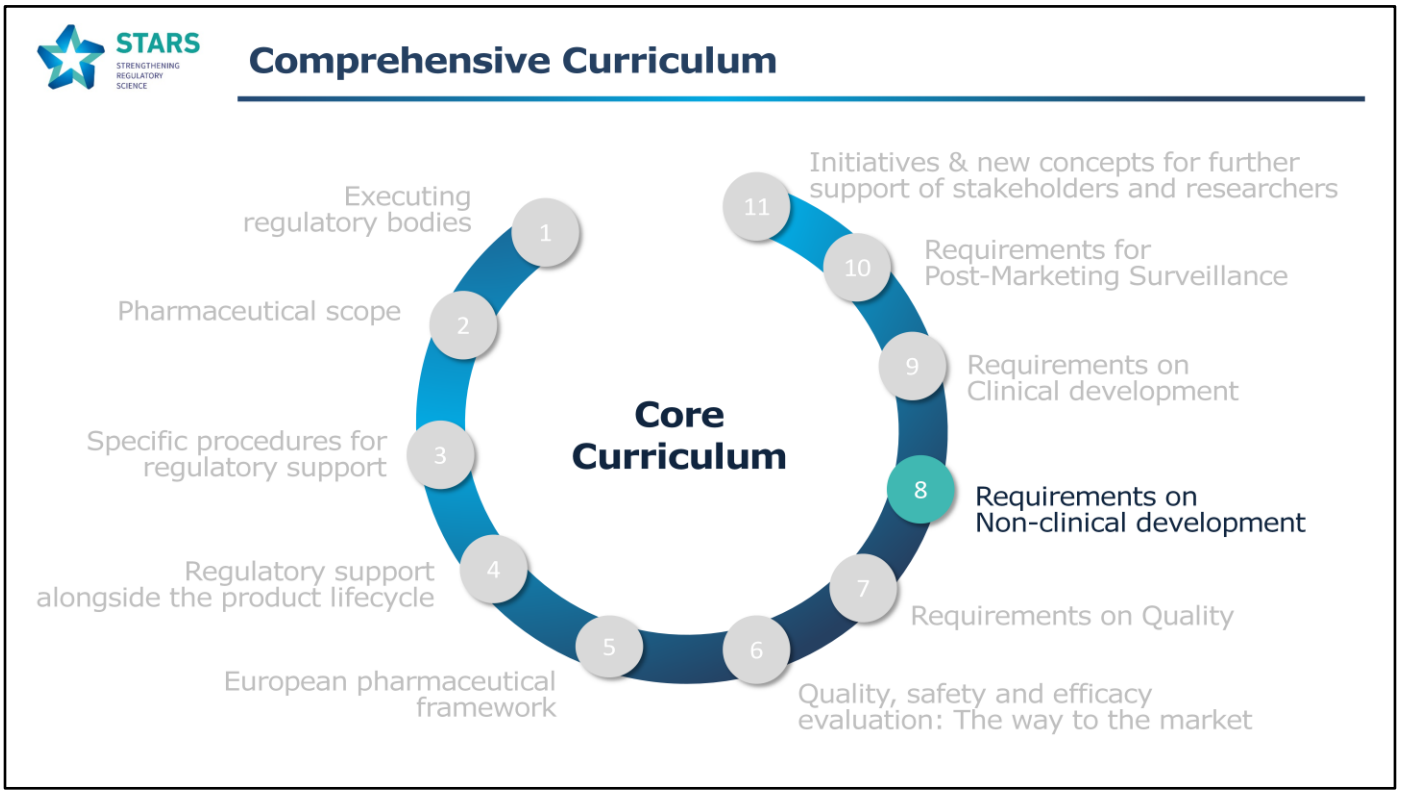


To conclude with the quality part, the following can be emphasised:

- The nature of the product, stage of development, patient population, nature and severity of the illness should be considered for each application
- It is responsibility of the sponsor to ensure quality and safety of the drug product
- And during the development process, the Pharmacopoeia, EMA and ICH guidelines should be taken into consideration.

It is highly recommended to communicate with the regulatory authority because asking for scientific advice would be really useful if some development issues occur.

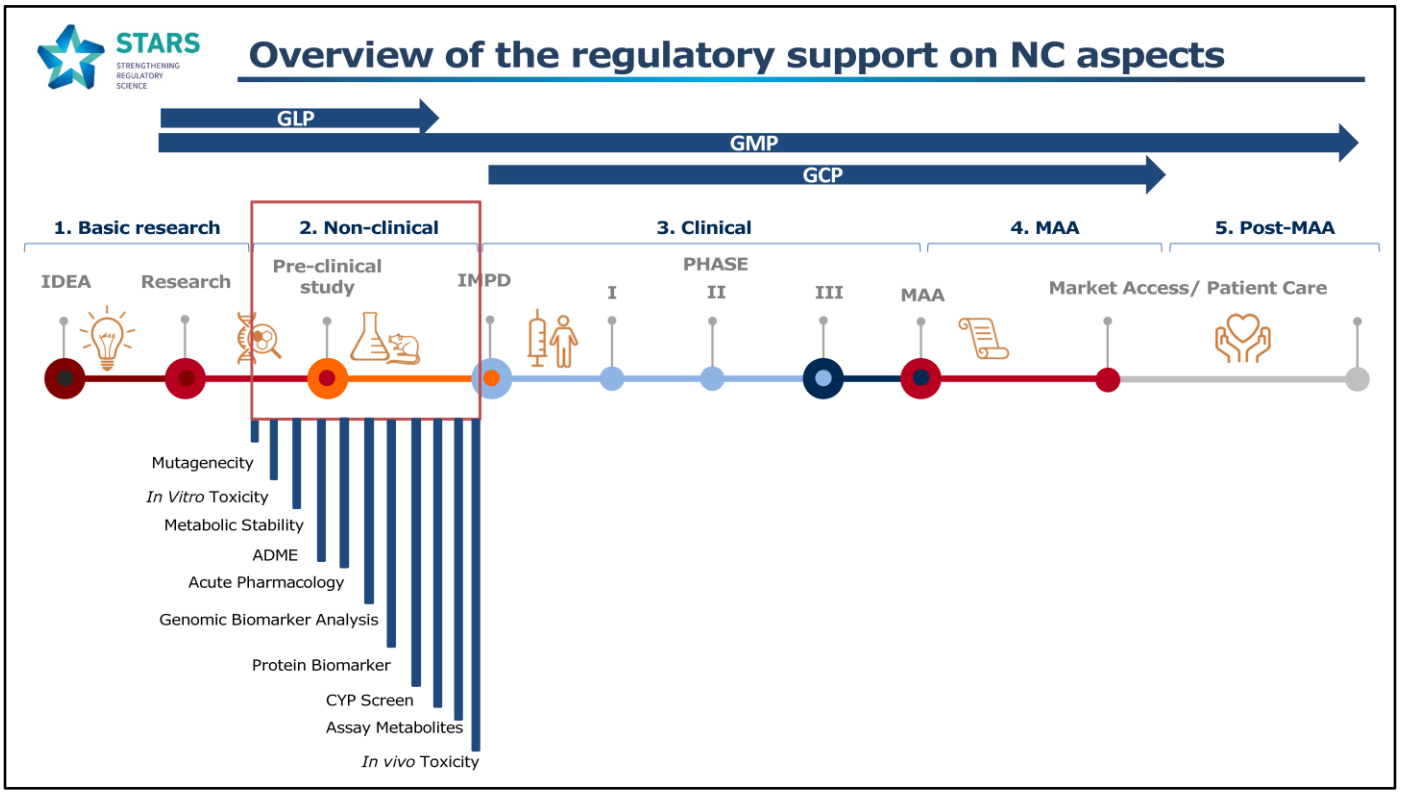
Finally, if there are any missing information in the IMPD it always should be properly justified.



Requirements on Non-clinical development.

Abbreviations – NC part

ADME	Absorbtion, Distribution, Metabolism, Excretion
AE	Adverse Event
API	Active Pharmaceutical Ingredient
CAT	Committee for Advanced Therapies
CHMP	Committee for Human Medicinal Products
CPMP	Committee for Proprietary Medicinal Products
EC	European Commission
EMA	European Medicines Agency
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GTWP	Gene Therapy Working Party
HED	Human Equivalent Dose
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMPD	Investigational Medicinal Product Dossier
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MABEL	Minimal Anticipated Biolocigal Effect Level
MAD	Mutual Acceptance of Data
NC	Non-clinical
NOAEL	No Observable Adverse Level
OECD	Organisation for Economic Co-operation and Development
PD	Pharmacodynamics
PK	Pharmacokinetics
SWP	Safety Working Party
WOCBP	Women of Childbearing Potential Authorisation


STARS
STRENGTHENING REGULATORY SCIENCE
Overview of the regulatory support on NC aspects
GLP
GMP
GCP
1. Basic research
2. Non-clinical
3. Clinical
4. MAA
5. Post-MAA
IDEA
Research
Pre-clinical study
IMPD
PHASE
I
II
III
MAA
Market Access/ Patient Care
Mutagenecity
In Vitro Toxicity
Metabolic Stability
ADME
Acute Pharmacology
Genomic Biomarker Analysis
Protein Biomarker
CYP Screen
Assay Metabolites
In vivo Toxicity

Legal Framework

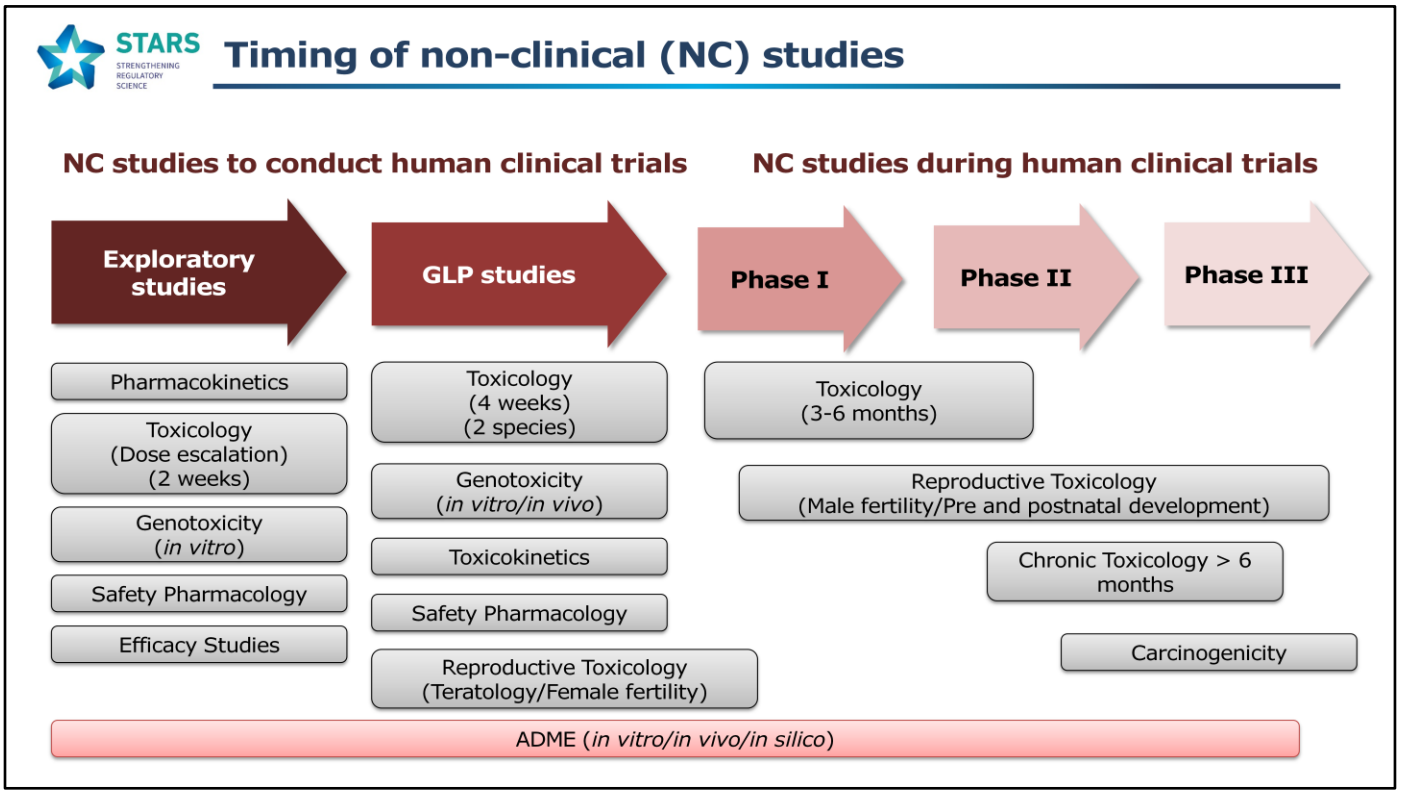
- Directive 2001/20/EC
  Clinical Trials & GCP
- ICH Guidelines
  "Community documents intended to fulfill a legal obligation laid down in the Community pharmaceutical legislation" **ICH S1-S12** & **ICH E1-E20**
- ICH M3 (R2)
  "Non-clinical safety studies for the conduct of human clinical trials & MA for pharmaceuticals"
- EMEA/CHMP/SWP/28367/07 Rev.
  "Guideline to identify & mitigate risks for first-in-human & early clinical trials with investigational medicinal products"
- Directive 2009/120/EC
  Advanced therapy medicinal products
- EMA/CAT/571134/2009
  Reflection paper on stem cell-based medicinal products
- EMA/CAT/80183/2014
  Gene Therapy
  Quality, non-clinical & clinical aspects of medicinal products containing genetically modified cells
- CHMP/GTWP/125459/06
  Non-clinical studies required before first clinical use of gene therapy medicinal products

The non-clinical (NC) studies have to fulfill the sets of requirements found in the guidelines, which are implemented by **EMA** working parties. Specifically, the Safety Working Party (SWP) is the one in charge for the NC field. Besides, International guidelines (**ICH**) should be followed on safety and efficacy. These guidelines show the path to be followed and the data that has to be presented. Therefore, it is important to justify the data that is requested by the guidelines and which of this data are missing. Some of the important chapters are listed here. For biotechnological IMPs (ATMPs, Gene Theraphy, Tissue and cell products) special guidelines are available.

The **Directive 2001/20/EC** is the main regulation behind the non-clinical requirements for an Investigational Medicine Product (IMP) that intends to enter a clinical trial (CT). It is a very general law framework so it is highly recommended to also follow the above-mentioned guidelines.

Both, European and International regimen guidelines, serve for academy, industry and assessors to transparently and consistently lead through the process of non-clinical drug development. Guidelines address issues coming up within the drug development in general and are dynamically improved according to the state of the art scientific knowledge.

It is important to emphasise that these guidelines are recommendations to be followed, they are not mandatory but they serve as a framework. However, proper scientific justification has to be done if the research is going beyond.



This slide shows the non-clinical studies that have to be carried out prior to entering first-in-human (**FIH**) clinical trial and during the clinical trial. After conducting these studies the safety, efficacy, toxicology profile and starting dosage of the drug product can be determined.

Hence, non-clinical studies can be divided into the ones **needed to conduct the clinical trial** and into the ones **needed to be done during it**.
The first set of non-clinical trials, likewise, are divided into two:

a) **Exploratory studies**. They include the study of the pharmacodynamics of the molecule, as well as, efficacy, safety, preliminary pharmacokinetics (ADME process) and toxicology studies. No GLP is needed. These studies allow to characterise how the API acts in live organisms so as to find the right dosage for the pivotal toxicological studies.

b) **GLP studies**. As it is named, GLP is required. They continue with the toxicology studies (over a longer period) and safety pharmacology. Besides, toxicokinetics are also studied. In case Women of Childbearing Potential Authorisation (WOCBP) shall be included, reprotox studies must be conducted.

During the clinical trial, non-clinical research continues. Longer toxicological studies have to be initiated in order to be allowed to proceed to the next phases of the clinical trial, which are differed in Phase I, Phase II and Phase III (see clinical part).

Relevance of NC studies in the drug development

- **EFFICACY**: Pharmacodynamics (PD) (mode of action)
  Pharmacokinetics (PK) (metabolism)
- **SAFETY**: Toxicological profile & reversibility of Adverse Events (AE)

- Establish a safe initial dose
- Identify parameters for clinical monitoring of potential adverse effects in clinical trials

To summarise, the two most important attributes that have to be determined are **safety** (toxicological profile) and **efficacy** of the API, which are characterised by toxicological studies and pharmacodynamics and pharmacokinetics, respectively.
Therefore, these studies allow to determine the mode of action, the ADME profile, the desired plasma concentration, and the toxicological effects (adverse events) of the IMP. With this knowledge a **safe initial dose** can be set up for starting the FIH CT.

In conclusion, with the non-clinical studies it is known, on the one hand, if the IMP is effective by the characterisation of its mode of action, ADME profile and the plasma concentration needed for being efficient. On the other hand, it is also determined whether the IMP is safe or not by obtaining the toxicological profile.

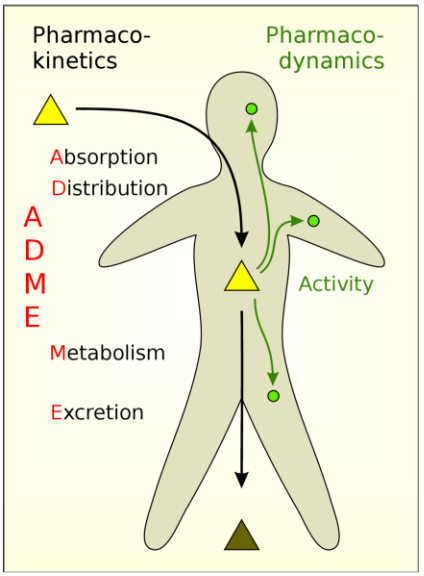
On the basis of this knowledge, the **safe initial dose** is calculated by the escalation dose step and calculating the maximal dose that could be administered in the first-in-human study. The goals of the non-clinical safety evaluation generally includes a characterisation of the adverse effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential of reversibility.

It should be also identified suitable adverse effects parameters for an appropriate monitoring in the clinical trial. It is important to always make a benefit/risk balance of the drug product.

Pharmacokinetics & Pharmacodynamics

ICH S3A, **ICH S3B**, **ICH S7A**

- **A**bsorption
  - Route of administration
- **D**istribution
  - Where will it go?
- **M**etabolism
  - How is it broken down?
- **E**xcretion
  - How does it leave?



- Mechanism of action on molecular, cellular, tissue and body level
- Bound interaction
- Specificity, selectivity
- Irreversibility
- Duration of action
- Proof of concept – *in vivo* on relevant animal model
- Same target with same potency
- Mechanism of action comparable to human
- Dosage

Concerning the **pharmacodynamics** (PD), the evaluation of mechanism of action on molecular, cellular, tissue and body level should be done first to define what the drug does to the body.
The following aspects about the API should be described:

- Bound interaction
- How specificly and selectively is it bound
- The potential irreversibility of binding to its receptor. There may be the risk to increase its activity leading to adverse outcomes (e.g. BIAL studies, in France)
- The duration of action in order to establish proper dosing schedule

In the picture shows, how a molecule acts on molecular and cellular level. It illustrates the prove of concept on relevant animal model. **Relevant animal model** is one that expresses same target and is targeted with the same potency by the API. This animal model should be as close to the pathophysiology of the human disease as possible to allow a correct evaluation of the API's efficacy. Metabolism and PK parameters should be also evaluated to allow comparison between animal models and humans. This should be the basis for the recommendation of the human dose.

The recommended guideline to conduct these studies is **ICH S7A**.

Not only what drug does to the body, but also what the body does to the drug should be evaluated: the **pharmacokinetics** (PK). It means how it is systemically **absorbed** by the intented route of administration, how it is **distributed** within the body, in which extend is **metabolised** and if the metabolites are active, or not and how it is **eliminated** from the body.
It should be evaluted by the applicant how much of active substance gets on-target to

correct PD site of action, how much of API could act on-target but on different tissue (inappropriate) , and how much of administered API could act on off-target causing side effect.

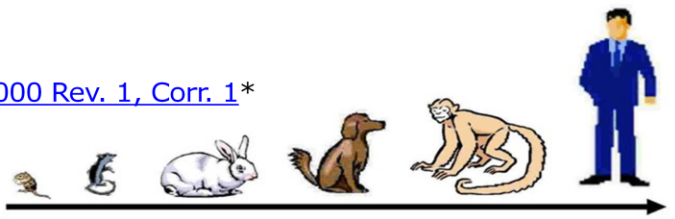
On that basis the evaluation of the **risk assessment** of the drug substance is established.

Toxicology - Guidelines

- Relevant animal species selection → planned to be minimised-3R (Reduce/Replace/Refine)
- Replacement of animal studies by *in vitro* models → CPMP/SWP/728/95 Feb 1997
- Comparative physiology (affinity to target, distribution of target)
- ADME → extrapolation of animal data to human

ICH M3

- **Single Dose Toxicity** (EMA/CHMP/SWP/81714/2010 Jun 2010)
- **Repeat Dose Toxicity** (CPMP/SWP/1042/99 Rev. 1 Corr Nov 2010)
- **Genotoxicity** → ICH S2 (R1)
- **Reproductive & Developmental Toxicity** → ICH S5 (R3) (WOCBP)
- **Juvenile Toxicity** ICH S11→ API for children
- **Local Tolerance** → EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1*
- **Carcinogenicity** → ICH S1



First, relevant animal species should be selected. Research with animal models for medicinal product development is crucial, but number of animals should be minimised as far as possible during toxicological studies (**3Rs**: Replacement, Reduction and Refinement) – **LD 50** (median lethal dose) is not allowed any more.

The duration of toxicological studies depends on the API application in the clinical trial.

For **single dose toxicity**, the duration of the studies is up to 2 weeks: usually sufficient to enable the evaluation of safety FIH single dose studies. It strongly depends on its plasmatic half life.

- The duration of the toxicological studies should be based on the duration of the administration in the clinical trial.
- The duration of the non-clinical studies also depends on the type of animal model where the API is evaluated (**ICH M3**)

For **repeated dose toxicity studies**, it is critical to find the right dose to be evaluated. Control and 3 dose levels to see dose response relationship should be included in main toxicological studies:

1. The lower dose should be selected to ensure the equal exposition in human dose administration.
2. The higher dose should should allow to see possible adverse outcomes and covered safety factors (discrepancy between animal and humans).

Genotoxicity studies are investigating chromosomal damage using rodent hematopoietic cells.

Reproductive and developmental toxicity studies should ensure mothers' fertility and child's early embryonic development.

In case of the **Juvenile Toxicity studies** (testing in support of development of paediatric pharmaceuticals) CNS and Bone systems, among others, have to be investigated.

Local tolerance studies should be carried out in case of topical administrations: inhalation and direct skin and eye contact.

The carcinogenicity studies address the risk of human carcinogenicity of small molecule pharmaceuticals.

Summary of the NC studies - Determination of Dosage

Toxicology

Determine «No Observable Adverse Level» (NOAEL)

Convert NOAEL to a «Human Equivalent Dose» (HED)

- Adjust for anticipated exposure in man
- Adjust for inter-species differences in affinity/ potency

Apply ≥ 10-fold safety factor

Pharmacology

Estimate human «Minimal Anticipated Biologicgal Effect Level» (MABEL)

- Justify based on pharmacology
- Adjust for anticipated exposure in man
- Include anticipated duration of effect
- Adjust for inter-species differences in affinity/ potency

«Maximum Recommended Starting Dose»

- Define anticipated safety window based on NOAEL & MABEL
- Appropriate safety factor, if necessary, based on potential risk

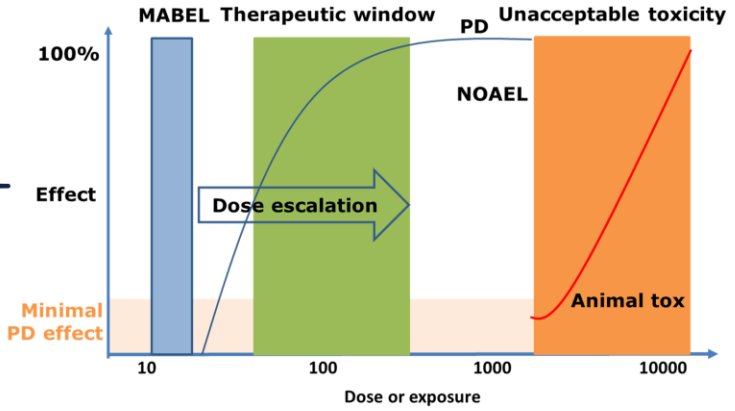


Figure is adapted from this link
https://link.springer.com/article/10.1007/s13238-017-0408-4/figures/7

On the margin of NC studies: “All substances are poison: there is none which is not a poison. The right dose differentiates a poisin from a remedy.” Paracelsus (1493-1541).

After all available non-clinical information **dosage** can be determined to have a safe API. Graph shows the way of calculation.

In order to further limit the potential for adverse reactions in humans, **safety factors** are generally applied in the calculation of the starting dose in humans. Safety factors should take into account **potential risks** related to:

• the novelty of the active substance;
• its pharmacodynamic characteristics, including irreversible or long lasting findings and the shape of the dose-response curve;
• the relevance of the animal models used for safety testing;
• the characteristics of the safety findings;
• uncertainties related to the estimation of the **MABEL**, **PAD** (Pharmacologically Active Dose) and the **expected exposure** in humans.

Information about API’s PD, PK, TK and toxicological profiles, dose or exposure/effect relationships, etc. should be taken into consideration for the calculation of the **starting dose**, **dose escalation** steps and **maximum exposure**.

The most important exposure level that is obtained from toxicity studies is **NOAEL** – on this basis **therapeutic range** could be established.

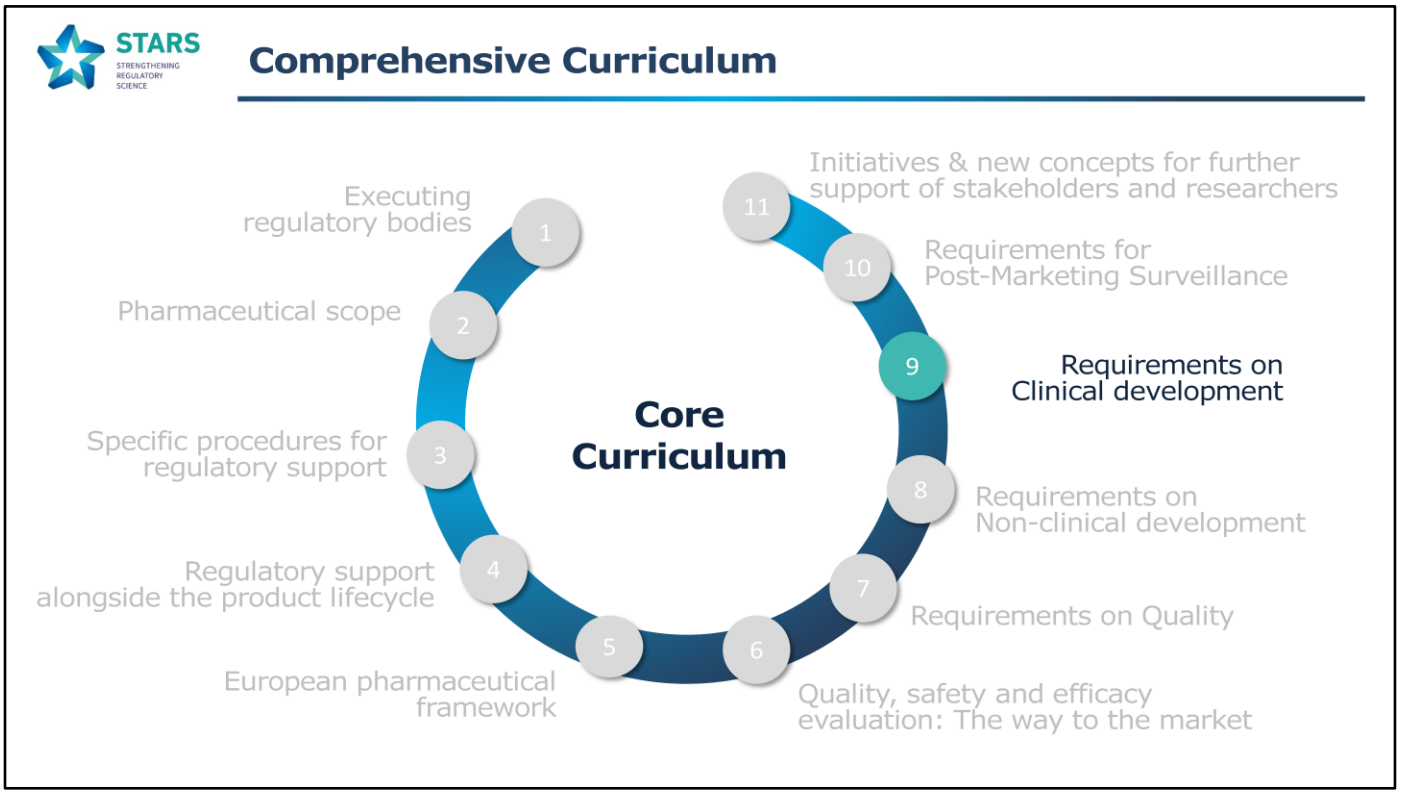
Therapeutic window could be created and recalculated to Human Equivalent Dose (**HED**).

Good Laboratory Practice (GLP)

- Directive 2004/10/EC
- GLP applies to non-clinical safety testing of test items contained in pharmaceutical products
- Comparable quality of test data forms the basis for the mutual acceptance of data among countries OECD MAD
- Define rules & criteria for a quality system concerned with the organisational process & conditions under which non-clinical health & environmental safety studies are planned, performed, monitored, recorded, reported & archived
- Promote the development of quality test data
- GLP laboratories are inspected by National Authorities

As mentioned at the beginning, the NC safety work has to be done according to the **GLP**.

GLP: sets of rules that have to be applied in laboratory (facility) where NC safety studies are carried out to ensure quality of the results obtained. The rules are strict, but need to be followed because human safety will be justified based on these results. GLP facilites are inspected by national authorities and their certificate enables to accept the results mutually around OECD sigantures.

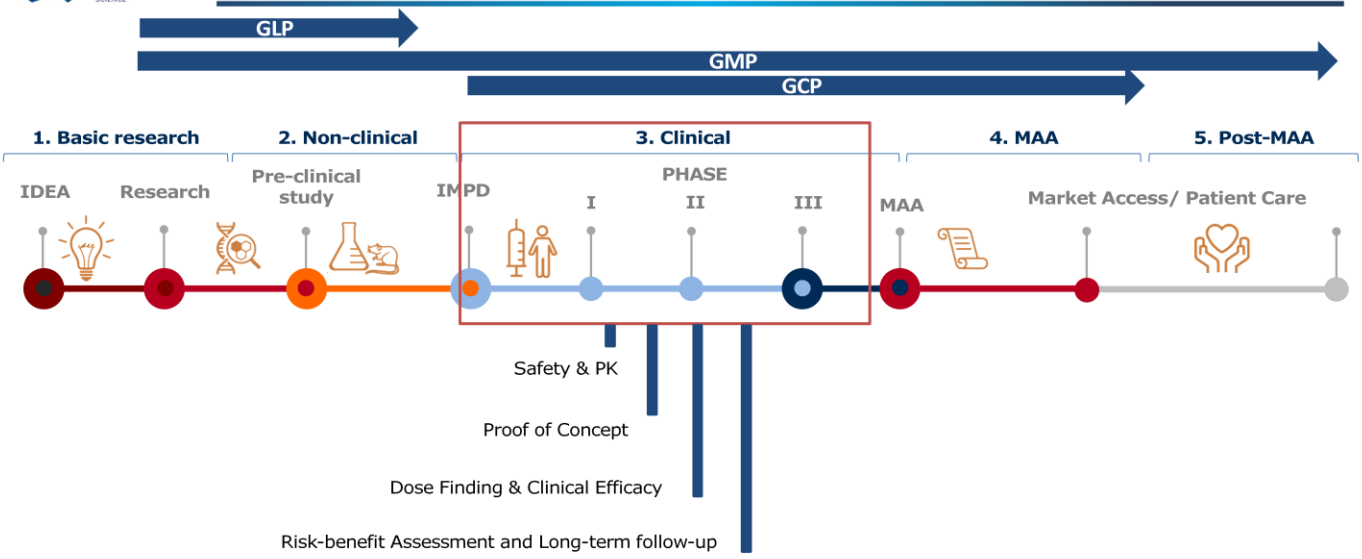


Requierements on the Clinical development.

Abbreviations – NC part

AMP	Auxiliary Medicinal Product
CT	Clinical Trial
CTA	Clinical Trial Application
CTR	Clinical Trial Regulation
DSMC	Data & Safety Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FIH	First-in-Human
GCP	Good Clinical Practice
GLSP	Good Lay Summary Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MAA	Marketing Authorisation Application
MS	Member State
NC	Non-clinical
PAES	Post-Authorisation Efficacy Studies
PASS	Post-Authorisation Safety Studies
PD	Pharmacodynamics
PK	Pharmacokinetics
PRAC	Pharmacoviligance Risk Assesment Committee
RSI	Reference Safety information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpeted Serious Adverse Reaction

Overview of the Regulatory Support on the Clinical



Clinical trial definition

Any investigation in human subjects

- intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s)
- identify any adverse reactions
- study absorption, distribution, metabolism, and excretion
- of an **investigational product(s)** with the object of ascertaining its **safety and/or efficacy**.

CTs: all studies with a non-authorised drug product

Elements of intervention

- randomisation
- blinding
- use of placebo
- modification of dosage
- change of dosage form
- change of route of administration
- examination for study purpose only
- sampling of biological material (blood, urine, tumour tissue…) for research purposes

A **clinical trial** shall mean any systematic testing of one or more investigational medicinal product(s) conducted in human subjects with the objective of ascertaining its (their) safety and/or efficacy, including clinical trials conducted at one or more trial sites in one or more of the European Member States intended to:

- discover or verify the clinical, pharmacological or other pharmacodynamic effects,
- identify any adverse reactions,
- study absorption, distribution, metabolism or excretion.

The intervention itself is the aspect that is being investigated in clinical research. The different elements that are defined as interventions are listed on the right.

Clinical trial with pharmaceuticals vs clinical studies

Rapid identification of the interventional clinical trial

Drug Product

- Administration of a medicinal product or active substance
- Non-authorised/authorised medicinal product

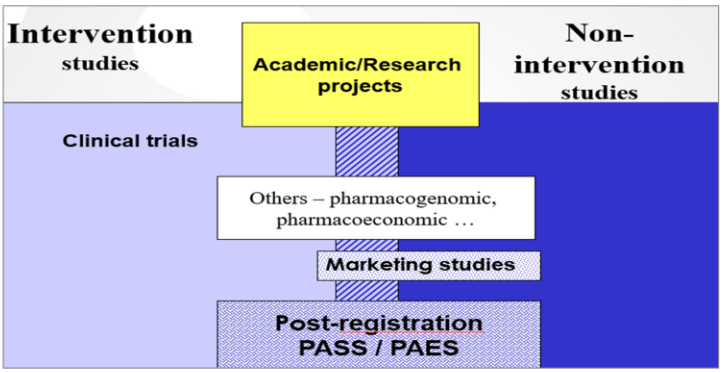
Intervention subject

- Anything beyond routine medicinal practice
- Everything trial subject undergoes for research, not routine medicinal practice (treatment)

Trial subject

- Healthy volunteer
- Patient

3 x YES = CLINICAL TRIAL (Directive 20/2001/EC)



The key questions to identify if the definition of a clinical trial applies are as follows:

1. Is the medicinal product **used or administered** the active substance in the study?
2. Is a human **research study** being done?
3. Is there an intervention that a **patient / healthy volunteer** would not undergo in routine practice?

If the answer is three times confirmed, the definition of a clinical trial applies. If not, this could be a non-interventional study.

In short, intervention studies differ from observational studies in that the investigator assigns the exposure after study enrolment.

Legal Framework

- Directive 2001/20/EC (**in transition**) Clinical Trials & GCP
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (repealing Directive 2001/20/EC) (entering into application on Jan. 31, 2022)
- Regulation (EC) No 2017/556 on the detailed arrangements for the good clinical practice inspection procedures
- Regulation (EC) No 1394/2007 on advanced therapy medicinal products (ATMP)
- Regulation (EC) No 1901/2006 on medicinal products for paediatric use
- **National legislations** (Law, Decree)
  - on implementations of Directives
  - on national specific requirements
- ICH E6 (R2) - Guideline for good clinical practice

Directive 2001/20/EC relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use has been repealed by regulation number **(EC) 536/2014 on January 31, 2022**.

The new EU regulation introduces novel concepts and requirements, such as risk proportionate approaches in clinical trials, the provision of layperson summaries of clinical trial results, and the definition of Auxiliary Medicinal Products (formerly referred to as Non-Investigational Medicinal Products) in clinical trials. The European clinical trial environment will benefit from the EU Regulation No. 536/2014 in several ways. The most important improvements and advantages of the new regulation are the harmonisation in study application procedures and the partial mutual recognition of review procedures across the Member States.

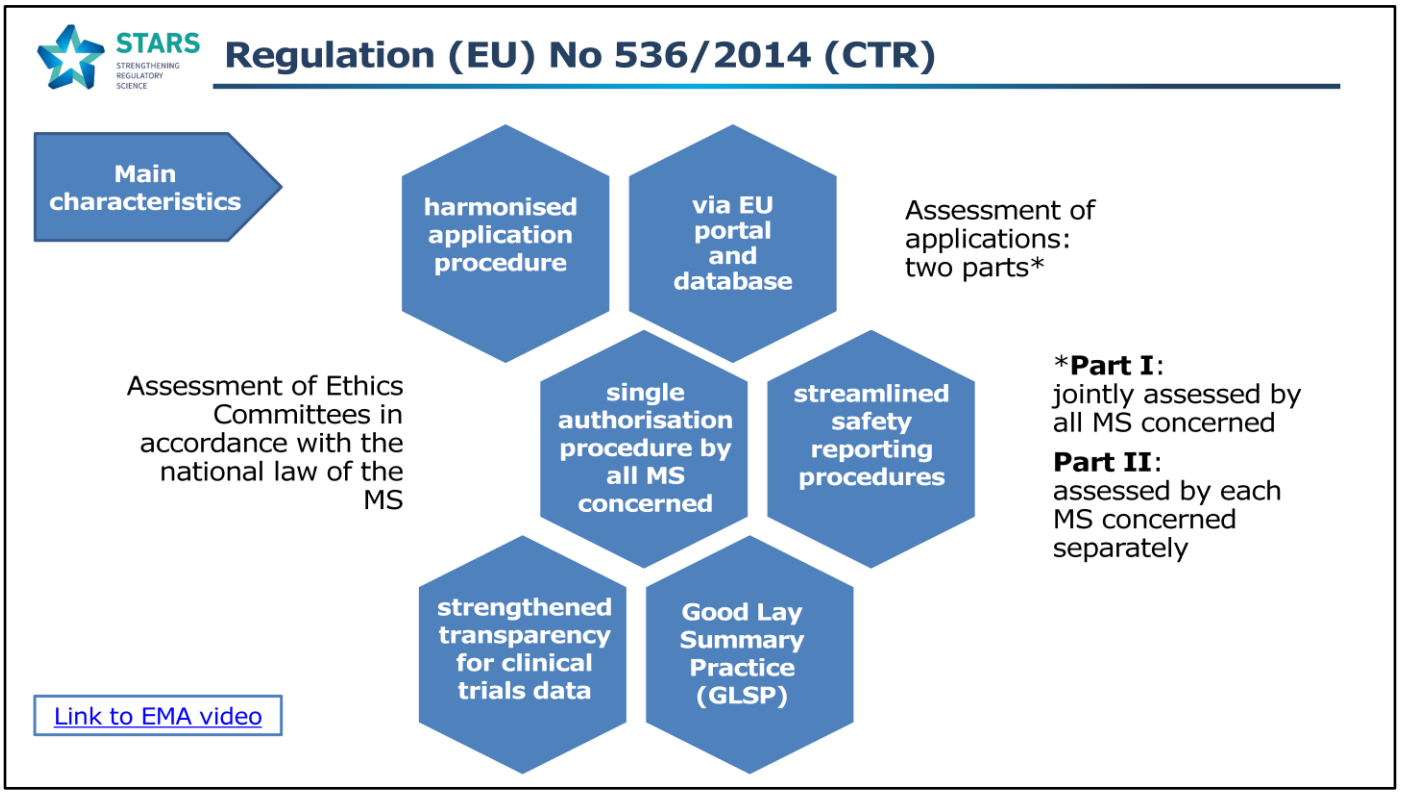
Regulation (EC) No 2017/556 details arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014.

Regulation (EC) No 1394/2007 comprises gene therapy medicinal products (GTMP), somatic cell therapy medicinal products (SCT) and tissue engineered products (TEP) as well as combined ATMP (combination of one of the afore-mentioned ATMP with a medical device component). For definitions please refer to Part IV of Annex I to Directive 2001/83/EC. Scientific progress has brought about a new type of medicinal products based on gene therapy, somatic-cell therapy or tissue engineering. To provide a common framework for the marketing of so-called advanced therapy medicinal products (ATMPs), Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products was adopted in 2007.

The ATMP Regulation was designed to ensure a high level of human health protection as well as the free movement of ATMPs in the EU. The cornerstone of the Regulation is that a marketing authorisation must be obtained prior to the marketing of ATMPs. In turn, the marketing authorisation can only be granted if, after a scientific assessment of the quality, efficacy and safety profile, it is demonstrated that the benefits outweigh the risks.

The **European Regulation (EC) 1901/2006** relating to medicines for children came into force on 26 January 2007, and is directly applicable in the Member States. The Regulation aims to make high-quality, safe and efficient medicines accessible to children and adolescents. Therefore, the regulation specifies the requirements for the development and authorisation of new medicinal products. It further requires the submission of line listings of studies already conducted with children and adolescents in connection with authorised products (see Articles 45 and 46 of the Regulation).

Guideline **ICH E6 (R2)** on GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.



The aim of the **new CTR** applicable in all Member States is to almost complete harmonisation of the approval process for clinical trials and the introduction of a common assessment for multinational clinical trials. The general aspects of harmonisation include:

- a harmonised authorisation dossier;
- a single portal managed by the European Commission, to submit an application for authorisation to conduct a clinical trial linked to a European database;
- a faster assessment procedure involving all the Member States where the sponsor intends to conduct the trial;
- precise and shortened timelines for both, the applicants and the assessors;
- and it includes a requirement for the submission of lay summaries.

Directive 2001/20/EC remains valid for a maximum of 3 years after the date of application of the Regulation. There will be a transition period for the old and the new procedures, so that both procedures will be in parallel for a maximum of 3 years. An application for approval may be submitted one year after its entry into force, in accordance with the old or the new legislation.

The assessment of the procedures are divided into 2 parts:

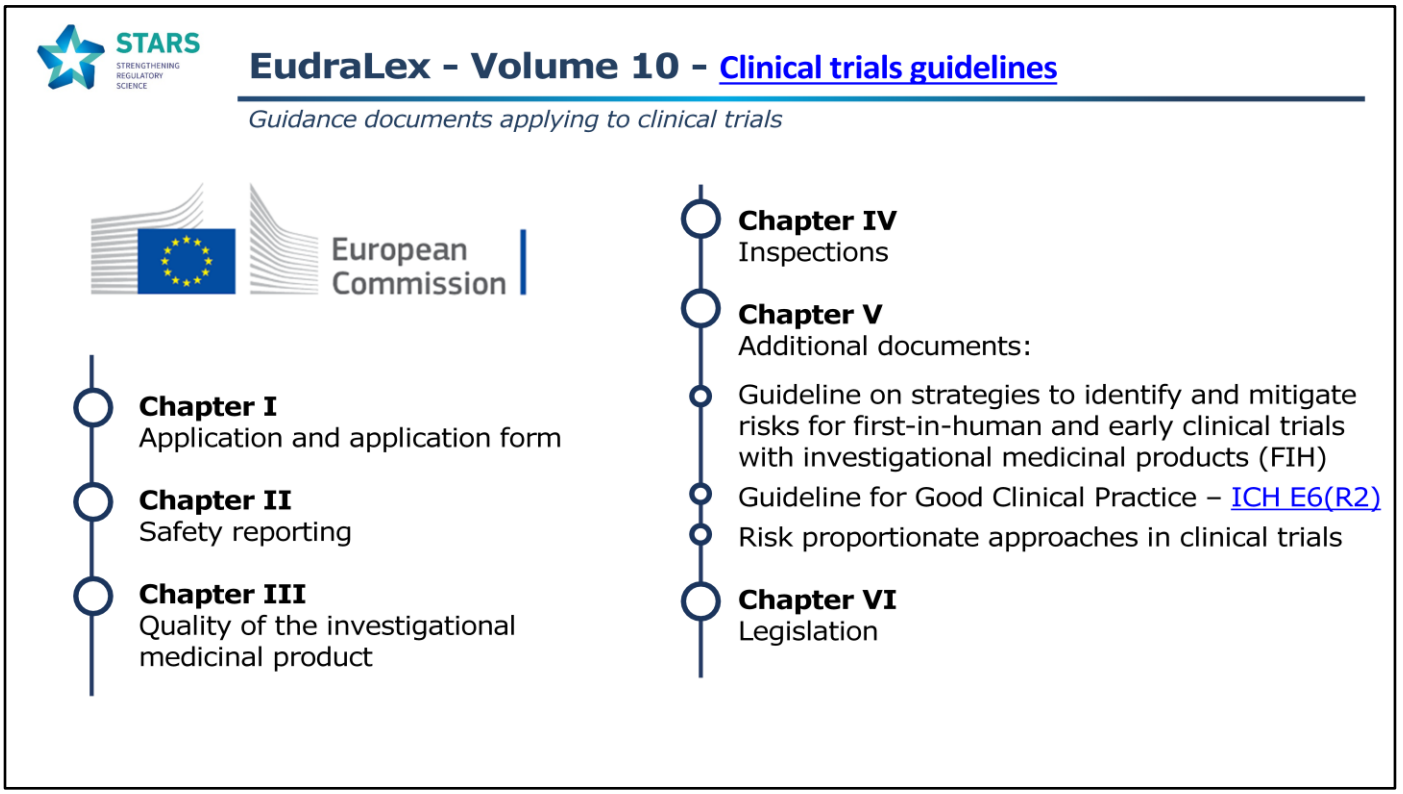
- **Part I**: on technical, scientific, non-clinical and clinical quality. State of knowledge, clinical question, hypothesis to be tested, clinical relevance, goals, endpoints, safety measures, risk/benefit.
- **Part II**: ethical aspects and local feasibility (patient information/informed consent, letter to the treating physician, how to enroll, insurance, PI fitness and clinical center, any refunds).

ICH E6 (R2 Guideline for GCP) (Link)

- CT - should be conducted in accordance with the **ethical principles** (*Declaration of Helsinki, GCP ICH E6 and regulatory requirements*)
- Risks and inconveniences should be weighed → **benefits justify the risks**
- The **rights, safety**, and **well-being of the trial subjects** → interests of science and society
- Adequate **non-clinical** and **clinical information** on an IMP
- CT - scientifically sound, and described in a clear, detailed **protocol**
- A CT should be conducted **in compliance** with the protocol
- A **qualified** physician or a qualified dentist (when appropriate) – is responsible for the medicinal care
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)
- Freely given **informed consent** – obtains prior to clinical trial participation
- Link to ICH Guidelines: https://www.ich.org/page/ich-guidelines

Clinical trials on human medicinal products involving natural persons as trial subjects shall be governed by the rules of **good clinical practice**.

This guideline addresses the good clinical practice and describes the **responsibilities and expectations** of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. It sets an international ethical and scientific **quality standard** for designing, conducting, recording and reporting trials that involve the participation of human subjects. The aim is to provide a unified standard for the ICH regions to facilitate the **mutual acceptance** of clinical data by the regulatory authorities in these jurisdictions.



A number of documents in **Volume 10** are being revised and updated to bring them in line with the changes required by the Clinical Trials Regulation (EU) No 536/2014. Additionally, new documents were prepared to cover new aspects introduced by the same Regulation.

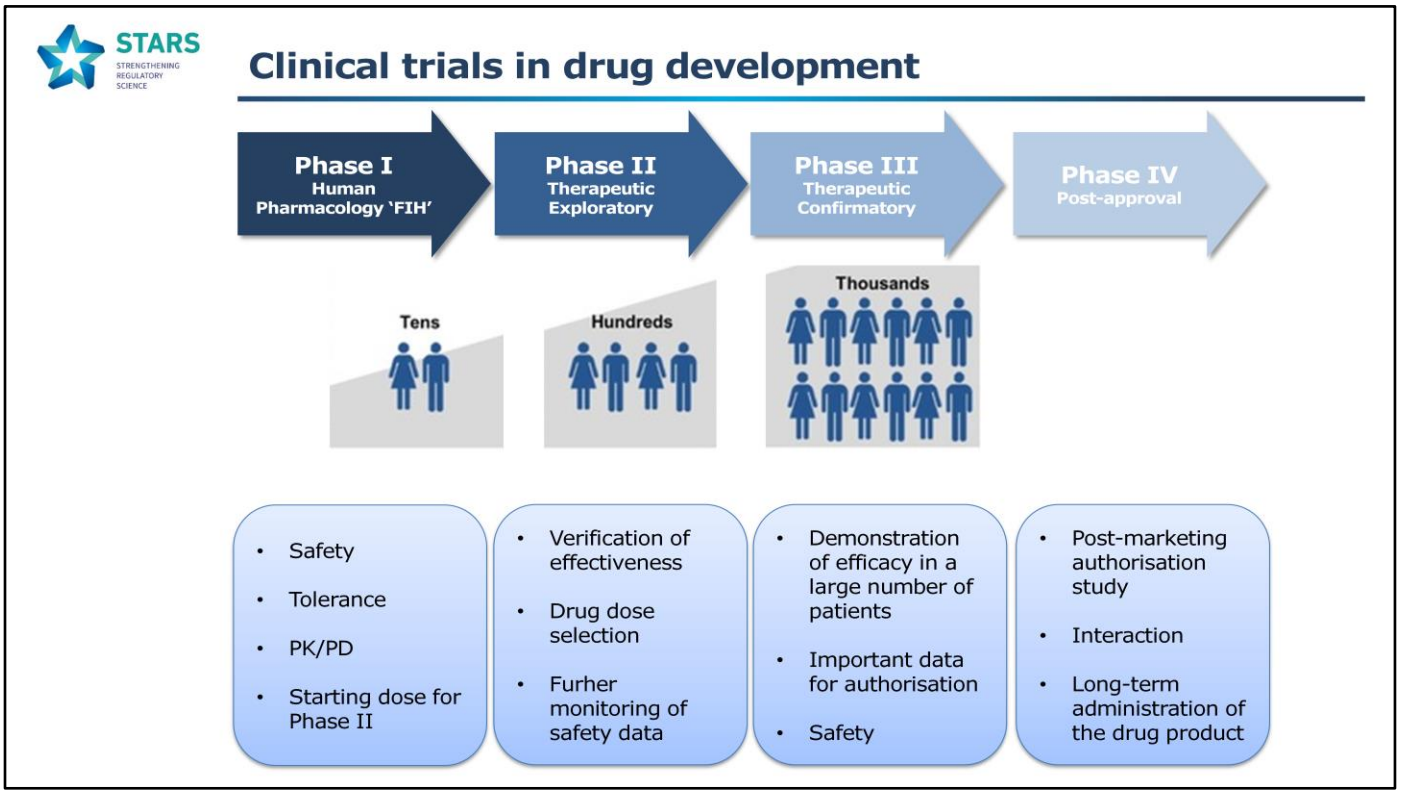
In order to make a distinction between documents applicable to clinical trials authorised under Directive 2001/20/EC (i.e. the current applicable documents) and documents relevant to clinical trials authorised under Regulation (EU) No 536/2014, these documents will be listed in **two separate pages** on the Eudralex Volume 10 website.

Until the Clinical Trials Regulation becomes applicable sponsors should follow the documents relevant to the Clinical Trials Directive.

During the transitional period, which will last for a period of **3 years** starting from when the Regulation becomes applicable, both sets of documents will apply accordingly and should be referred to respectively according to the legislation under which the Clinical trial is conducted.

At the end of the transitional period all clinical trials shall be conducted under the **Regulation** and should follow only the set of documents applicable to the Regulation.

Although it is not mandatory, stakeholders are encouraged to take already into consideration a number of aspects that are outlined in the new or updated documents published in the page dedicated to the Clinical Trial Regulation and apply them to those clinical trials authorised under the Directive, to the extent possible and in compatibility with the legal framework of the Directive.



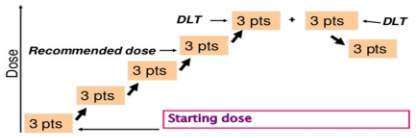
Following the "classic" product life cycle, clinical trials are divided into **four phases** at different stages of the drug development. Clinical trial data are included in clinical study reports that form a large part of the **application dossiers** submitted by pharmaceutical companies applying for a marketing authorisation via EMA.

The first three phases aim to obtain data with view to the application of a marketing authorisation. The phases start in **Phase I** with the exploration of safety data respect to the side effects. **Phase II** studies focus on data on efficacy and finding the optimal dose and **Phase III** studies are supposed to confirm the data and may also aim to test whether a new treatment is better than existing ones. **Phase IV** studies take place after the marketing authorisation has been granted to learn more about safety and efficacy of the drug in more patients and/or explore long-term effects.

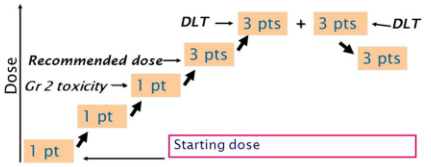
Clinical trials – Phase I

- Investigational Medicinal Product (**IMP**) in humans for the first-time use
- Study the human **pharmacology**, **tolerability** and **safety** of the IMP
- **FIH** is often undertaken in healthy volunteers but can also include patients
- **Starting dose determination** - based on the non-clinical studies

Phase I Standard 3 + 3 Design



Phase I trial design: accelerated titration



The key aspects of the **Phase I** design are to select an appropriate population and to clearly and unambiguoulsy define **inclusion and exclusion criteria**, e.g. healthy volunteers (preferably 18-65 years) or patients in an open and unblinded design.

The **initial and maximum dose**, **exposure** and the **maximum duration** of treatment need to be fixed as well as the number of subject in to cohort. A transition period between cohorts with a new dose needs to be planned and stopping rules as well as monitoring safety parameters need to be clearly stated.

Clinical trials – Phase II

- **Pilot** Clinical trials
- **Therapeutic exploratory**
- Evaluate **efficacy** (and safety)
  - in selected populations of patients with disease or condition to be treated, diagnosed, or prevented
- **Objectives**
  - dose-response,
  - type of patient (sub)groups,
  - frequency of dosing, or other characteristics of safety and efficacy

Subsequent to positive results on safety data in Phase I, **Phase II** trials focus on the **efficacy** of an IMP and if it works well enough to be tested in a larger Phase III CT.

Phase II trials are usually **larger** than Phase I and can comprise different cohorts with different doses and different treatment regimes to identify **dose optimisation** and **best treatment effects**. Approaches often occur in an adaptive design with a staggered approach, in which different treatments enter the same trial at different times for safety reasons. Sometimes, in a Phase II trial, a new treatment is **compared** with another treatment already in use or with the placebo and they can also be **randomised**.

In practice, Phase I and II can be combined in one study protocol, the same as Phase II studies can be divided into a **Phase IIa** with less often than 200 patients and **Phase IIb** extended to a larger patient group.

Clinical trials – Phase III

- CTs conducted **before** submitting the application for marketing authorisation
- Generate additional data of both **efficacy** and **safety**
- **Large numbers of patients** selecting populations of patients with disease or condition to be treated, diagnosed, or prevented
- **Phase III main investigational features**
  - different formulations
  - dosages
  - durations of treatment
  - new age groups
  - new indication
  - different route of administration…

Phase III trials are conducted with view to submitting a **CTA** and are based on a **large population** carried out as **pivotal trials** to provide the necessary robust data basis to meet regulatory requirements. Assessments are based on purely scientific criteria and determine whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements in accordance with EU legislation. Most Phase III trials are randomised and randomisation is regarded as the gold standard trial for evaluating the effectiveness of interventions.

Phase III trials can be based on a completely new treatment, different doses, durations or forms of application of the same treatment or also with view to new patient populations or indications.

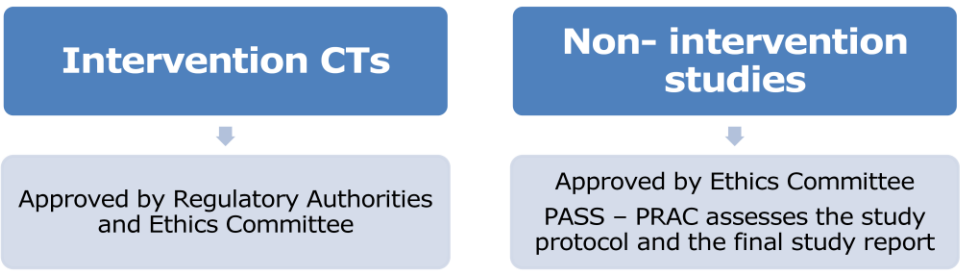
Clinical trials – Phase IV

- CT conducted **after** marketing authorization
- IMP - must be used in accordance with **SmPC**
  - dose,
  - route of administration,
  - diagnosis,
  - age groups…
- **Additional** details about the medicine´s efficacy or safety profile
- Possibility of simplified labelling for **open CT**

Phase IV trials are conducted to find out more about the safety and efficacy of the authorised medicinal product or treatment. They are conducted after the MA is obtained. This can specially be the case with view to gaining more data from **long-term follow-up** to better outweigh the risks and benefits and/or to gather more data from larger patient populations. This can apply, for example, to conditional marketing authorisations, when additional data need to be shown to the Regulatory Authorities to confirm that the medicine's benefit-risk balance remains positive.

Post-authorisation studies

- **PAES** - Post-authorisation efficacy studies
  - EMA Guidance – Post-Authorisation Efficacy Studies: Questions and Answers
- **PASS** - Post-authorisation safety studies – either imposed or voluntary
- PAESs and PASSs can either be **clinical trials** or **non-interventional studies**



A **post-authorisation safety study** (**PASS**) is a study that is carried out after a medicine has been authorised to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures. The EMA's Pharmacovigilance Risk Assessment Committee (**PRAC**) is responsible for assessing the protocols of **imposed PASSs** and for assessing their results.

The purpose of the information in PASSs is to evaluate the **safety** and **benefit-risk profile** of a medicine and support regulatory decision-making. They aim to:

- identify, characterise or quantify a safety hazard;
- confirm the safety profile of a medicine, or;
- measure the effectiveness of risk-management measures

Marketing-authorisation holders (**MAHs**) can be obliged to carry out imposed PASSs. These include studies that are a specific obligation for a marketing authorisation granted under exceptional circumstances and other studies that the PRAC requests the company to carry out.

Voluntary PASSs are sponsored or conducted by MAHs on their own initiative. They include non-imposed studies that are requested in risk management plans.

Post-authorisation efficacy studies (**PAES**) are carried out with the same framework and focus on obtaining more data on the efficacy of the medicine.

Required documents for the CTA

- **Cover letter**
- **Protocol** and all amendments
- **CTA form**, confirmation of assignment
- **Investigator´s Brochure**
- **IMPD**
- **Case Report Form** (if required)
- Patient Information Sheet / **Informed Consent Form**
- **Approval of Ethic's Committees** based on national law

Fore more detailed information please refer to A**nnex I of the Regulation (EU) 536/2014**.

Clinical Trial Protocol

- Description of objective(s), design, methodology, statistical considerations and organisation of a clinical trial
- General Information: title, code, version no. & date, sponsor name&address, phase of CT
- Name and description of the IMPs
- Summary findings NC-studies and relevant CTs
- Evaluation of Benefit/Risk profile
- Description of objectives and purpose of the trial
- Primary endpoints and secondary endpoints
- Description of the trial design (e.g. double-blind or open, randomised, placebo-controlled, parallel design) and a schematic diagram of trial design

Detailing:

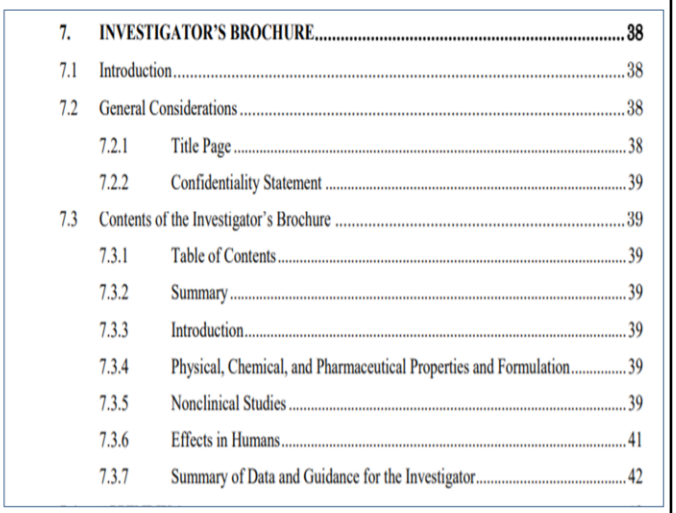
- Subjects population - inclusion and exclusion criteria, including stopping rules or discontinuation criteria from the trial
- Treatment of subjects - names of all the products (IMP, AMP), dose, route of administration, treatment period, follow-up period
- Concomitant treatment - permitted and prohibited, including regimen measures
- Schedule of procedures - flowchart – time of visits, investigations, blood samples, compliance, adverse event/reaction
- Pharmacovigilance - reporting adverse event, SAE, SUSAR
- Statistics
- Parameters of efficacy / safety
- Other info – substudies; DSMC etc.

This slide shows the key information to be included on a **clincial trial protocol**.

Investigator's Brochure

RSI – Reference Safety information

- Data file of the clinical and non-clinical data on the IMP provides investigators with available data on IMP (according the **section 7 ICH E6** (R2))
- Separate section in **IB**
- Includes a list of **expected serious adverse reactions** (SARs), e.g. in the form of a table (preferable)
- All related serious adverse reactions are listed by **nature** and **severity** including **frequency** (see CT-1 section 2.3. (32.), CT-3 section 7.2.3.2. (51 to 53))
- Any change to an RSI is considered a **substantial amendment** and it requires to be justified with supportive data



Usually **one IB for one IMP** in all indications – exceptions need to be properly justified – e.g. oncological vs non-oncological indications.

Sponsor

- Can be an individual, company, institution or organization, which takes **responsibility** for the initiation, management and/or financing of a CT
- Must be located in a **EU** Member State or has a "legal representative" in the EU
- **Full responsibility** for performing the CT
- Preparation and continuous updating of **documentation**
- Standard procedures introduction (**SOP**)
- **Selection** of investigator and clinical trial site
- **GCP** assurance
- Risk management plan (**RMP**)
- **Pharmacovigilance** during CT (*SUSAR, DSUR*)
- Ongoing **reporting** (*initiation of the CT, Urgent Safety Restriction, Deviation of protocol, notification of the end of CT in MS and global, Clinical Study Report*)

The slide describes the role requeriments and tasks of the **sponsor** of the clinical trial.

Investigator

- Responsible for the **conduct** of the clinical trial at a trial site
- Relevant **qualifications**
- **Training and experience** for the proper conduct of the clinical trial
- **Experience** in performing CT
- **GCP** and **regulatory** requirements knowledge (e.g. at national level of concerned MS)
- Selection of **investigator´s staff** (*sufficient experience and adequate qualifications*) – delegation log (*the tasks entrusted to the individual members of the study team are indicated; their training is recorded - everyone confirms with their signature*)
- In charge of **IMP**
- Responsible for obtaining **informed consent** according to national law(s)

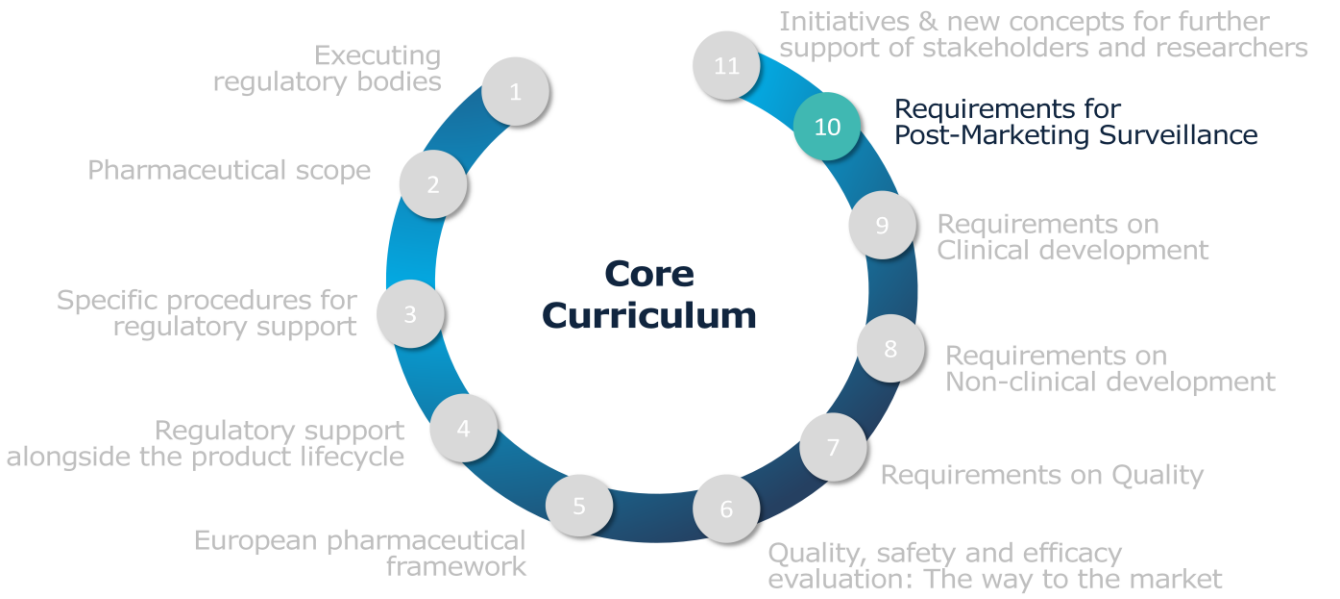
The slide describes the role requeriments and tasks of the **investgator** of the clinical trial.

Regulation of CTs – summary of objectives

- ✓ Testing under **standard conditions**
- ✓ Obtaining objective and valid data for **market access**
- ✓ Information about achievement of balanced **risk/benefit ratio**
- ✓ **Protection** of human subjects
- ✓ Confirmation of drug product **quality**

Quality and safety of marketing authorisation of medicinal products

Comprehensive Curriculum- Core Module

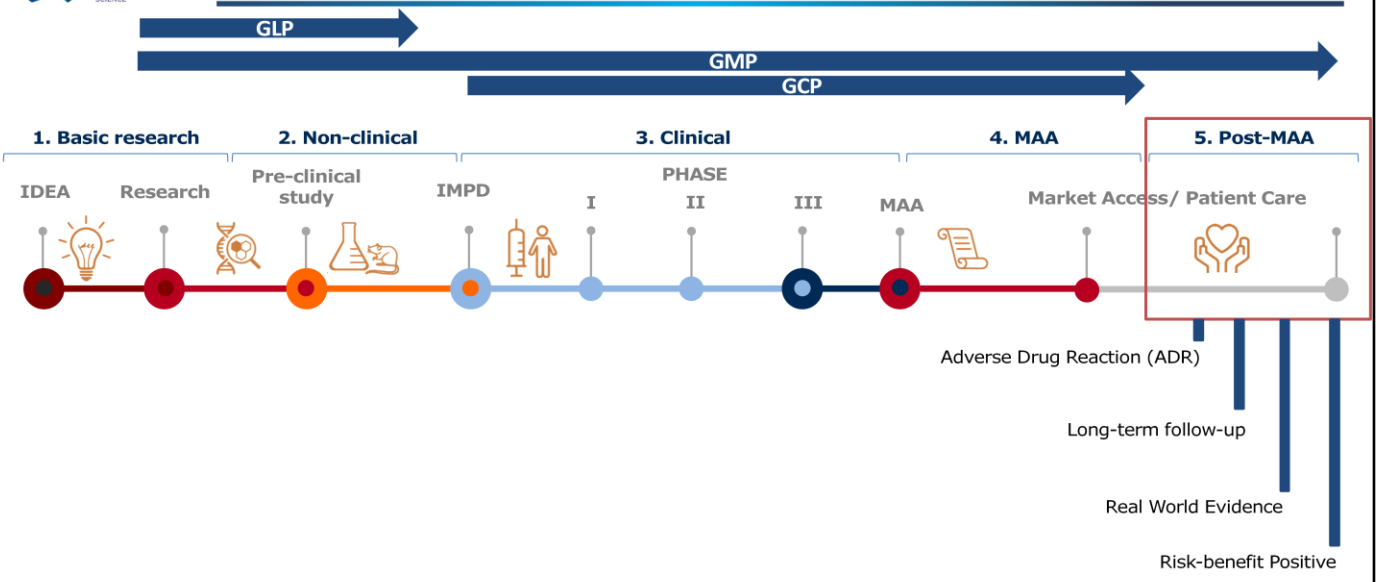


Requirements for Post-Marketing Surveillance.

Abbreviations – Pharmacovigilance part

ADR	Adverse Drug Reaction
EC	European Commission
EU	European Union
FIH	First-in-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IMPD	Investigational Medicinal Product Dossier
MAA	Marketing Authorisation Application
PAES	Post-Authorisation Efficacy Studies
PASS	Post-Authorisation Safety Studies

Overview of the Regulatory Support on the Clinical



Legal framework - Pharmacovigilance

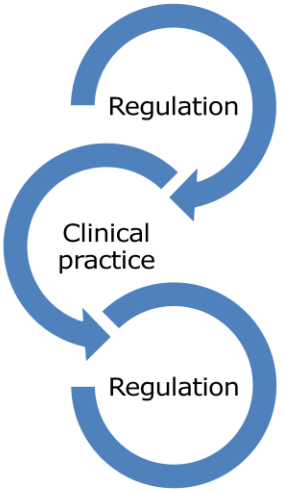
"The development of the pharmacovigilance legislation was based on the observation that adverse drug reactions (ADRs), 'noxious and unintended' responses to a medicine, caused around 197,000 deaths per year in the EU".

- Regulation (EU) No 1235/2010 and Regulation (EU) No 1027/2012 amending, as regards pharmacovigilance, Regulation (EC) No 726/2004;
- Directive 2010/84/EU and Directive 2012/26/EU amending, as regards pharmacovigilance, Directive 2001/83/EC.
- Commission Implementing Regulation No 520/2012, which concerns operational aspects of implementing the new legislation.

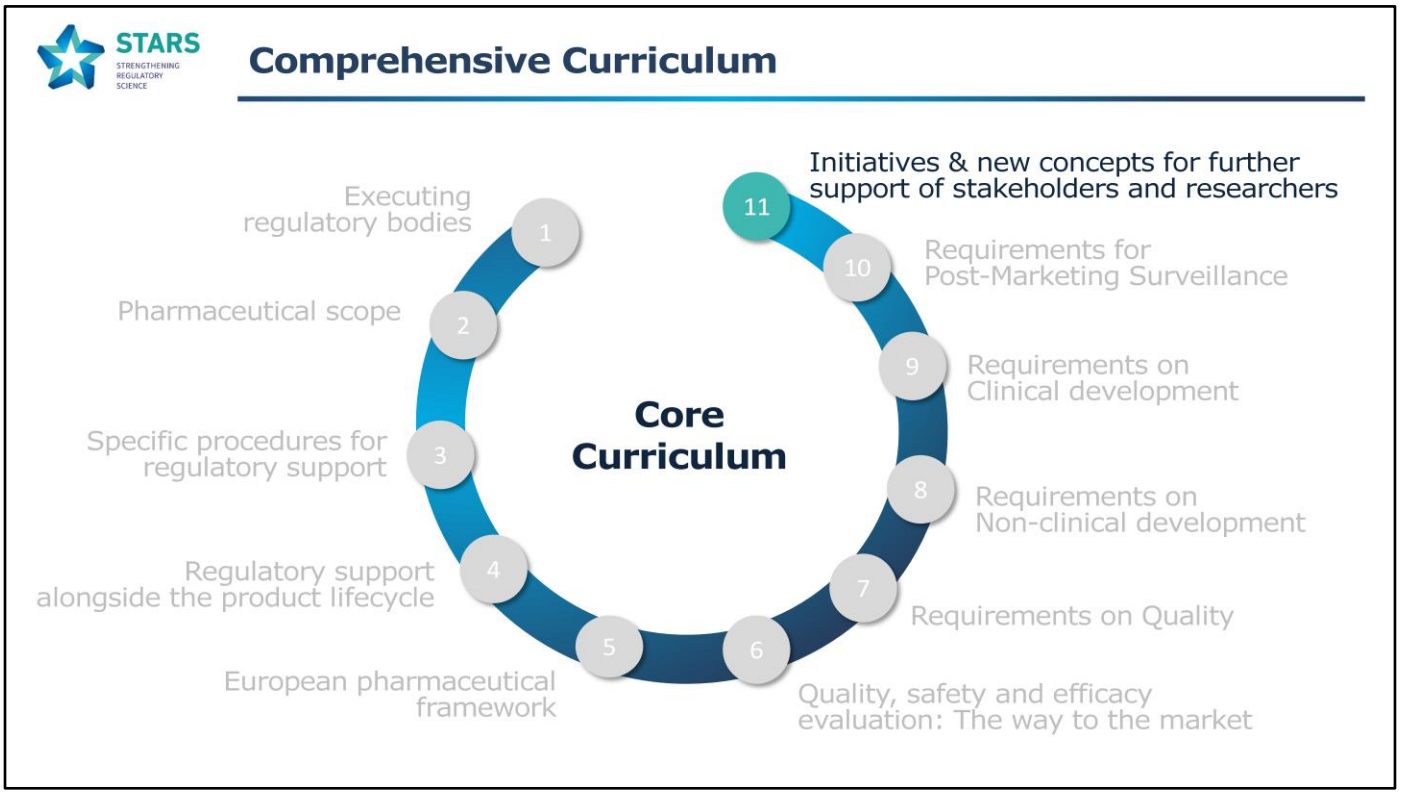
The development of the **pharmacovigilance legislation** was based on the observation that adverse drug reactions (**ADRs**), 'noxious and unintended' responses to a medicine, caused around 197,000 deaths per year in the EU.

Post-Marketing Surveillance Measures

- Continuous surveillance to monitor the benefit/risk remains positive
- Regulation is nourished by clinical practice, clinical studies (among them PASS and PAES) & registries
- Increasingly supported by data analysis coming from patient registries (Real World Evidence)
- Regulation & clinical practice is not the same but should not differ as they support each other

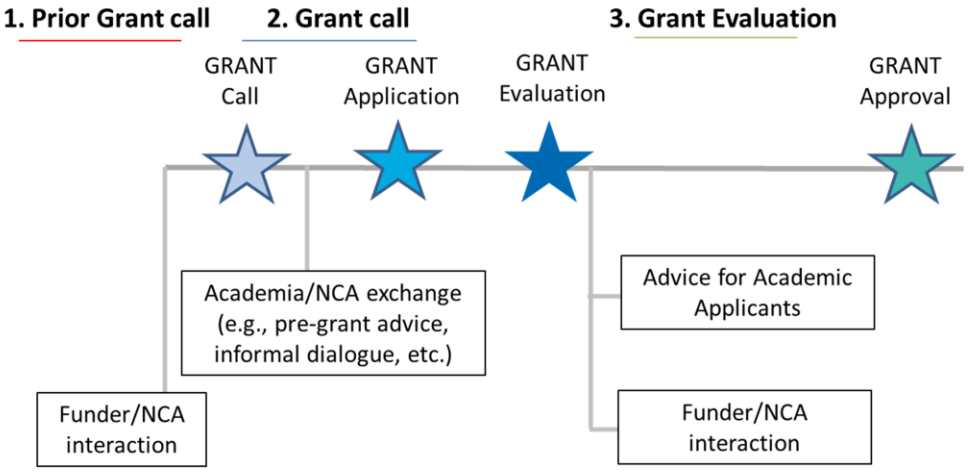


During the post-marketing surveillance measures regulation is more closely related to data from **clinical practice** and measures can include **real word data** as well as **observational studies**. More details were explained in the part on Phase IV studies.



Initiatives & new concepts for further support of stakeholders and researchers.

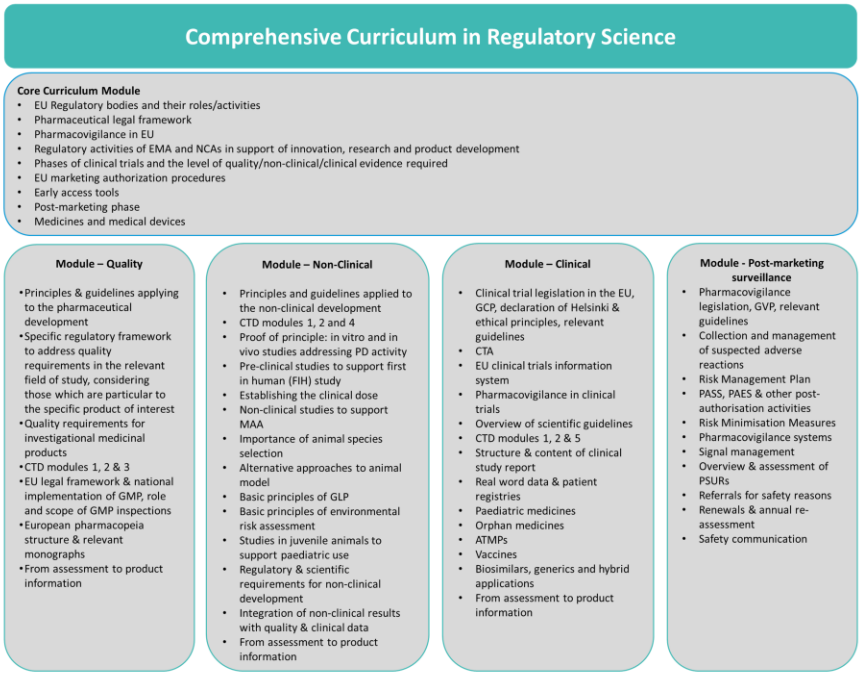
Further Support Tools for Academia- Pre-grant advice



The **pre-grant advice** is a recommendation developed by the STARS partners to support academia during the grant application process.

1. The first aim is that the **regulators have a close interaction with the funding bodies** to discuss regulatory requirements needed to adequately inform the grant call, which means that already in the call academia should get a regulatory advice on their project. This includes also a **payment strategy** for academia as a refundable advice concept offered by the funders.
2. Second aim would be a **close interaction between regulators and academic applicants** to discuss the regulatory requirements to be provided in the grant call is envisaged.
3. The third step aims to:
    1. provide **direct advice to academic applicants** on regulatory matters between the two evaluation stages when foreseen by the grant call.
    2. discuss **between the funders and regulators** the pre-selected grant applications from the regulatory point of view to optimise the application in a regulatory perspective up front.

Overview- STARS Comprehensive Curriculum



This slide gives you an **overview** of the content of the STARS Comprehensive Curriculum. If you would like to have more input on certain topics that were not addressed within the presentation, please complete the **survey** after going through the document and give us feedback how to optimise the curriculum in the future.