Submission Packages and Changes to Regulatory Guidelines in EU Region

AGENDA

- What is EU
- Who are the key players, including the role of the EMA
- Definitions
- SUBMISSION CONTENT
- Overview of procedures available
- Types Of Variations AND TIMELINES
- REFERENCES
- QUESTIONS

An introduction to EU

- The European Union (EU) is unique: it is not a federation like the USA, nor an organisation for co-operation between governments, like the United Nations.

- The countries that make up the EU ("Member States") remain independent sovereign nations but at the same time, they delegate some of their decision-making powers to common institutions, so that decisions on specific matters of joint interest can be made democratically at European level.

- The European Institutions were created to reflect the ever closer Union of European nations. At present, there are five EU institutions, each playing a specific role:

  - European Parliament (representing the EU's citizens)
  - Council of the European Union (representing the governments of the Member State)
  - European Commission (driving force and executive body)
  - Court of Justice (ensuring compliance with the law)
  - Court of Auditors(controlling sound and lawful management of the EU budget).

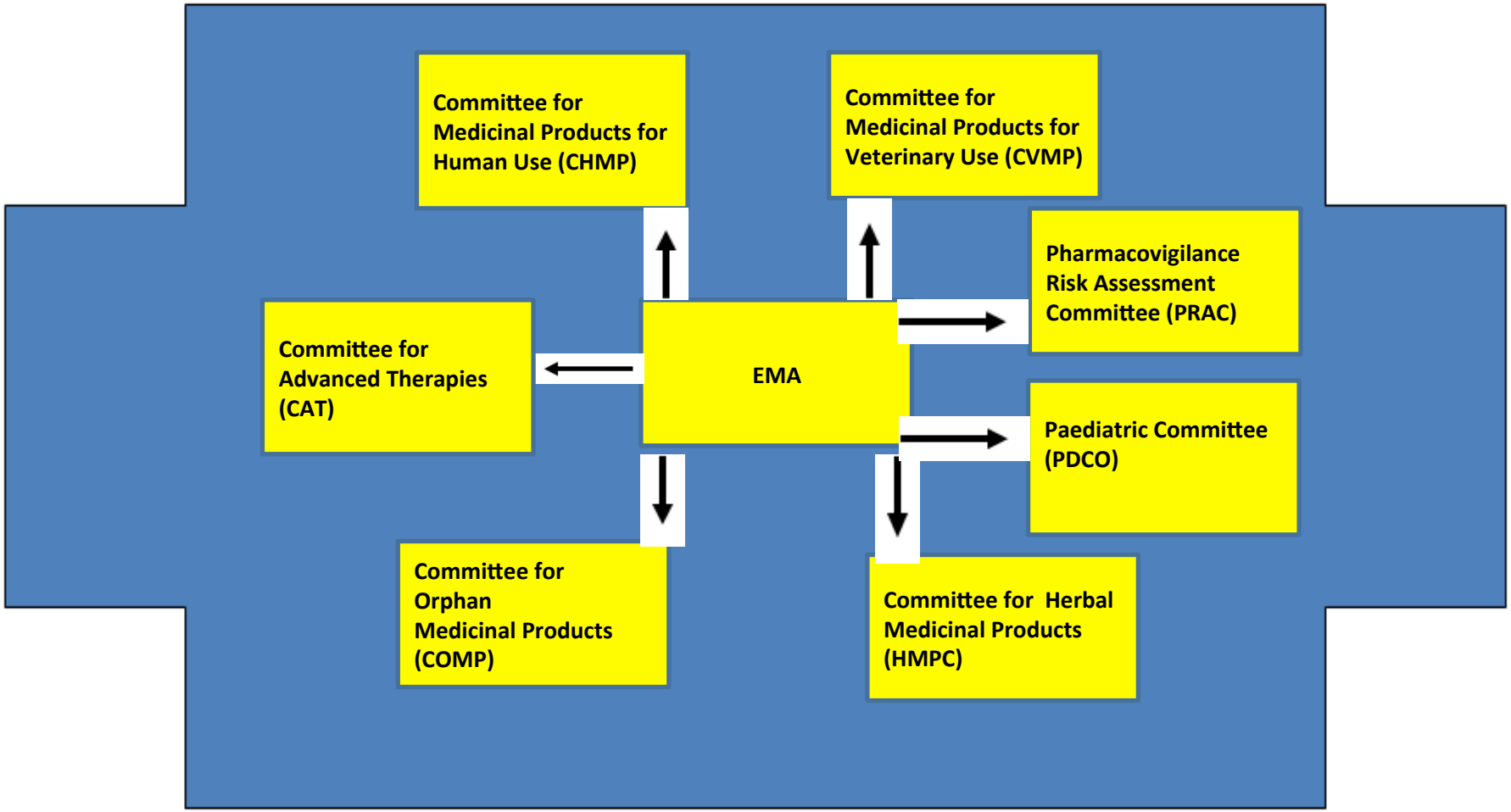
European regulatory network

- **European Medicines Agency**
  - The EMA is conceived as an interface of co-operation and co-ordination of Member States' activities with respect to medicinal products
  - EMA is a decentralised agency of the EU but is not part of the European Commission
  - CHMP within EMA performs scientific assessment of dossiers
  - EMA/CHMP adopts opinions on basis of scientific criteria which are relayed to European Commission

- **28 national competent authorities**
  - Network of 6,000 European experts
  - Assess dossiers for national and MRP/DCP
  - Provide scientific expertise to EMA assessors

- **European Commission**
  - Takes decisions based on EMA opinion and issues European Marketing Authorisations
  - Must fully justify decision when it is not in accordance with EMA opinion

Committees, working parties and other groups of EMA



Committees, working parties and other groups of EMA

CHMP - Responsible for preparing opinions on questions concerning medicines for human use.

- The CHMP replaced the former Committee for Proprietary Medicinal Products (CPMP).

CVMP - Responsible for preparing opinions on questions concerning medicines for veterinary use.

COMP : Responsible for reviewing applications from people or companies seeking 'orphan-medicinal-product designation'.

HMPC - Responsible for preparing the Agency's opinions on herbal medicines.

PRAC: - Responsible for assessing and monitoring safety issues for human medicines.

PDCO : Responsible for assessing the content of paediatric investigation plans and adopting opinions on them. This includes assessing applications for full or partial waivers and assessing applications for deferrals.

CAT : Responsible for assessing the quality, safety and efficacy of advanced –therapy medicinal products (ATMPs) and following scientific developments in the field.

EU Countries

Memberstates of the EU (year of Entry)

1. Austria (1995)
2. Belgium (1958)
3. Bulgaria (2007)
4. Croatia (2013)
5. Cyprus (2004)
6. Czech Republic (2004)
7. Denmark (1973)
8. Estonia (2004)
9. Finland (1995)
10. France (1958)
11. Germany (1958)
12. Greece(1981)
13. Hungary (2004)
14. Ireland (1973)
15. Italy (1958)
16. Latvia (2004)
17. Lithuania (2004)
18. Luxembourg(1958)
19. Malta(2004)
20. Netherlands (1958)
21. Poland (2004)
22. Portugal (1986)
23. Romania (2007)
24. Slovakia (2004)
25. Slovenia (2004)
26. Spain (1986)
27. Sweden (1985)
28. United Kingdom (1973)

On the Road to EU membership

Candidate Countries

1. Albania
2. Montenegro
3. Serbia
4. The former Yugoslav Republic of Macedonia
5. Turkey

Potential Candidates

1. Bosnia and Herzegovina
2. Kosovo

DEFINITIONS

- A regulatory submission for a health care product includes any documentation or information submitted to a regulatory agency for review, for notification or in response to a request for additional information related to a healthcare product.

- Variations are defined as changes to marketing authorization i.e., administrative, quality, safety and efficacy. Variations to medicinal products can be classified in different categories, depending on the level of risk to public or animal health and the impact on the quality, safety and efficacy of the medicinal product concerned, which needs to be notified, approved depends on the type of variation.

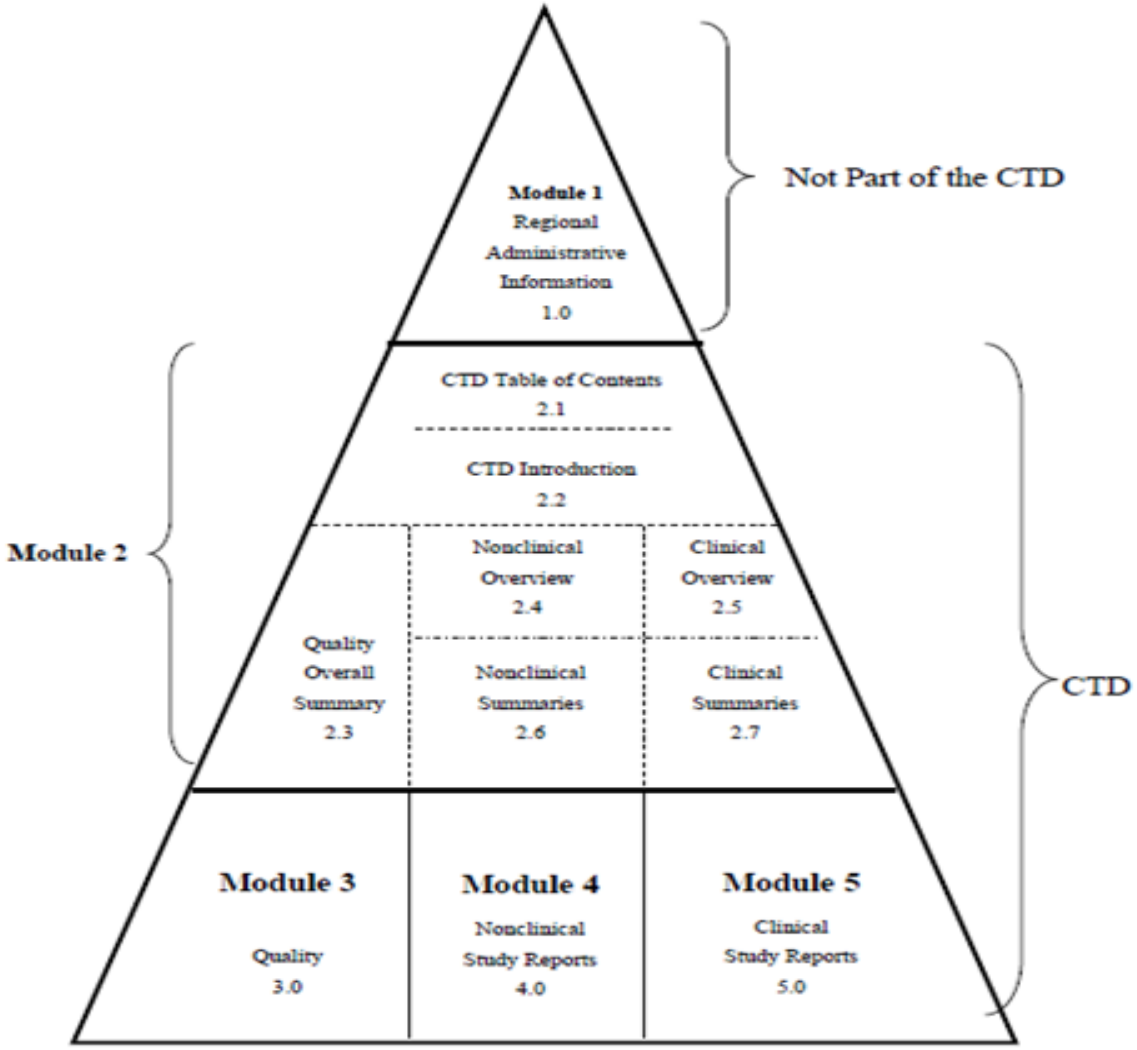
Key Elements of the CTD

- A Common structure has been agreed for EU and US Marketing Authorisation dossiers
- US = NDA (New Drug Application)
- EU = MAA (Marketing Authorization Application)

Structure of Common Technical Document (CTD)

- Module 1: Administrative Information and Prescribing Information (Regional)
  - For EU include Summary of Product Characteristics, Labelling, Package Leaflet and Mock-ups
- Module 2: CTD Overviews and Summaries
- Module 3: Quality
- Module 4: Nonclinical Study Reports
- Module 5: Clinical Study Reports

Dossier Structure



Registration procedures available

- **National route**
  - Used to maintain nationally approved products (variations, line extensions)
  - For NCE, only for a single MS registration

- **Mutual Recognition (MRP)**
  - 1 MS (RMS) assess data/dossier; other MS mutually recognise within 90 days the MA granted by RMS
  - CMS chosen by company (not all EU MS required –can be selective)
  - Marketing authorisations issued on national basis in each of the countries concerned but identical SmPCs for all MS completing procedure

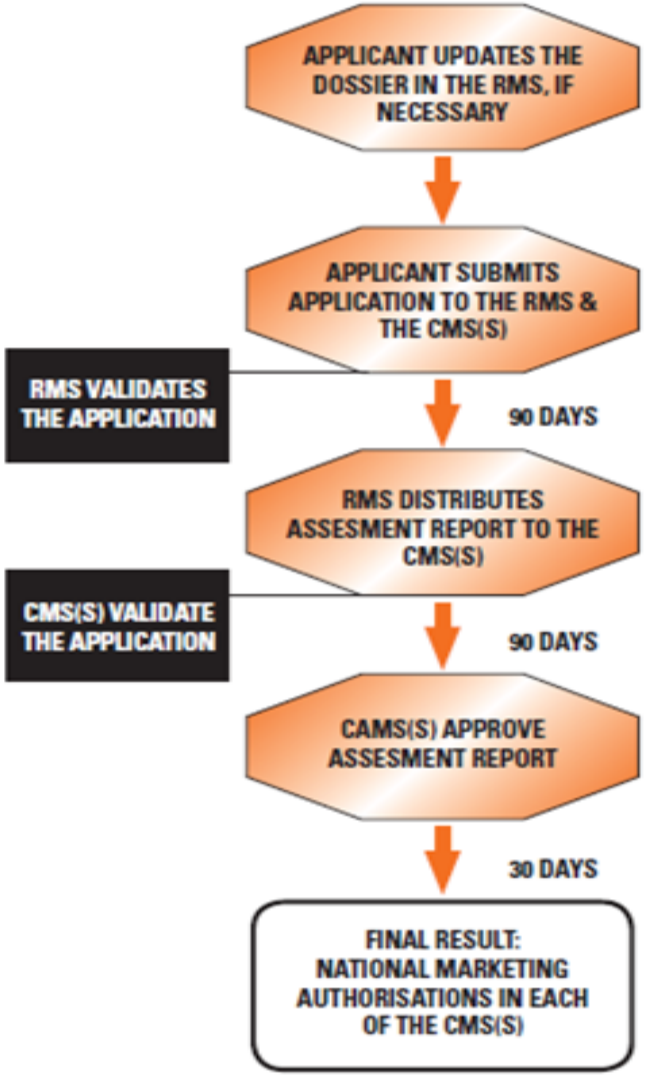
Registration procedures available

- **Decentralised Procedure (DCP)**
  - Same principles/outputs as MRP but different timelines

- **Centralised Procedure (CP)**
  - Single marketing authorisation with identical label valid throughout EU (cannot select countries)
  - Marketing authorisation granted by EU Commission based on opinion delivered by CHMP

MRP Principles and Overview

- The **M**utual **R**ecognition **P**rocedure is based on the principle of the mutual recognition by EU Member States of their respective national marketing authorisations.
- The objective of this procedure is to obtain marketing authorisations in one or several Member States, when the medicinal product has already been granted authorisation by at least one country in the European Community (this member state would then become RMS).
- The **R**eference **M**ember **S**tate acts as the main contact point for the applicant and the CMS. They act as a scientific assessor, a regulatory advisor and a moderator during the process.
- The **C**oncerned **M**ember **St**ate(s) are the countries selected by the applicant to participate in the MRP.
- Each member state has their own national authorisation so can choose their own local trade name.
- MRP can only be initiated once
  - •RMS approval granted
  - •AR produced by RMS
  - •Dossier and all relevant documents received by all CMS



MRP Timelines

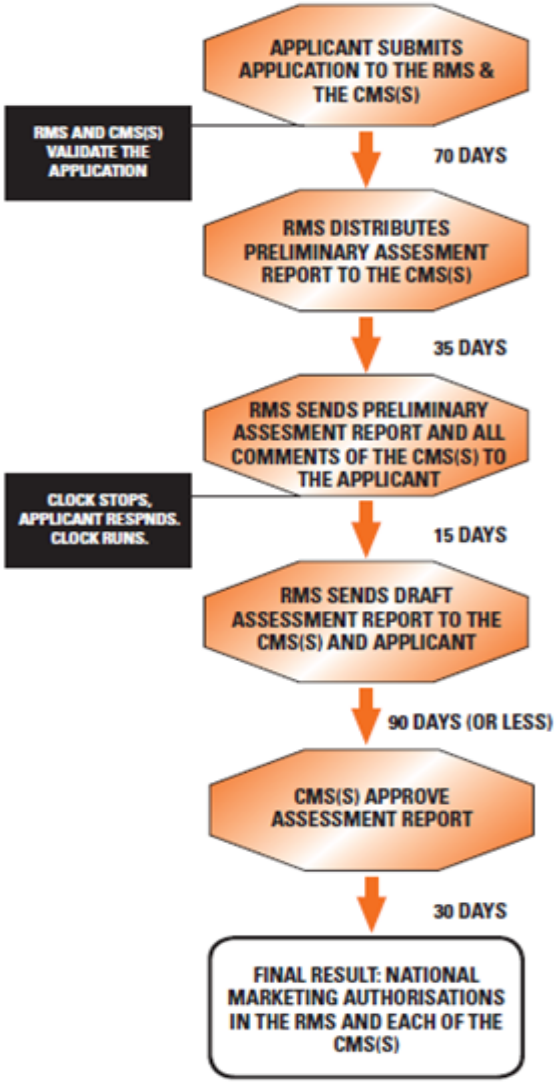
Approx. 90 days before submission to CMS	Applicant requests RMS to update Assessment Report (AR) and allocate procedure number.
Day -14	Applicant submits the dossier to CMS. RMS circulates the AR including SmPC, PL and labelling to CMSs. Validation of the application in the CMSs.
Day 0	RMS starts the procedure
Day 50	CMSs send their comments to the RMS, CMSs and applicant
Day 60	Applicant sends the response document to CMSs and RMS
Until Day 68	RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 75	CMSs send their remaining comments to RMS, CMSs and applicant.
Until Day 80	A break-out session (BOS) can be organised around Day 75 (but may take place between days 73 – 80).
Day 85	CMSs send any remaining comments to RMS, CMSs and applicant.
Day 90	CMSs notify RMS and applicant of final position (and in case of negative position also the CMDh secretariat of the EMA). If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMSs are referred to CMDh by the RMS within 7 days after Day 90.
Day 150	Final position adopted by the CMDh: If consensus is reached at the level of CMDh, the RMS closes the procedure. If consensus is not reached at the level of CMDh, the RMS refers immediately the matter to EMA for CHMP arbitration
5 days after close of procedure	Applicant sends high quality national translations of SmPC, PL and labelling to CMSs and RMS.
30 days after close of procedure	Granting of national marketing authorisations in the CMSs subject to submission of acceptable translations.

DCP Principles and Overview

- The objective of this procedure is to obtain marketing authorisations in several Member States, when no marketing authorisation has been granted in the European Community.
- The applicant may designate a country to act as the Reference Member State (RMS). Selection of the RMS depends on many considerations including workload, previous experience and acceptance of the dossier by the RMS.
- Each member state has their own national authorisation so can choose their own local trade name.
- Four steps:
  - •Pre-procedural step, including validation phase
  - •Assessment step 1
  - •Assessment step 2, including discussion at the CMD, if needed
  - •National step

Why DCP?

- •Applications containing a NCE which is not mandatory for CP.
- •When optional use of CP is not the choice.



DCP Timelines

Before Day -14	Applicant discussions with RMS RMS allocates procedure number. Creation in CTS.
Day –14	Submission of the dossier to the RMS and CMSs Validation of the application. Positive validation should only be indicated in CTS, not via e-mail.
Assessment step I	
Day 0	RMS starts the procedure. The CMS are informed via CTS.
Day 70	RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SmPC, PL and labelling) on the dossier to the CMSs and the applicant
Until Day 100	CMSs send their comments to the RMS, CMSs and applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments
Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.
Clock-off period	Applicant may send draft responses to the RMS and agrees the date with the RMS for submission of the final response. Applicant sends the final response document to the RMS and CMSs within a period of 3 months, which can be extended by a further 3 months.
Day 106	RMS restarts the procedure following the receipt of a valid response or expiry of the agreed clock-stop period if a response has not been received. The CMS are informed via e-mail and CTS will be updated accordingly.
Assessment step II	
Day 120 (Day 0)	RMS sends the DAR, draft SmPC, draft labelling and draft PL to CMSs and the applicant
Day 145 (Day 25)	CMSs send comments to RMS, CMSs and the applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments.
Day 150 (Day 30)	RMS may close procedure if consensus reached Proceed to national 30 days step for granting MA
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification, prepare a short report and forward it to the CMS's and applicant

DCP Timelines

Day 195 (at the latest)	A Break-Out Session (BOS) may be held at the European Medicines Agency with the involved MSs to reach consensus on the major outstanding issues
Between Day 195 and Day 210	RMS consults with the CMSs and the applicant to discuss the remaining comments raised.
Day 210 (Day 90)	Closure of the procedure including CMSs approval of assessment report, SmPC, labelling and PL, or referral to Co-ordination group. Proceed to national 30 days step for granting MA.
Day 210 (at the latest)	If consensus on a positive RMS AR was not reached at day 210, points of disagreement will be referred to the Co-ordination group for resolution
Day 270 (at the latest)	Final position adopted by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement
National step	
5 days after close of procedure	Applicant sends high quality national translations of SmPC, labelling and PL to CMSs and RMS
30 days after close of the procedure	Granting of national marketing authorisation in RMS and CMSs if outcome is positive and there is no referral to the Co-ordination group. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).
30 days after close of CMD referral procedure	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the Co-ordination group and no referral to the CHMP/CVMP. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable
5 days after close of procedure	Applicant sends high quality national translations of SmPC, labelling and PL to CMSs and RMS

When the Member States Disagree

- Where one or more Member States cannot recognise an authorisation already granted in an MRP or a final assessment and product information prepared in a DCP, the disagreement is referred to the Coordination Group for Mutual Recognition and Decentralised Procedure for Human Medicinal Products (CMDh).

- If the Member States still fail to reach an agreement within the CMDh, the matter is referred to the Committee for Medicinal Products for Human Use (CHMP).

Principals & Scope of the Centralised Procedure

- The centralised procedure, which came into operation in 1995, allows applicants to obtain a marketing authorisation that is valid throughout the EU.

- It is compulsory for medicinal products manufactured using biotechnological processes, for orphan medicinal products and for human products containing a new active substance which was not authorised in the Community before 20 May 2004.

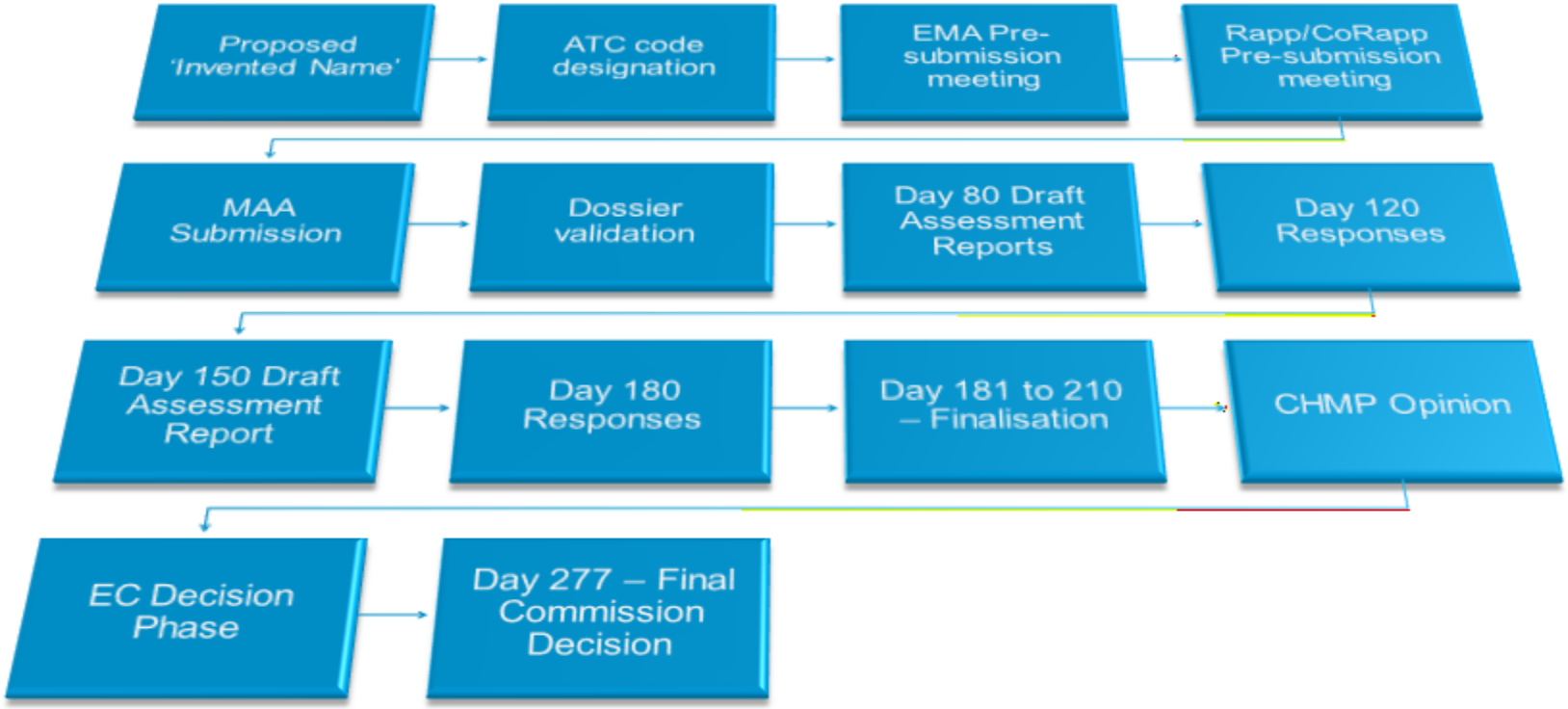
- It is also compulsory for products which are intended for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes.

- 1 central trade name is selected and is identical in all markets.

- **Key players**

  •Rapporteur and Co-rapporteur: lead the review process and produce assessment report (AR)

CP Submission – the steps to approval



Post-Authorisation Activities

➢ Amendments to Marketing Authorisations

- **Minor Variations:** No or minimum impact on the quality, safety or efficacy of the medicinal product
  - ✓ Notification - 'DO and Tell' Procedure (do not require HA prior approval)

    Type IA_{IN} – Event date should be within 30 days from the implementation date

    Type IA - to be submitted to HA within 12 months of event.
  - ✓ Variations - 'Tell , Wait and Do' Procedure

    Type IB - Date of approval = date of implementation or within set date after approval (usually 6 months
- **Major Variations:** Impact on the quality, safety or efficacy of the medicinal product

  Type II - Date of approval = date of implementation, Local Product Documentation needs to be provided within 5 days to each CMS
- **Extension Application**
  - Changes to the active substance
  - Changes to the strength, pharmaceutical form and route of administration
- **Renewals**
  - Applications shall be valid for five years and then need to be renewed for five year periods
- **Safety Reporting**
  - Periodic Safety Update Reports (PSURs) required (6 monthly to 2 years, every year for next 2 years and then every 3 years).

Type IA Notification

EX:

- Minor change in the manufacturing process of active substance
- Change in the Specification parameters of finished product (tightening of specification limits)
- Minor changes to approved test procedure of finished product
- Reduction of the shelf life of the finished product

Day 0	Start of Procedure
Until day 30	RMS validates the dossier
Day 30	RMS notify outcome of review On behalf of CMSs If no response MAH can assume change was acceptable

MRP: Type IB Notification

EX:

- Increase in the batch size
- Changes in scoring/break lines intended to divide into equal doses limits)
- Addition or replacement of a specification parameter
- Change in storage conditions of the finished product or the diluted/ reconstituted product

Day 7 to 1	Validation check
Day 0	Start of Procedure
Until Day 20	CMS notify RMS any objection
Day 30	RMS notify outcome of review
Clock stop for 30 days	RMS send notification with ground
New Day 0	Restart of Procedure
New Day 30	Final Decision by RMS

MRP: Type II Variation

EX:

- Deletion of an in-process test which may have a significant effect on the overall quality of the active substance
- Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product
- Addition of a new therapeutic indication or modification of an approved one

Day 14 to 1	Validation Check
Day 0	Start of Procedure
Day 15/40/70	RMS circulate the PVAR
Day 20/55/85	CMC comments on PVAR
Day 21/59/89	RMS send RSI
Clocked off period 10+10/60+60/90+60	
Day 22/60/90	RMS circulate the FVAR
Day 27/85/115	CMC comments on FVAR
Day 30/90/120	End of Procedure

REFERENCES

http://ec.europa.eu/health/documents/eudralex/index_en.htm

http://www.ema.europa.eu/ema/

http://europa.eu/about-eu/institutions-bodies/

Questions

Thank you