Introduction to the EU Regulatory Framework

David McCoubrey
Regulatory Affairs Lead
Almac Group

ALMAC

Objectives

1) Regulatory procedures in Europe

2) Overview of Centralised Procedure
   - Main features
   - Submission requirements
   - Timelines
   - Procedural options

3) EU Orphan Medicinal Product Designations

European Union

- 28 Member States
- 24 official national languages
- Population of 512 million
- Plus three additional EEA countries
  - Norway, Iceland and Liechtenstein

EU Marketing Authorisation Procedures

There are four different routes to obtaining a Marketing Authorisation in the EU/EEA

1) **Centralised Procedure**

- One application assessed by the European Medicines Agency
- Results in one Marketing Authorisation valid in all EU/EEA Member States

EU Marketing Authorisation Procedures

2) Decentralised Procedure (DCP)

- An application is made to a number of EU/EEA States
- The assessment is carried out by one Member State (the Reference Member State)
- The authorisation is agreed with the other Member States (the Concerned Member States)

EU Marketing Authorisation Procedures

3) Mutual Recognition Procedure (MRP)

- An existing authorisation in one EU/EEA State is "mutually recognised" in a number of other EU/EEA States

4) National Procedure

- A single application to an individual EU/EEA State

HPRA AIFA Agenzia Italiana del Farmaco ansm Agence nationale de sécurité du médicament et des produits de santé MHRA Regulating Medicines and Medical Devices

MA Application Submission Strategy

Product type may influence EU submission route

- **Mandatory for Centralised**
  - New active substances for:
    - Oncology, Diabetes; Neurodegenerative, Autoimmune and Viral disorders; AIDS
  - Biotech products
  - Advanced Therapy Medicinal Products
    - Gene Therapy
  - Orphan Medicinal Products

MA Application Submission Strategy

- **Optional for Centralised**
  - New active substances
  - Significant therapeutic, scientific or technical innovation, or in the interest of patients
  - Certain paediatric products
  - Generics or hybrids of Centralised products
- **Conditional/Exceptional/PRIME/Accelerated procedures**
  - Mostly only available via the Centralised route

Centralised Procedure

ALMAC

Output of EU Centralised Review

Licence: One European Marketing Authorisation

Product Name: One name

Prescribing Info: Identical Summary of Product Characteristics (SPC) and Identical Package Leaflet (PL) each in all EU official languages

Centralised Procedure – Who does what?

- **European Medicines Agency (EMA) in London**
  - Coordinates the scientific evaluation
  - Utilises the existing scientific resources of Member States

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Centralised Procedure – Who does what?

- **Committee for Medicinal Products for Human use (CHMP)**
  - Scientific Committee of the EMA
  - Perform scientific review and provide a scientific opinion
  - One representative / 28 Member States + Norway and Iceland (Each EU Member State has an alternate/back-up member)
  - Up to five co-opted members with specific areas of expertise

Centralised Procedure – Who does what?

- **Rapporteur and Co-rapporteur**
  - Members of the CHMP
  - Review the application and prepare assessment report(s) for the CHMP
- **EU Commission in Brussels**
  - Issues EU Commission Decision ('Licence') based on the Scientific Opinion
  - Legally binding to all Member States

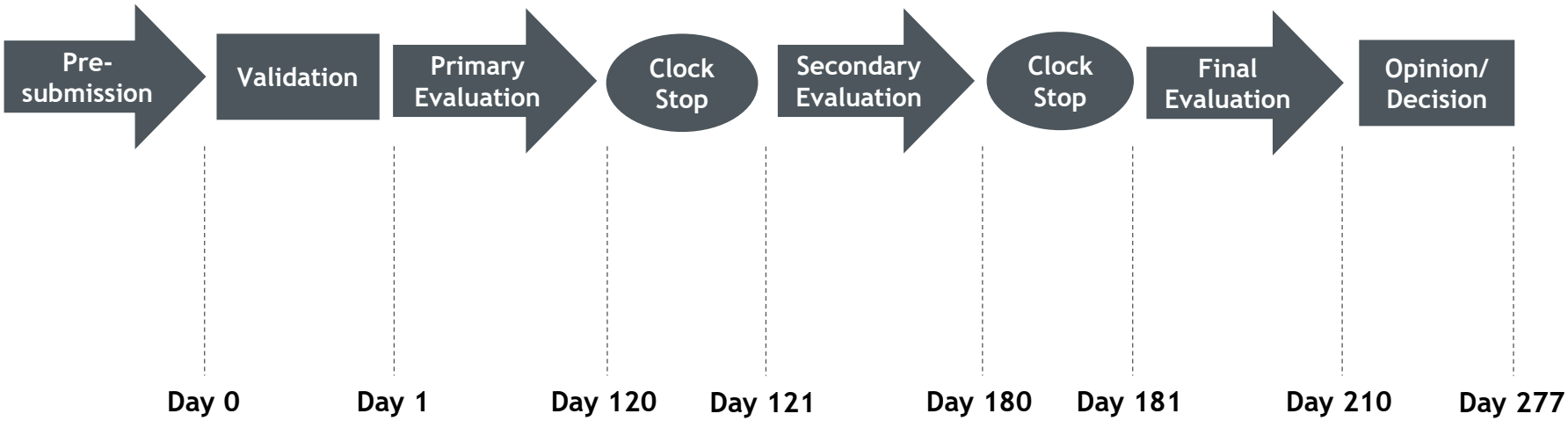
Key Information for Submission

- **Applicant:** Must be registered in EU/EEA
  - Provide proof of establishment
- **Application form:** Names of key personnel
  - Qualified Person for Pharmacovigilance
  - Scientific Service
- **Drug substance/product manufacturing sites**
  - Including EU Batch Testing and Batch Release Site(s)
- **Risk Management Plan**

Key Information for Submission

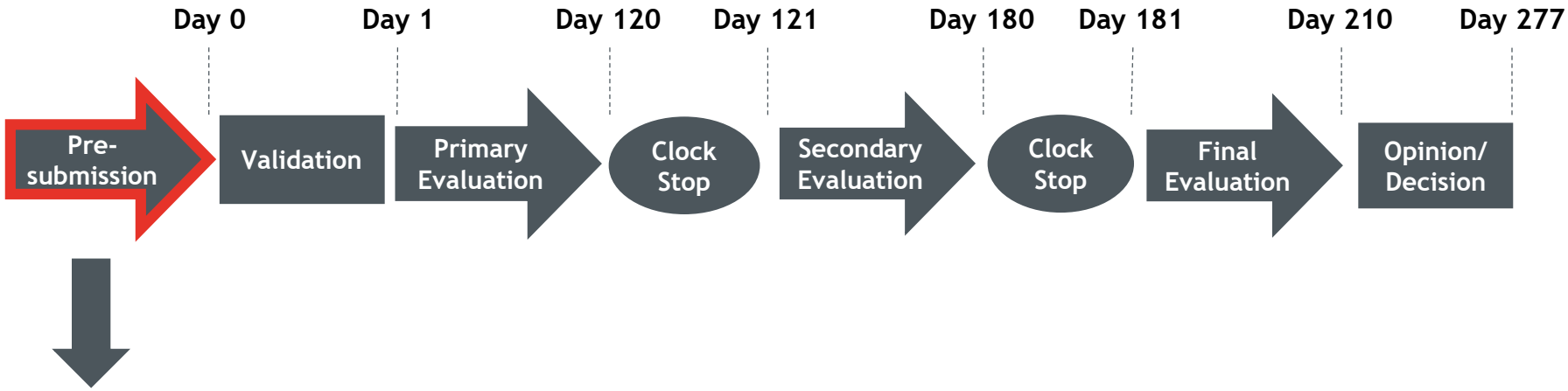
- **Labelling Mock-Ups**
  - English mock-up and Multi-lingual mock-up (i.e. a worst-case mock-up) of outer and immediate packaging in each strength and container type in the smallest pack size
- **Package Leaflet and User Testing Report**
  - Optional at the time of initial MAA submission (at the latest with the Day 121 responses)
- **CTD structure**
  - eCTD submission format is mandatory

Centralised Procedure Overview



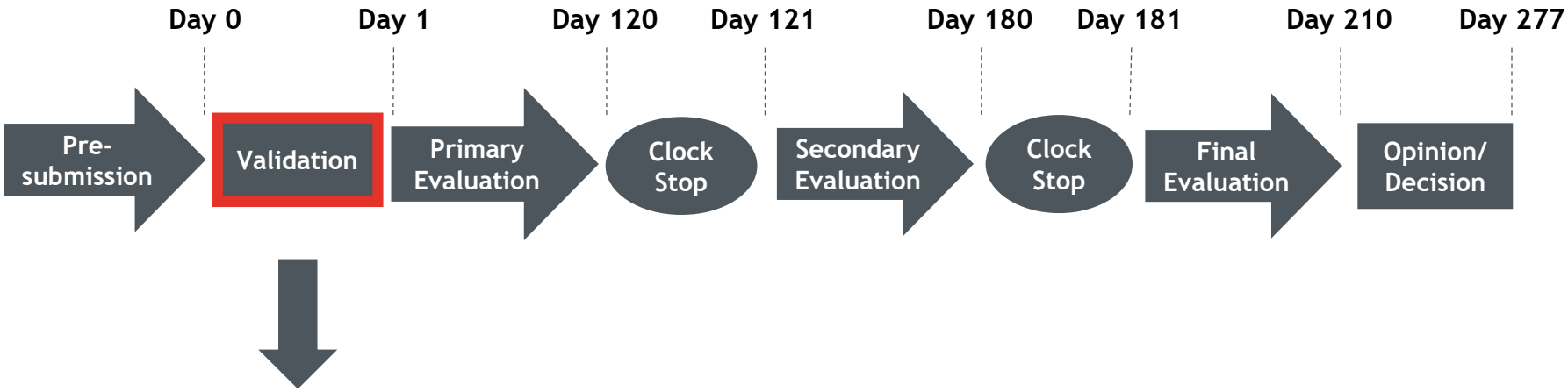
- Legal requirement for CHMP Opinion within 210 days (not including validation and clock stop periods)

Pre-submission



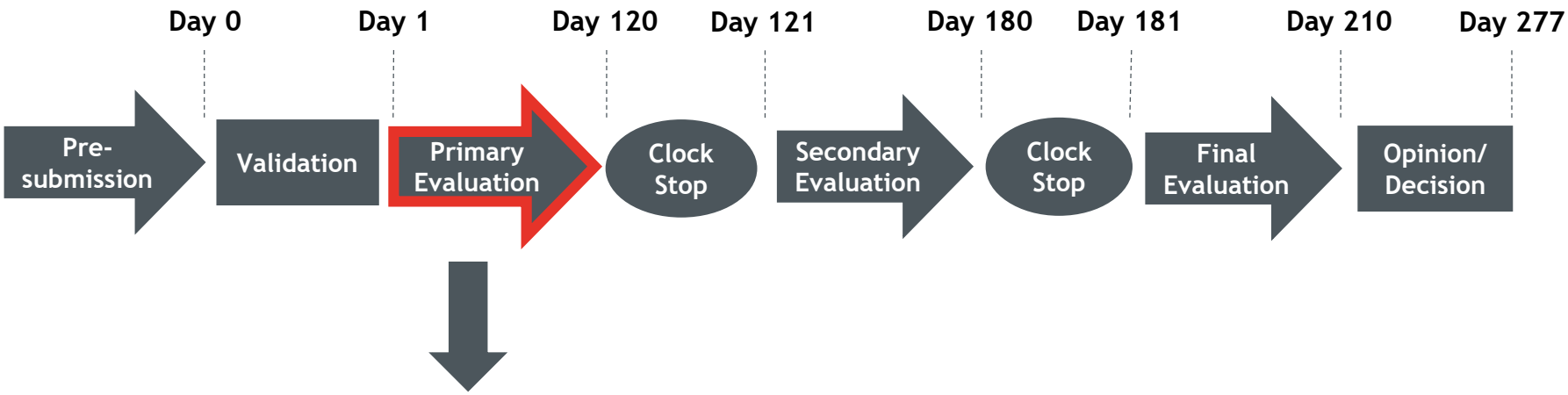
- Activities in advance of the dossier submission
- They start at least seven months before the submission date
- Eligibility request
- Letter of intent to submit
- Pre-submission meeting

Validation



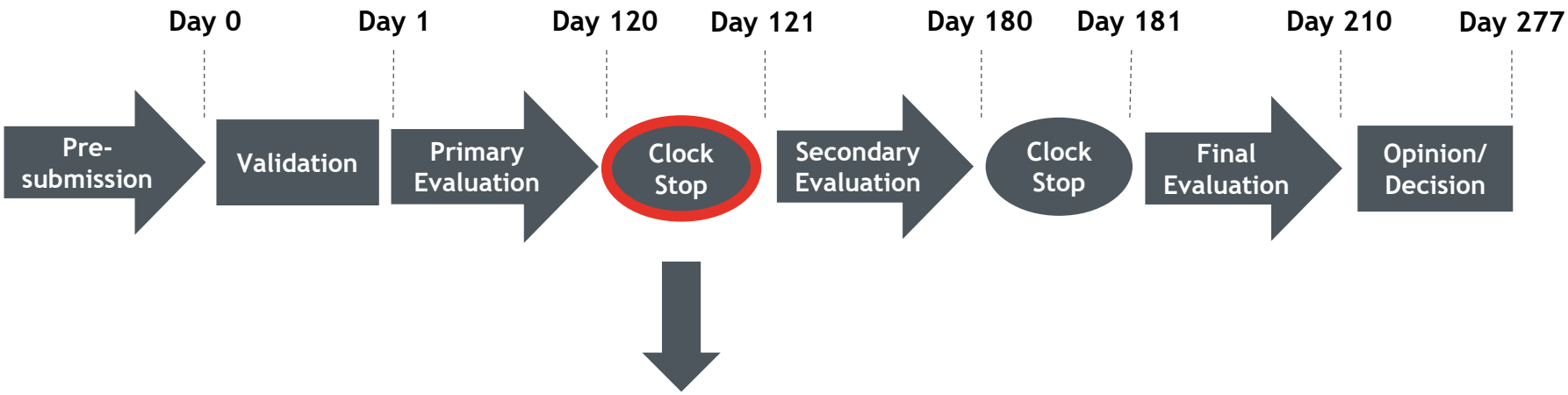
- Electronic submission via the eSubmission Gateway
- Technical validation
- Regulatory and administrative validation
- 13 working days timeline – but potential for delays

Primary Evaluation



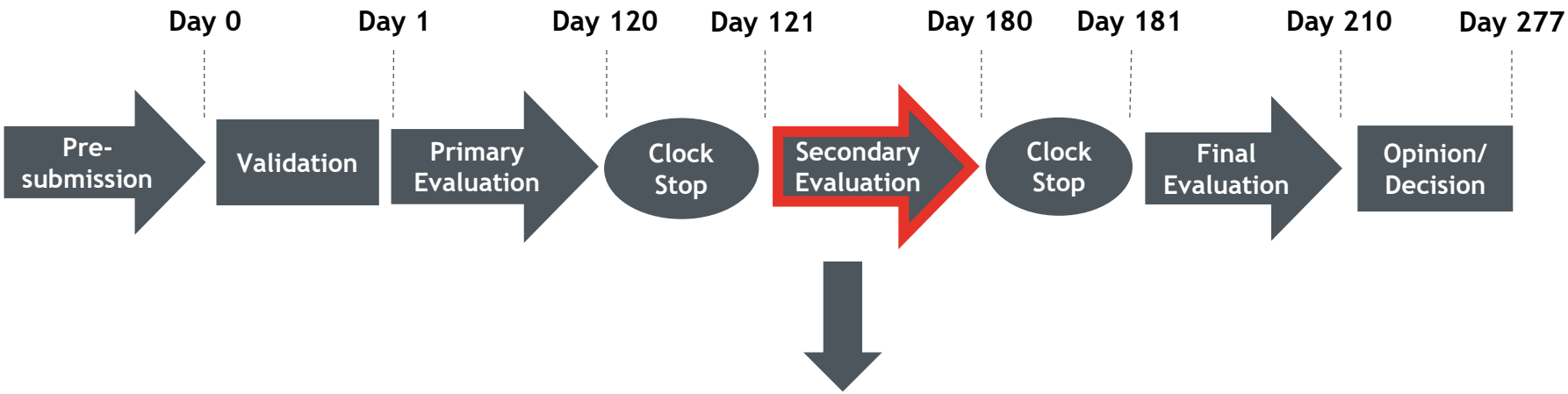
- Day 1 – Start of Procedure
- Day 80 – Receipt of initial assessment report by applicant
- Day 100 – CHMP receives comments from committee members
- Day 120 – Formal CHMP overview and list of questions sent to applicant

First Clock Stop



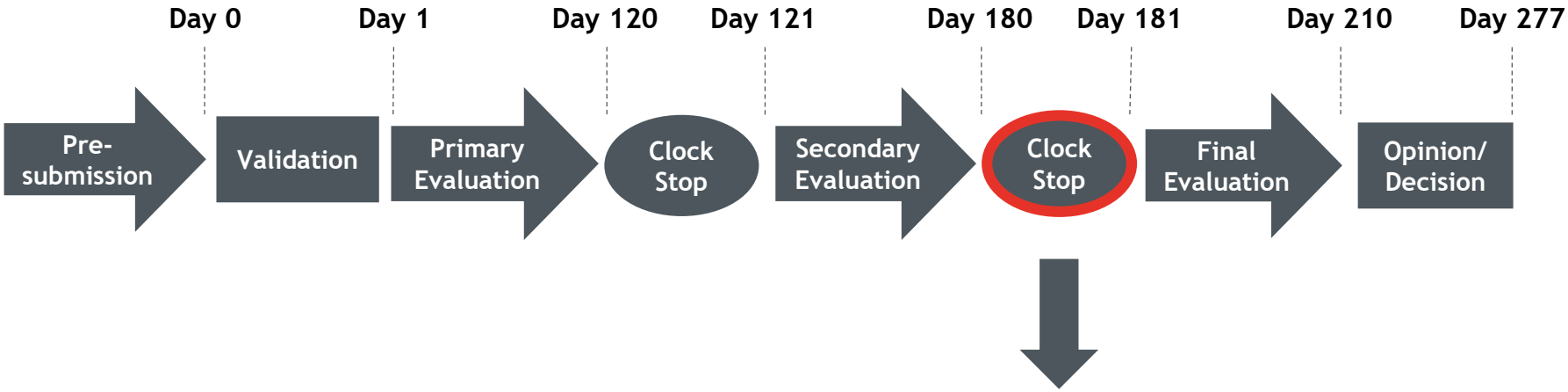
- Day 120 – Clock stops
- Applicant's responses expected within 3 months
- Includes revised English SPC, PL and pack labelling texts
- Day 121 – Clock restarts

Secondary Evaluation



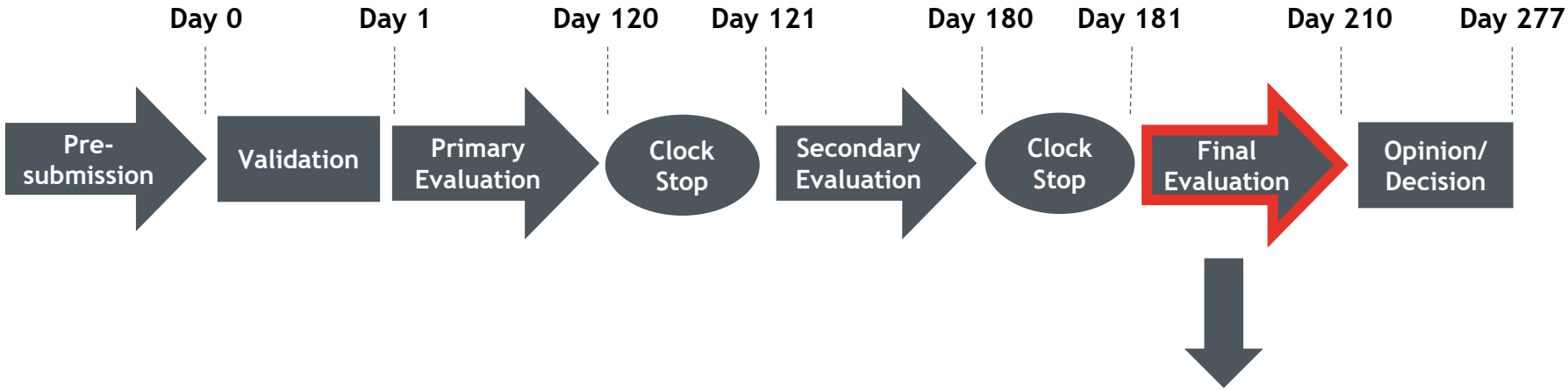
- Day 140 – English product information review by EMA/QRD
- Day 157 – Joint assessment report received by applicant
- Day 170 – CHMP receives comments from committee members
- Day 180 – List of outstanding issues adopted by CHMP

Second Clock Stop



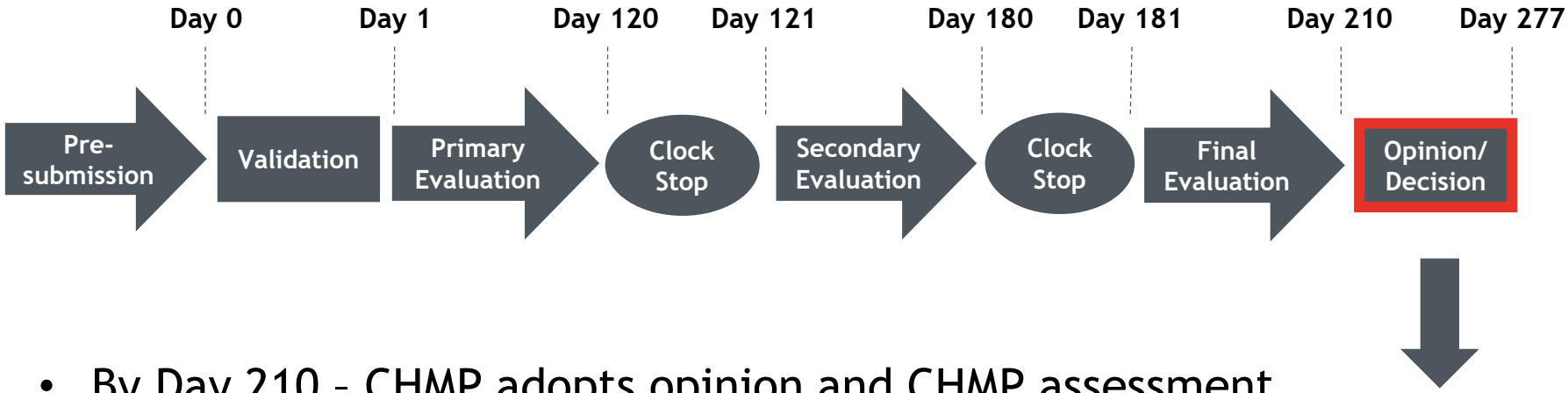
- Day 180 – Clock stops
- Applicant's written responses expected within one month
- EMA decide if oral explanation is also required
- Day 181 – Clock restarts and oral explanation meeting (if needed)

Final Evaluation



- Day 181 to Day 210 – Final draft of English SPC, PL and labelling to be submitted by applicant

Opinion / Decision

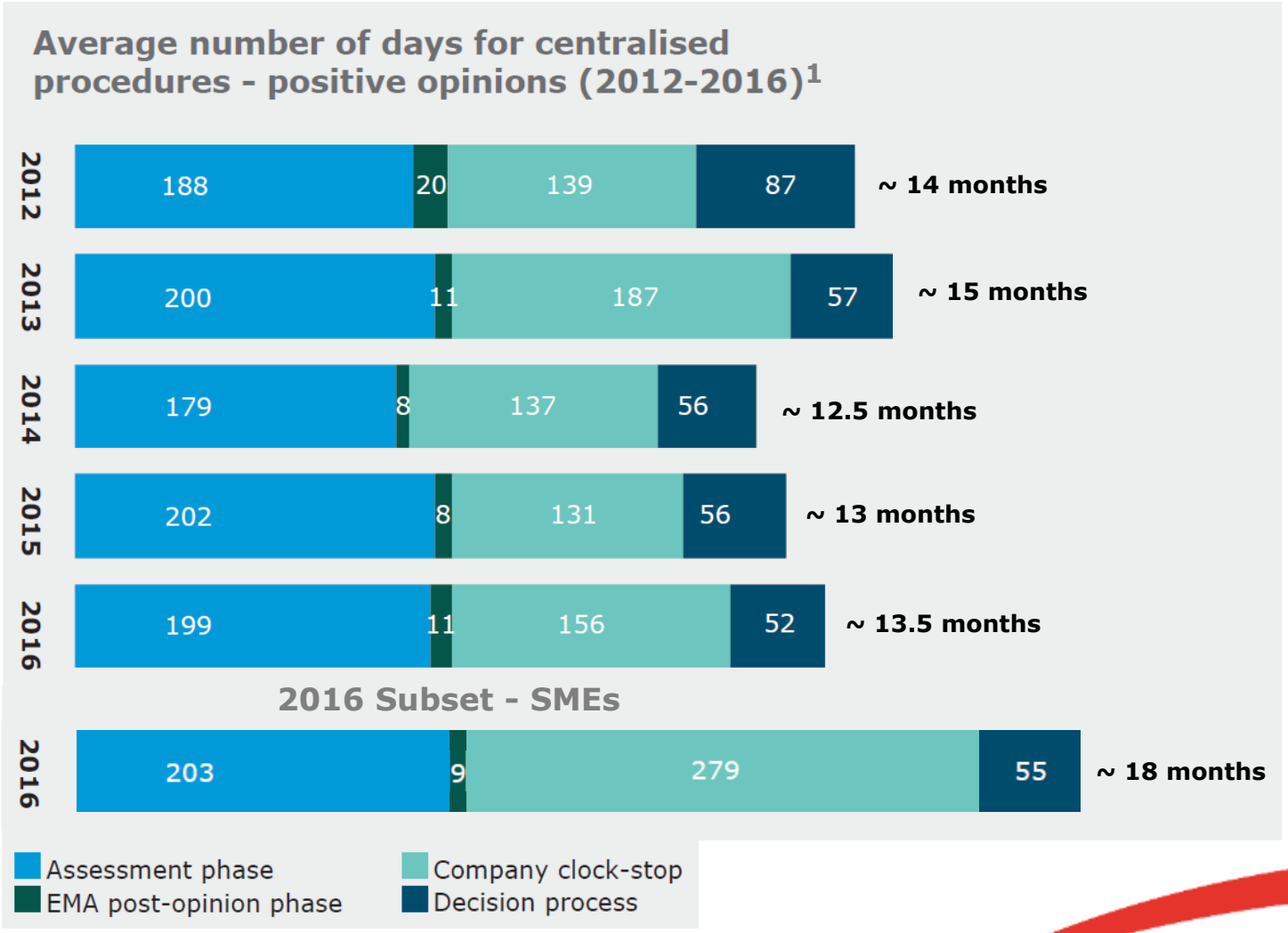


- By Day 210 – CHMP adopts opinion and CHMP assessment report issued (CHMP opinions are based on majority voting)
- By Day 215 – Product information in all EU languages (plus Icelandic and Norwegian) to be submitted by applicant
- Day 229 – Member States send comments on translations
- Day 235 – Final translations to be submitted by applicant
- Day 277 – EU Commission Decision issued

Specimens and Samples

- **Specimens**
  - Sales presentation of the product
    - Packaging and leaflet
  - Required to be submitted:
    - Before product is marketed
    - If number of languages used increases
- **Samples**
  - Drug product or ingredients
  - Required to be submitted:
    - Only on request during the assessment

Centralised Procedure: Practical Timelines



1. European Medicines Agency Annual Report 2016

Centralised Procedure: Practical Timelines

EITHER: Total duration ~14 months

No oral explanation

Val 1 M	Assessment 4 M	Clockstop + Restart 3+1 = 4 M	Assess't responses 2M	Final SPC 1M	MAs ~2M

Majority of launch related activities

With oral explanation

Val 1 M	Assessment 4 M	Clockstop + Restart 3+1 = 4 M	Assess't responses 2M	Oral Expn 2 M	Final SPC 1M	MAs ~2M

Majority of launch related activities

OR: Total duration ~16 months

Accelerated Assessment

- CHMP opinion in 150 days instead of 210 days
- EU equivalent of Priority Review in the US
- Justification based on major public health interest
  - Unmet needs
  - Therapeutic innovation
  - Major impact on medical practice

Priority Medicines (PRIME) Scheme

- Supports the development of medicines that target an unmet medical need
  - The request is made based on preliminary clinical evidence
- EU equivalent of ‘Breakthrough Therapy Designation’ in the US
- Gives early engagement with the EMA
- Eligibility criteria are those of the accelerated assessment

Conditional Approval

- Additional clinical data required but benefit to public health of immediate availability outweighs risk
- Can apply to:
  - Products for seriously debilitating or life-threatening diseases
  - Orphan designated medicinal products
- Valid for one year on a renewable basis
  - Required to complete ongoing or new studies
  - Once the studies are provided it can become a ‘normal’ MA

Exceptional Circumstances Approval

- Comprehensive data cannot be provided e.g.
  - Extremely rare indications
  - Against medical ethics to collect data
- The MA may be granted subject to specific obligations e.g. additional studies or advice in Product Information
- Reviewed annually to assess the risk-benefit balance
- Will not normally lead to the completion of a full dossier and become a ‘normal’ MA

Orphan Designated Products

- Medicines for serious rare diseases
  - Application to EMA for designation
- Procedural and marketing benefits
  - Mandatory access to centralised procedure
  - Eligible for Conditional Marketing Authorisation
  - Extended marketing exclusivity
- Financial benefits
  - Lower fees (further reductions available for Small and Medium-sized Enterprises)

Summary of Centralised Procedure

- One Application, One Evaluation, One Authorisation
- EU-wide authorisation (plus Liechtenstein, Norway and Iceland) that is binding and identical in all Member States
- Set timelines
  - Scientific opinion in 210 days (plus clock stops)
  - Authorisation about two months later
- Options for innovative products
  - PRIME Scheme/Accelerated Assessment
  - Conditional Approval
  - Exceptional Circumstances Approval

Questions…

Thank you