TOPRA Module 1

EU Regulatory Procedures – Strategic Choices

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Learning Outcomes

- **Knowledge of EU regulatory procedures;**
- **Basics of Mutual Recognition (MRP) and Decentralised Procedure (DCP);**
- **Basics of Centralised Procedure (CP);**
- **Understanding factors influencing the choice of a regulatory procedure;**

In This presentation we will cover

- Legal Basis for a Marketing Authorisation Application
- Principles MRP/DCP procedure;
- Role of Reference Member State;
- Centralised Procedure;
- Mandatory and optional scope of centralised procedure
- Role of Rapporteur;
- Special circumstances;
- Strategic Choices

A Marketing Authorisation

- **A license to sell a medicine**
- **License granted by "Competent Authorities"**
- **Assessment is benefit/risk based on:**
  - Quality
  - Safety
  - Efficacy

Positive risk-benefit balance in favour of patients and users of products once they reach the market place

How to obtain a marketing Authorisation

National

- Application in individual countries

MRP/DCP

- National application intended for more than one country
  - Mutual recognition
  - Decentralised procedure

Centralised Procedure

- 1 marketing authorisation
- 1 (invented) name
- 1 common product information

Legal Basis

Article 8(3) Full Application

- Full dossier; quality, nonclinical and clinical data

Article 10 (1) Generic

- Reference product on the market no less than 8 years
- Same qualitative, quantitative compositions
- Same pharmaceutical form
- Bioequivalence

Legal Basis

Article 10 (3) Hybrid (mixed) Application

- Additional non-clinical/clinical data in case:
  - Product does not meet definition of generic
  - No bioequivalence
  - in case of changes in the active substance(s),
  - Change to active substance, therapeutic indications, strength, pharmaceutical form or route of administration

Article 10 (4) Biosimilars

- Additional non-clinical/clinical data required in case of:
  - product does not meet definition of generic, esp. differences relating to raw materials or differences in manufacturing processes of biological product and reference biological product

Legal Basis

Article 10(a) Well established use

- Well-established medicinal use of active substance for at least 10 years
- Non-clinical and clinical trial results replaced by appropriate scientific literature

Article 10(b) Fixed combination products

- Active substances used in composition of authorised medicinal products but not in combination
- New non-clinical and clinical data relating to the combination are required

Article 10 (c) Informed consent / Duplicate

- MAH allows reference to data on file to support assessment of other medicinal products with same qualitative and quantitative composition of active substance and same pharmaceutical form

How to obtain a marketing Authorisation - procedures

National

- Application in individual countries

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Competent Authorities

National Health Authorities in each Member State

ansm
Agence nationale de sécurité du médicament et des produits de santé

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

cBG MEB

famhp
federal agency for medicines and health products

AIFA

MHRA
Regulating Medicines and Medical Devices

The European Medicines Agency

- Partners national competent authorities

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Nationale Procedure

- **Until 1998**
- **Currently only for:**
  - Marketing authorisation in a single EU Member State
    (No MA in any other Member State and no pending application in a Member State)
  - National phase Mutual Recognition Procedure
- **Timelines: national**
- **Result:**
  - National approval, national SPC

(difference between Member States)

Mutual Recognition (MRP) Decentralised procedure

Principle of Mutual Recognition/ Decentralised procedure

- Relying upon principle of mutual recognition

- A Marketing authorisation in one Member State ought in principle to be recognised by the authorities of other member States.

As opposed to CHMP opinion by majority of votes (CP)

As opposed to every HA doing their own procedure, assessment (National)

MRP and DCP

Mutual Recognition procedure (MRP)

Where the medicinal product has **already** received in a MS a MA at the time of application

Decentralised Procedure (DCP)

Where the medicinal product has **not** received in a MS a MA at the time of application

Eligibility

- **Applications for MA in more than one Member State**
- **Open for all applications not falling under mandatory scope of Centralised procedure:**
  - New active substances; Generic medicinal products; Informed consent applications; Bibliographic applications; Known substances in new combinations; Line extensions; Herbal medicinal products; Homeopathic products

- **Flexible -** choice of MSs, with different trade names and MA holder
- **Possibility of repeating procedure**
- **Applicant to choose RMS**

Overview of MRP and DCP

MRP	DCP
•National registration in RMS	•Submission to RMS and CMS
•(Updated) Assessment Report	
•Dossier submission to CMS	
•Validation (14 days)	•Validation (14 days)
•90 Day assessment	•Assessment I – 120 days
	•Assessment II – 90 days
•Discussion at CMDh (if necessary)	•Discussion at CMDh (if necessary)
90 days	*210 days*
•National phase	•National phase

Timelines MRP

210 Days - National Registration

90 Days – preparation AR

Day 0 – Start procedure

Day 50 - CMS Comments

Day 60 - Applicants's Response

Day 75 - CMS Comments

Day 85 - Final CMSs position

Day 90 - Consensus/close of procedure

Timelines DCP

Assessment I

Day 0 – Start procedure

Day 70 - Preliminary AR

Day 100 - CMS send comments/questions

Day 105 - Clockstop

Day 106 - Applicants responses

Day 120 - Consensus/ close of procedure

- No Consensus/ AR to applicant

Assessment II

Day 150 - RMS + CMS comments to Applicant

Day 160 - Applicant Responses

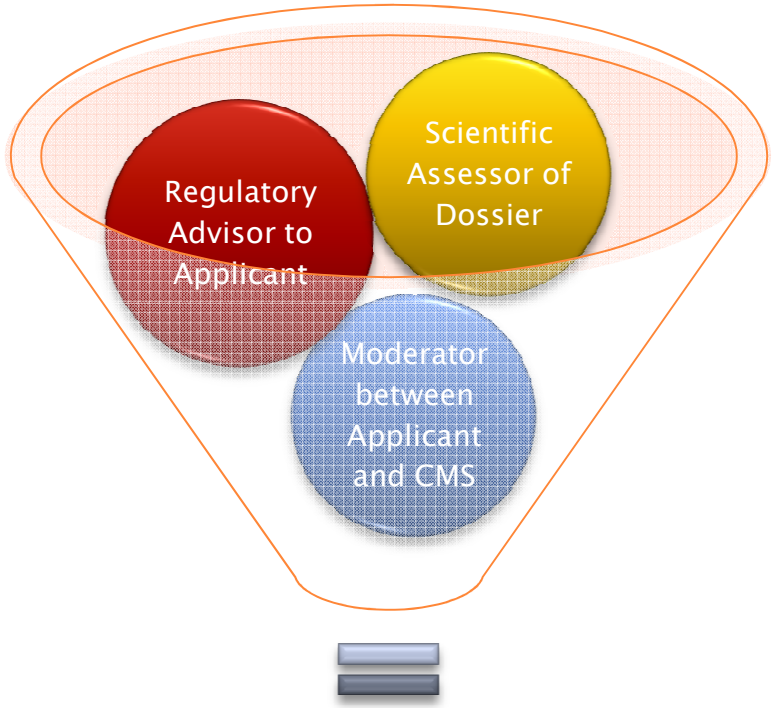
Day 180 - Consensus/Close of Procedure

Day 195 - Break-out session if required

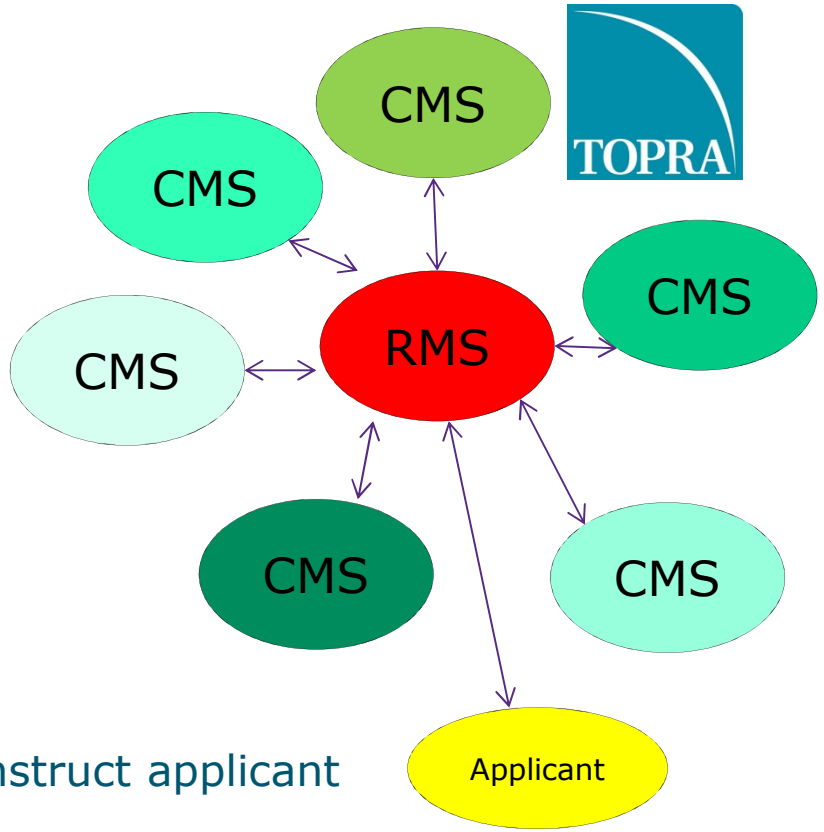
Day 195 – 210 Resolution of any minor outstanding comments

Day 210 - Consensus/Close of Procedure

Role of Reference Member State



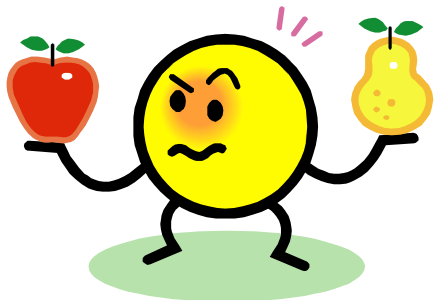
Role of RMS



- Provide regulatory and scientific advice
- Decides timetable
- Scientific assessment – assessment report
- Evaluation responses
- Central point between applicant and CMS
- Organises and chairs break-out sessions, instruct applicant
- Refers to CMDh
- Informs EMA if after referral no consensus
- Informs applicant and CMS after positive conclusion and prepares final assessment report
- Public assessment report

Choosing RMS and CMSs

- **Based on regulatory, strategic and commercial reasons**
- **Availability of RMS in DCP**
  - Were they supportive of product/dossier during scientific advice
  - Expertise of RMS for certain type of product
  - Availability of slot
- **For MRP, RMS is where dossier was filed and approved nationally**



Referral

- Automatic in the absence of consensus
- Aim is to resolve PSRPH which have not been resolved during the procedure, and must be explained in detail
- Applicant cannot ask for a referral to appeal a negative consensus
- Written response is always necessary, oral hearing possible
- No new data can be submitted, elaboration or clarification of existing data is acceptable
- CMS not included in the DCP/MRP will be involved in the discussions but not the formal agreement
- If agreement is not reached move to CHMP Referral EMA
- MSs agreeing with AR at Day 60 proceed to national phase

Withdrawal

MRP

- At any time
- Except after a PSRPH has been raised
- If PSRPH is dealt with by CMDh or if failed in an arbitration procedure in the CHMP an opinion will be given
- After withdrawal automatic referral to CMDh

DCP

- At any time
- Except during assessment Step II, once PSRPH has been raised,
- If PSRPH is dealt with by CMDh or if failed in an arbitration procedure in the CHMP an opinion will be given
- Withdrawal after day 120 –automatic referral to CMDh

Repeat-use MRP

To include further CMSs

All ongoing procedures (e.g. variations and renewals) to be finalised and dossier updated

Dossier update to include

- Responses to previous procedures; variations/renewals
- Commitments fulfilled without a variation procedure
- Additional data to comply with recent regulatory requirements, e.g. Risk Management Plan, Environmental Risk Assessment. These must be added by variation
- Formatting to CTD structure if dossier is in 'old' EU format
- Consider conducting new studies according to current standards, or provide updated evaluation of risk-benefit
- Discuss issue with RMS before submission of RU-MRP

Centralised Procedure

The European Medicines Agency

- **Protection and Promotion of Public and Animal Health**
  - Evaluation and supervision of medicines
- **Marketing Authorisations**
  - Responsible for the scientific evaluation of applications for medicines in the centralised procedure
- **EU's safety-monitoring or 'pharmacovigilance' system**
- **Referrals**
- **Coordinating inspections: GMP, GCP, GLP, PhV**
- **Stimulating Innovation and research**
  - Scientific advice, Guidelines, SME office,

    Orphan designation, Innovation Task Force

CHMP – Scientific Committee EMA

Composition

- Chair (Tomas Salmonson, Sweden)
- One member and alternate from 28 member states
- One member and alternate from Iceland and Norway
- Up to five co-opted members to provide additional expertise
- 3 year mandate renewable

CHMP Tasks

- **Scientific advice**
- **Preparation of opinion of EMA on questions relating to the evaluation of medicinal product for human use**
  - Initial assessment
  - Post-authorisation and maintenance (variations)
- **Urgent opinions**
  - (pharmacovigilance, Serious concerns on public health, Quality defects, Urgent Safety Restriction)
- **European Public Assessment Report**

Centralised Procedure: Mandatory and optional scope

Legal Basis: Regulation (EC) No 726/2004, Article 3 (references to Annex)

- Mandatory Scope: Art 3(1)
- Optional Scope: Art 3 (2)

Mandatory scope of CP

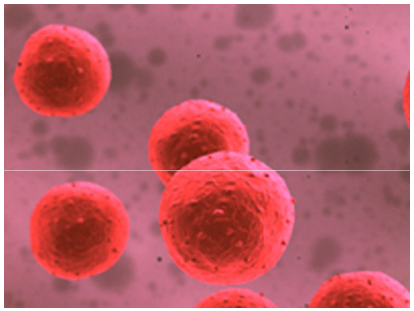
Biopharmaceuticals

- recombinant DNA technlogy
- Controlled expression of genes coding for biologically active proteins
- Hybridoma and monoclonal antibody cells
- biosimilars

Mandatory Scope of CP

Advanced Therapy Medicinal Products (ATMPs)

- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products



Certain therapeutic areas

- Aids, Cancer, Neurodegenerative disorders, Diabetes, Autoimmune diseases, Viral diseases

Orphan medicinal products

Optional Scope of CP

New active substances (outside mandatory scope indications)

- A new chemical, biological or radiopharmaceutical active substance, as defined in Annex III to Chapter 1 of Notice to Applicants, includes:
  - A chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union

Steps to obtain an EU marketing Authorisation

- **Submission of eligibility request**
  - between 18 to 7 months before submission
- **Notification of intention to submit an application**
  - 7 months before submission
- **Appointment of Rapporteurs**
  - 7 months before submission
- **Pre-submission Meeting**
  - 7 months before submission
- **Submission of Application**
- **Scientific evaluation**
  - 210 days of assessment
- **CHMP scientific opinion**
- **European Commission decision**

Role of the Rapporteur

- **Spokesperson of the CHMP**
- **Assessment Report**
- **Can be important for the applicant**
  - Good and open relationship is important

Rapporteur/co-Rapporteur appointment

- **Appointment from CHMP members**
- **Expert team**
- **Appointment normally in accordance with expertise (therapeutic area)**
  - Supported by their national experts
- **Applicant's proposal/preferences are not considered**

  - ATMPs: (Co-)Rapporteurs appointed amongst CAT Members
  - PRAC Rapporteur and Co-Rapporteur appointed

EMA Product Team

Product Team Leader (PTL) and Product Team Members

- Nominated by EMA
- Responsible for handling procedural aspects
- Both pre- and post- authorisation Phase

PTL primary contact point for the applicant

Liaison between EMA, (Co-) Rapporteur, Applicant

Centrale Procedure - Timelines

Day 1	– Start Procedure
Day 80	– Preliminary Assessment Report
Day 120	– List of questions
Clockstop	
Day 121	- Submission responses
Day 157	– Joint Assessment Report
Day 180	– CHMP discussion
Day 181	– Restart of the clock and oral explanation
Day 181 – 210	- Preparation final product information
Day 210	– CHMP opinion

Potential options

- Accelerated review
- Exceptional circumstances
- Conditional approval
- Orphan drugs
- Options for Small and medium sized enterpises (SME)

Accelerated assessment

- **Request before submission, at least 10 working days before submission**
- **Reduced timeline from 210 to 150 days**
- **Major Public Health Interest**
  - particularly from the point of view of therapeutic innovation
- **Justification of public health interest, case-by-case**
  - Unmet need, new methods of therapy, improves on existing methods
- **If at day 120 or 150 CHMP or applicant consider accelerated assessment no longer appropriate, assessment may continue under standard timelines**

Conditional Approval

Extensive studies/data may not be required in case of:

- Seriously debilitating/ life-threatening diseases
- Emergency products for Public Health threats
- Orphans

Requirements:

- Positive benefit/risk balance
- Unmet medical need
- Possibility to provide comprehensive data
- Benefit to public health outweighs the risks of placing on market without comprehensive studies

Prerequisite: MA subject to specific obligations (to provide comprehensive data)

Exceptional Circumstances

- **Applicant is <u>unable</u> to provide comprehensive data**
  - Indication so rare that no large phase III trial can be performed
  - present state of scientific knowledge prohibits provision of comprehensive information
  - Ethical concerns
- **MA also subject to specific obligations**
- **Annual reassessment of risk-benefit**
- **Particular emphasis on safety of product**
- **Formal application to be submitted before MAA**

Differences conditional approval and exceptional circumstances

Conditional approval:

- temporary authorisation with eventually a full dossier.
- Valid for one year
- can become “normal” marketing authorisation

Approval under exceptional circumstances:

- comprehensive development cannot/will not be provided
- annual review
- will not lead to “normal marketing authorisation

Only one legal basis can be chosen

Adaptive Licensing

- **Prospectively planned, adaptive approach to bringing medicines to patients**
  - Timely patient access
  - Providing adequate evolving information of benefit and risks

- **Prospectively designed development plan, subject to early dialogue with stakeholders (authorities, patients, HTA)**
- **Unmet medical need**
- **Build on existing regulatory processes**
- **Pilot started in March 2014**

How to liaise options for dialogue

Scientific advice

- Early in development
- can (and should) be repeated
- national HA or EMA
- combined with HTA

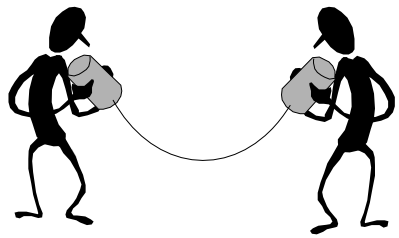
Pre-submission meeting

first opportunity to meet product team

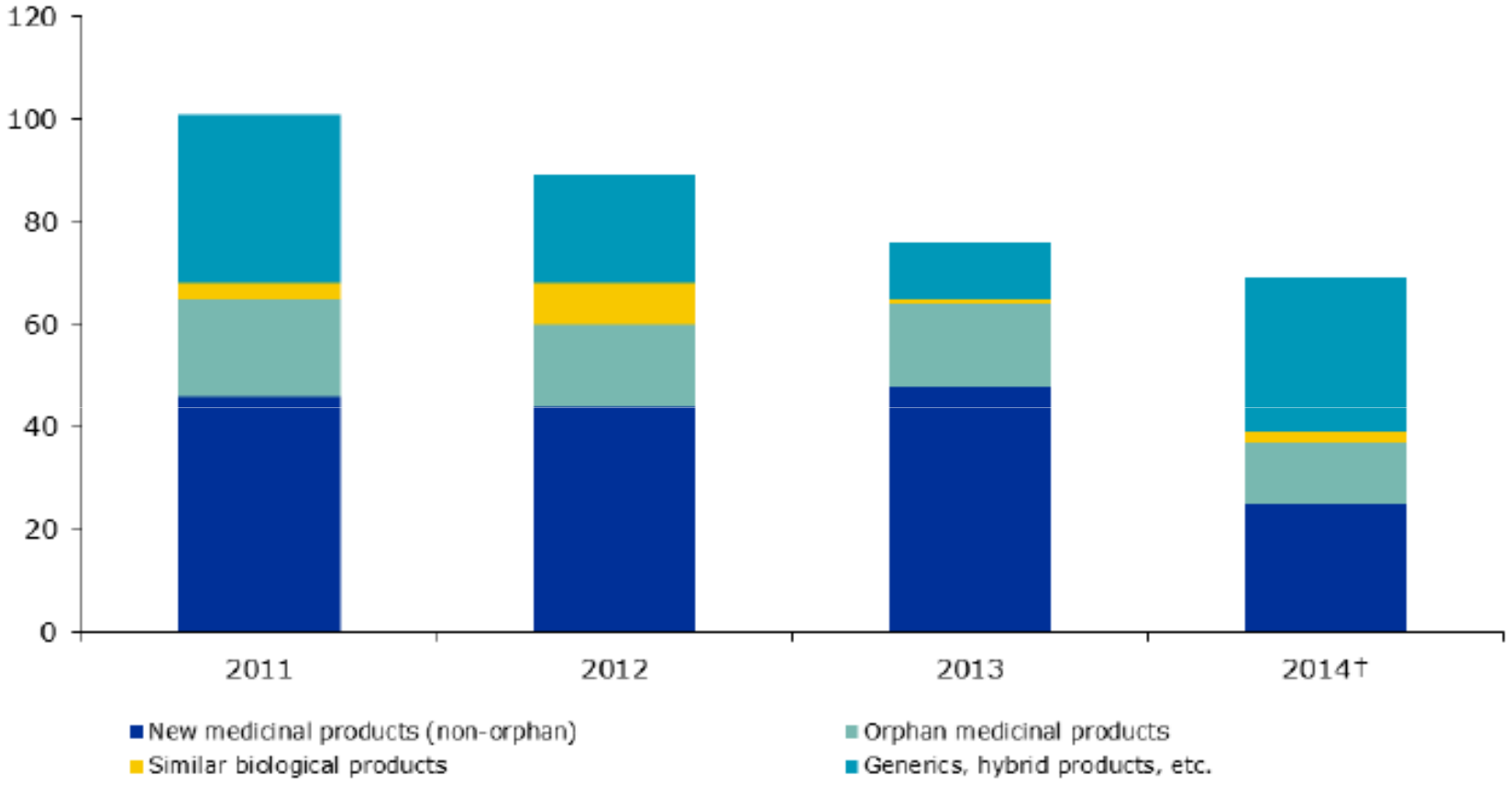
Clarification meeting

- upon receipt of questions

Oral explanation, SAG



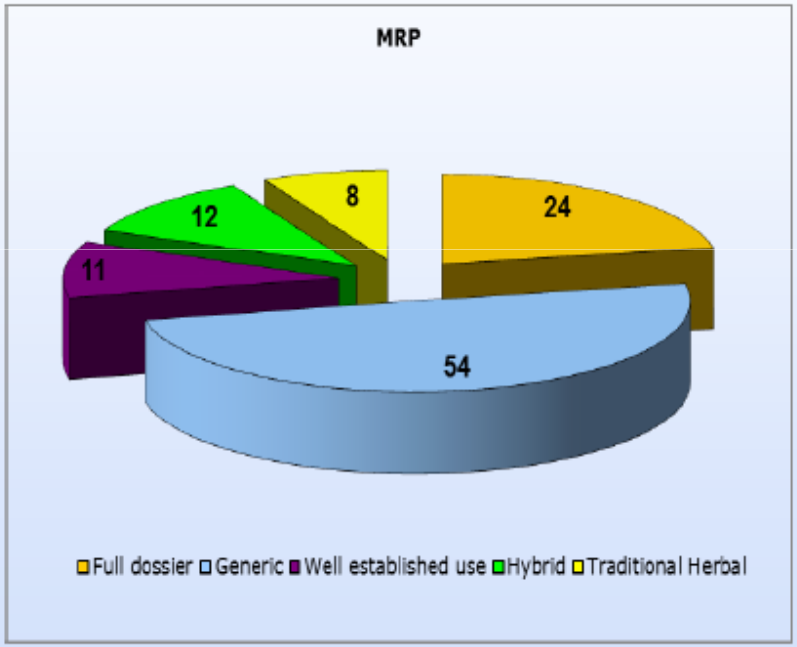
Marketing authorisation application evaluations started by type of application

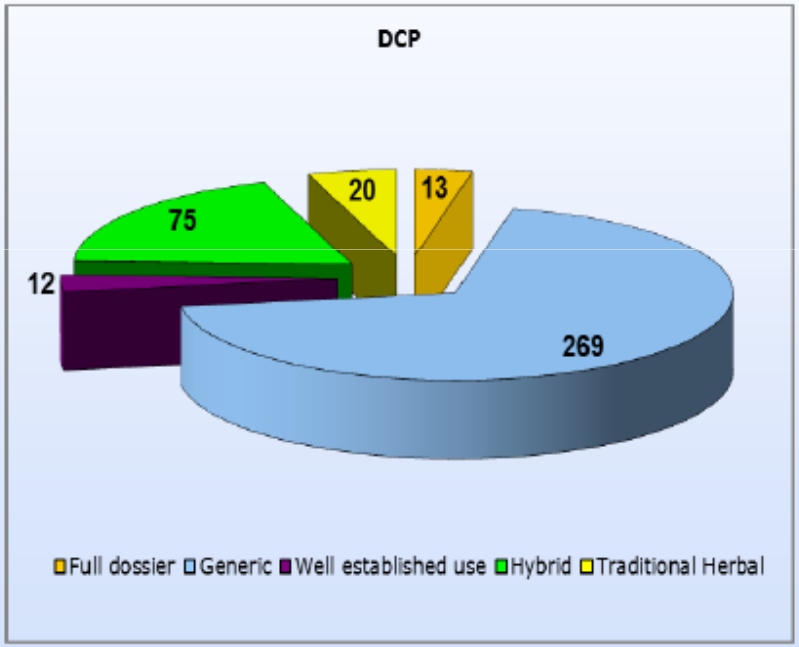


MRP/DCP New applications
January to June 2014

FINALISED Procedures – MRP/DCP per legal basis*

Total: 109 MRP and 389 DCP (regarding 201 and 802 products respectively)





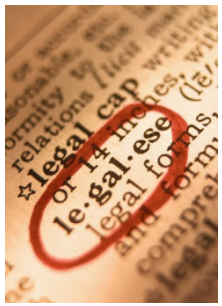
** Due to late database updates cumulative yearly figure differs from the monthly figures. Cumulative yearly figure includes late database updates on finalised procedures not captured in the monthly figures published in press releases. The applications referred to CHMP are included in the 'new applications finalised*

Slide 4

Strategic choices
Type of Application

- **Mandatory scope of Centralised Procedure**

- **Legal Basis**
  - Complete
  - Biobliographic
  - generic



Strategic Choices
Market considerations

Where will the product be marketed ?

All EU member states ⇔ Limited number of countries

Expand later: repeat use MRP

- Decentralised Procedure to target main markets.
- Repeat Mutual Recognition procedure(s) to add new Member States as required

Capability of the organisation

- Ability to market throughout EU
- CP more efficient to market in all or majority of MS

Existing license in one MS ⇨ Mutual Recognition Procedure

Strategic choices fees

Centralised Procedure

One fee

Mutual Recognition, Decentralised procdure

Fee per member state

Fee RMS, Fee CMS

Strategic choices
Fees

Applications for which a full dossier needs to be submitted in CP

Basic fee	278 500 EURO For a single strength associated with one pharmaceutical form and one presentation.
Additional fee	+ 27 900 EURO For each additional strength or pharmaceutical form including one presentation, submitted at the same time as the initial application for authorisation.
	+ 7 000 EURO For each additional presentation of the same strength and pharmaceutical form, submitted at the same time as the initial application for authorisation.

Strategic Choices
Timelines

Is there a faster procedure?

MRP: national plus 90 days

national timelines in MRP not defined

DCP: 210 days

Centralised Procedure: 210 days

Accelerated assessment: from 210 to 150 days

Strategic Choices Procedure

Is there an “easier” procedure?

- only data count
- withdrawal of a MS in MRP/DCP
- withdrawal or negative opinion in CP

Choice of names

Centralised Procedure

one single name

MRP/DCP

names can be different in MS

name flexibility

Strategic Choices
Special cases

Conditional approval

Exceptional circumstances

- Not to be mistaken for an easier option when in fact data are deficient
- Need sufficient data for positive risk/benefit
- Conditional approval: condition imposed should be able to be met

Strategic choices Rapporteur – Reference Member State

Centralised Procedure

Applicant can not choose rapporteur

MRP/DCP

- choose based on scientific expertise
- availability
- supportive of your product (during scientific advice)

Should you try to influence the choice of the Rapporteur?

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- Understanding factors influencing the choice of a regulatory procedure;

Recommended references

- www.ema.europa.eu
- ec.europa.eu/health/documents/eudralex/
- www.hma.eu/
- http://www.hma.eu/cmdh.html

QUESTIONS?

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