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Fundació Doctor Robert
UAB

Regulatory Procedures

Patrick Salmon
HPRA

Regulatory Procedures

- **Types of Procedure**
- **The “usual” procedure**
- **Compassionate Use**
- **Accelerated Review**
- **Conditional Approval**
- **Marketing Authorisation under Exceptional Circumstances**
- **PASS/PAES**

Life Cycle

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A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of that Member State or by the European Medicines Agency.

The process for obtaining a marketing authorisation is very detailed and highly regulated.

Scientific Life of a Drug

Assessment based on Quality, Safety and Efficacy

Dossier

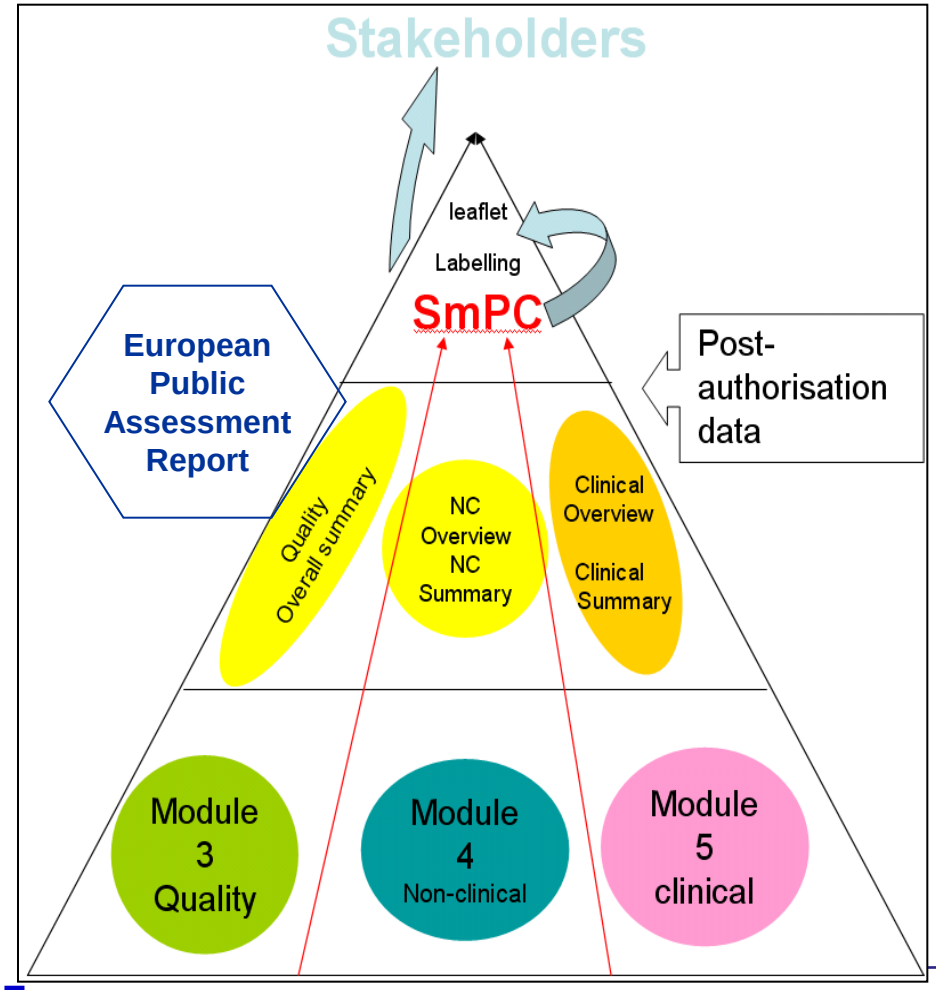
- Quality
- Pre-clinical
- Clinical

Summary Product Characteristics (SmPC)

Modules of the CTD

1. Specific administrative data including application form, summary of product characteristics (SmPC), labelling and package leaflet (PL)
2. Quality overall summary, non-clinical overview/summaries and clinical overview/summaries
3. Quality – chemical, pharmaceutical and biological information
4. Safety (Pharmacology/Toxicology) - non-clinical reports
5. Efficacy - clinical study reports

SmPC: The cornerstone between assessment and information



- The scientific assessment should evaluate how the SmPC will optimise the benefits and manage the risks.
- The SmPC is the *agreed* position on the medicinal product, as distilled during the course of the assessment process, before (and after) marketing authorisation.
- Detailed information and benefit-risk assessment is provided in public assessment report

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The European System

Optimised utilisation of resources
Harmonised scientific opinions
Harmonised information to healthcare professionals & patients

Authorisations

National

- **National**
- **Mutual recognition**
- **Decentralised**

- **Centralised**

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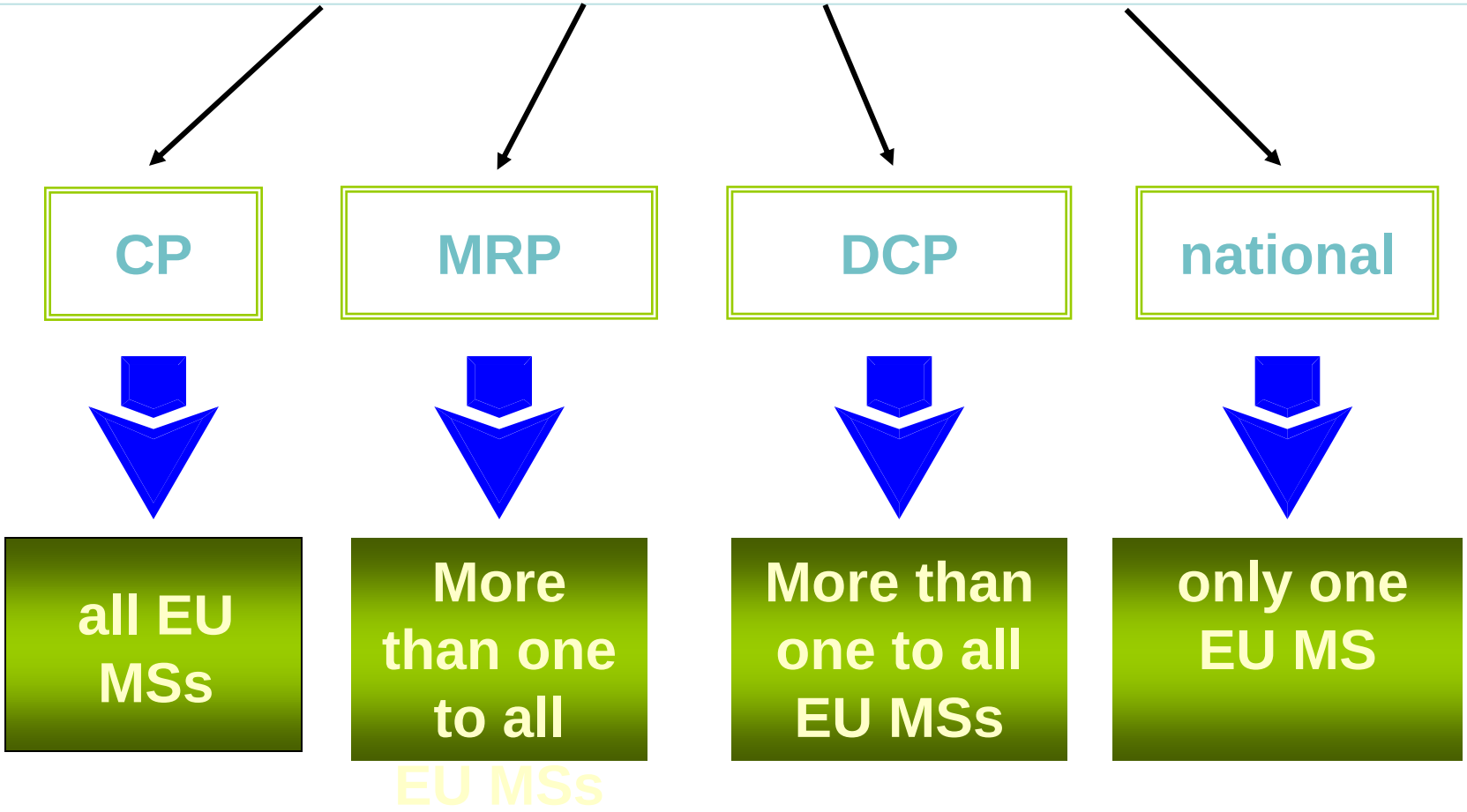
- In the EU, a company may submit a single application to the European Medicines Agency (EMA) for a marketing authorisation (licence) that is valid simultaneously in all EU Member States, plus Iceland, Liechtenstein and Norway....the ***centralised*** authorisation procedure.

- Each EU Member State has its own ***national*** procedures for the authorisation of medicines that fall outside the scope of the centralised procedure. Applicants must submit an application to the competent authority of the Member State.

- In the **mutual recognition procedure (MRP)**, a medicine is first authorised in one EU Member State, in accordance with the national procedures of that country. Following this, further marketing authorisations can be sought from other EU countries in a procedure whereby the countries concerned agree to recognise the validity of the original, national marketing authorisation.

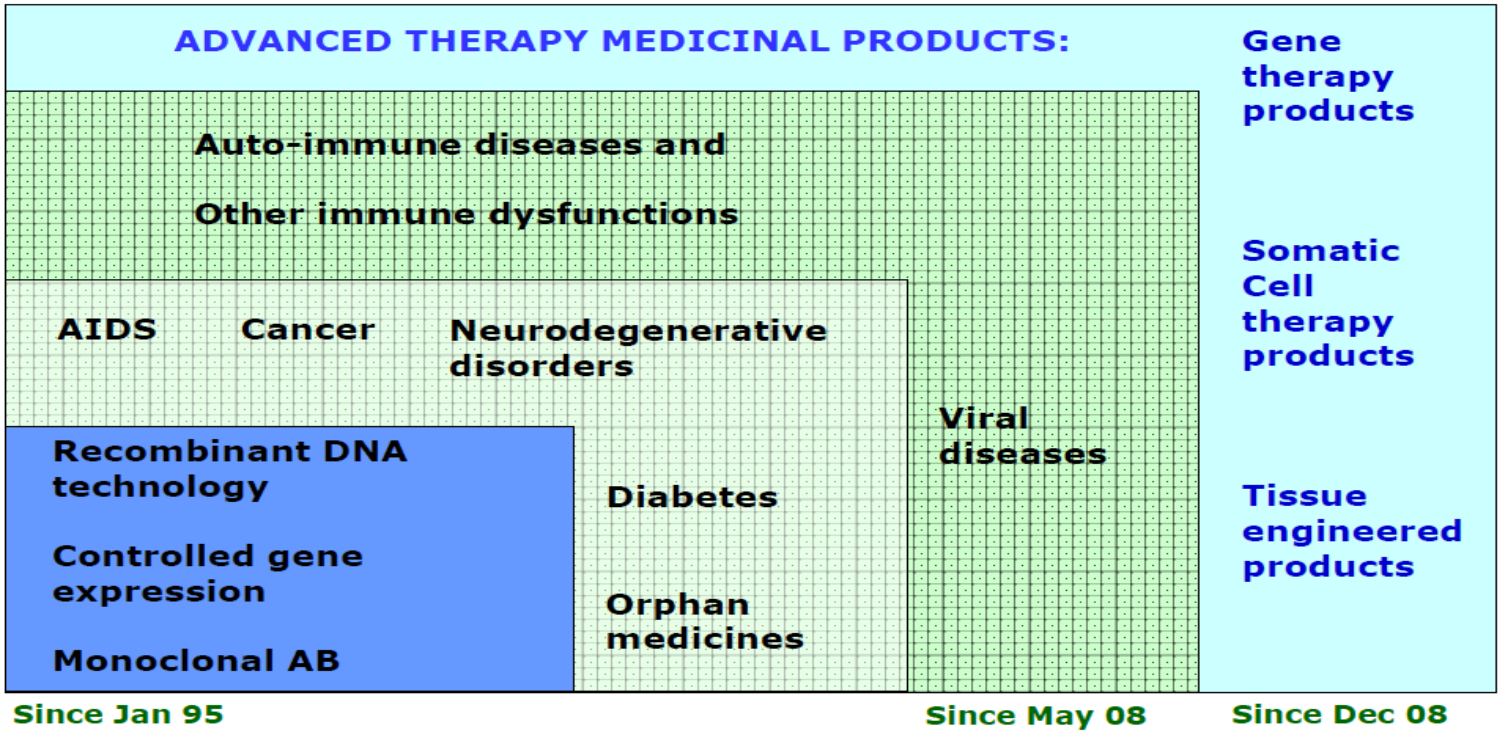
- Using the **decentralised procedure (DCP)**, companies may apply for simultaneous authorisation in more than one EU country of products that have not yet been authorised in any EU country and that do not fall within the mandatory scope of the centralised procedure.

EU MA Procedures



Centralised

Eligibility: "Mandatory Scope"



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Centralised

Eligibility "Optional Scope"

Art 3(3) Generic of a product authorised via EMA

The centralised procedure attracts most innovative medicines.
Decentralised and MRP mainly do generics and new indications for existing products

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Mutual Recognition Procedure - MRP

- This procedure is based on the mutual recognition by CMSs of a national MA granted by a RMS
- An identical application for mutual recognition is to be submitted to all concerned member states
- RMS prepares an assessment report or updates any existing one within 90 days
- Copies of the assessment report are sent to all CMSs, together with the approved SmPC, package labelling and package leaflet
- CMSs then have 90 days to recognise the decision of the RMS
- National marketing authorisations will be granted within 30 days after acknowledgement of the agreement

Decentralised Procedure - DCP

- The DCP is available for new products which have not yet been authorised in any EEA country and do not fall within the mandatory scope of the CP
- One member state acts as the RMS and takes the lead
- Submission of an application in all the Member States involved at the same time
- RMS prepares an assessment report within 120 days
- CMSs then have 90 days to recognise the decision of the RMS
- National marketing authorisations will be granted within 30 days after acknowledgement of the agreement
- The product will be nationally authorised in the RMS and each CMS with a harmonised SmPC, package leaflet and package labelling

Types (legal bases) of applications for a MA

- Stand alone (full) application
- “informed consent” application… piggyback
- Generic application
- “well established use” application
- “Mixed” application
- Hybrid application

- Similar biological product application
- application for “new combination” containing active substances used in already authorised products

Compassionate Use

- Medicinal products must be authorised in order to be marketed

BUT

- Compassionate use programmes are intended to facilitate the availability to patients of new treatment options under development.

- National compassionate use programmes, making medicinal products available either on a named patient basis or to cohorts of patients, are governed by individual Member States legislation.

Compassionate use

Compassionate use is a treatment option that allows the use of an unauthorised medicine. Compassionate-use programmes are for patients in the European Union (EU) who have a disease with no satisfactory authorised therapies or cannot enter a clinical trial. They are intended to facilitate the availability to patients of new treatment options under development.

Compassionate-use programmes are often governed by legislation in individual EU Member States, to make medicines available on a named-patient basis or to cohorts of patients.

In addition to this, **EU legislation** provides an option for Member States to ask the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) to provide an opinion to all EU Member States on how to administer, distribute and use certain medicines for compassionate use. The CHMP also identifies which patients may benefit from compassionate-use programmes. This is described in Article 83 of Regulation (EC) No 726/2004 and is complementary to national legislation.

The **objectives** of Article 83 are to:

- facilitate and improve access to compassionate-use programmes by patients in the EU;
- favour a common approach regarding the conditions of use, the conditions for distribution and the patients targeted for the compassionate use of unauthorised new medicines;
- increase transparency between Member States in terms of treatment availability.

Contact point:
compassionateuse@
u

Compassionate Use

London, 19 July 2007
Doc. Ref: EMEA/27170/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON COMPASSIONATE USE OF MEDICINAL PRODUCTS, PURSUANT TO ARTICLE 83 OF REGULATION (EC) No 726/2004

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Compassionate Use

For unauthorised products, products undergoing clinical trials in the EU or elsewhere

For products applying through centralised procedure

For *groups of patients* suffering from a chronically or seriously debilitating disease or whose disease is considered to be life threatening, who cannot enter a clinical trial, and who cannot be treated satisfactorily by an authorised medicinal product

Not a substitute for clinical trials

Not for off-label use

Compassionate Use

According to the current legislation, member states (MS) can request EMA-CHMP opinion on the conditions for use, and distribution and on the patients targeted for compassionate use.

In this case, CHMP can adopt an non-binding opinion on member states (add reference of legislation)

Compassionate use (CU) opinions from the CHMP

Member state notifying the Agency	Name of product Active substance Dosage(s) and form	CHMP opinion on Conditions of use Conditions for distribution and Target population	Date of opinion	Company details
Finland	Tamiflu IV Oseltamivir phosphate 100mg - Powder for solution for infusion	EMA/45566/2010 Summary on compassionate use	20 January 2010	F.Hoffmann-La Roche Ltd. Pharmaceuticals Division PBMV Bldg 74/3O 104 CH-4070, Basel, Switzerland Tel: +41 61 688 5522 Fax: +41 61 687 2239 basel.tamifluquestions@roche.com
Sweden	IV Zanamivir 10 mg/ml - solution for infusion	EMA/110920/2010 Summary on compassionate use	18 February 2010	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford, Middlesex TW8 9GS UK Tel: +44 (0) 208 047 5000 Tel: +44(0) 208 990 3885 Email: julie.c.kerrison@gsk.com

Compassionate Use

Name of medicine	Ledipasvir/Sofosbuvir
Active substance	ledipasvir, sofosbuvir
Dosage	90mg / 400 mg
Pharmaceutical form	Film coated tablet
Member State notifying the Agency	Ireland
CHMP opinion documents	Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring Summary on compassionate use
Date of opinion	20/02/2014
Company contact information	Gilead Sciences Limited Granta Park Abington Cambridgeshire CB21 6GT United Kingdom Tel. +44 (0)208 5872206 Fax +44 (0)1223 897233 E-mail: eamemed.info@gilead.com
Status	Ongoing

Name of medicine	Daclatasvir
Active substance	daclatasvir
Dosage	30 and 60 mg
Pharmaceutical form	Film coated tablet
Member State notifying the Agency	Sweden
CHMP opinion documents	Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring Summary on compassionate use
Date of opinion	21/11/2013
Company contact information	Bristol-Myers Squibb Pharma EEIG Uxbridge Business Park Sanderson Road Uxbridge UB8 1DH United Kingdom Tel. +44 (0)1895 523 740 Fax +44 (0)1895 523 677 E-mail: medical.information@bms.com
Status	Ongoing

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Accelerated Assessment

When a marketing application is submitted for a product:

- that is of major interest from the point of view of public health
- that is of particular interest from the viewpoint of therapeutic innovation,

Accelerated assessment procedures should be set up to:

- meet the expectations of patients
- take account the increasingly rapid progress of science and therapies for medicinal products of major therapeutic interest,

Accelerated assessment should be requested by the applicant and once authorisation is granted is subject to certain annually reviewable conditions.

Accelerated Assessment

- Applicant requests time limit reduction 210 days to 150 days
- Applicant justifies:
  - Major Public Health Interest….therapeutic innovation
  - Consider unmet medical needs and available methods
  - Extent to which product is expected to have a major impact on medical practice, added value, addressing unmet needs
  - Outline available evidence
- CHMP decides
- During assessment, standard timeline may be considered (major objections, long clock-stop, need for Good Manufacturing Practice or Good Clinical Practice inspections)

Road Map 2015.. A more appropriate use of

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 17 July 2006
Doc. Ref. EMEA/419127/05

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE PROCEDURE FOR ACCELERATED ASSESSMENT PURSUANT TO ARTICLE 14 (9) OF REGULATION (EC) No 726/2004

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Accelerated

European Medicines Agency recommends first-in-class medicine for treatment of cystic fibrosis

Press release

25/05/2012

European Medicines Agency recommends first-in-class medicine for treatment of cystic fibrosis

New medicine offers therapeutic innovation for treatment of cystic fibrosis; review under accelerated assessment

The European Medicines Agency has recommended Kalydeco (ivacaftor), an orphan-designated medicine, for the treatment of cystic fibrosis in patients age 6 years and older who have a *G551D* mutation in the cystic fibrosis transmembrane regulator (*CFTR*) gene.

The Agency's Committee for Medicinal Products for Human Use (CHMP) reviewed Kalydeco under accelerated assessment, in 150 days. Accelerated assessment is one of the Agency's tools to speed up access by patients to new medicines that are of major public health interest.

Kalydeco offers an innovative therapeutic approach for patients with cystic fibrosis:

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Accelerated?

Br J Clin Pharmacol. 2013 Jan 31. doi: 10.1111/bcp.12085. [Epub ahead of print]

A Fresh Perspective on Comparing the FDA and the CHMP/EMA: Approval of antineoplastic tyrosine kinase inhibitors.

Shah RR, Roberts SA, Shah DR.

Rashmi Shah Consultancy Ltd, Gerrards Cross, UK.

Abstract

We compared, and determined the reasons for any differences in, the review and approval times of tyrosine kinase inhibitors (TKI) by the FDA and the EMA/CHMP. Applications for these novel cancer drugs were submitted to them within a mean of 31.2 days of each other, providing a fair basis for comparison. The FDA had granted priority review to 12 TKIs but the EMA/CHMP did not grant the equivalent accelerated assessment to any. The FDA granted accelerated approvals to 6 (38%) and CHMP granted (the equivalent) conditional approvals to 4 (29%) of these agents. On average, the review and approval times were 205.3 days in the US compared to 409.6 days in the EU. The active 225.4 days in the EU and 205.3 days in the

Conditional

EC grants conditional marketing authorisatio to Pfizer's Sutent in two indications

(Ref: Bloomberg, Forbes, finanzen.net)
July 27th, 2006

EC grants conditional marketing authorisation for ADCETRIS to treat hematological cancers

Published on October 31, 2012 at 5:28 AM · No Comments

Communities / MDR-TB Treatment & Prevention

EMA conditional authorization for marketing Deltyba 50 mg for MDR-TB treatment

By Masoud Dara, MD | 24 Nov, 2013

> *"Conditional marketing authorisation by the European Commission signifies an important advancement in the treatment of adult patients with these rare CD30 positive hematological cancers who are relapsed or refractory and previously had limited options."*

MolMed TK therapy submitted for Conditional Marketing Authorisation in EU

Novartis to request conditional marketing authorisation in EU

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Conditional

The legal framework: scope and requirements

Scope

This Regulation shall apply to medicinal products for human use that fall under Article 3(1) and (2) of Regulation (EC) No 726/2004 and belong to one of the following categories:

1. medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;

2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC;

3. medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

Requirements

1. A conditional marketing authorisation may be
where the Committee finds that, although compre
clinical data referring to the safety and efficacy
medicinal product have not been supplied, all the fo
requirements are met:

(a) the risk-benefit balance of the medicinal product, as
in Article 1(28a) of Directive 2001/83/EC, is positiv

(b) it is likely that the applicant will be in a position to
the comprehensive clinical data;

(c) unmet medical needs will be fulfilled;

(d) the benefit to public health of the immediate availab
the market of the medicinal product concerned ou
the risk inherent in the fact that additional data
required.

Commission Regulation (EC) No 507/2006

Conditional Approval

May be granted where, although comprehensive clinical data have not been supplied, the following apply:

(a) The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive

(b) It is likely that comprehensive data can be provided

(c) Unmet medical needs will be fulfilled (no satisfactory methods or major therapeutic advantage)

(d) Benefits of immediate availability outweigh risks due to additional data to be provided

Conditional Approval

- When the CHMP has based a positive opinion on data which, while not yet comprehensive, indicate that the medicine's benefits outweigh its risks.
- The company is given obligations to fulfil, such as the performance of further studies.
- The approval is renewed on a yearly basis until all obligations have been fulfilled, and is then converted from a conditional approval into a normal approval.
- Conditional approvals can only be granted for medicines that satisfy an 'unmet medical need', meaning the medicine is intended to be used for a disease or condition for which no treatment is readily available, and it is therefore important that patients have early access to the medicine concerned.

Conditional Approval

- Conditional MA will be subject to **specific obligations** to complete ongoing studies, or to conduct new studies with a view to confirming the positive Benefit/Risk balance.

  Applicant to provide reassurance on the **feasibility** and quality of additional studies to be performed

  "*where (timely) completion of further studies required for the confirmation of the Benefit/Risk can not be expected, this may lead to a negative opinion on the granting of a conditional MA*"

- Financial **penalties** in case of infringement of the specific obligations
- Nature of approval, obligations and timeframes **publicly available**
- Conditional MA only for **initial MA** Applications, not for variations (supplements)
- Conditional MA **valid for one year**, renewable

Obligations of Conditional Approval

- Pharmacovigilance data
- Other required data important for understanding of benefit-risk, e.g.:

  Confirm final clinical outcome for likely surrogate endpoints

  Confirm long-term effects

  Study effect in subgroups

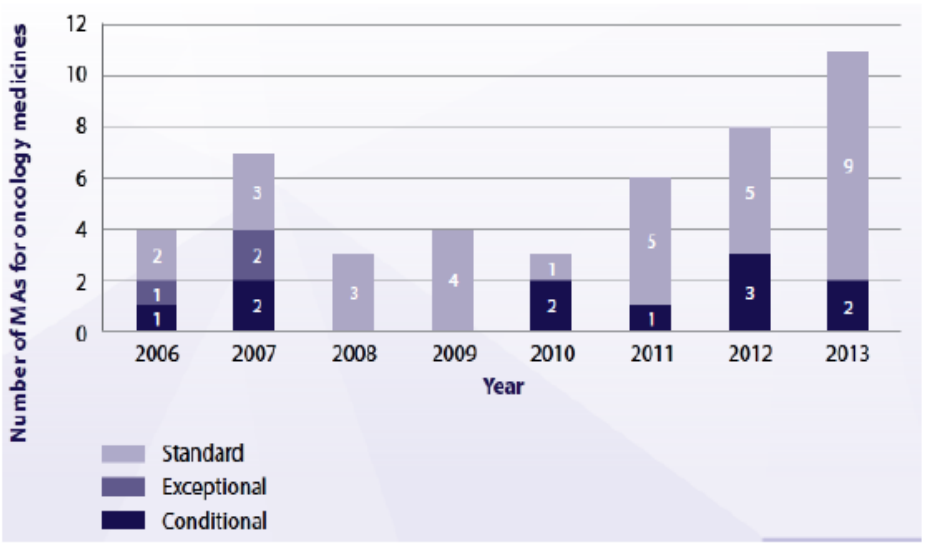
  Confirm results of interim analysis

Conditional

An external analysis …

3.3 Use of the conditional marketing authorisation pathway for oncology medicines

Jarno Hoekman, Marie L De Bruin, Wouter PC Boon



Conclusion

CMA is given to oncology medicines with less comprehensive data available upon MA, compared with oncology medicines that receive standard MA. The MA procedures resulting in CMA are challenging, possibly because CMA use is often initiated relatively late during the MA procedure. Companies do not seem to have sufficient incentives to request CMA upfront, which leads in a substantial number of cases to a situation in which regulators initially use standard evaluation criteria for data assessment. In these cases, the option of CMA is only discussed once there is initial consensus that a standard MA cannot be granted. As a consequence, the use of CMA for oncology medicines is sometimes perceived as a 'rescue' option by regulators and companies rather than as a prospectively planned pathway to grant early access to medicines that show promising effects, but for which comprehensive data is not yet available.

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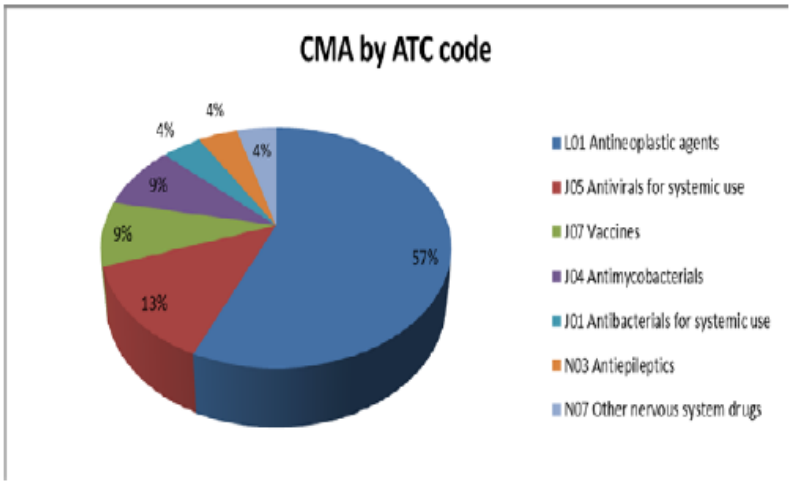
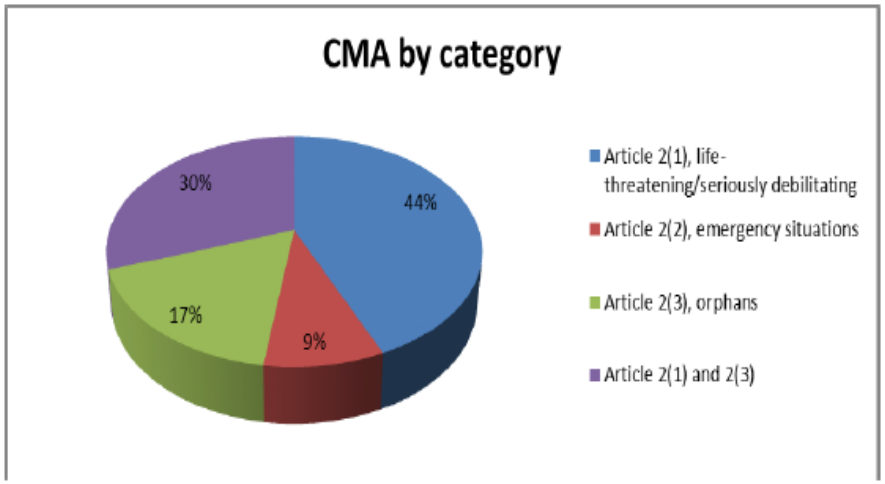
Conditional

Experience to-date

- 23 medicinal products were authorised as conditional marketing authorisation (CMA) mainly in the area of oncology (57%).
- 21 are currently authorised (2 withdrawn for commercial reasons)





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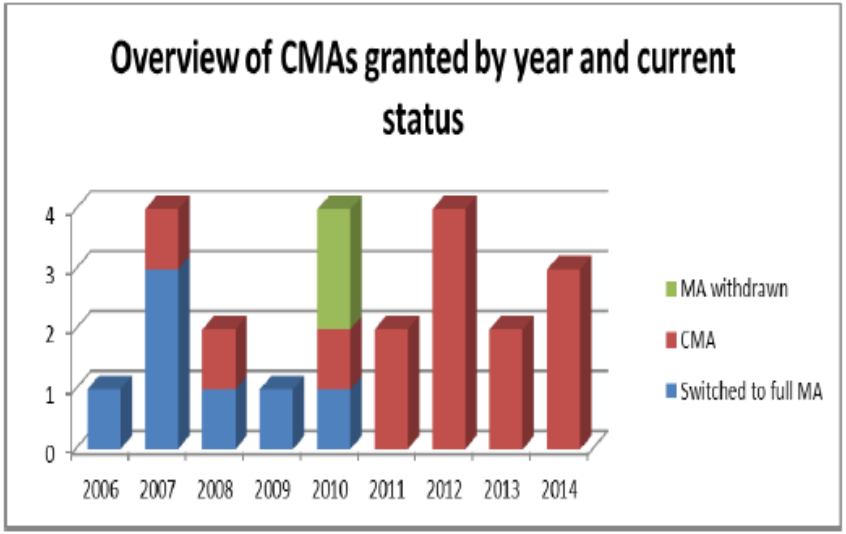
Conditional

Current status of the marketing authorisations initially approved as CMA (since 2006)



- 7 have fulfilled all specific obligations (SOB) imposed and switched to full marketing authorisation
- 5 were subject to modifications in the scope of the SOB and deadlines
- 1 was subject to modifications in the deadline only

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Exceptional Circumstances

Unable to provide comprehensive data on the efficacy and safety of the medicine

- Indication so rare that cannot reasonably be expected to provide comprehensive evidence
- In the present state of scientific knowledge, comprehensive information cannot be provided
- Contrary to medical ethics to collect such information

Authorisation may be granted subject to certain obligations

Usually evaluation involves external expert groups (to determine clinical relevance)

Obligations of Exceptional Circumstances

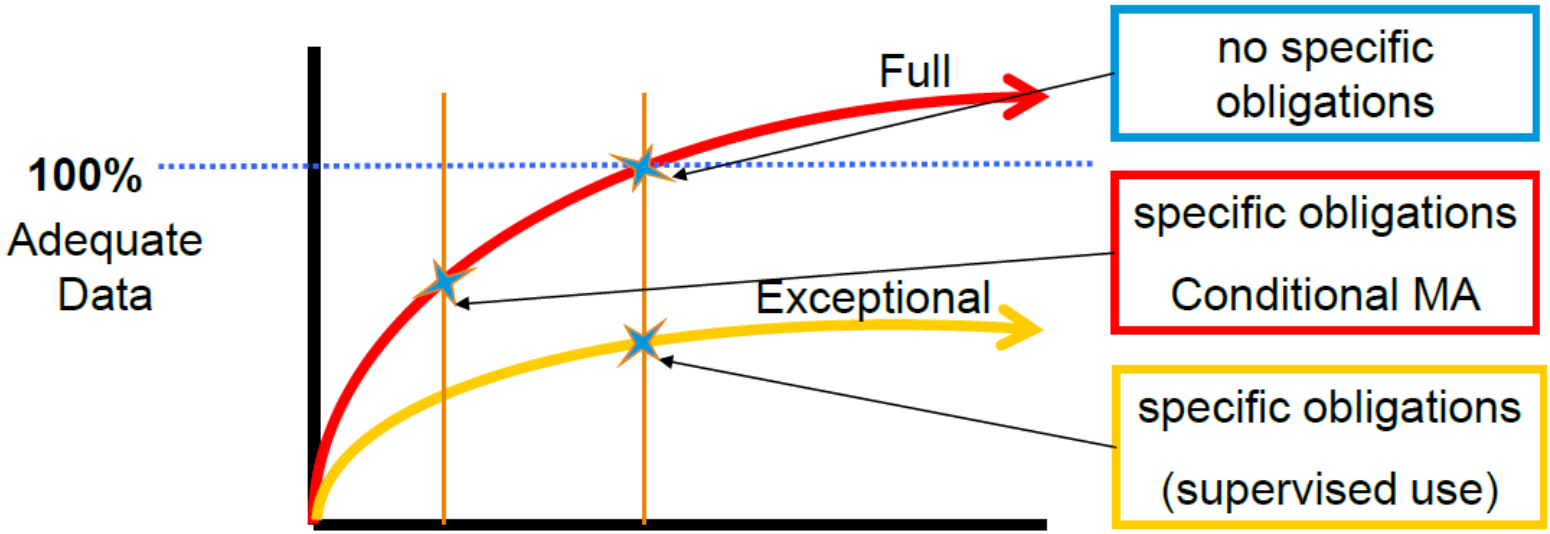
Specific Obligations may include

- Complete an identified programme of studies within a specified period of time
- Supply by prescription only and possibly under strict supervision
- Package leaflet will point out that particulars concerning the product are inadequate in certain respects

Conditional Approval	Approval under Exceptional Circumstances
Demonstration of positive benefit:risk, based e.g. on early evidence of effects predictive for clinical outcome from comprehensive data	Comprehensive data cannot be provided
Valid for one year, renewable	Validity and renewal as for "normal" MA; annual reassessment of the benefit:risk
Temporary authorisation not intended to remain conditional, becomes "normal" MA once data confirming positive benefit:risk are provided	Will normally **not** lead to the completion of a full dossier (NB: in rare cases may become "normal" MA)

Exceptional circumstances not to be granted if conditional approval is more appropriate

Reminder of the concept of different MA types



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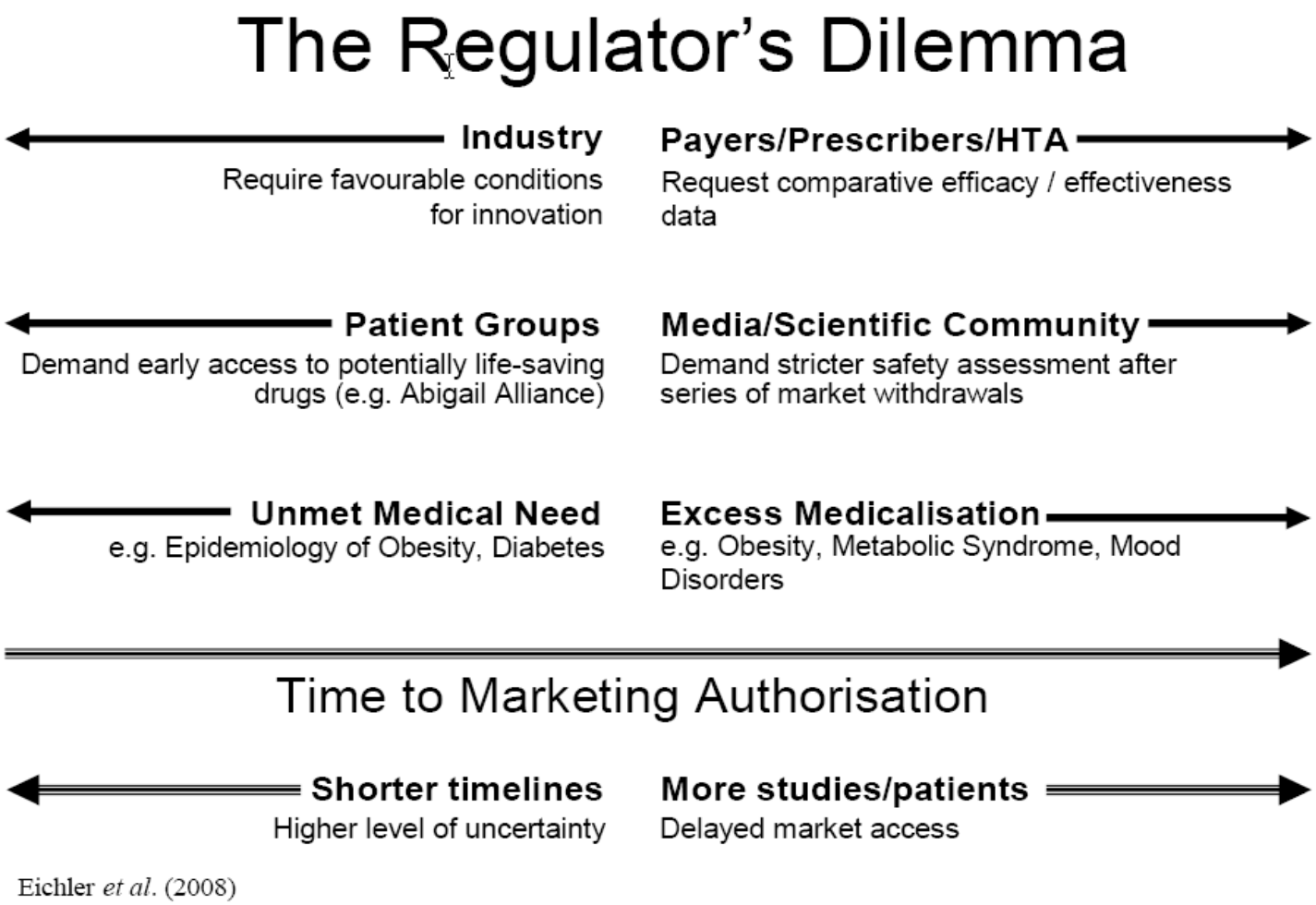
Balance



Eichler *et al*. (2008)

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Articles

Clinical Pharmacology & Therapeutics **88**, 848-853 (December 2010) | doi:10.1038/clpt.2010.207

Conditional Approval and Approval Under Exceptional Circumstances as Regulatory Instruments for Stimulating Responsible Drug Innovation in Europe

W P C Boon, E H M Moors, A Meijer and H Schellekens

The need for fast drug innovation and the public demand for risk-free drugs creates a dilemma for regulatory authorities: less restrictive procedures involve uncertainties about benefit/risk profiles of new drugs. The European Union has introduced two instruments that regulate early market access: conditional approvals (CAs) and approvals under exceptional circumstances (ECs). We have studied whether these instruments compromise the safety of new drugs and whether they lead to earlier access to innovative drugs. Our study shows that neither of these regulatory pathways accelerates the approval process for innovative drugs. However, the CA pathway shortens the clinical development period. Approvals under ECs are associated with longer clinical development periods, but this regulatory pathway may open up opportunities for specific drugs to be admitted into the market because less comprehensive data are required. Despite the fact that these advanced approvals are based on limited safety databases, there are no special safety issues associated with using these pathways.

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Br J Clin Pharmacol. 2011 Sep;72(3):490-9. doi: 10.1111/j.1365-2125.2011.03995.x.

Additional safety risk to exceptionally approved drugs in Europe?

Arnardottir AH, Haaijer-Ruskamp FM, Straus SM, Eichler HG, de Graeff PA, Mol PG.

Department of Clinical Pharmacology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands.
a.h.arnardottir@med.umcg.nl

Abstract

AIMS: Regulatory requirements for new drugs have increased. Special approval procedures with priority assessment are possible for drugs with clear 'unmet medical need'. We question whether these Exceptional Circumstances (EC) or Conditional Approval (CA) procedures have led to a higher probability of serious safety issues.

CONCLUSION: The EC/CA procedure is not associated with a higher probability of DHPCs despite limited clinical development data. These data do not support the view that early drug approval increases the risk of serious safety issues emerging after market approval.

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EMA Workplan

6 October 2011
EMA/MB/550544/2011 Endorsed

Implementing the European Medicines Agency's Road map to 2015: The Agency's contribution to Science, Medicines, Health

"From Vision to Reality"

Facilitating Access

Exploring the balance between early approval with limited data and later approval with more extensive data package

Considering the merits and mechanics of an optional approach to early authorisation of medicines in a restricted population e.g. based on early information from good responders. Exploring the broader applicability of 'staggered' approvals and preparing guidance on the applicability of such approaches.

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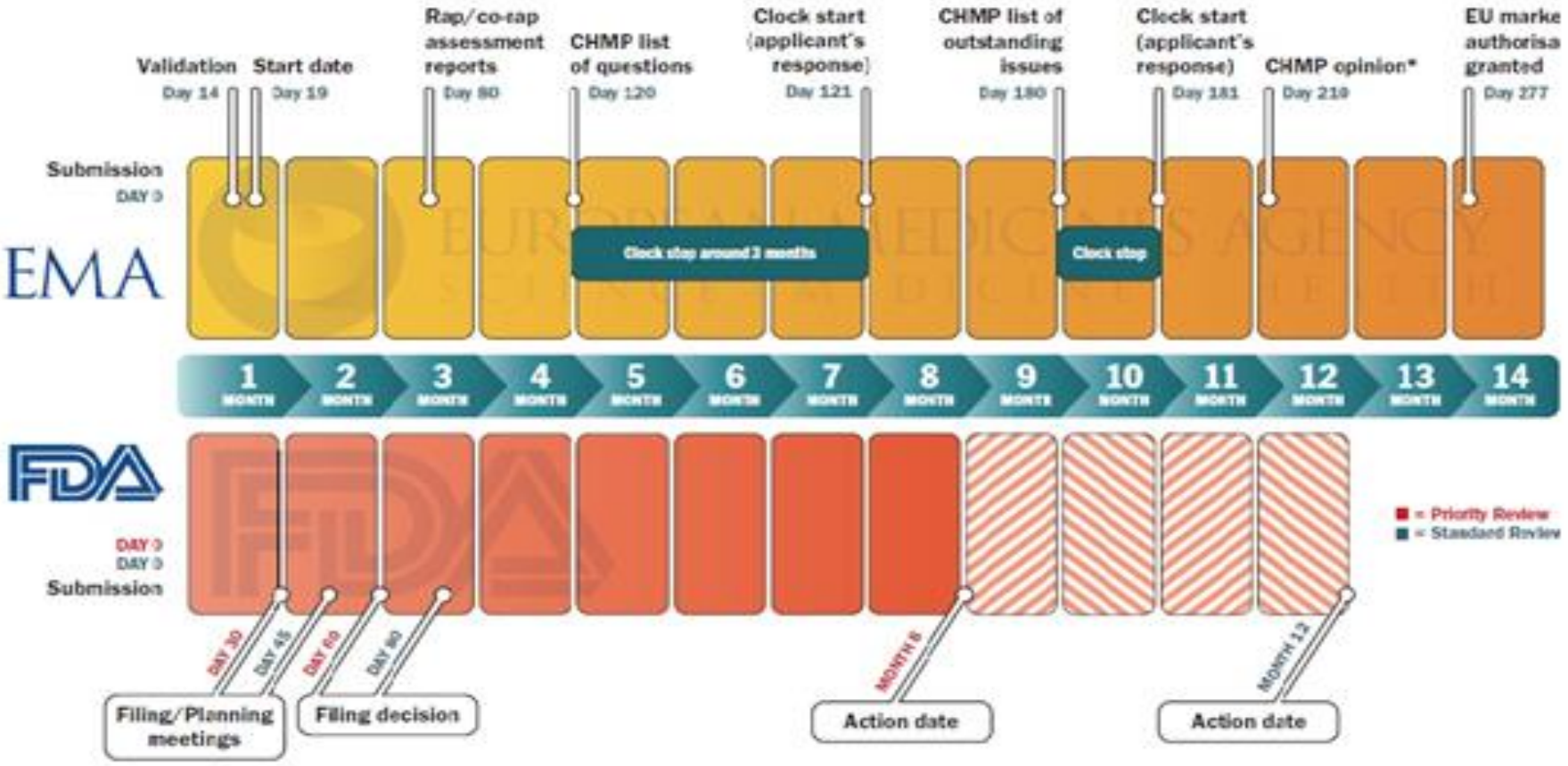

On average the EMA takes around six months more than the FDA to approve a new drug or new indication for a dreg. This is mainly cue to time lost to cloc stop and the delay between getting a positive CHMP opinion and approval from the European Commission. Furthermore, in the US almost all cancer drug are approved under priority review, whereas accelerated assessment is rarely used by the EMA

Source: CDER 21st Century Review Process (www.fda.gov); User Guide for Micro, Small and Medium-sized Enterprises (www.ema.europa.eu)
*Day 150 for accelerated assessment; Rap – Rapporteur

PASS

- **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 European Medicines Agency'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.**
- **PASSs can either be clinical trials or non-interventional studies.**

PASS

PASSs are either imposed or voluntary:

- **Marketing-authorisation holders (MAHs) are 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 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.**

Guideline on good pharmacovigilance practices (GVP)

Module VIII – Post-authorisation safety studies (Rev 1)

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PAES

- **A post-authorisation efficacy study (PAES) is a study that aims to clarify the benefits of a medicine on the market including efficacy in everyday medical practice.**
- **They aim to address concerns related to the efficacy of a medicine in certain situations, such as everyday medical practice, in specific populations, or over time. This type of study already existed, however, the EU pharmacovigilance legislation that came into force in July 2012 has extended the legal framework in which they can be required.**
- **The aim is to enable regulators to request such studies when there are important questions about the efficacy of the medicine that can only be answered once the product is in general use, or when questions arise in the post-authorisation period.**

Conclusion

- **Several procedures for authorisation**
- **If “full/usual” authorisation not possible, several options exist**
- **If drug has public health implications, additional options for authorisation exist**