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SCIENCE MEDICINES HEALTH

The Centralised Procedure

Instrument for Pre-accession Assistance Programme (IPA)
European Medicines Agency, London UK

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Presented by: George Wade
Quality of Medicines Sector : Section Head - Chemicals

An agency of the European Union

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The Centralised Procedure

- Rapid and EU-wide authorisation of medicines
  277 days (210 days + 67 days)
- Emphasis on innovative medicines, but now we have an increasing number of generics
- 1 Scientific Opinion
- 1 Marketing Authorisation, valid in all Member States
- 1 Product Name, identical in all Member States

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Some Key Words

- The EU is a Single Market for pharmaceuticals approx. 0.5 billion people : bigger than USA
- There are a number of ways (Procedures) for a company to obtain a Marketing Authorisation.
- Conditions for the use of an authorised medicine are defined in the Summary of Product Characteristics (The SPC)
- The main scientific principle used in the evaluation of medicines is the benefit/risk balance which may be favourable or unfavourable for authorisation, based on efficacy and safety and quality considerations
- Following evaluation of the benefit risk balance, there will be a Scientific Opinion which will be sent to the Commission to convert it into a Commission Decision.

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Key Principles

The majority of medicines authorised in the EU are NOT authorised via the Centralised Procedure.

- they go into the National procedures handled by the Member States without involving EMA.
- But..there should be Harmonisation in the use of medicinal products in the EU.
- The main scientific committees who give scientific opinions on approvability (or not) and who ensure harmonisation in the EU are based at the EMA:
  - CHMP –Medicinal Products for Human Use
  - CVMP –Medicinal Products for Veterinary Use

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CHMP – Human Medicines

- Chairman (Dr Eric Abadie) & Vice-Chairman (Thomas Salmonson)
- **1** scientific expert **member** nominated by each MS **and 1 alternate**
- **1** scientific expert **member** from NO and IS **and 1 alternate** (observers)
- **5 co-opted members** as appointed by Management Board

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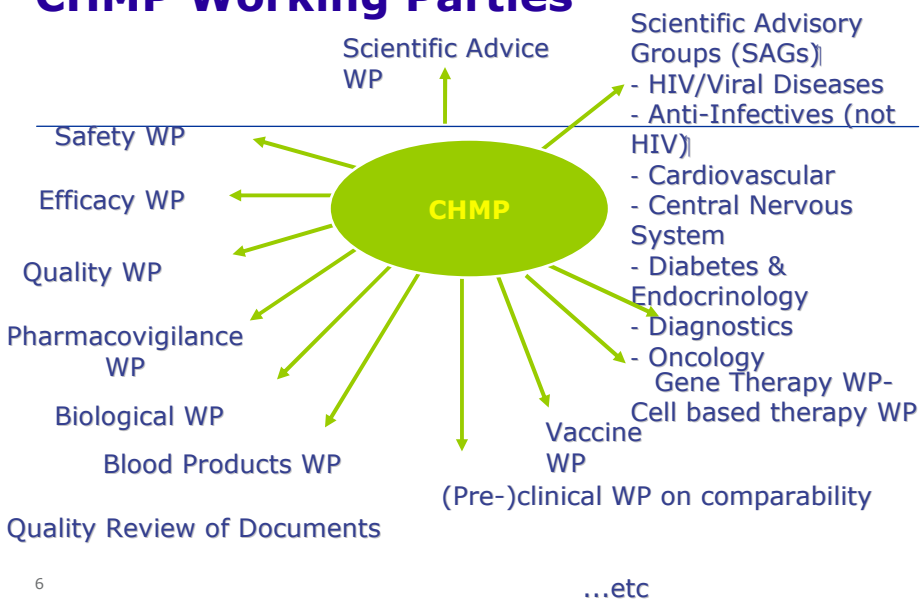
CHMP Working Parties



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Scope of the CP – a club for new products?

The CP is not open to all products
(Annex to Regulation 726/2004)

It is mandatory for some products and optional for others.

We have the condept of 'eligibility'

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Scope of the CP - Mandatory

- Biotechnology products
- Orphan medicines
- New active substances for the treatment of certain diseases (726/2004, Annex : 3)
  - Oncology, AIDS, Diabetes, & CNS
  - Since May 2008 : Autoimmune diseases, Viral diseases

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Scope of the CP - Optional

- Other types of products may apply but the applicant must prove eligibility, e.g.
  - New active substance, in a non-mandatory therapeutic area (726/2004, Art 3.2.a)
  - Significant scientific/technical/therapeutic innovation (726/2004, Art 3.2.b).
  - In the Interest of patients at the level of the Community (726/2004, Art 3.2.b). – e.g. Non-Prescription Medicines,
  - Generics have their own entry under Art 3.3, i.e. Generics of Centrally authorised reference products.
  - Generics of National Reference products are also allowed, but under the 'Community Interest' option above.

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Eligibility

New Active Substance (NAS) for ulcerative colitis…YES?

Old established products are generally not eligible for the CP, unless there is something significantly new, or unless there is "Community Interest".

Paracetamol for headache .....NO

Paracetamol for Alzheimers Disease ….....YES?

("significant therapeutic innovation")

Fentanyl injection for analgesia……..NO

Fentanyl by transdermal iontophoretic delivery..YES?

("significant scientific/technical innovation")

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Basic Procedure

- The system forsees :
  - A two-phase evaluation, 120 + 90 days, leading to an opinion within 210 days net time.
  - Evaluation may be accelerated by agreement (approval from CHMP), but not usually in the first phase.
  - 2 Rapporteur teams to do the evaluation
  - 2 separate reports @day80, in the 1st phase , and a single joint report @ day150
  - CHMP Peer Review Team to check the reports
  - EMA Peer Review Team to check the reports

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Before Submission

- Applicants are encouraged to meet with the EMA or apply for Scientific Advice, early in the development of their product – most of them do.
- There is a Scientific Advice group at the EMEA and an expert Working Party to decide development issues.
- ~2yrs later, we have the applicant's intention to submit
- The EMA Product Team is defined to coordinate the application, PTL, PTM roles assigned
- EMEA meetings (Pre Submission)
- Request for eligibility must be approved by CHMP in advance for non-mandatory products
- CHMP Members apply to be rapporteur, and a provisional choice is made by EMEA, sent to EMEA chairman
- Appointment of Rapporteurs by CHMP.

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Rapporteurs

- Who are the Rapporteurs ? - **YOU, if you join the EU**
- Normally TWO for new products, ONE for generics
- What do they do ?
- They write the scientific evaluation reports (day 80) and circulate to all other CHMP Members for comment
- CHMP Peer Review Team, EMEA Peer Review Team will assist them
- **Critical exposure is high !**
- Define the draft List of Questions for the applicant and make an initial judgement on 'approvability' – confirmed by CHMP at day 120
- Evaluate the applicant's responses and generate a JOINT report at day 150
- Guide the evaluation process to the end
- All of these activities are coordinated and facilitated by EMA Secretariat

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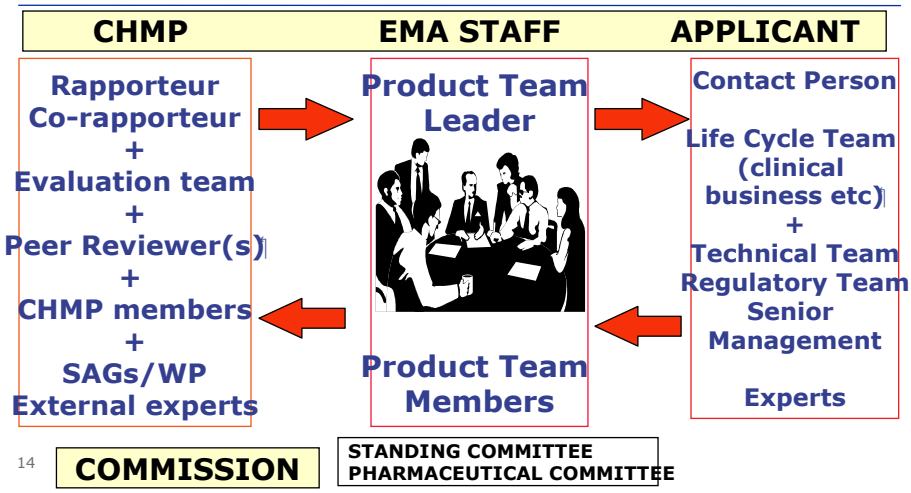
Partners in the Centralised Procedure



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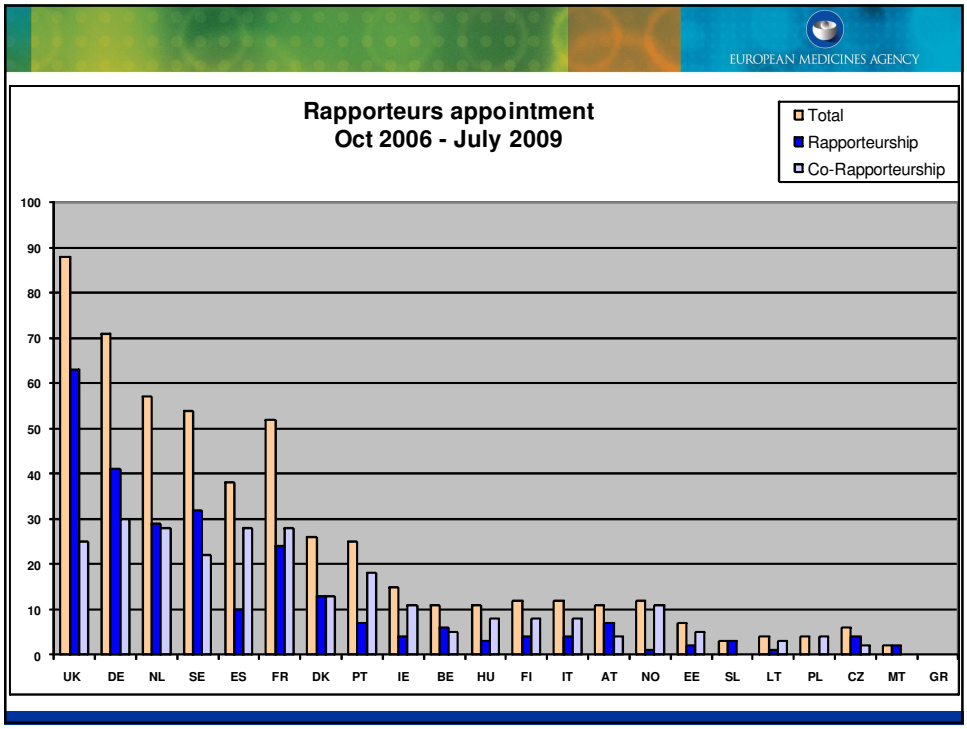
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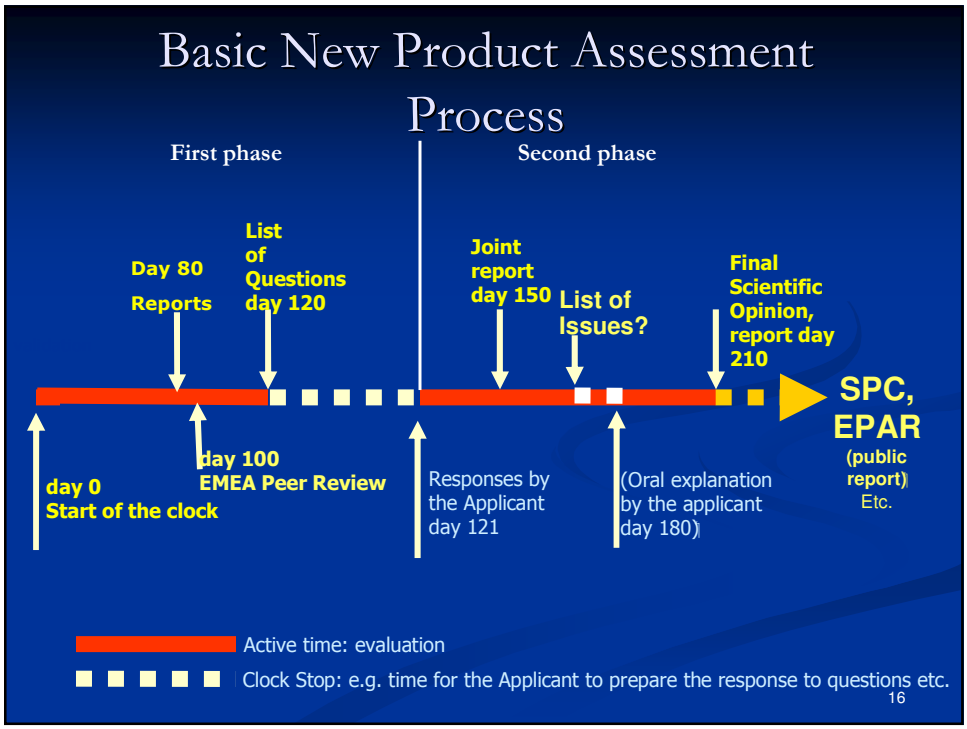
Rapporteurs appointment
Oct 2006 - July 2009
Total
Rapporteurship
Co-Rapporteurship
100
90
80
70
60
50
40
30
20
10
0
UK DE NL SE ES FR DK PT IE BE HU FI IT AT NO EE SL LT PL CZ MT GR


Basic New Product Assessment Process
First phase
Second phase
Day 80
Reports
List of Questions day 120
Joint report day 150
List of Issues?
Final Scientific Opinion, report day 210
SPC, EPAR
(public report)
Etc.
day 0
Start of the clock
day 100
EMEA Peer Review
Responses by the Applicant day 121
(Oral explanation by the applicant day 180)
Active time: evaluation
Clock Stop: e.g. time for the Applicant to prepare the response to questions etc.
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The CHMP Opinion

CHMP/CVMP reaches an Opinion on the benefit /risk ratio involving evaluation of all Q/S/E aspects :

- by consensus - everybody agrees – no problem
- by majority - allowing for dissent

The names of the CHMP Members who dissent must be mentioned in the Opinion

All CHMP Members must accept a majority opinion.

Opinion is adopted in English

Opinion page + (divergent positions)

Annexes :

Annex A – the different pharmaceutical forms of the product

Annex I – The SPC – Summary of product Characteristics

Annex II – other conditions, manufacturers, etc.

Annex IIIA – labels of the product – text only

Annex IIIB – Package Leaflet – text and relevant graphics

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Types of CHMP Opinion

The scientific basis for all types of opinion must be described in the CHMP Assessment Report. Companies can appeal against ALL types of opinion.

Positive : may often have 'followup measures' - mostly chem/pharm which do not affect benefit /risk ratio. Company provides a 'letter of committment' to solve them later.

Under Exceptional Circumstances: where the data are not comprehensive, and not likely to be provided , e.g. small clinical trials in rare diseases,

Conditional approval, with obligations. It is expected the deficiencies will be repaired with a program of obligations. Conditional status is renewable annually until converted into a 'full' Positive Opinion.

Negative – must state the reasons.

Company can appeal ('re-examination of the opinion'). If the appeal fails the negative opinion and scientific report will be published in a negative EPAR.

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Between the Opinion and the Commission

The CHMP Opinion in EN must be available in All EU languages and must be confirmed by the Commission

Within 5 days after the Opinion, Translations are prepared by the Company

(except SMEs, EMA does this)

Checked by MS / EMA & sent to Commission

Commission's Decision Making Phase: 67 days

draft decision, internal consultation, standing committee, respecting the 'droit de regard' of the Eur. Parliament, etc.

The Commission will then issue a DECISION which is sent to the company and EMEA, this is the Marketing Authorisation.

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Post-Authorisation Activities

Authorisations do not stand still – there are many changes

Variations: Type I

These simple variations – mostly quality - do not involve the CHMP and there is no Opinion

Type IA (14 days) handled and approved entirely by EMEA. No questions, no stopclock, just yes or no.

Type IB (30d, 60d or 90d) rapporteur's report needed, questions if necessary, approved by EMA

Variations: Type II

More complex. Can be either quality or non/clinical (30d, 60d +) rapporteur's report needed, Request for Supplementary Info is possible (RfSI), stopclock, response, Final rapporteur's report, A CHMP Opinion is needed.

Line extensions

may be based on quality, e.g. new strength, or a change from tablets to oral suspension needs a new authorisation, i.e. an extension in the line of the same product 'family'. Same product name.

Guideline gives demarcation between Type II and Line Extension.

Urgent Safety Restrictions,USR

20 may arise from unforeseen events during marketing. May be based on quality problems.

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Post-Authorisation Activities

Ongoing monitoring of safety after authorisation - Pharmacovigilance

We can

- suspend, pending investigation
- revoke, if benefit/risk ratio becomes unfavourable

In all cases, our reports and conclusions are published on the EMEA website

We are transparent !

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Thank You

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