The mission of the European Medicines Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

Key Principles

- The EU is a Single Market for pharmaceuticals
  ~ 0.5 billion people
- In order to market a medicinal product in the EU, a company needs a Marketing Authorisation
- There are different ways ('Procedures') for a company to obtain a Marketing Authorisation
- The main scientific principle used in the evaluation of medicines is the **benefit/risk balance**, based on quality, efficacy and safety aspects
- Economic considerations are excluded from the assessment

European Marketing Authorisation Procedures

Centralised Procedure (via EMA)

Mutual Recognition or Decentralised Procedure (national licences)

Both Systems allow

Better Resource Utilisation
Harmonised Scientific Opinions
Harmonised Information to Doctors / Patients

CHMP
(Committee for Human Medicinal Products)

PRAC
(Pharmacovigilance Risk Assessment Committee)

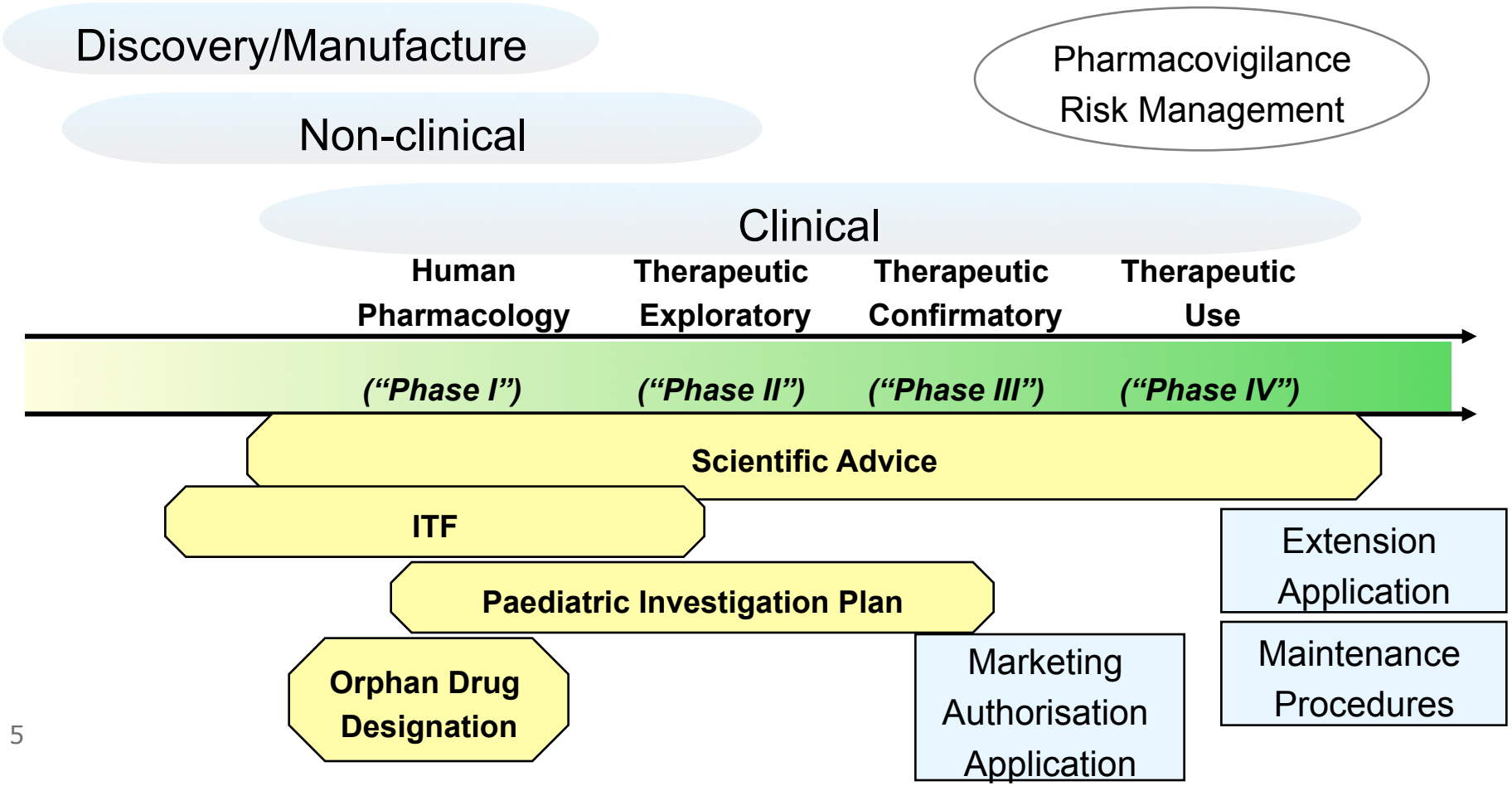
COMP
(Committee for Orphan Medicinal Products)

HMPC
(Committee for Herbal Medicinal Products)

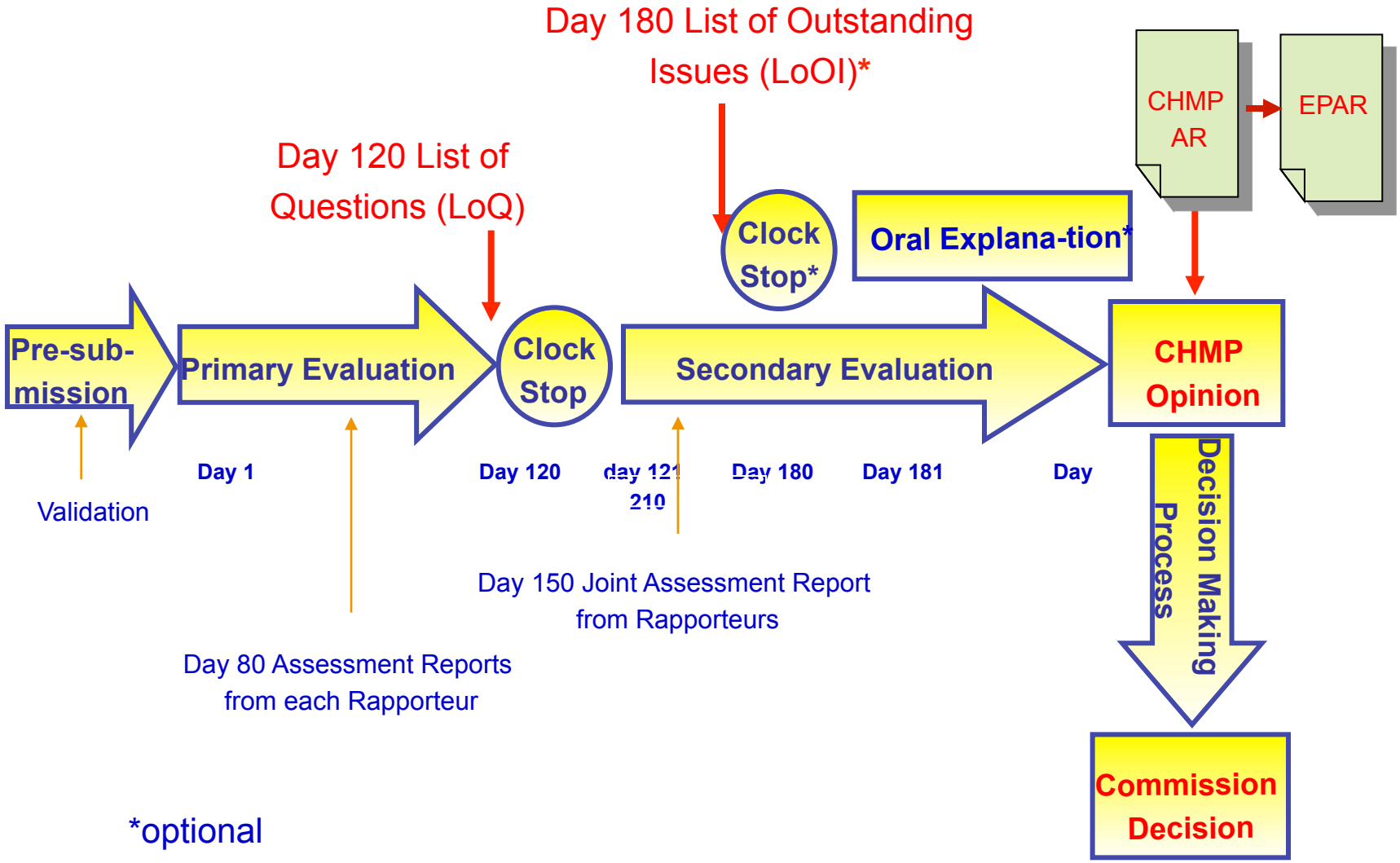
PDCO
(Paediatric Committee)

CAT
(Committee for Advanced Therapies)

EMA support of Drug Development



Assessment procedure



*optional

European Public Assessment Report (EPAR)

EPAR → increased transparency / openness to public

- CHMP assessment report
(without annexes and commercially confidential information)

- summary understandable by the general public

- Authorised Presentations, Summary of Product Characteristics, Labelling and Package Leaflets

Regularly updated

Available on EMA Homepage
http://www.ema.europa.eu/index/indexh1.htm

Women in Clinical Trials

EUROPEAN MEDICINES AGENCY

Phase I/II registration trials: traditionally mainly healthy males 18-35 years old

FDA guideline 1977: excluded premenopausal women from early phase clinical trials

Trial population was therefore not very representative: in the 1990ies young women were excluded from HIV trials

FDA took steps to facilitate their inclusion

NIH Revitalization Act 1993

mandated sample size adequate to support valid analysis of gender & racial subgroup effects

1995: establishment of the EMA

ELSEVIER

Women's Health Issues 19 (2009) 89–93

WOMEN'S HEALTH ISSUES

INCREASING PARTICIPATION OF WOMEN IN EARLY PHASE CLINICAL TRIALS APPROVED BY THE FDA

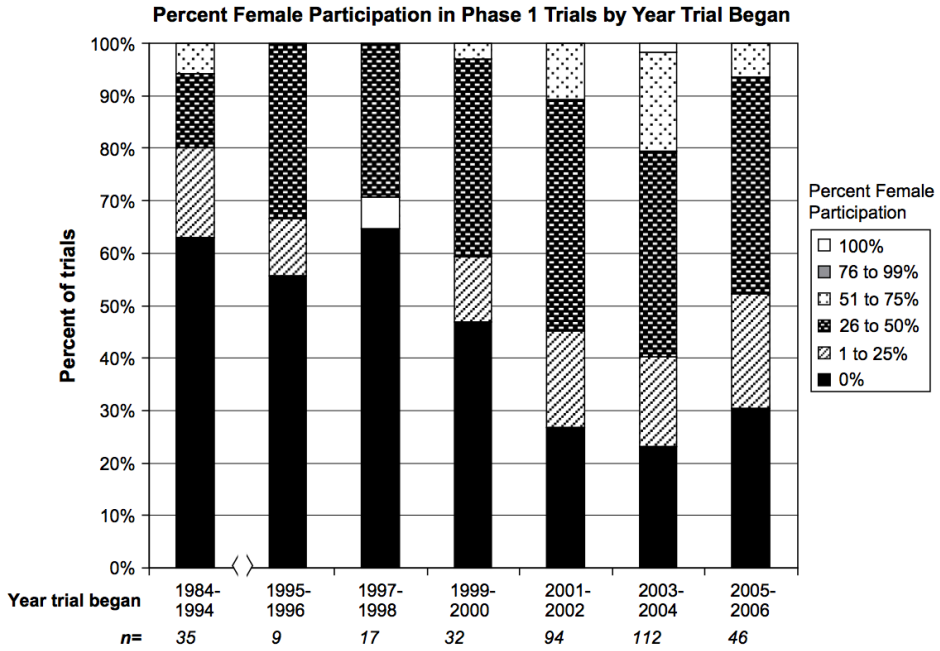


Figure 1. Percent female participation in Phase I trials by year trial began.

Conclusion. **Females subjects have traditionally been underrepresented in phase 1 trials. The number trials enrolling women and the number of women participating in phase 1 trials has increased since 2001, however, women are still underrepresented.**

EMA/ICH Analysis on gender bias in 2004

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- Analysis of all products, which received marketing authorisation in the EU between January 2000 and December 2003: **ICH Step 5** (EMEA/CHMP/3916/2005 – ICH)
- only pivotal trials included (confirmatory studies for the risk/benefit)

Point estimates and CI were confronted with expected women proportion.

Conclusions were:

generally there seemed to be no or only negligible gender bias.

Exceptions:

Under-representation of women in hypertension- and diabetes trials
Overrepresentation of women in rheumatoid arthritis- and allergy trials

FDA Report

Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products August 2013

U.S. Department of Health and Human Services
Food and Drug Administration

2. CDER – Sex Composition

All of the applications approved in CDER during 2011 and examined reported trial composition by sex.

Overall, **the percentage of patients by sex who participated in clinical studies tended to reflect the prevalence of the disease in men and women**.

e.g. no female representation in the prostate cancer trial,

whereas SLE, which is predominantly a disorder of women, had a high percentage of female participants.

Why do studies suggest that women may be underrepresented in clinical trials?

Possibly many of the cited studies are not registration/confirmatory trials.

Women may be more difficult to recruit and retain, e.g.:

- Family/carer role
- Different risk perception from men (?)
- Recruitment/cohort issues (particularly in USA, e.g. veterans health administration, Medicare access)

Vulnerability mind-set is still prevailing (CTA, investigators): legitimate protection needs to be balanced with possible collection of important data in women

Powered subgroup analysis require increased sample size

Lower mortality decreases event rates requiring increased sample sizes in outcome trials

EMA Geriatric medicines strategy (2011): TWO PRINCIPLES

Medicines used by geriatric patients must be of high quality, and appropriately researched and evaluated… **for use in this population**.

⇨ Evidence based medicine

Improve the availability of **information** on the use of medicines for older people

⇨ Informed prescription

Lessons for gender issues:

- who are our patients, and
- are we helping them with relevant information?

CHMP assessment report template

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Baseline characteristics

Baseline demographic and clinical characteristics of each group. Describe particularly any asymmetry in characteristics across treatment arms.

- *Discuss how study population reflects intended indication (or defer to overall conclusions).*

Special populations

Exploratory analysis of data across studies that may contribute to the ***understanding of variations in drug pharmacokinetics*** *and possible statements on the consequences may be displayed here. These variations may be related to extrinsic or intrinsic factors such as age, gender,race, smoking status, metabolic polymorphism, renal function and hepatic insufficiency*

EPAR/SmPC information

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- The SmPC (Summary of product characteristics) is the main source of information for healthcare professionals on how to use the medicinal product safely and effectively, including in special populations, such as children, older people and pregnant women.
- Differences in PK or efficacy should be mentioned as appropriate.
- In accordance with the SmPC guideline, efforts should be made by the Marketing Authorisation Applicant or Holder to provide the reasons for the recommendations for use in pregnant or lactating women and in women of childbearing potential.
- All available knowledge should be taken into account, including clinical studies and post-marketing surveillance, pharmacological activity, results from non-clinical studies, and knowledge about compounds within the same class.

SmPC guideline:
http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

EPAR information

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CHMP assessment report template:

A tabular overview of the relevant clinical studies; study number, design and number of patients in treatment arms, baseline characteristics such as age, gender and severity of disease, efficacy parameters and efficacy results should be included. Such a table should be in accordance with the CTD table 2.7.3.1, as appropriate.
Example table for study details:

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint

3.6. Analysis performed across trials (pooled analyses AND meta-analysis)

Criteria used for these analyses should be stated and may involve exploratory analysis on the whole database considering ***different effect modifiers (gender****, age, drug-disease interactions, smoking etc.).*
In addition dose-effect relationship in special

4.6. Safety in special populations

Short summary of all available information both derived from preclinical and clinical studies in order to substantiate the specific statements in the SPC (e.g. ***gender related differences****, risks for the use in pregnant women, breast feeding, potential effects on fertility, etc).*

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Draft Clin Trial Regulation

Art 10

MS will assess… "the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial **represent** the population to be treated, or if not, explanation and justification is provided in accordance with Annex I…"

…….

Annex I

- if a specific gender or age group is **excluded from or underrepresented** in the trials, an explanation of the reasons and justification for these exclusion criteria…
- ..justification for the gender and age allocation of trial subjects.

Identifying knowledge gaps:

1) Elderly women:

- the majority of older, multimorbid patients
- EMA geriatric medicines strategy

2) pregnant and lactating women

- The vulnerable subject is embryo/foetus/baby
- IMI/PROTECT
- EMA pregnancy and lactation strategy

3) Sex-Genetically linked issues

- Have sufficient sample sizes to detect (as per guidelines)
- Personalised medicine initiatives

How can we get better data?

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- Increase attention to unjustified exclusion criteria (Scientific advice and during MAA assessment)
- Analyse ALL data we have and provide relevant and transparent information
- Application of new European Pharmacovigilance legislation
  - Missing data at the time of MAA (RMP/ Post Authorisation Safety/Efficacy studies)
  - ADR hospitalisations
  - Adherence to treatment
  - (in)appropriate prescription
  - Real life data (comorbidities, drug interaction)
- EMA participation in IMI projects

Thank you