EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Workshop with stakeholders on support to quality development in early access approaches

Session 9.
Regulatory tools to support early access

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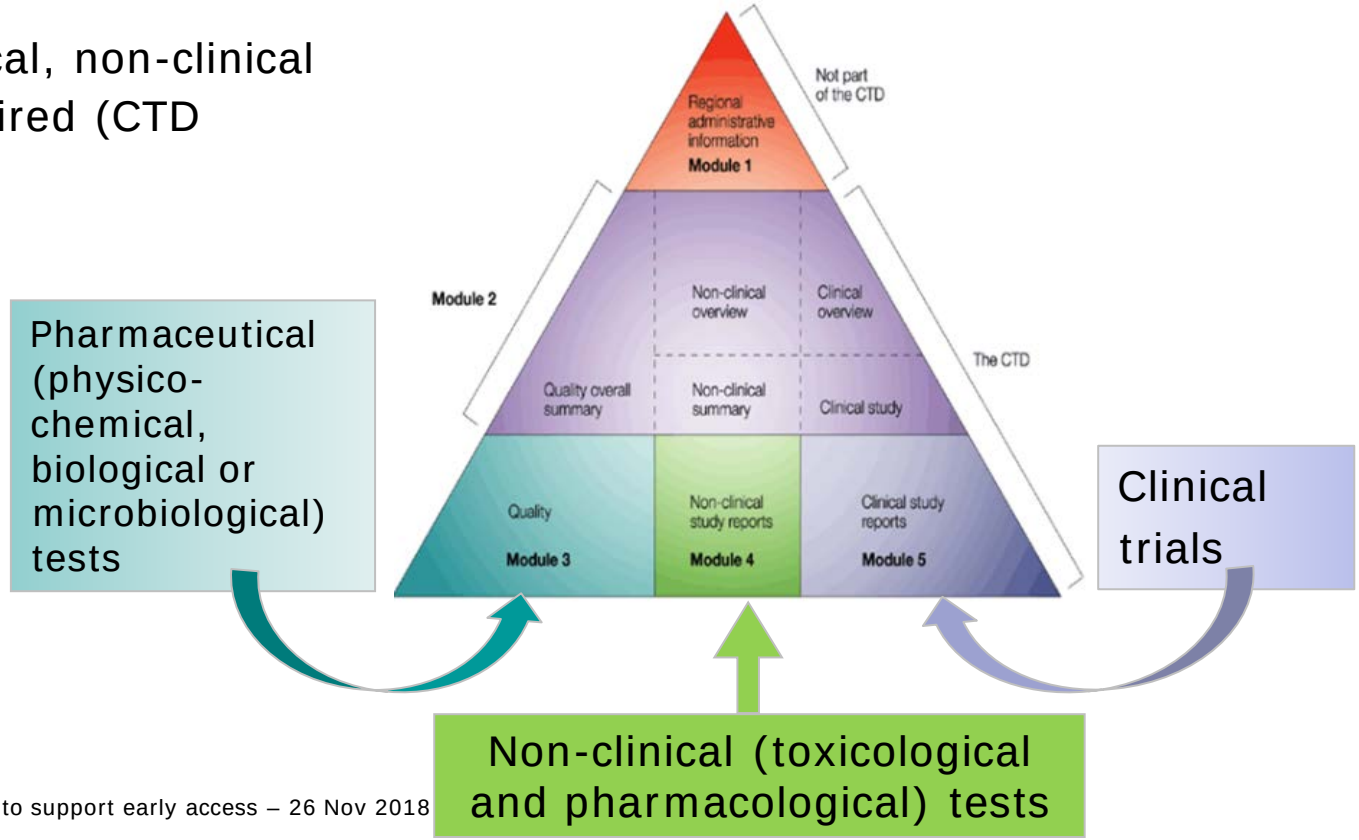
An agency of the European Union

Early Access Tools

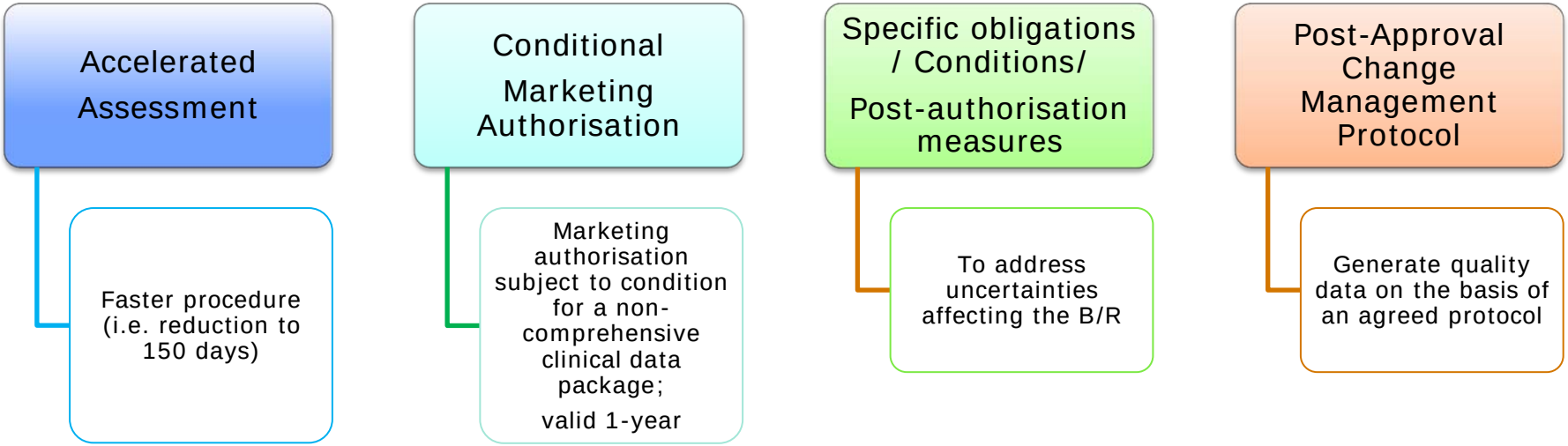
Marketing authorisation application – Data requirements

- Detailed pharmaceutical, non-clinical and clinical **data** required (CTD format).

- Need to properly and sufficiently demonstrate quality, safety and efficacy & establish a positive B/R balance.
- Specified in Annex I of Directive 2001/83/EC; further clarified in scientific guidelines.



Early tools within the regulatory framework



Accelerated Assessment

What to consider for an Accelerated Assessment

- **Medicinal products with major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation**
- Faster procedure : Active time reduced to 150 days (90 + 30 + 30 / ATMPs 120 + 30) [The CHMP can revert to standard timetable when AA can no longer be maintained]
- **Discuss proactively with regulators issues related to the dossier**, to ensure appropriateness of an accelerated assessment procedure and possible way forward to address any potential issues

Article 14 (9) of Regulation (EC) No 726/2004

CHMP guideline EMEA/419127/05

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004136.pdf

Accelerated assessment: key-messages

- Accelerated assessment **allows for a faster evaluation procedure** but **does not reduce the data requirements at time of the MAA submission**
- There is no concept of rolling review, nor principle that data needed to demonstrate quality, safety or efficacy can be provided post-authorisation.
- **Early preparedness and dialogue is strongly recommended through:**
  - Scientific advice
  - pre-submission meeting with the EMA, CHMP and PRAC rapporteurs (6-7 months before submission) to present the data package

Conditional Marketing Authorisation

Conditional Marketing Authorisation – scope and requirements

Scope (at least one):

- Intended for treatment, prevention or diagnosis of **seriously debilitating diseases or life-threatening diseases**;
- To be used in **emergency situations**, in response to public health threats;
- Designated as **orphan** medicinal products.

Requirements (all):

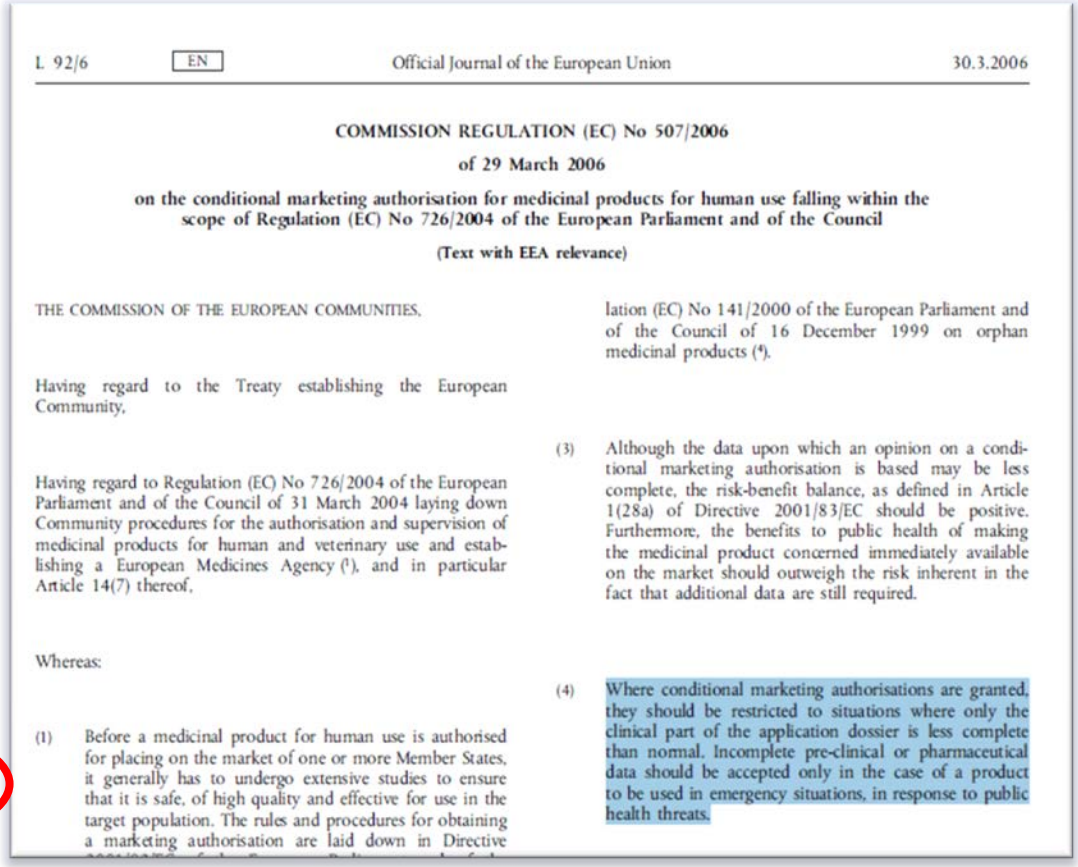
- The **benefit-risk balance** is **positive**;
- It is **likely** that the applicant can **provide comprehensive clinical data**;
- **Unmet medical needs** will be fulfilled;
- The **benefit to public health of the immediate availability** of the medicinal product outweighs the risk inherent in the fact that additional data are still required.

Conditional MA

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

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

In **emergency situations** as referred to in Article 2(2), a conditional marketing authorisation may be granted, subject to the requirements set out in points (a) to (d) of this paragraph, also where **comprehensive pre-clinical or pharmaceutical data have not been supplied**.



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COMMISSION REGULATION (EC) No 507/2006

of 29 March 2006

on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (1), and in particular Article 14(7) thereof,

Whereas:

(1) Before a medicinal product for human use is authorised for placing on the market of one or more Member States, it generally has to undergo extensive studies to ensure that it is safe, of high quality and effective for use in the target population. The rules and procedures for obtaining a marketing authorisation are laid down in Directive

lation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (4).

(3) Although the data upon which an opinion on a conditional marketing authorisation is based may be less complete, the risk-benefit balance, as defined in Article 1(28a) of Directive 2001/83/EC should be positive. Furthermore, the benefits to public health of making the medicinal product concerned immediately available on the market should outweigh the risk inherent in the fact that additional data are still required.

(4) Where conditional marketing authorisations are granted, they should be restricted to situations where only the clinical part of the application dossier is less complete than normal. Incomplete pre-clinical or pharmaceutical data should be accepted only in the case of a product to be used in emergency situations, in response to public health threats.

Post-Authorisation Measures

Post authorisation measures

- Adopted **at time of approval of a procedure** (new marketing authorisation or variation/extension); the Agency's Committee(s) request that applicant/MAH should provide **additional data post-authorisation**, as it is **necessary from a public health perspective** to complement the available data with additional data about the safety and/or the efficacy of the medicinal product.
- The legislation foresees **post-authorisation efficacy and safety studies** but does not foresee conditions on quality.
- **Quality** of medicinal product **needs to be sufficiently demonstrated** at time of **regulatory approval**

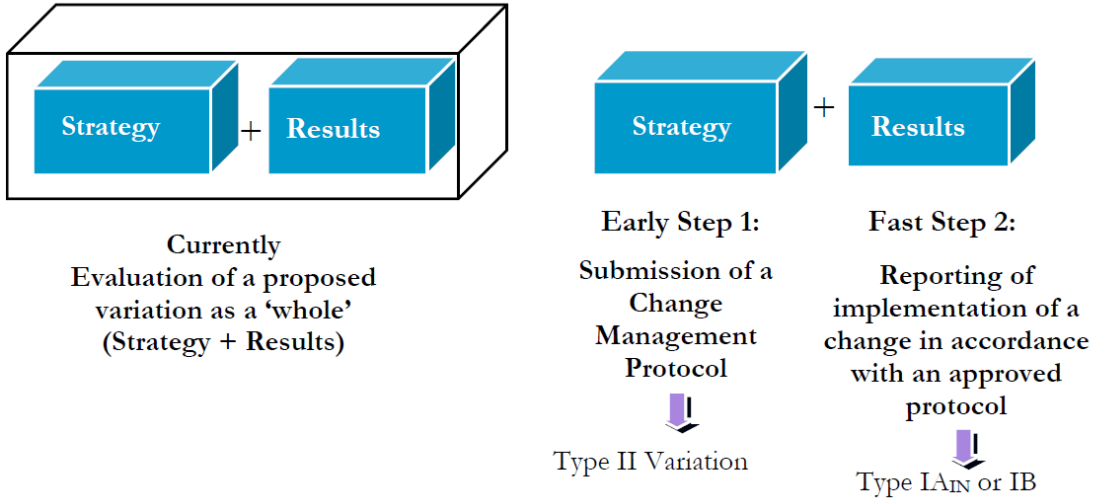
What about quality conditions?

- Only **very exceptionally, quality related conditions have been imposed** where the quality concern may impact the safety and efficacy profile of the product and can be **linked to the benefit-risk balance**.
- Exceptionally, Quality conditions have been considered, in particular, :
  - to increase the knowledge in this area, to allow confirmation of the quality criteria established at the time of MA, or
  - to better qualify and/or mitigate the potential risks
    - e.g. medical device, characterisation, stability, comparability, either in the active substance or in the finished product, batch-to-batch consistency or comparability resulting from changes in the manufacturing process (for biotechnologically derived products) where it could lead to a safety concern

Post-Approval Change Management Protocol

Post-Approval change management protocol

Figure 1: Post Approval Change Management Protocols



Perceived benefits:

- Early assessment of strategy to implement a change
- Removal of extended type II assessment from **critical path**
- Reduction of overall regulatory review time

PACMP EU Experience * – by Product Type

SCOPE	TYPE II	MAA	Line Extension
New site for manufacture and/or QC testing of drug substance	Bio: 15	Bio: 1 Chem: 5	
New site for manufacture and/or QC testing of drug product	Bio: 27 Chem: 3	Bio: 8 Chem: 1	Bio: 2
Change to the manufacturing process of the drug substance	Bio: 14	Bio: 6 Chem: 1	
Scale up of the drug substance manufacturing process	Bio: 7	Bio: 2	
Change to the cell bank preparation		Bio: 2	
Change to the manufacturing process of the drug product	Bio: 3 Chem: 4	Bio: 1 Chem: 3	
Change to the container closure system (drug substance or product)	Bio: 1 Chem: 1	Chem: 1	
Other	Bio: 4	Bio: 2	Chem: 2
Totals	Bio: 95 (Type II 71, MAA 22, LE 2) Chem: 21 (Type II 8, MAA 11, LE 2)		

*2010-2016

Other tools to support development and MA application for early patient access

- Scientific Advice / Protocol Assistance
- PRIME
- Parallel EMA-FDA scientific advice
- MAA Pre-submission meetings
- Clarification meeting (during evaluation with Applicant / Rapporteurs / EMA)

Features of the PRIME scheme

Early access tool, supporting patient access to innovative medicines.

- Written confirmation of PRIME eligibility and potential for accelerated assessment;
- **Early CHMP Rapporteur appointment** during development; Appointment of **EMA quality specialist**
- **Kick off meeting** with multidisciplinary expertise from EU network;
- **Enhanced scientific advice** at key development milestones/decision points;
- **EMA dedicated contact point**;
- Fee incentives for SMEs and academics on Scientific Advice requests.

Scientific Advice

Voluntary, not mandatory procedure

Pre-submission meeting for SA, as needed

40-day or 70-day SA procedure when face-to-face meeting

Scope: to advise developers on specific questions they have during development of medicines to meet regulatory and scientific requirements, e.g.:

- Manufacturing processes
- Control strategy
- how to test them in humans in clinical trials.
- how to study them in specific populations e.g. rare diseases and children
- prospective in nature

EMA-FDA Parallel Scientific Advice

- To provide a mechanism for EMA and FDA to ***concurrently exchange with sponsors their views on scientific issues*** during the development phase of new medicinal products
- Increased dialogue between the two agencies and sponsors from the beginning of the lifecycle of a new product, provide a ***deeper understanding of the bases of regulatory decisions***, ***optimize product development***, and ***avoid unnecessary testing replication*** or ***unnecessary diverse testing methodologies***.
- After a PSA procedure, ***each agency will retain its individual regulatory decision-making authority regarding drug development issues and marketing applications***. However, ***both agencies will strive to provide PSA responses that are convergent***.

New element: Consultative Advice

- Alternatively both agencies can engage in a "***consultative advice***". In this case, a limited number of experts from either side will be invited to participate in the discussions of the other agency.
- Allows sponsors to request scientific advice from one regulatory agency and **concurrently notify the other regulatory agency** of the request. At the invitation of the first agency, the **second will participate in the sponsor meetings or teleconferences as able**. Unlike the parallel scientific advice process, the **second** agency will be expected to **only engage on top level issues**. The review and sponsor meeting will follow the timelines of the regulatory agency from whom the sponsor initially seeks scientific advice. **Only the initially contacted regulatory agency will provide written scientific advice**

Conclusion

Early dialogue and prospective planning

Discuss in advance the overall development plan including quality programme **before authorisation**

Prospective **scenario building**, planning the impact of future outcomes on next steps (including PACMP)

Expected benefits

- Optimised development timings
- Be prepared on how to address uncertainties
- Avoiding delays in assessment procedure
- Enable accelerated assessment
- Successful MAAs

Any questions?

Further information

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