EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The regulatory framework for licensure of medical countermeasures during public health emergencies

Preparedness for emerging diseases, consultation workshop, Brussels

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Regulatory framework

- **Use in EU**
  - Compassionate use
  - Conditional Marketing Authorisation (CMA)
  - Marketing Authorisation under exceptional circumstances (EC)
  - Paediatric Investigational Plans (PIP) required for MA
  - Specific provisions for a pandemic influenza situation
- **Use only outside EU**
  - Article 58 procedure including options of CMA or EC MA
- **Opinion on scientific matter for the evaluation of medicinal products**
  - Article 5(3) procedure

Compassionate Use

- Article 83 of Regulation (EC) No 726/2004 introduced legal framework for Member State to ask the CHMP when **compassionate use for group of patients** is envisaged to adopt opinions on the conditions for use, conditions for distribution and the patients targeted for a medicinal product in the EU

- Article 83 of Regulation (EC) No 726/2004 further states that when a Member State makes use of the possibility for compassionate use for group of patients it shall notify the Agency

- Since the introduction of Article 83 of Regulation EC No 726/2004 in 2005, the CHMP adopted 5 scientific opinions for Compassionate Use for two conditions (hepatitis C and influenza)

- Guideline on compassionate use of medicinal products, pursuant to Article 83 of Regulation (EC) no 726/2004

- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac058007e691

CHMP Scientific Opinions on Compassionate Use to Date

Product	Country	Year
ledipasvir, sofosbuvir	Ireland	2014
daclatasvir	Sweden	2013
Sofosbuvir	Sweden	2013
Zanamivir	Sweden	2010
Oseltamivir phosphate	Finland	2010

Conditional Marketing Authorisation

On the basis of less comprehensive data and subject to specific obligations

Scope (at least one):

- for **seriously debilitating diseases or life-threatening diseases**;
- to be used **in emergency situations**;
- **orphan** medicinal products.

Criteria (all):

- the **risk-benefit balance is positive**;
- it is likely that the applicant **will be in a position to provide comprehensive clinical data**;
- **unmet medical needs** will be fulfilled;
- the **benefit** to public health **of the immediate availability** on the market of the medicinal product concerned **outweighs the risk** inherent in the fact that additional data are still required.

'**unmet medical needs**' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected

Regulation (EC) No 507/2006

Missing elements* of comprehensive data**

Data at the time of CMA	Data generated through specific obligations
Data based on an intermediate endpoint (e.g. overall response rate)	Data on clinically most relevant efficacy endpoint (e.g. survival data)
Data from limited study/-ies	Data from a larger database or for longer duration, with the same endpoint(s) (e.g. response rate at a later time cut-off)
Data in overall population	Further data in important sub-populations (e.g. in patients with resistance or a particular biomarker)
Data on certain endpoints	Further data on additional endpoints / specific issues identified
Data in a certain combination therapy	Data with other co-medication for combination therapies
Immunogenicity data	***Vaccine effectiveness data***

* justified based on the strength of available results and taking into account the requirement for a positive B/R balance

** data requirements laid down in Annex I of Directive 2001/83/EC, including confirmatory studies normally required in the particular indication for respective type of the medicinal product

Marketing authorisation under exceptional circumstances

- *Article 14 (8) of Regulation (EC) No 726/2004:* In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted **subject to certain conditions**, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can **show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use**, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the **annual reassessment** of these conditions.

  http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

- *CHMP Guideline EMEA/357981/2005*
  http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf

Criteria of MA under exceptional circumstances

Criteria as per Annex I to Directive 2001/83/EC :

- the indications for which the product in question is intended are encountered so **rarely** that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the **present state of scientific knowledge**, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical **ethics** to collect such information

Conditional MA

- Comprehensive data expected after authorisation
- To later switch to 'full' MA
- Valid for 1 year only
- Annual renewals
- Only in centralised procedure

MA under exceptional circumstances

- Comprehensive data not possible
- To remain such indefinitely
- Normal validity of MA
- Annual re-assessments
- Possible in all registration procedures

Article 58 of Regulation (EC) No. 726/2004

1. *"The Agency may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with the provisions of Articles 6 to 9. The provisions of Article 10 shall not apply.*
2. *The said Committee shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice."*

L 136/24 Official Journal of the European Union 30.4.2004

Article 58

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2. The said Committee shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.

Article 59

1. The Agency shall take care to ensure early identification of potential sources of conflict between its scientific opinions and those of other bodies established under Community law carrying out a similar task in relation to issues of common concern.

Article 61

1. Each Member State shall, after consultation of the Management Board, appoint, for a three-year term which may be renewed, one member and one alternate to the Committee for Medicinal Products for Human Use and one member and one alternate to the Committee for Medicinal Products for Veterinary Use.

The alternates shall represent and vote for the members in their absence and may act as rapporteurs in accordance with Article 62.

Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate and shall represent the competent national authorities.

2. The committees may co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

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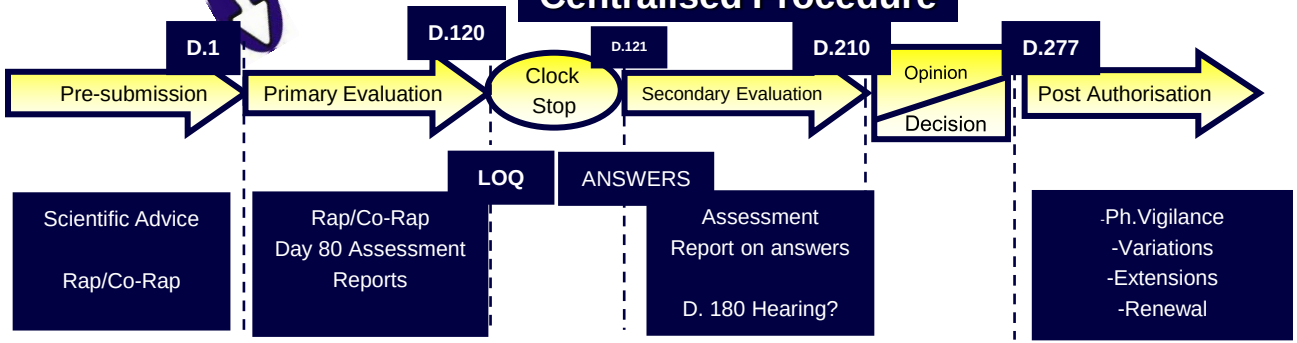
Centralised Procedure



Examples of different approval pathways for vaccines

- **Conditional marketing approval** (e.g. H5N1 LAIV vaccine for use in a declared pandemic)
- **Approval under exceptional circumstances** (e.g. smallpox vaccine)
- **Art. 58 Scientific Opinion** for use outside of EU (e.g. malaria vaccine)

Paediatric Legislation -Regulation (EC) No 1901/2006

- Obligation and incentives to study medicinal products in children
- **Paediatric Committee (PDCO)** to provide scientific opinions on PIPs/Waivers applications
- **Paediatric Investigation Plan (PIP)** is a development plan to ensure that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children in an age-appropriate formulation
- All applications for marketing authorisation for **new medicines** in EU have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a waiver or the paediatric development is delayed because of a deferral (**art7**).
- Not required for art. 58 procedures

Rapid "Scientific Advice" procedure

- The Rapid SA procedure is a process managed by EMA and initiated by ED in light of public health need for specific products directed towards the disease.
- It is an *ad hoc* procedure which aims to follow the principles of the standard SA wherever possible.
- The scope of the questions are intended to be the same as for standard SA. It is not a pre-review although the Agency will make every effort to assist the development of the products by providing relevant rapid feedback.
- There is usually only one co-coordinator's report (different coordinators for different areas are possible, e.g. quality /clinical/non-clinical) , which is reviewed by an Ad hoc group of experts (which have been agreed by the EMA/CHMP chair/ED). Extra experts/ WPs may be involved as considered necessary.
- Where similar requests are submitted to another international regulatory body with whom we have a confidentiality agreement, there might be discussion of the advice to be provided although the advice may not necessarily be identical.
- The final advice is always adopted by CHMP (even if by written procedure).

Rolling Review principles for pandemic applications

- Evaluation of data as it becomes available (preceding MAA submission or post-authorisation procedures)
- Applicant/MAH should present in advance an overview of upcoming data packages
- Two-weeks cycles or multiples, depending on amount of data to review (to agree with Rap. assessors)
- Repeat rolling review cycles as many time as needed
- Responses to be incorporated into rolling review submissions
- Each RR cycle foresees the possibility of TC with experts
- Committee discussion if there is a scheduled meeting, Rapp consolidates comments, opinion adopted.
- Once Committee considers that the data package is complete, the submission of the variation/MAA is made and processed via an accelerated TT.

Scientific question – article 5(3) referrals

- Where relevant, an opinion on a scientific matter concerning the evaluation of medicinal product for human use can be drawn up by the CHMP.

Assessment report for Article-5(3) procedure: Medicinal products under development for treatment of Ebola

Core labelling

Lessons learned from the review of the labelling of centrally authorised pandemic vaccines - final (EMA/467700/2014)

- Timing for the printing of final labelling material
- Use of generic labelling
- English only labelling
- Prominence of key information on the outer labelling
- Readability of the information displayed on small immediate labelling
- Use of multi-dose vials
- Labelling impact for a posology change from full dose to half dose
- Outdate of the Package leaflet

Thank you for your attention

Further information

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