Federal Institute
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory update from Europe:

Procedures to promote early access of medicinal products to the market

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The views expressed in this presentation are primarily those of the author and do not necessarily express those of the BfArM, nor of the EMA

Regulatory update from Europe - Overview

- Current tools for „early access“
  - Conditional approval
  - Accelerated assessment
    - Planned updates

- Initiatives to improve early access:
  - Adapative pathways approach
  - PRIME („proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines”)

Current tools for early access

- **Conditional approval**
  - Regulation (EC) No 726/2004
    - Article 14 (7)
  - Regulation (EC) No. 507/2006
- **Accelerated assessment**
  - Regulation (EC) No 726/2004
    - Recital 33 and Article 14 (9)
  - Regulation (EC) No 507/2006
    - Recital 7 referring to Article 14 (9)
- **„Other" procedure outside „regular" licenses:**
  - „Exceptional circumstances" („unable to generate comprehensive data")
    - Article 14 (8) of Regulation (EC) No 726/2004 – not applicable for NASH

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Current tools for early access - Overview

Accelerated assessment

- Medicine is of **major interest** from the point of view of **public health** and in particular from the viewpoint of **therapeutic innovation**

- Objective: **Faster assessment** of marketing authorisation application

Conditional approval

- Medicine fulfills **unmet medical need**
- Medicine targets seriously **debilitating or life-threatening** disease, rare disease or is for use in emergency situations in response to a public health threat
- **Benefit-risk balance of the product is positive**, and benefit to public health of its immediate availability outweigh the risk related to need for additional data
- **Comprehensive data** expected to be provided **after authorisation**

- Objective: **Early Authorisation** on the basis of less complete clinical data

Current tools for early access

Planned changes with current ongoing update

(end of consultation phase for draft updated guidelines was: End of September 2015

Conditional approval

- Can be applied for by the applicant or requested by the CHMP
- Application and justification to be submitted as part of Module 1.5.5. EU-CTD
- Specific obligations part of the license; yearly re-evaluation of risk-benefit
- Necessary content:
  - justifications to show that the medicinal product falls within the scope of the conditional marketing authorisation Regulation
  - that the requirements for conditional marketing authorisation are fulfilled (see overleaf)
  - applicant's proposal for completion of ongoing or new studies andspecific proposals for collection of pharmacovigilance data

Current tools for early access

Conditional approval

- Requirements for conditional approval :
  - Demonstration of a positive risk-benefit on the basis of the available data
  - Display/discussion of the missing evidence („comprehensive data not yet available“)
    - E.g. more „reliable“ endpoints, long-term efficacy and safety, further sub-populations etc.
  - Demonstration of the likelihood that „comprehensive“ data can be provided
  - Fulfillment of the „unmet medical need“
    - Critical review of current standards, quantification of the problem (epdiomiology), justification how the new medicinal product will meet the unmet needs
  - The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required
    - impact of immediate availability on public health, potential risks associated with the fact that “comprehensive data” are not available.

Current tools for early access

Conditional approval

- Update of the Guideline :
  - Consultation phase ended 9/2015; finalisation expected end of 2015
  - Proposed changes:
    - Emphasis on importance of **planning** conditional marketing authorisation prospectively to ensure swift assessment procedure
    - Emphasis on advantages of engaging in **early dialogue** with EMA on the development programme, in particular in the context of joint scientific advice with health technology assessment bodies
    - Clarification of how a **positive benefit-risk** balance should be **substantiated** wherethere are less complete data
    - Examples and further guidance on the **level of evidence** that must be provided **at the time of authorisation** and data that can be provided p**ost-authorisation**
    - Updated guidance on **extent and type of data** required to be included in **annual renewal** submissions
    - Guidance on when a **condition** could be considered **life threatening** or **seriously debilitating** if these effects are in the long-term
    - Clarification on **fulfillment of unmet medical needs**, i.e. medicines providing major improvements in patient care over existing therapies can be eligible in certain cases

http://ec.europa.eu/health/files/committee/stamp/2015-10_stamp3/stamp_3_14_3a_guideline_on_conditional_ma_-_public_consultation.pdf

Current tools for early access

Accelerated Assessment

- Reduces Assessment time from 210 to 150 days
- Has to be requested by the Applicant
- Accelerated Assessment and Conditional Approval may be combined
- Content of the Justification of the “major public health interest”
  - Unmet medical need, available standards
    - Epidemiological data, literature overview, registries etc.
  - The extent to which the new product is expected to meet the unmet medical need
    - Effects of the new product (reference to the data), potential use in clinical practice
  - Display of the strength of the evidence from the point of view of public health
  - A new mechanism of action or a technical innovation per se may not necessarily represent a valid argument

Current tools for early access

Accelerated Assessment

- Update of the guideline:
  - Consultation phase ended 9/2015; finalisation expected end of 2015
  - Proposed changes
    - More detailed guidance on how to **justify major public health interest**, i.e. fulfillment of unmet medical need
    - Acknowledgment that **comprehensive clinical data** may **not** be **available** in certain situations, allowing accelerated assessment in the context of a conditional marketing authorisation for example
    - **Optimisation of the assessment timetable** by better balancing evaluation phases to reach a CHMP opinion within 150 days after the start of the marketing authorisation application procedure
    - Intent to request accelerated assessment to be indicated 6-7 months in advance and submission of accelerated assessment request encouraged to take place **2-3 months ahead** of marketing authorisation **application** instead of 10-30 days ahead
    - **Importance of early dialogue** with EMA so that accelerated assessment can be planned well ahead of the submission, e.g. by detailed discussion of the data package at pre-submission meetings

http://ec.europa.eu/health/files/committee/stamp/2015-10_stamp3/stamp_3_16_3b_guideline_on_accelerated_assessment_-_public_consultation.pdf

Adaptive Pathways Approach

- **Pilot Project on Adaptive Licensing**
  - Idea: An iterative development plan (gradual expansion of target population, progressive reduction of uncertainty, Conditional Marketing Authorisation, maybe surrogate endpoints and confirm)
    - (See e.g.: Eichler et al 2012; Woodcock JU et al 2012, Forda SR et al 2013, Baird L et al 2013)
  - Started in March 2014
    - Background: Timely access to promising medicines potentially addressing unmet medical needs
    - Discussion of “live assets”
    - Exploration and Development of potential new pathways
    - Including different stakeholders (HTA bodies, academic societies, patient organisations)
    - Help develop an understanding of how future adaptive pathways might be designed

Adaptive Pathways Approach

- Invitation to Sponsors sent out in March 2014
  - Submission of ongoing development programmes
  - Should be early stage of development (prior to phase III)
  - „Informal interaction“, no formal scientific advice, no binding decisions; „safe harbour brainstorming“
    - Criteria for drug candidates/Content of submissions:
      - Sufficient promise to meet an unmet medical need
      - Evidence to support a positive benefit-risk in a sub-population for initial licensing
      - Commitment for further studies/widening of population
      - Observational part (e.g. registries, e-health records) after initial licensing
      - Role of other stakeholders to be defined
      - Mitigation of off-label use (plans to be presented)

Adaptive Pathways Approach

- Statistics (up to 7/2015)
- (for initial evaluation, see also „Adaptive pathways to patients: report on the initial experience of the pilot project": EMA/758619/2014 , 15 Dec. 2014)

- 58 products submitted as candidates
- 19 selected for in-depth discussion with company (Stage I)
- 12 Stage I discussions have taken place

  Of the 19 selected products:
  - 4 SMEs
  - 5 are Orphan drugs
  - 4 are ATMP (Advanced Therapy Medicinal Products)
  - 5 Anticancer
- 9 proposals selected for Stage II (in-depth meeting after Stage I)
  - (1 ATMP, 5 Orphan, 3 SME; 2 anticancer)
- Main reasons for rejection were:
  - Development too advanced (too late to change anything)
  - Limited learning potential for a pilot (no developed proposal for use of RWD, limited iteration)

Adaptive Pathways Approach

- Current Status:
  - Renamed as „Adaptive Pathways Approach“
  - Stage I closed end 2/2015
  - Stage II open to further submissions under the condition of presenting „well-developed“ plans
    - Plans for expansion of target population or reduction of uncertainty
    - Ability to engage HTAs an other „downstream“ stakeholders
    - Well developped plans for collection of „real-world“ post-authorisation data.

PRIME

proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines

- Project started 6/2015
- Aims and Objectives:
  - Better informed development plans,
  - improve quality of marketing authorisation applications
  - promote regulatory awareness
  - Reinforce early dialogue and regulatory support to stimulate innovation,
  - optimise development
  - enable accelerated assessment of Priority Medicines
- Pre-condition for access: availability of adequate non-clinical and exploratory clinical data to justify a potential major public health interest prior to the initiation of confirmatory clinical studies at proof of concept stage
- Earlier Access possible for SMEs
- Just entered public consultation phase (until 23 December)
- Planned Start: March 2016

PRIME

proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines

- Procedures:
  - Eligibility assessed by SAWP/CHMP
  - Compulsory repeated Scientific Advice
  - Early assignment of CHMP-Rapporteur
  - Early application/decision for accelerated assessment
- Conditions:
  - Product fulfills the conditions for accelerated assessment
  - Data to support eligibility should show:
    - Potential for major therapeutic advantage
      - impact on the onset and duration of the condition, or
      - improving the morbidity or mortality of the disease

PRIME

proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines

- Support features:
  - Scientific advice including multiple stakeholders (e.g. patient representatives; HTAs)
  - Initial kick-off meeting of all involved network bodies
  - Early assignment of Rapporteurship
  - Early decision on accelerated assessent with confirmation shortly before submission

Further reading:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002424.jsp&mid=WC0b01ac058004d5c1

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Summary: Comparison FDA-EMA

EMA

- **Conditional approval**

  Approval of a drug for serious debilitating/life threatening diseases, less complete data; unmet medical need, positive risk-benefit ratio

- **Accelerated assessment**

  CHMP opinion given within 150 days instead of 210 days

- **No direct equivalent**

  ITF/SME office, Scientific Advice and Protocol Assistance, Biomarker Qualification

  New: PRIME

- **No direct equivalent**

  ITF/SME office, Scientific Advice and Protocol Assistance, Biomarker Qualification

  New: PRIME

FDA

- **Accelerated approval**

  Approval of drug for serious lor life threatening conditions based on effect observed on surrogate endpoint reasonably likely to predict clinical benefit

- **Priority review**

  Regulatory review period shortened from standard 10 months to 6 months

- **Fast track designation**

  Facilitate development and expedited review of drugs through more frequent FDA interaction and rolling of review data

- **Breakthrough designation**

  Expedite the development and review through more intensive FDA guidance and commitment to involve senior management

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Take home message:

- Talk to the regulators early -

Thank you for your attention!

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