EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Incentives and regulatory considerations:

Situation in Europe

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Post-designation is complex field

- European legislation regarding post-designation is spread over several pieces of legislation.
- Covers support for:
  - Product development.
  - Small to medium enterprises.
  - Licencing
  - Post-licencing: 10yr Market Exclusivity +2yr Market Exclusivity with endorsed PIP.
- Specific regulatory considerations for Orphan Medicines;
  - Orphan Similarity

Product Development

- Product development for Rare Diseases offers challenges which are unique.
- In order to foster development, Europe offers assistance through its incentives mechanisms enshrined in EU regulations.
- Development support through:
  - Protocol Assistance
  - Paediatric Investigational Plan
  - Compassionate Use Guidance
- These are centralised services which are operated by the EMA involving SAWP, PDCO, COMP and CHMP primarily.

Protocol Assistance.

- Article 6 of EC Regulation No 141/2000 is the basis for Protocol Assistance before submitting for a Market Authorisation.
- The EMA operates a centralised Protocol Assistance system for these products through the SAWP.
- Sponsors can submit questions on quality, pre-clinical and clinical development.
- SAWP meets once a month and operates a 70 Day procedure. **Fee reductions** are applicable on status. There is no limit to the number of times a sponsor can request this service.
- CHMP endorses quality, pre-clinical and clinical development answers
- COMP endorses Significant Benefit answers.
- The EMA operates a parallel Scientific Advice Service with the FDA on request.

Paediatric Investigational Plan

- *EC Regulation (EC) No 1901/2006 Article 37 states that "a Marketing Authorisation Application for an Orphan Medicinal product which includes the results of all studies conducted in compliance with an agreed paediatric investigation plan will be eligible for a **2yr extension** onto the 10yr Market Exclusivity."*
- Sponsors' should come and establish the need for a Paediatric Investigational Plan (**PIP**) with the PDCO.
- The PDCO operates a 120Day procedure with clock-off periods for a PIP. The service is **free**.
- Sponsor's should integrate this consultation into their development planning as failure to have a PIP may invalidate their application at the time of submission for MAA.

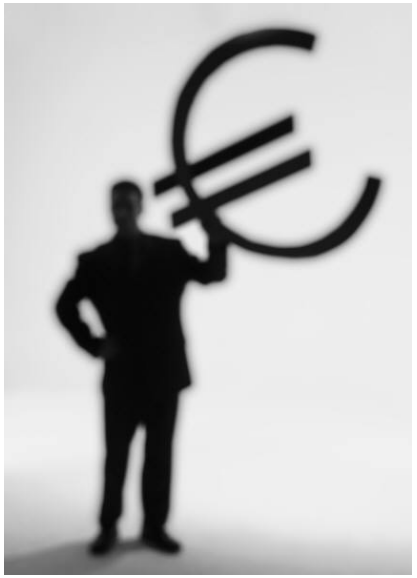
Compassionate Use Advice.

- *EC Regulation (EC) No 726/2004 Article 83 states that "By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use."*
- There is a guideline available for sponsors on the EMA website: *GUIDELINE ON COMPASSIONATE USE OF MEDICINAL PRODUCTS, PURSUANT TO ARTICLE 83 OF REGULATION (EC) No 726/2004*
- Sponsor's can approach their National Competent Authorities to request that the CHMP provide Advice for compassionate use programmes for a given product. This coordinated by EMA.

Regulatory Support for Small to Medium Size Enterprises

- EC Regulation No 2049/2005 specifically addresses assistance of pharmaceutical SMEs in Europe.
- The EMA operates a Small to Medium Size Enterprises Office whose role is defined in Article 11 of the Regulation No 2049/2005.
- Companies who qualify need to register with the SME Office in order to benefit from these incentives more information is available on the EMA website.
- Article 7 of EC Regulation No 2049/2005 is the basis for free Scientific Advice and Scientific Services for Small and Medium Size Enterprises (SMEs) who have a product with an Orphan Medicinal Designation.

Orphan Fee Incentives



SMEs - 100% fee waiver for:

- scientific advice
- scientific services
- marketing autorisation application
- pre-authorisation GMP, GLP, GCP, PhVig inspections
- 1st year post-licensing fees (variations etc.)

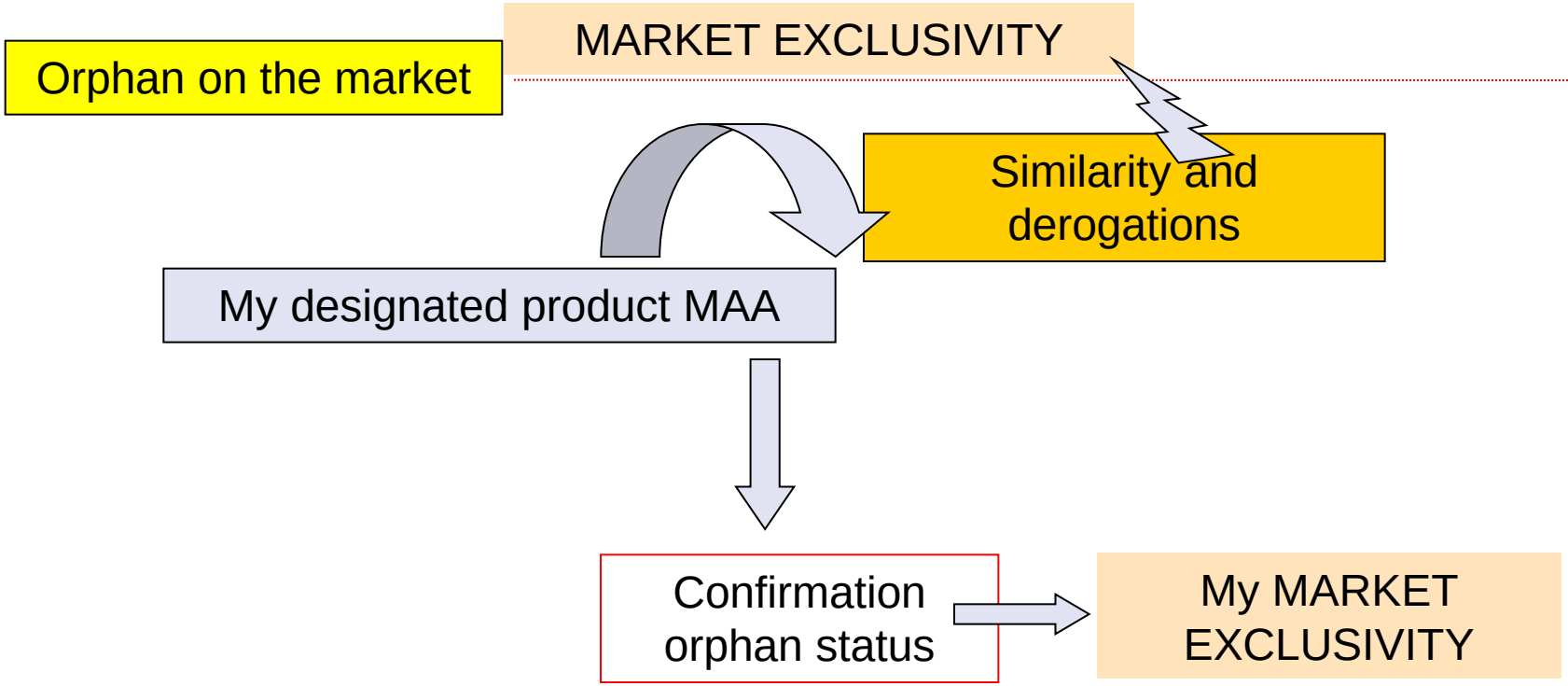
Non-SMEs – 70% fee reduction for:

- scientific advice

Marketing Authorisation

- *EC Regulation (EC) No 726/2004* establishes the basis for the centralised procedure for products which have obtained an Orphan Medicinal Designation.
- Specific considerations for Orphan Medicinal Designation Products:
  - Centralised Procedure for Products with Orphan Medicinal Designation.
  - Conditional Licencing
  - Orphan Similarity
  - Review of the Orphan Medicinal Designation at the time of MAA
  - Establishing Significant Benefit for the purpose of the 10yr Market Exclusivity.

Specific requirements



Authorisation of an orphan drug

- Based on same standards as for non orphan products (quality / safety / efficacy)
- Authorisation only centralised procedure: Regulation 2004/746
- CHMP responsible for assessment
- A completed valid PIP or waiver at the time of MAA submission.
- Authorisation within designated condition
- More than one designation possible per product (independent incentives)

Conditional Approval

- *EC Regulation (EC) No 507/2006* establishes the basis for the conditional marketing authorisation for products which have obtained an Orphan Medicinal Designation.
- MA on the basis of less complete data

➢ subject to **specific obligations**

- Well motivated in CHMP
- B/R balance positive
- Benefits of immediate availability outweigh risk of incomplete data

Conditional Approval

- Only clinical part of the application dossier is less complete (Incomplete pre-clinical or pharmaceutical data only in the case of emergency situations)
- **Specific Obligations**: initiate or complete certain clinical studies
- Valid for 1 year
- Only for initial MAA
- Significant benefit is assessed by the COMP at the time of initial MAA.

Other Licencing Considerations

- Although Orphan Medicines are not specifically mentioned in the relevant legislation companies can consider:
  - An accelerated Centralised Procedure providing the Applicant submits adequate argumentation the CHMP to support the basis for this procedure.
  - A submission based on Exceptional Circumstances which can be considered in very rare conditions where very few patients have the condition.

Orphan Similarity

- Paragraph 3 of Article 8 of EC Regulation 141/2000 establishes the basis for Orphan Medicinal Similarity.
- Orphan Similarity involves a orphan designation product which is applying for an MAA where another Orphan Product already has an MAA for the same indication and has the 10yr Market Exclusivity.
- CHMP determines at any stage before EC approval whether there is Orphan Similarity.
- EC Guideline exists which is available on the EMA Orphan Designation legal basis webpage which explains how it works.

Assessment of Orphan Similarity

- Applies if other orphan medicines authorised for same designated condition

- Need to submit report in module 1.7
  - Molecular structure
  - Mechanism of action
  - Similarity of indication (“significant overlap of populations”?)
- Assessment by CHMP working party competent
- Final opinion by CHMP
- Similarity can be triggered any time before EC decision
- Proactive publication on-going procedures

Derogations to market exclusivity

Applicable if product is similar

Assessed based on sponsor's report

- Specific timetable (parallel to QSE assessment)

Three derogations (Art 8(2))

- First MAH's consent (agreement market sharing)
- Insufficient supply: long term and clinical consequences (presumably)
- Clinical superiority: better efficacy, better safety or exceptionally major contribution to patient care

Specific requirements for an Orphan Medicinal MAA

Confirmation designation criteria

- Report to orphan medicines section
  - At time of submission MA
  - Possible to update
- Need to address all designation criteria
- Standard set at time of authorisation
- Assessment by COMP; opinion in parallel with MA opinion by CHMP

Procedure

- Sponsor submits report at the same time submission marketing authorisation application
- Procedure allows two discussions at COMP
- COMP adopts opinion only after CHMP has adopted opinion on marketing authorisation
- Possibility to invite sponsor for oral explanation
- COMP opinion can be subject to appeal
- Final COMP opinion is sent to Commission
- The Commission grants the 10yr Market Exclusivity
- A valid an completed PIP which is +ve another 2yr can be added by the Commission.

····· Opinion

Market Exclusivity

- The Commission grants the 10yr Market Exclusivity based on the recommendation of the COMP.
- Sponsors should ensure that Significant Benefit is adequately addressed at the time of MAA submission (Protocol Assistance answer from the COMP on Significant Benefit should be sought)
- A valid and completed PIP should be available at the time of Market Authorisation Submission for evaluation by the CHMP.
- Based on the outcome of the MAA the Commission grants the additional 2yr Market Exclusivity.

Conclusions

- European Legislation provides the basis of the framework for Post-Orphan Medicinal Designation Incentives and Regulatory Guidance.
- Support of product development through Protocol Assistance, Paediatric Investigational Plans and Compassionate Use Guidance.
- Specific Regulatory support and fee reductions exist for SMEs.
- Centralised Marketing Authorisation with specific consideration to Conditional Authorisation, Orphan Similarity Issues, review of Orphan Designation and granting of 10yr+2 Market Exclusivity.