Clinical Development and enabling Regulatory Steps: “How to obtain ODD and Scientific Advice at EMA”

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Why this session?

European and National granting applications (i.e., H2020, Bando AIFA, etc) requires *in-depth and early dialogue* with Regulatory Agency on the Clinical Development to ”validate” the data and the program
Agenda

- EMA Scientific Committees
- EMA Scientific Advice
- EMA Orphan Drug Designation
EMA Scientific Committees
EMA Interaction during development

EMA Committees

- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Committee for Advanced Therapies (CAT)
- Paediatric Committee (PDCO)

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**CHMP Working Parties & Expert Groups**

- **PERMANENT WPs**
  - Scientific Advice Working Party (SAWP)
  - Safety Working Party (SWP)
  - Quality Working Party (QWP)
  - Patients' and Consumers' Working Party
  - Biologics Working Party (BWP)
  - Healthcare Professionals' Working Party

- **TEMPORARY WPs**
  - Biosimilar Medicinal Products Working Party
  - Biostatistics Working Party
  - Blood Products Working Party
  - Cardiovascular Working Party
  - Central Nervous System Working Party
  - Infectious Diseases Working Party
  - Oncology Working Party
  - Pharmacogenomics Working Party
  - Pharmacokinetics Working Party
  - Rheumatology/Immunology Working Party
  - Vaccines Working Party

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EMA Scientific Advice
EMA Interaction during development

Legal basis of Scientific Advice

✓ Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004: one of the tasks of the Agency is "advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products". As such, scientific advice may be requested for all medicinal products for use in humans, [as defined in Directive 2001/83 (as amended)], irrespective of the medicinal products eligibility for the centralised procedure, on aspects of the design of studies, trials and programs to support quality, safety and efficacy of a medicinal product.

Legal basis of Protocol Assistance

✓ Article 6 of the Regulation on Orphan Medicinal Products (EC) 141/2000 after ODD granted

- SA or PA received from EMA is not legally binding with regard to any future MAA of the product concerned, neither on the Agency/CHMP nor on the sponsor. However, the advice provided is taken into consideration during MAA and any deviations from the advice given need to be well justified!
- Scientific advice received from EMA is applicable throughout the EU
- A SAWP/CHMP consultation does not preclude the possibility of consultations with national competent authorities.
What falls under SA?

• SA is when the Agency gives **advice to a company** on the **appropriate tests** and **studies** in the development of a medicine. This is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients.

• Companies can request SA from the **EMA at any stage of development** of a medicine, whether the medicine is eligible for the centralised authorisation procedure or not.

• SA helps the company to make sure that it performs the **appropriate tests and studies**, so that **no major objections** regarding the design of the tests are likely to be raised **during evaluation of the marketing-authorisation application**. Such major objections can significantly delay the marketing of a product, and, in certain cases, **may result in refusal** of the marketing authorisation. Following the Agency’s advice increases the probability of a positive outcome.

• SA may be given on issues relating to **interpretation and implementation of (draft) EU guidelines**

• Scientific advice is prospective in nature

• The Qs posed to SAWP/CHMP should address scientific issues and may relate to the following:
<table>
<thead>
<tr>
<th>Aspects</th>
<th>Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any QUALITY aspects</td>
<td>• characterization, specifications, manufacturing, chemical, pharmaceutical and biological testing, quality by design, comparability</td>
</tr>
<tr>
<td>Any NON-CLINICAL aspects</td>
<td>• toxicological and pharmacological tests, choice of animal</td>
</tr>
<tr>
<td>Any CLINICAL aspects</td>
<td>• FIM, bioequivalence studies, dose finding, paediatric geriatric development, clinical pharmacology, pivotal trials, post approval trials including risk-management programmes</td>
</tr>
<tr>
<td>Any METHODOLOGICAL issues</td>
<td>• use of biomarkers as surrogate endpoints, modelling and simulation, statistical analysis plan, adaptive design, post-approval trials</td>
</tr>
<tr>
<td>Focuses on OVERALL DEVELOPMENT strategy</td>
<td>• development strategy to support MAA, Conditional MAA or Authorisation under exceptional circumstances, risk management plan, etc</td>
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Focuses on OVERALL DEVELOPMENT strategy rather than pre-evaluation of data to support a Marketing Authorisation application.
Protocol Assistance particular issues (1)

- the Qs and proposed development plan should be within the scope of the designated orphan indication to access fee reductions
- As SA, the PA should contain Qs on Quality, Non-Clinical and Clinical

Related to the criteria for Marketing Authorisation

1) Request concerning the proposed development plan of medicinal products for rare conditions (where by definition the population is small) to demonstrate efficacy and safety

2) Request concerning study design to demonstrate clinical superiority over a similar orphan product authorised for the same indication based on EC 141/2000, Art. 8.3(c) and EC 847/2000, Art. 3.3(d) in order to justify a derogation from Market Exclusivity:
   2) [...] the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior. (EC 141/2000, 8.3(c))
   3) Clinically superior means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more ways [...] (EC 847/2000, Art. 3.3(d))
Protocol Assistance particular issues (2)

Related to the criteria for designation of Orphan Drug status (Significant benefit criterion)

3) When another satisfactory method exists in the Community (including authorised medicinal products) for the same orphan indication, the designation is based on the criterion of significant benefit.

- **Significant benefit** means (Article 3.2 of Regulation (EC) No 847/2000) “a clinically relevant advantage or a major contribution to patient care”

- An assumption of significant benefit at the time of designation has to be demonstrated at the time of marketing authorisation (Article 5.12 of Regulation EC No 141/2000 states “if it is established before the market authorisation is granted that the criteria laid down in Article 3 (criteria for designation) are no longer met ... a designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products”.

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How to submit a scientific advice or protocol assistance request

Applicants wishing to apply for scientific advice or protocol assistance from the European Medicines Agency should follow the procedure below:

**EudraLink account:** secure File Transfer System designed to enable users to send large amounts of information securely over the Internet to EMA (the Agency only accepts electronic submissions)

**Letter of intent:** template letter of intent + briefing document (+ annexes + references) giving an introduction to the medicine under development, and the applicant's questions and positions

**Attend a pre-submission meeting, if requested**

Draft Package: introduce their proposed development programme and receive feedback from Agency staff;

receive feedback on the list of questions to be included in the request for scientific advice, with a view to obtaining satisfactory answers;

identify additional issues to be included in the request for scientific advice;

obtain more detailed information concerning the procedure for obtaining scientific advice or protocol assistance

**Electronic Final Package for validation**

to: scientificadvice@ema.europa.eu

Timing: ≈ 7 wks in advance before the intended submission date in case of pre-submission meeting required or ≈ 3 wks in advance

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## Submission Deadlines for SAWP Meetings in 2017

<table>
<thead>
<tr>
<th>Start of procedure SAWP meeting</th>
<th>Presubmission meeting</th>
<th>Final briefing package by</th>
<th>SAWP 1 start of procedure</th>
<th>SAWP 2 reports discussed</th>
<th>Finalisation day 40 adoption at CHMP</th>
<th>SAWP 3 if needed meeting with applicant</th>
<th>Finalisation day 70 adoption at CHMP</th>
<th>Finalisation for PASS procedures only</th>
</tr>
</thead>
<tbody>
<tr>
<td>09 – 12 Jan 17</td>
<td>YES</td>
<td>14 Nov 16 – 23 Dec 16</td>
<td>09 – 12 Jan 17</td>
<td>06 – 09 Feb 17</td>
<td>20 – 23 Feb 17</td>
<td>06 – 09 Mar 17</td>
<td>20 – 23 Mar 17</td>
<td>03 – 06 Apr 17</td>
</tr>
<tr>
<td>06 – 09 Feb 17</td>
<td>NO</td>
<td>19 Dec 16 – 27 Jan 17</td>
<td>06 – 09 Feb 17</td>
<td>06 – 09 Mar 17</td>
<td>20 – 23 Mar 17</td>
<td>03 – 06 Apr 17</td>
<td>18 – 21 Apr 17</td>
<td>02 – 05 May 17</td>
</tr>
<tr>
<td>06 – 09 Mar 17</td>
<td>YES</td>
<td>23 Jan 17 – 24 Feb 17</td>
<td>06 – 09 Mar 17</td>
<td>03 – 06 Apr 17</td>
<td>18 – 21 Apr 17</td>
<td>02 – 05 May 17</td>
<td>15 – 18 May 17</td>
<td>06 – 09 Jun 17</td>
</tr>
<tr>
<td>03 – 06 Apr 17</td>
<td>NO</td>
<td>20 Feb 17 – 24 Mar 17</td>
<td>03 – 06 Apr 17</td>
<td>02 – 05 May 17</td>
<td>15 – 18 May 17</td>
<td>06 – 09 Jun 17</td>
<td>19 – 22 Jun 17</td>
<td>03 – 06 Jul 17</td>
</tr>
<tr>
<td>02 – 05 May 17</td>
<td>YES</td>
<td>20 Mar 17 – 21 Apr 17</td>
<td>02 – 05 May 17</td>
<td>06 – 09 Jun 17</td>
<td>19 – 22 Jun 17</td>
<td>03 – 06 Jul 17</td>
<td>17 – 20 Jul 17</td>
<td>29 Aug – 01 Sep 17</td>
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<tr>
<td>03 – 06 Jul 17</td>
<td>NO</td>
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Overview of the SA/PA Procedures

Fixed procedure timelines
## EMA fees

- SA/PA procedures **not paid in advance**
- the Agency **issue an invoice on the date of the notification** of the **administrative validation** to the applicant and fees are payable within 45 calendar days

<table>
<thead>
<tr>
<th>Scientific Advice/Protocol Assistance (Initial Request)</th>
<th>EMA std Fees</th>
<th>Fees with ODD granted (-75%) Non-SME</th>
<th>Fees for ATMP (-65%) Non-SME</th>
<th>Fee for Pediatrics ONLY (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level III</td>
<td>€83.700,00</td>
<td>€20.925,00</td>
<td>€29.295,00</td>
<td>€0,00</td>
</tr>
<tr>
<td>Quality, Safety and Clinical Dev or Quality &amp; Clinical Dev or Safety &amp; Clinical Dev</td>
<td>€62.700,00</td>
<td>€15.675,00</td>
<td>€21.945,00</td>
<td>€0,00</td>
</tr>
<tr>
<td>Level II</td>
<td>€41.800,00</td>
<td>€10.450,00</td>
<td>€14.630,00</td>
<td>€0,00</td>
</tr>
<tr>
<td>Quality Dev or Safety Dev only</td>
<td>€41.800,00</td>
<td>€10.450,00</td>
<td>€14.630,00</td>
<td>€0,00</td>
</tr>
</tbody>
</table>
KEY TAKE-HOME ON MESSAGE on SA/PA

1) **GRANT ACCESS** (i.e., H2020, Bando AIFA, etc)
2) Plan well in advance as the **procedure** has **fixed timelines**
3) Plan this procedure when you have developed a **Concept Clinical Protocol** and a **clinical development plan** (recruitment strategy is often requested)
4) **Secure the right resources** to work on this procedure
5) **Secure budget** for this procedure as it is costly

**EMA SA/PA feedback is not legally binding**, however you have **to justify** up to the Marketing Authorization Application **if/why** you have **not implemented them into the Clinical Protocol/Clinical Development Plan**
EMA Orphan Drug Designation
What are orphan products?

'Orphan' medicinal products are for diagnosing, preventing or treating life-threatening or very serious conditions that are rare and affect not more than 5 in 10,000 persons in the European Union (EU).

Pharmaceutical companies are unwilling to develop such medicinal products under normal market conditions, as the cost of bringing them to market would not be recovered by the expected sales of the products without incentives.
Orphan Drug Designation

Orphan designation is based on the criteria laid down in Regulation (EC) No 141/2000.

Designation is free of charge, and may be obtained at any stage of development before an application for marketing authorisation is made, provided proper scientific justification of the intended use is submitted.

Designation as an orphan medicinal product does not indicate that the product has already satisfied the efficacy, safety and quality criteria necessary for the granting of a marketing authorisation. As with any medicine, these criteria can only be assessed once the application for marketing authorisation has been submitted.

Criteria evaluated by COMP

**Rarity** (a condition affecting no more than 5 in 10,000) / Insufficient Return of investment

**Seriousness** (Life-threatening or chronically debilitating)

**Medical plausibility** an implicit criterion (“intended for...”)

Existing Methods: If satisfactory methods exist the sponsor should establish that the product will be of **significant benefit**

**Review at the Marketing Authorisation stage**
Orphan designation procedure (EMA)

[0. Sponsor notifies the Agency of intent to file – no more required]

1. Pre-submission meeting *(if required)*
2. Submission of full application
3. Validation by the Agency (day 0)
4. Assessment:
   - COMP meeting
   - possible hearing
   - COMP opinion adopted (by day 60 or 90)
5. Opinion sent to the European Commission
6. EU Commission decision granted *(within 30 days)*
7. Publication
   - in EU Register on the EU Commission's website;
   - publication of public summary of opinion on the EMA's website
EU ODD – Outline procedure for Designation

**Day 1**
- Submission
- Validation

**Day 60**
- COMP Meeting
- List of questions / oral explanation
- Decision

**Day 90**
- COMP Meeting
- Opinion

Publication
- Of the ODD in EU Register on the EU Commission's website
- Of public summary of opinion on the EMA's website
What are the **EU incentives**?

<table>
<thead>
<tr>
<th>Market exclusivity</th>
<th>• For 10 years after the granting of a marketing authorisation (approval for sale), orphan medicinal products benefit from market exclusivity in the EU. During that period, directly competitive similar products cannot normally be placed on the market.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol assistance</td>
<td>• The Agency can provide scientific advice to optimise development and guidance on preparing a dossier that will meet European regulatory requirements. This helps applicants to maximise the chances of their marketing authorisation application being successful.</td>
</tr>
<tr>
<td>Fee reductions</td>
<td>• A special fund from the European Commission, agreed annually by the European Parliament, is used by the Agency to grant fee reductions. Reduction of fees will be considered for various centralised activities, including applications for marketing authorisation, inspections and protocol assistance. Additional fee reductions apply for small and medium-sized enterprises (SMEs).</td>
</tr>
<tr>
<td>EU-funded research</td>
<td>• Sponsors developing orphan medicinal products may be eligible for grants from EU and Member State programmes and initiatives supporting research and development, including the Commission's framework programme.</td>
</tr>
</tbody>
</table>
Orphan similarity: decision tree at the time of MAA

- Are there any OMPs authorised for the same condition?
  - Yes
    - Is the product under evaluation “similar” to authorised OMP(s)?
      - Yes
        - Does any derogation apply?
          - Consent of the original MAH or Inability of the original MAH to supply sufficient quantities or The new OMP is safer, more effective or clinically superior
            - No
              - Marketing authorisation not possible
            - Yes
              - Marketing authorisation may be granted
      - No
        - Marketing authorisation not possible
  - No
    - Marketing authorisation may be granted

Source: TopRA RR
Regulatory incentives associated with EU and US orphan designation

- Specific support for small and medium-sized enterprises (SMEs)
- Eligibility for protocol assistance
- Eligibility for specific grants
- Financial incentives
- Centralised Procedure (CP)
- EU 10-year market exclusivity
- PIP completion + 2 years of market exclusivity

**MAA**
- Eligibility for specific grants
- Waiver for user fees
- Tax credits
- PREA waiver

**YEAR 7**
- 7 years of market exclusivity

**YEAR 10**
- Free of change

**YEAR 12**
- Free of change, but.... Legal entity established in Us

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1) **GRANT ACCESS** (i.e., H2020, Bando AIFA, etc)
2) Plan well in advance as the procedure has **fixed timelines**
3) This procedure can be submitted anytime during the product development, however you need to have **robust functional data**
4) **Secure the right resources** to work on this procedure
5) **NO budget** needed *(ODD free of charge)*

*ODD granted during development* will be *re-evaluated* at the *time of the Marketing Authorization Application*
EU economical incentives

• Fee reductions

• 10-year market exclusivity – protection against:
  - similar products (structure/mech. of action) for
  - same indication

• Three derogations:
  ✓ Sponsor’s consent
  ✓ Lack of supply
  ✓ Clinical superiority
Thank you!