The EU Scientific Advice Process: Roadmap for Clinical Development Success

Michael Rozycki, Ph.D
Vice President and Head
Global Regulatory Affairs Asia
Bayer HealthCare Pharmaceuticals
Complying with EMA Scientific Advice is Associated with Positive MAA Outcomes*

- **188 MAAs** to EMA (2004 - 2007) analyzed
  - Positive outcome: positive opinion by CHMP
  - Negative outcome: negative opinion by CHMP or withdrawal

- Obtaining Scientific Advice (SA) *per se* WAS NOT associated with positive outcome

- **BUT**, complying with SA WAS
  - Choice of primary endpoint
  - Selection of control
  - Statistical methods

Timing of EMA Scientific Advice

• Possible at any time during development or post-authorization
  - *Novel Methodologies*
  - *Pre-CTA*
  - *End of Phase II*
  - *Pre-Submission*
  - Also multiple times → *Follow-up advice*
  - *Orphan Drug (Protocol Assistance)*

• Should be coordinated with advice sought in other regions
• Recommended at least after end of Phase 2, prior to Phase 3

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5*
EMA Advice can be Preceded by Advice from Local European Authorities

- Possibility to “preview” response from one or more authorities
  - Local procedures often shorter timeframe
  - Build consensus from multiple points of view
  - Fine-tune proposal for discussion with EMA

- Depending on situation, may decide to forego EMA procedure
  - If advice conflicting, “back to the drawing board”
  - If pressed for time, and advice from several countries confirms what we already thought we knew
  - But consider the risk
Topics for Advice

• Development questions not covered at all or in detail by EU guidelines/guidances
• Deviations from existing guidances
• Scientific issues regarding quality, non-clinical or clinical aspects
• Examples:
  - Quality (comparability, specification, stability, manufacturing, etc.)
  - Non-clinical (carcinogenicity, reprotox, animal model, etc.)
  - Clinical (dose finding, controls, strategy, pediatric development, statistical analysis, safety program, endpoints, QT, inclusion / exclusion criteria, etc.)

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5
Overview of Timelines and Procedures

**Deadlines during pre-submission phase:**

<< D -120: WHO collaboration submission (MIP intended to be marketed exclusively outside EC)
D -60: Submission of Letter of Intent (LoI) if pre-submission meeting requested
<< D -60: Submission of LoI if FDA Parallel Advice
D -30: Submission of LoI if no pre-submission meeting requested
D -15: Submission of draft SA or PA request to EMEA and start of Validation at EMEA
~ D -10: Submission of final SA or PA request to EMEA
D 0: Start of Procedure (SAWP 1)

**Timelines during evaluation phase:**

D +30: SAWP 2 – Discussion of the first reports from the co-ordinators
      Decision regarding further procedure (Day 40 or Day 70 procedure)
      In case of Day 70 procedure: list of issues adopted & sent to applicant
D +40: In case of Day 40 procedure: final advice letter adopted by CHMP
D +60: SAWP 3 – Discussion meeting with applicant
D +70: In case of Day 70 procedure: final advice letter adopted by CHMP

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5*
Pre-submission Phase

• Letter of intent (D -30)
  - Formal notification of intent to submit Scientific Advice or Protocol Assistance request
  - Consists of at least Cover Letter and Form
  - Submission of draft briefing document is only necessary in case of request for pre-submission meeting

<table>
<thead>
<tr>
<th>Start of procedure SAWP meeting</th>
<th>Pre-submission meeting</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 company)</th>
<th>Finalisation day 70 (adoption at CHMP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter of Intent (^1) by Dates of pre-submission meeting</td>
<td>Final request by</td>
<td>Letter of Intent (^2) by</td>
<td>Final request by</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>10-12 Jan 07</td>
<td>13 Oct 06</td>
<td>27 Oct – 15 Dec 06</td>
<td>02 Jan 07</td>
<td>17 Nov 06</td>
<td>18 Dec 06</td>
<td>10-12 Jan 07</td>
</tr>
<tr>
<td>31 Jan – 02 Feb 07</td>
<td>16 Nov 06</td>
<td>30 Nov 06 – 17 Jan 07</td>
<td>22 Jan 07</td>
<td>14 Dec 06</td>
<td>15 Jan 07</td>
<td>31 Jan – 02 Feb 07</td>
</tr>
</tbody>
</table>

• Next steps:
  - Appointments of the SA Administrator (EMA) and the Coordinators
  - Submission of draft briefing package at least 1 w before deadline for final request

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5*
D 40 Procedure

- **D 0:**
  - SAWP 1: Coordinators introduce the company’s request
  - Additional expert appointment

- **D +20:**
  - First reports sent to EMA Secretariat by the Coordinators
  - Reports forwarded to SAWP

- **D +30:**
  - SAWP 2: Discussion of the first reports of the Coordinators
  - Decision between Day 40 or Day 70 procedure → Day 40 procedure
  - Information of the company regarding the next steps/timelines

- **D +33:**
  - Joint report available
  - CHMP/SAWP/EMA peer review

- **D +40:**
  - Adoption of the final advice letter by the CHMP
  - Advice is sent to the company

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5*
D 70 Procedure

- **D +30:**
  - SAWP 2: Discussion of the first reports of the Coordinators
  - Decision between Day 40 or Day 70 procedure → Day 70 procedure
  - Decision if applicant is invited to discussion meeting or not
  - Information of the company regarding the next steps/timelines
  - List of issues is sent to the applicant

- **Ahead of the discussion meeting the applicant may …**
  - … also propose additional points for discussion (strictly related to topics initially raised!)
  - … notify the EMA/SAWP about amendments/changes to the development program

- **D +50:** joint report is distributed to EMA/SAWP (and COMP if applicable)

- **D +60:** SAWP 3: Discussion meeting with the company

- **D +63:**
  - Joint report available
  - CHMP/SAWP/EMA peer review

- **D +70:**
  - Adoption of the final advice letter by the CHMP
  - Advice is sent to the company

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5*
Presubmission Meeting

- Requested at time of submission of Letter of Intent
- Purpose:
  - Introduce program and receive initial feedback
  - Feedback on content and scope of intended questions
  - Identify additional issues to be included in the request
  - Ask regulatory questions outside scope of SA
  - Establish personal contact with the authority

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5*
Briefing Package

- Critical document: “begin with the end in mind”
- Purpose:
  - Tell agency what you want to discuss (request letter, background information)
  - Tell agency again what you want to discuss (questions)
  - Provide clear, concise scientific / medical rationale
- The briefing package sets the tone
  - Set expectation for science-based discussion
Briefing Package Contents

• Background information (mechanism, chemistry, preclinical, clinical, etc.)

• Intended indications

• Regulatory status

• Stage of development of program, stage of clinical development of studies

• Geographical location of clinical studies

• Overview of data requirements, if program intends use of published literature

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5
Briefing Package: Questions and Company Position

• Format different from FDA package, but idea is similar
• Questions should be detailed and precise
• Each question is followed by a separate company’s position including
  - justification of the company’s strategy
  - all relevant information about the topic
  - cross-references to the relevant annexes
Discussion Meetings

- D+30: SAWP discusses first reports, decides whether to ask company to Discussion Meeting.
  - Case-by-case basis, depends on issues which need to be discussed with the company
  - SAWP will ask for Discussion Meeting in case of disagreement with the company’s development plans

- Detailed list of issues to be addressed by the company during the Discussion meeting is sent to company following the SAWP meeting

- Two categories of issues:
  - Addressed during the Discussion Meeting
  - Addressed in writing by the company prior to the Discussion Meeting

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5*
Discussion Meetings - More

• The company may also propose additional points for discussion at the meeting.
  - Must strictly relate to topics initially raised in the request
• If company intends to present major amendments to the initial proposal, these must be submitted one week in advance of the meeting
• The Discussion meeting will take place at EMA at D+60 during the SAWP meetings
• Presentation should focus exclusively on issues list sent by the EMA
  - Preliminary conclusions drawn at the end of the Discussion Meeting
  - Following the meeting, further internal discussion by SAWP
• The company should provide minutes 2 WD after the Discussion Meeting.
  - Regarded as a company's record; NOT endorsed by SAWP

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5
Ground Rules for Discussion Meetings

• Listen carefully!
• Plan carefully…
  - Who does the speaking
  - Anticipate questions and expected responses
• Do not use non-scientific generalizations and qualification statements
• Maintain formality of the interaction
Clarification Procedure

- Opportunity to clarify the meaning of CHMP advice:
  - Misunderstandings
  - Contradictions within the advice
  - Precision

- New information is not a topic for clarification, but part of a follow-up request!

- Procedure
  - Contact the SA Administrator at the EMA first to discuss the further procedure
  - Send the clarification request to the SA Administrator via Eudralink
  - Minor clarification will be addressed with the Coordinators
  - Major clarifications will be addressed at the following SAWP meeting

*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5*
Example 1: Situation

- Planned phase III study in VTE prevention in non-surgical/medically ill patients
  - Based on the dose-finding from VTE prevention in surgical patients
  - Enroll medium- to high-risk pts
- Propose **superiority study design** comparing 35 days of drug treatment to 14 days comparator followed by placebo for 21 days
- Submitted to the SAWG/CHMP for evaluation SA
Example 1: SAWG Feedback

- **SAWG/CHMP disagreed:**
  - Superiority of 35 days treatment with drug over 14 days with comparator could not necessarily be attributed to drug or prolonged treatment
  - Rebound phenomenon likely to occur after anticoagulation withdrawal – likely to introduce a bias

- **CHMP recommended non inferiority trial** vs. comparator, with extension phase for drug vs. placebo
  - Study should be positive for day 14 (non-inferior to standard of care) and day 35 endpoint (superior over standard of care plus placebo)
Example 1: Outcome

• Because of more positive feedback from FDA, the team had already started the study and submitted CTAs

• However, upon receipt of CHMP/SAWG feedback, the protocol was changed as a major amendment

• Used clarification letter with SAWG to make sure that all components of the response were well understood

• After the clarification response, the protocol was changed.
Example 2: Situation

- Clinical development program for a new indication for an already-approved drug

- A single, two-armed (agent + comparator vs. comparator only) Phase 3 global trial was planned
  - 500 patients in Europe, South Africa, South America and Asia-Pacific.

- Considered local-patient requirements in Asia:
  - 75 - 100 Japanese patients as per PMDA guidance
  - For China, Category 3 NCE submission, therefore 100 Chinese patients per treatment arm, for a total of 200

- US FDA and EMA Rapporteur (from Swedish MPA) were consulted regarding the acceptability such a large proportion of patients from Asia-Pacific
Example 2: HA Feedback

- **US FDA**
  - Concern that the study population not representative of US population
  - Recommended majority of patients to be from US

- **EMA Rapporteur**
  - No evidence of major differences in efficacy between the Asian countries and EU population
  - However, should differences be found between the two populations in the proposed study, the sponsor would bear the risk to approval
  - Therefore, suggested upper limit of 50% for Asia-Pacific patients, with at least 10% from EU
EMA / FDA Parallel Scientific Advice

• First parallel advice was issued in Oct 2003
• Focus on vaccines, medicines for children, orphan drugs, oncology, and pharmacogenomics
• Intention:
  - **Not** intended to provide combined or joint advice!
  - **But** opportunity for increased dialogue
• Procedure in general:
  - Preferably for End-of-Phase 2 or pre-IND meeting
  - Contact both agencies as early as possible
  - Synchronized submission to FDA and EMA
  - Similar procedural timelines allow for discussion (exchange of documents, teleconference or videoconference) before final decision is reached by each agency
  - Each agency will provide their independent advice to the applicant
  - Advice may still differ between agencies!
Conclusions

• As with FDA, EMA Scientific Advice procedure is data driven and science-based

• Complying with SA recommendations can increase chance of positive outcome

• As global drug development becomes more complex, coordination of discussion between authorities is critical, but addressing their concerns is challenging
Appendix: Useful Information
EMA Scientific Advice: Useful Links

• Overview:

• Guidance:

• Dates for 2010:
Directives, Regulations & Guidelines

• Basic Directive:

• Regulation:

• Guidances:
  - EMA/H/4260/01 Rev 4 - EMA Guidance for Companies Requesting Scientific Advice (SA) or Protocol Assistance (PA)
  - EMA/CHMP/267187/05 Rev 1 - New Framework for Scientific Advice and Protocol Assistance (final)
EMA Scientific Advice Fees

• Payable fees (status of April 2010):
  - Initial request:
    • Clinical and any other area: 76,300 €
    • Clinical alone or two other areas in combination: 57,200 €
    • Single area except clinical (quality, safety, bioequivalence): 38,100 €
  - Follow-up request:
    • Clinical and any other area: 38,100 €
    • Clinical alone or two other areas in combination: 28,600 €
    • Single area except clinical (quality, safety, bioequivalence): 19,100 €

• Fee reductions for orphan drug status

• Link: http://www.ema.europa.eu/htms/general/admin/fees/feesfaq.htm