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The EU Scientific Advice Process: Roadmap for Clinical Development Success

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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

*Source: Regnestrom et al. (2010) *Eur. J. Clin. Pharmacol.,* 66:39-48

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

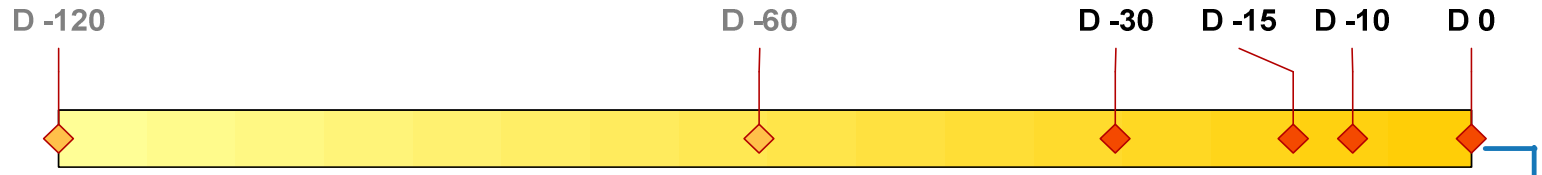
- Possibility to "preview" response from one or more authorities
  - Local procedures often shorter timeframe
  - Build consensus from multiple points of view
  - Fine-tune proposal for discussion with EMA
- Depending on situation, may decide to forego EMA procedure
  - If advice conflicting, "back to 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.)

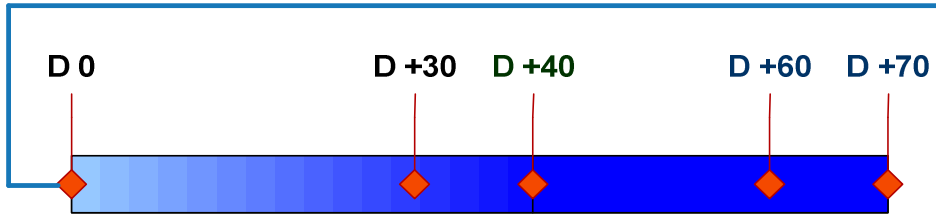
*Source: EMEA Guidance EMEA-H-4260-01-Rev. 5

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 for 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
  - Download of Form (Word format): http://www.ema.europa.eu/htms/human/sciadvice/Scientific.htm
  - Submission of draft briefing document is only necessary in case of request for pre-submission meeting
  - Deadlines for submission published by EMA, e.g.: http://www.ema.europa.eu/pdfs/human/sciadvice/13898708en.pdf

Start of procedure SAWP meeting	Presubmission meeting					SAWP 1 (start of procedure)	SAWP 2 (reports discussed)	Finalisation day 40 (adoption at CHMP)	SAWP 3 if needed (Meeting with company)	Finalisation day 70 (adoption at CHMP)
	YES			NO						
	Deadline for submission of:									
	Letter of Intent [1] by	*Dates of pre-submission meeting*	Final request by	Letter of Intent [2] by	Final request by					
10-12 Jan 07	13 Oct 06	*27 Oct –15 Dec 06*	03 Jan 07	17 Nov 06	18 Dec 06	10-12 Jan 07	31 Jan – 02 Feb 07	19-22 Feb 07	26-28 Feb 07	19-22 March 07
31 Jan–02 Feb 07	16 Nov 06	*30 Nov 06 - 17 Jan 07*	22 Jan 07	14 Dec 06	15 Jan 07	31 Jan – 02 Feb 07	26-28 Feb 07	19-22 March 07	28-30 March 07	23-26 April 07

- 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:
  - http://www.ema.europa.eu/htms/human/sciadvice/Scientific.htm
- Guidance:
  - http://www.ema.europa.eu/pdfs/human/sciadvice/426001en.pdf
- Dates for 2010:
  - http://www.ema.europa.eu/pdfs/human/sciadvice/13898708en.pdf

Directives, Regulations & Guidelines

- Basic Directive:
  - Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
- Regulation:
  - Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
- 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 cinical (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 cinical (quality, safety, bioequivalence): 19,100 €
- Fee reductions for orphan drug status
- Link: http://www.ema.europa.eu/htms/general/admin/fees/feesfaq.htm