How to efficiently leverage scientific advice - a joint statistical and clinical perspective

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The views expressed are personal views and not necessarily the views of Fimea or EMA

There are various types and levels of advice

- National advice (two levels in Finland)
- Simultaneous National Scientific Advice (SNSA)
- EMA-coordinated centralised Scientific Advice
  - Also joint regulatory / HTA advice
  - Parallel advice with US FDA
- Protocol assistance
- Qualification opinions (publicly available on EMA website)

Scientific Advice Working Party (SAWP)

- a standing working party, establish by the CHMP, with the sole remit of providing scientific advice and protocol assistance
- N=36 including
  - 3 members of the Committee for Orphan Medicinal Products (COMP)
  - 3 members of the Paediatric Committee (PDCO)
  - 3 members of the Committee for Advanced Therapies (CAT)
  - 1 member of the Pharmacovigilance Risk Assessment Committee (PRAC).
- representation of the following areas of expertise is ensured:
  - non-clinical safety;
  - pharmacokinetics;
  - methodology and statistics;
  - therapeutic fields for which there are frequent requests or which are defined in the Annex of Regulation (EC) No 726/2004

SAWP members

Dina Apele-Freimane
Caroline Auriche-Benichou
Ewa Balkowiec Iskra
Carin Bergquist
Nanna Borup Johansen
Minne Casteels
Marie Louise Schougaard Christiansen
Mario Miguel Coelho da Silva Rosa
Pierre Demolis (Vice-Chair)
André Elferink
Paolo Foggi (Chair)
Hrefna Gudmundsdottir
Sheila Killalea
Andreas Kirisits
Rune Kjeken
Armin Koch
Juha Kolehmainen
Andrea Laslop

Mette Linnert Jensen
Cristina Migali
Alexandre Moreau
Hans Ovelgonne
Gabriella Passacquale
Karri Penttilä
Vilma Petrikaite
Mair Powell
Livia Puljak
Jens Reinhardt
Rosalía Ruano Camps
Elmer Schabel
Brigitte Schwarzer-Daum
Olli Tenhunen
Anna Vikerfors
Kristian Wennmalm
Kerstin Wickström
Joerg Zinserling

Silvijus Abramavicius
Lukas Malte Aguirre Davila
Adriana Ammassari
Mikael Andersson
Elina Asikanius
Nicolas Beix
Karoline Buhre
Caoimhin Concannon
Valentina Conti
Macarena Gajardo Alvarez
Sara Galluzzo
Ivana Haunerova
Larissa Higgins
Karin Janssen van Doorn
Ebru Karakoc Madsen
Johanna Lähteenvuo

Anders Lignell
João Manuel Lopes de Oliveira
Serena Marchetti
Clemens Mittmann
Nathalie Morgensztejn
Flora Musuamba Tshinanu
Robert Nistico
Martin Oleksiewicz
Sif Ormarsdóttir
Elina Rönnemaa
Ingrid Schellens
Anja Schiel
Audrey Sultana
Martin Walter
Elisabeth Wischnitzki
Hilke Zander

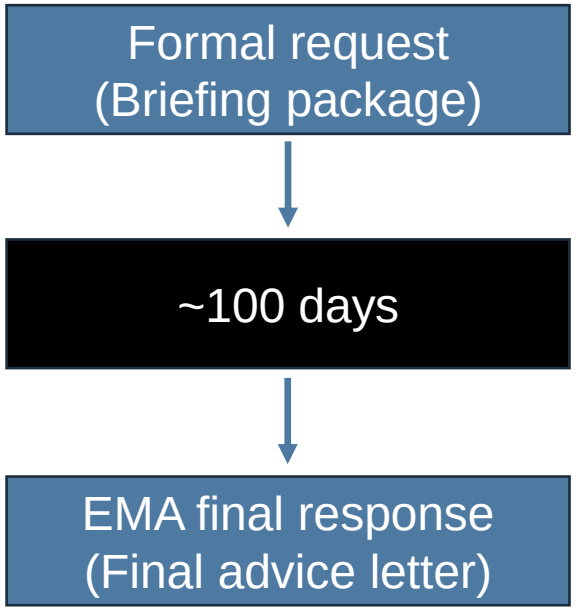
*as of 04 Sep 2023

https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/scientific-advice-working-party

The members are sourced from national agencies

Timelines

Typically:

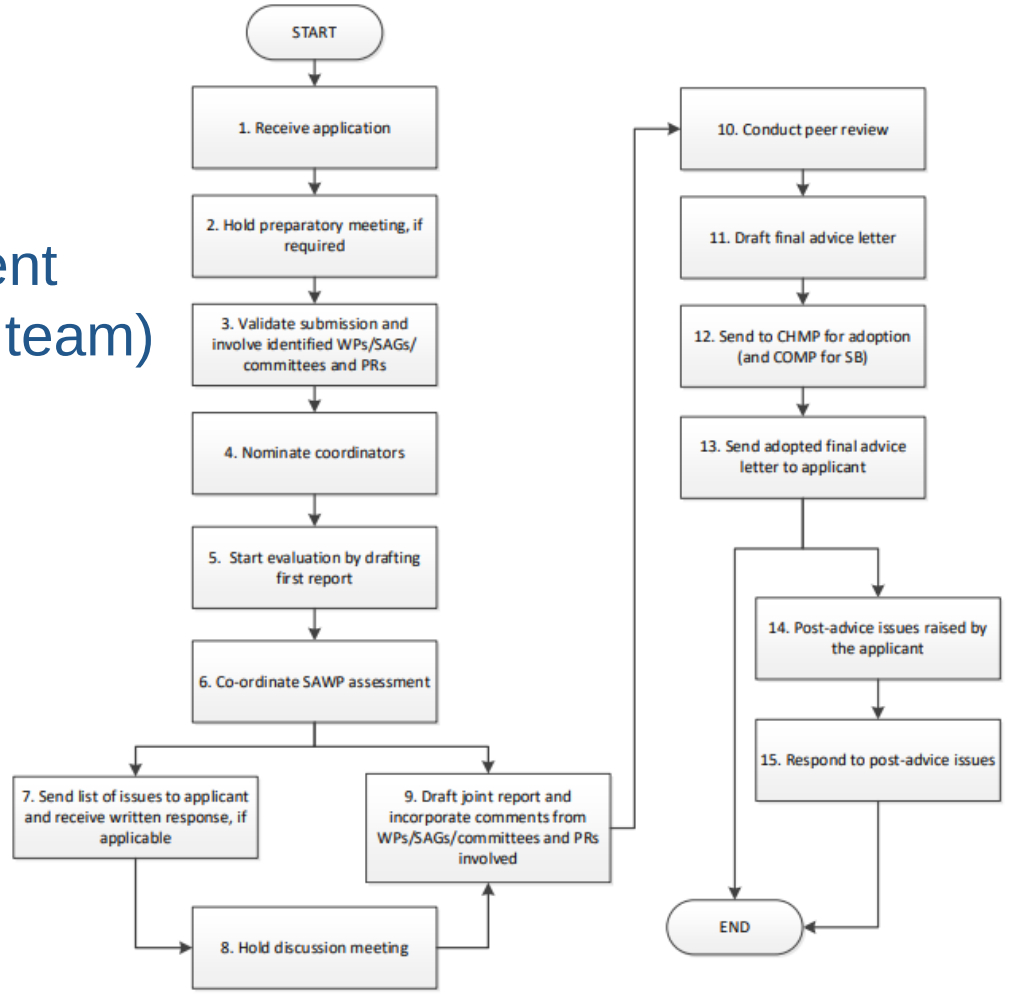


Not ideal for getting quick feedback. Ideally SA is planned early in advance to be part of the clinical development process.

- The timelines are longer if discussion meeting is organised
- Discussion meeting organised when SAWP does not agree with any important aspect of the applicant's plan or when no consensus within the SAWP members can be reached

How does EMA SA work in practice?

- 2 SAWP coordinators selected per process
- Each coordinator compiles an internal assessment team from NCA staff (sometimes a multinational team)
- 2 ”First reports” prepared
- SAWP meeting → discussion of critical topics / differing views
- First reports combined into Joint Report
- Peer review by a third SAWP member
- CHMP adoption → Final Advice Letter (FAL)



Source: SOP/H/3037, 13-FEB-23 (https://www.ema.europa.eu/en/documents/sop/standard-operating-procedure-scientific-advice-protocol-assistance-procedure_en.pdf)

Scientific advice vs. CTA and MAA assessment

- Assessors involved in SA are not necessarily the same assessors as who will perform CTA or MAA assessment.
- SA is not binding on CTA and MAA assessors
  - although definitely considered, and disagreements are (probably) relatively unusual.
  - acceptability of data into SmPC is a question that you will seldom get an answer to in SA

Statistician’s role in the SA process

- SAWP statistician appointed as coordinators
- At Fimea, a statistician always involved by default when there are clinical questions
  - Preparation of the first report:
    - collaborating with clinical assessor
    - drafting answers to “statistical” questions more independently
    - Where is the borderline between statistical and non-statistical consideration?
  - Biostatistics OEG BINGO for learning, feedback, sharing, consistency
- Biostatistician SAWP members representing their discipline in SAWP discussions

SA from statistical assessor’s perspective

- Always limited time, sometimes limited experience and knowledge of the specific therapeutic field
- Preconditions to take into account:
  - Guidelines from EMA but also from other regulatory bodies
  - Previous advice for the same product (when “Follow-up SA”)
  - Previous advice for other “similar” products in “similar” indications
  - SmPC and EPAR of “similar” products in “similar” indications
  - General ”regulatory memory”
- Scientific judgement + personal views (e.g. responder analyses, percentage changes)
- Anticipated views by SAWP and CHMP (e.g. preference for treatment policy)
- Feasibility from Clinical Trial Application perspective
- More difficult than MAA assessment: Have to imagine how results will look and be assessed.

Help us help you

At the time of SA, the applicant and SAWP have common interest: Good advice!

How to help assessment team give good advice in a multidisciplinary way?

- Explain how your protocols fit into the development and regulatory strategy
- Not only “what” will be done but also “why”
- “Because the U.S. FDA told so” is a valid reason to do or not do something.
  - But if EMA has different view, understanding Applicant’s position beyond what the FDA said is helpful.
- References to preconditions are helpful (not only to save assessor’s time but also to give ‘good’ advice)
- Particularly helpful if highlighted when e.g. guidelines are not followed (with justification)

Example: Interim analyses in oncology

- A typical SA procedure for an oncological trial includes a description of planned interim analyses.
- Explained:
  - expected number enrolled patients
  - follow-up time
  - required number of endpoint events

  at the time of interim analysis
  - technique for controlling type 1 error,
- Not explained
  - why it will be done
  - what will be done or claimed based on the results
  - how the study would continue following a positive result.
    - What does “stopping study” mean? Will the investigators and patients be unblinded?

Example: Phase 3 trial for a progressive disease

Q: Does the CHMP have comments about the design of the proposed Phase 3 study *HoldOn* to support authorisation of *A* for the treatment of the disease *D*? In particular, does the CHMP have comments about:

. . . c) Statistical methodology, including

i) the proposed estimand for the primary endpoint,

ii) . . .

In *HoldOn* study, the primary objective is the comparison of efficacy of treatment *A* to placebo in subjects with disease *D* who meet the enrolment criteria, with or without standard background medication.

The rate of progression will be measured in terms of change from baseline to Week 96 in outcome *Y* and compared between treatment *A* and matching placebo using the difference in the change from baseline to Week 96 between treatment *A* and placebo as a population-level summary.

??

In the case of (1) treatment discontinuation for any reason or (2) change in standard background medication, data after intercurrent events (1) or (2) will be not considered relevant and will be treated as missing. Data after events (1) or (2) will be assumed to be missing at random (MAR), envisioning that subjects continue on the prescribed treatment as if the events (1) or (2) did not happen (hypothetical strategy) . . . A linear mixed effects model will be used to estimate treatment effect under the MAR assumption.

Sensitivity analyses will be performed to evaluate the robustness of results to MAR. The missing data after treatment discontinuation will be imputed using a pattern mixture model control-based imputation under the missing not at random assumption.

Estimand, the key point associated with study objective is presented as a sub-bullet of statistical methodology section!

Example cont’d: Advice given

- CHMP advised to consider treatment policy strategy as being primary, because
  - *“ICE treatment discontinuation will occur in practice”*
  - “*the treatment effect regardless of discontinuations (treatment policy strategy) is of primary regulatory relevance.*”
  - “*treatment difference regardless of changes in background meds (treatment policy strategy) appears the appropriate target of estimation*”
- In absence of justification, SAWP recommendation of Phase 3 trials often defaults to treatment policy analysis (or ’ITT’ analysis if you like)

A few more attributes of estimand discussion

- *Estimand framework* is not successfully used to gain interdisciplinary understanding and agreement of how effects of treatments should be assessed.
- Estimands are described/defined in terms of algorithms and data handling rules.
  - (NB: What data will or won't be used does – this does not suffice to define the estimand)
- The word scares many clinical assessors
- Furthermore, the questions about estimand are presented as "statistical" --> Becomes a task for statistical assessor.
- On a positive note, some clinical assessors see it as a major area of collaboration between clinical and statistical assessors – but are currently dependent on this collaboration between assessors
  - More training needed on the regulatory side
  - The companies should motivate estimands better and describe them in understandable way
  - We applaud any efforts to describe estimand in natural language.

  - Academic work is being done to build the bridge between estimand framework and comprehension, e.g.

  The detailed clinical objectives approach to designing clinical trials and choosing estimands
  Pharm Stat 2021 Nov;20(6):1112-1124.
  James Bell, Alan Hamilton, Oliver Sailer & Florian Voss

Framing the question as *clinical* or *statistical*

Some topics tend to be considered as “clinical” although are arguably more “statistical”:

- Study design in general
- Randomisation stratification: Why is this not framed as a statistical question?
- Study population:
  - representativeness
  - heterogeneity
  - “gapping”, i.e. setting limits to proportion of participants with certain characteristic

  … more about this in the last year’s workshop.

  Why?!

Tips on preparing your materials

- Applicants are good at recycling text paragraphs between e.g. protocol, SAP and the briefing material and questions
- We would recommend to avoid redundancy in material
- On the other hand, searching between annexes takes time. Perhaps ideal to
  - include relevant text as verbatim copies from e.g. the protocol
  - provide further justification and context to facilitate substantive discussion.

When you should think twice before seeking SA

- It may help in getting your CTA approved in Europe, but may also make it more complicated if you deviate from the advice

- If you know beforehand that you are not going to follow the advice, or if you are seeking acceptance for something that you have already done, then it is better not to ask.
  - Engage in time!

Thank you!