



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Scientific Advice

SME Workshop April 26 2013

Presented by: Jane Moseley
Scientific Administrator / Scientific Advice

An agency of the European Union





Scientific Advice at the EMA

Basic activities

- Maximising the benefit
- Examples
- Committee and working party interactions

New Initiatives

- **Modelling & Simulation WG**
- **Wider patient involvement**
- **Biomarkers Qualification advice/opinion**
- **Parallel advice EMA/HTAs**
- **Draft Reflection paper on risk based quality management in clinical trials/SA**



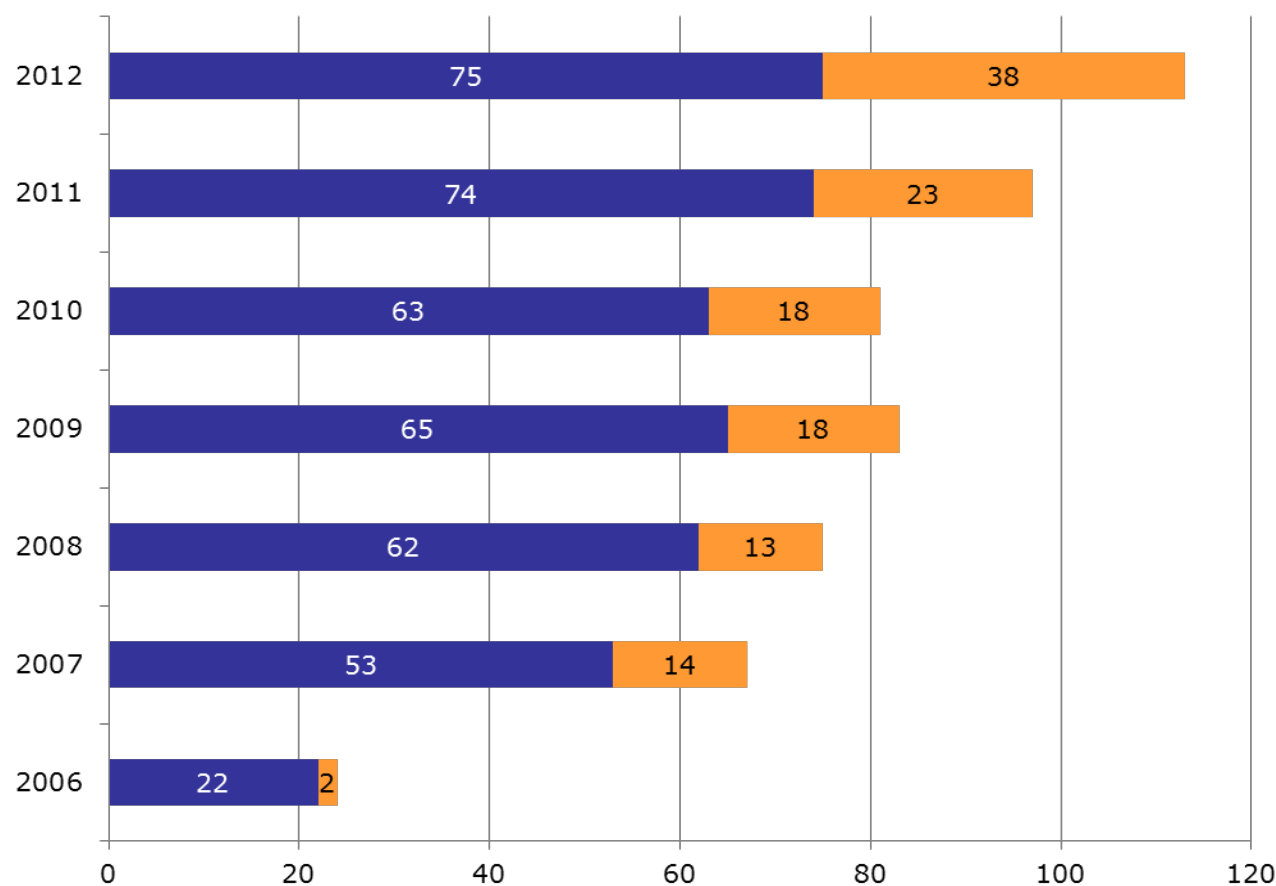
Basic Scientific advice

Voluntary procedure

- companies ask questions
- responses are prepared and discussed
- in 50% a face-to-face meeting with the company
- written responses adopted by the CHMP
- scientific advice letter, protocol assistance (Orphan/rare)
- 40 days or 70 days (face-to-face meeting)
- 100% fee reduction if SME-orphan, OR paediatric only
- 90% fee reduction if SME



Scientific Advice activity - product related for SMEs

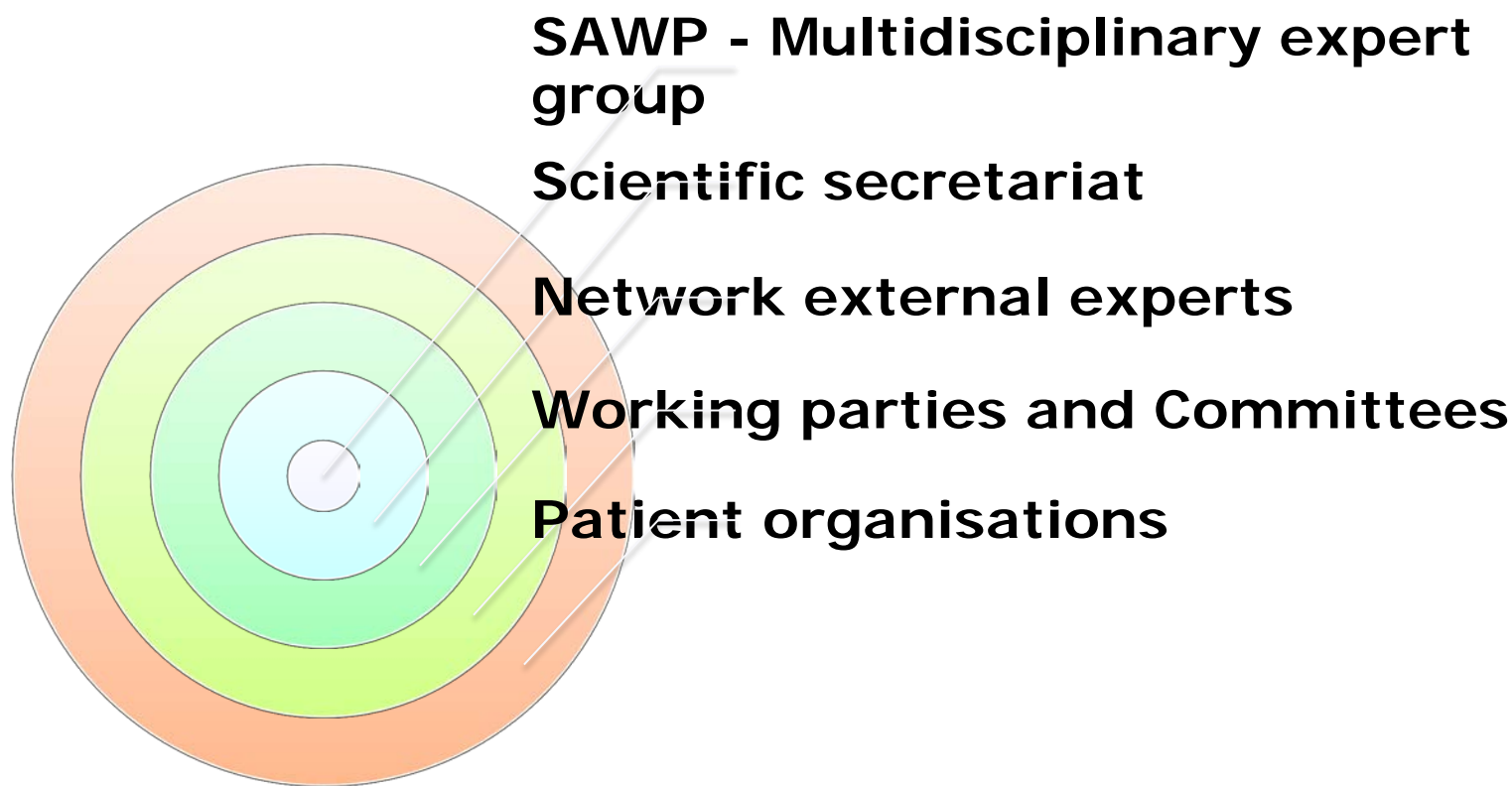


22% of SA = SME
47% of PA = SME
Overall 27% = SME

■ Scientific Advice SME
■ Protocol Assistance SME



Scientific Advice Network





What to ask in Scientific advice

- No relevant guideline available OR when deviating from the guideline
- PA for rare diseases
- SA for advanced therapies
- Quality issues – especially for SMEs and for biotechnology
 - Quality issues
 - Using novel approaches: quality by design
- Nonclinical issues
 - E.g. Pharmacological models for human specific targets



Anonymised examples of EMA interactions



Types of product, Types of Indications

Is it a follow up advice? – are fee reductions applicable?

Product A –

First advice - treatment of non-infectious posterior, and panuveitis.

Second - Adjunctive therapy in Behçet's disease **Different development programs and indications**

Autoinjector program for Product B **follow up- same discipline (Q/S/E)**



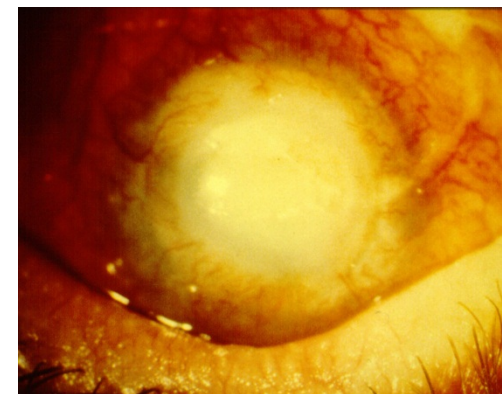
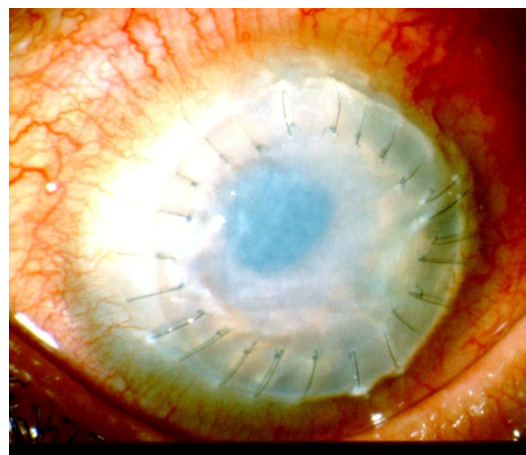
Types of Indication

Is the indication within the scope of orphan designation?

Product C

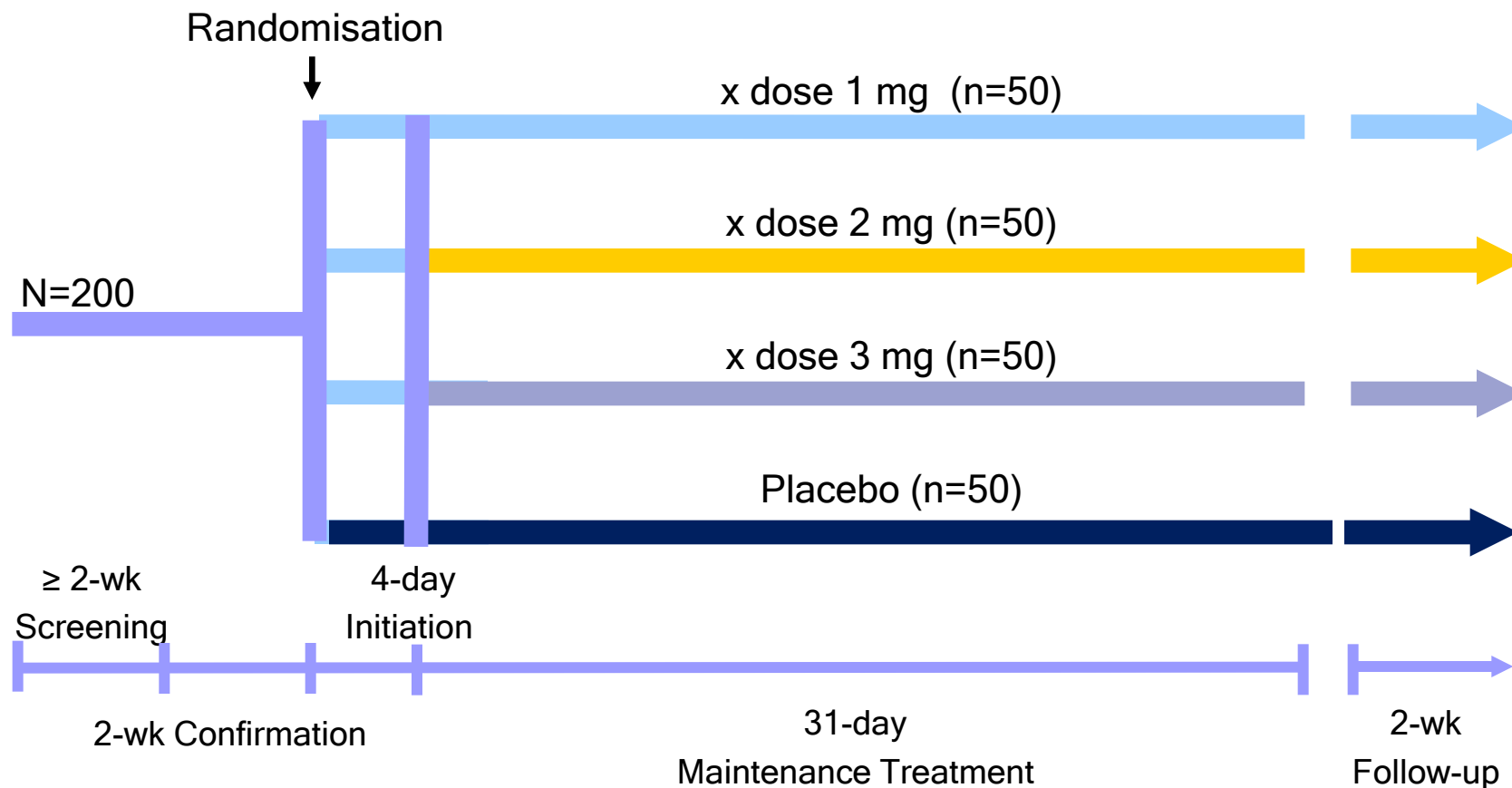
“Treatment of keratitis or kerato-uveitis of infectious or traumatic (e.g., alkali burns) origin developing or associated with corneal neovascularisation.”

Orphan Designation- *Prevention of graft rejection*

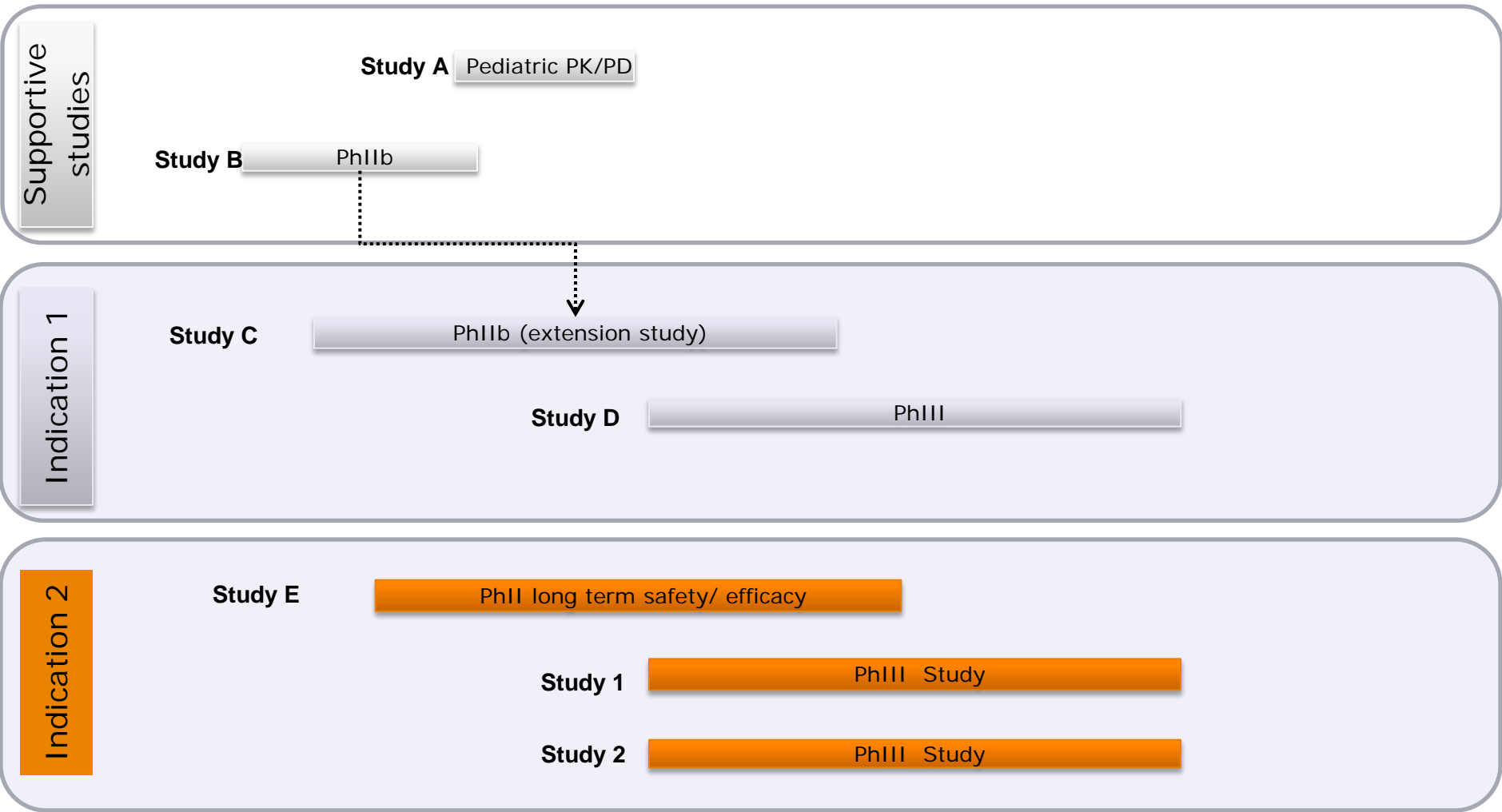




Phase 2 Study 12344



Include schematics of key trials and for overall development program





Types of Questions

Product F intended for Immunotherapy

“Following completion of the Phase III study the total number of subjects exposed to Product F will be 726. Does the Agency agree that a single Phase III study with the indicated design conducted in Europe and a total safety database of 726 subjects will be sufficient to support product registration?”

- Spilt into several questions
- Single pivotal study, safety database, study design parameters



Regulatory Questions

Product G is a **new medicinal product** that:

- contains a known active substance
- for a new therapeutic indication:
- is intended for a new route of administration
- A future MAA for G will be submitted according to Article 8.3 of Directive 2001/83/EC

- Discussed at presubmission meeting only
- Note Commission Communication 98/C229/03
- Choice of legal basis up to applicant



Product H Discussion Meeting

Issues to be clarified on Clinical development

- Related to the heterogeneous presentation of the disease, it may be considered to include patients according to disease severity rather than age.
- Related to this issue, the company is asked to elaborate on additional endpoints for the most severe patients
- The ratio of 1:4 in favour of the drug, is not considered optimal
- The choice of the dose to be used in the phase III study needs better justification.



Discussion meeting

Product I

Issues to be clarified on Clinical development

description of the patient population to be included into this first-line treatment trial so that the proposed trial for first-line treatment of patients then will be competent to justify the starting with a fixed combination medicinal product.

**GUIDELINE ON CLINICAL
DEVELOPMENT OF FIXED
COMBINATION MEDICINAL
PRODUCTS**

Under revision



Clarifications and Follow-up Product J

Intended for Treatment of acute gout flares

We also request clarification of the statement *“It may be argued that trial J----123 and trial J--456 should be regarded to be mutually supportive. However, the clinical situation is regarded to be different from several important aspects”*.

Can the Agency provide additional explanation of the important aspects that are different as alluded to above?



Advantages

- Unified opinion applicable across EU
- Vast array of scientific questions
- Network of Experts
- Reasonable timeframe – 40 or 70 days
- Impact on success on MAA
- Voluntary
- SME and Orphans fees / regulatory assistance

Maximising Benefit

- Come early in development
- Pre-submission meeting if first time
- Ask precise questions – no limit!
- Present concise but comprehensive data
- Review List of Issues carefully and approach discussion meeting in open manner
- Explore and present alternative approaches



Qualification of novel methodologies

New regulatory procedure

Scope

Acceptability of technology/biomarker for a specific use in pharmaceutical R&D

Applicants

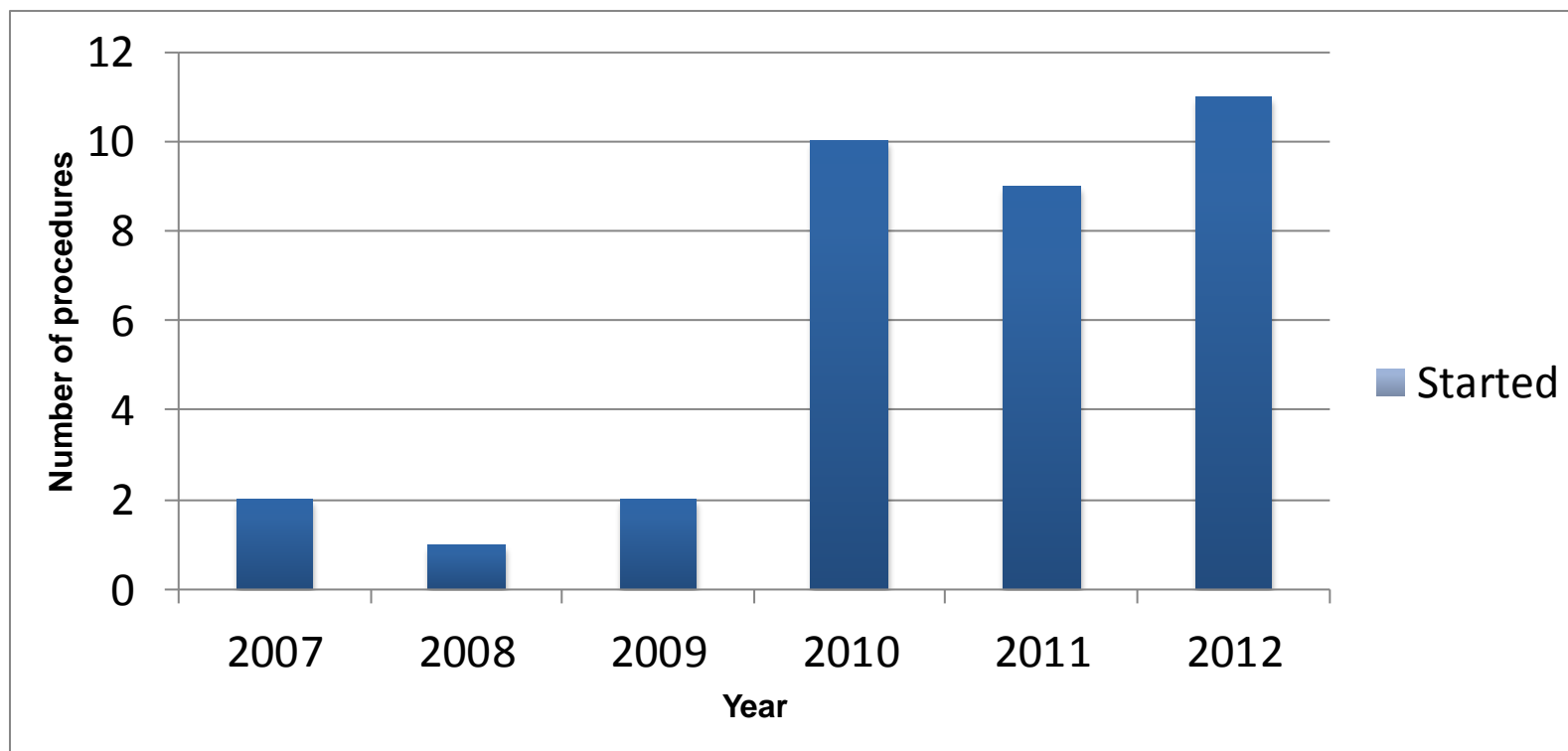
Consortia, networks, public/private partnerships, learned societies, pharmaceutical industry

Input

Protocols, study reports, raw data etc. to establish the use of the BM for a specific purpose



Qualification procedures





Qualification of novel methodologies

Preclinical development

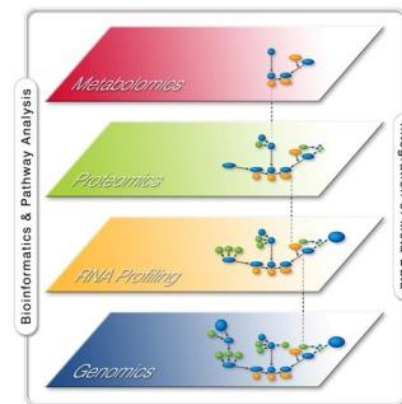
- pharmacological screening
 - mechanism of action
 - predict activity/safety
 - PK/PD modelling
 - toxicogenomics

Clinical development

- verify mechanism
 - dose-response
 - proof of concept
 - enrich population
- surrogate endpoint

Drug utilisation

- optimise target population
- guide treatment regimen





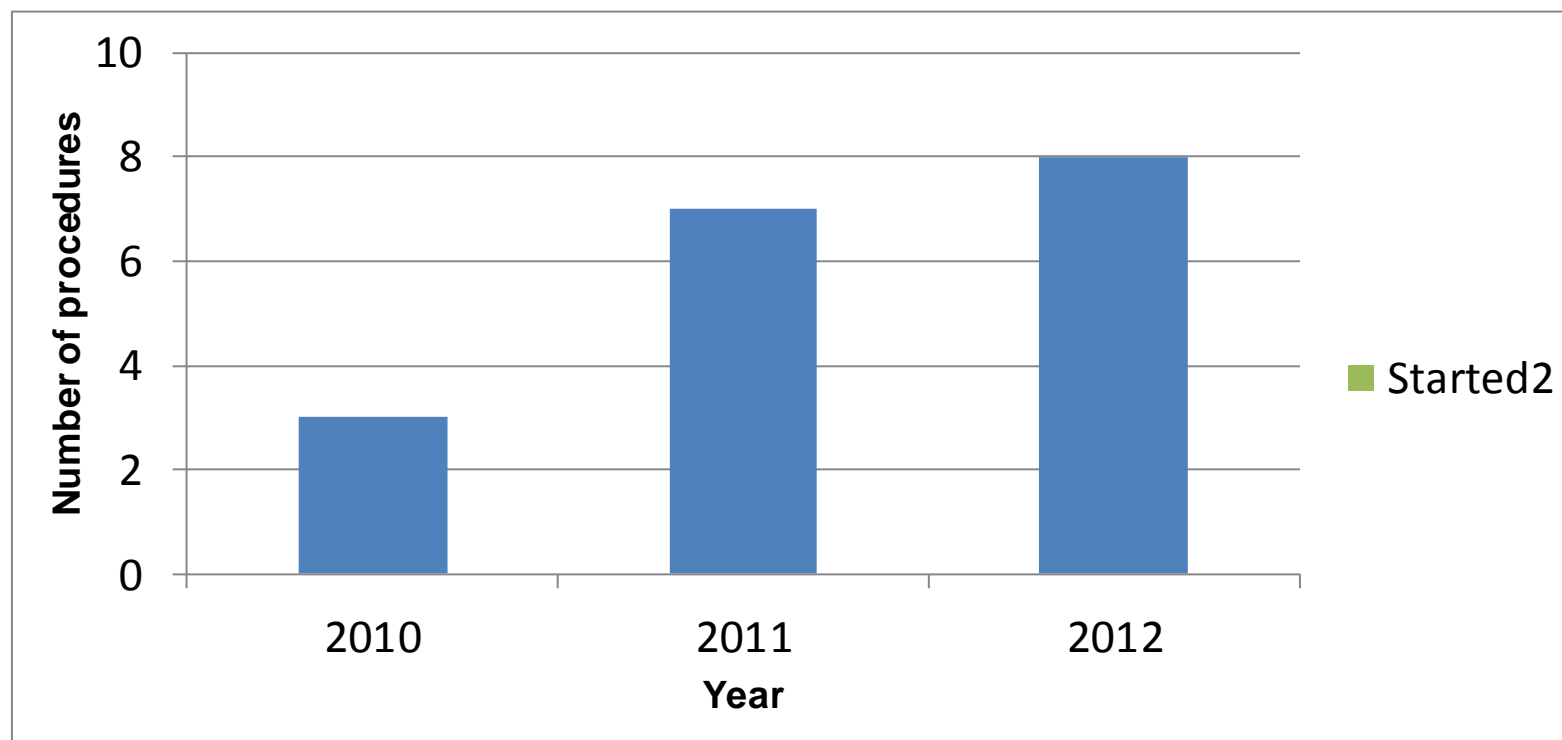
Parallel HTA Advice

Challenge today: new medicines do not reach all patients

- Regulators and HTAs appear to have different requirements in terms of evidence
- All stakeholders come together early to discuss how to investigate a new medicine
- Comparators/design of trial and endpoints/ measures to show added value
- Improve access to medicines for patients

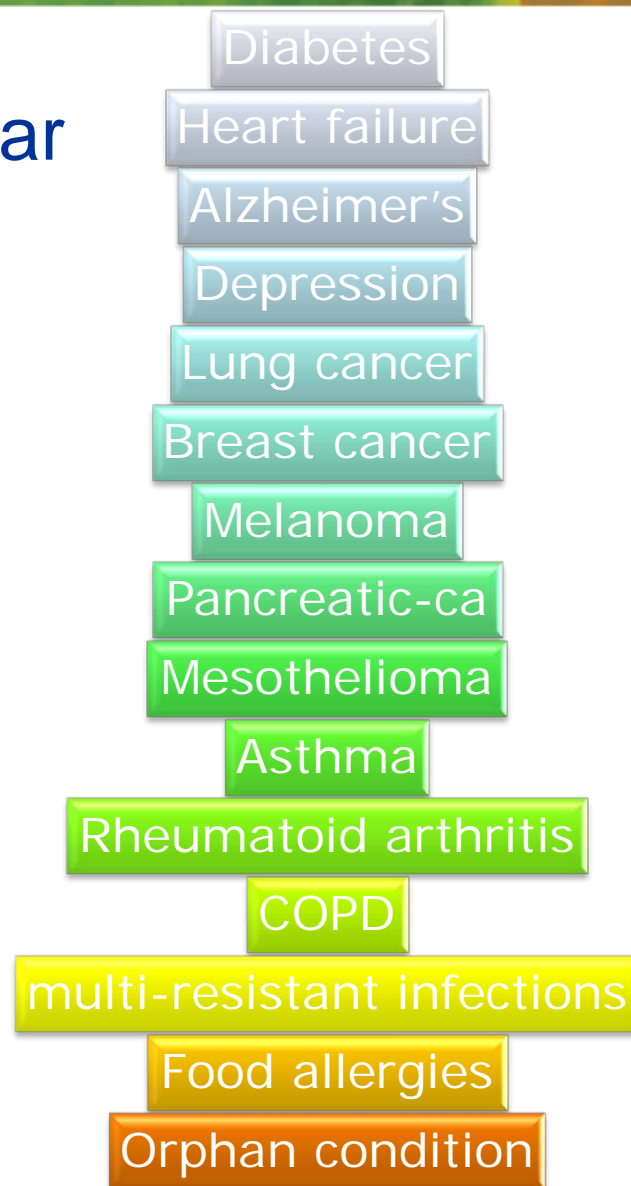


Parallel HTA EMA Procedures





Experience so far





Parallel HTA-EMA SA experience so far

HTAs and payers from UK, Sweden, France, Italy, Netherlands, Spain, Germany, Belgium

Most big companies, 2 SMEs.

Pre-Notification

Pre-Validation

Meeting

Outcome

Outcome: SA letter with the responses from the CHMP

Minutes circulated by the company for individual written HTA agreement on the views expressed during the discussion meeting



Advantages of HTA EMA parallel scientific advice

- **Interaction between HTA and regulators;** listening to each others views, improves understanding, and allows contemporaneous evolution of your development to satisfy all parties before development plans and HTA/EMA decisions have been finalised
- **Focus early** on how you will show value/ what is your place in therapy
- **Target fundamental issues**
Population/comparator/SOC/Intervention/outcomes
- Flexible in choice of HTAs- EMA can facilitate contacts
- EMA/HTAs equal partners



Advantages of HTA EMA parallel scientific advice

- External experts
- Uses experience administration/machinery of scientific advice
- Critical mass done/ no restriction in indications/Eligibility
- Comprehensive constructive discussions
- Written outcome
- Possible for Orphan and SME; populations limited/resources critical
- **Prenotify early and plan ahead** when study design parameters can still be changed



➤ Approaches for HTA EMA parallel advice very welcome

➤ Contact EMA

Prof Spiros Vamvakas, Section head, EMA Scientific Advice

email spiros.vamvakas@ema.europa.eu Tel +44 (0)20 7523 7006

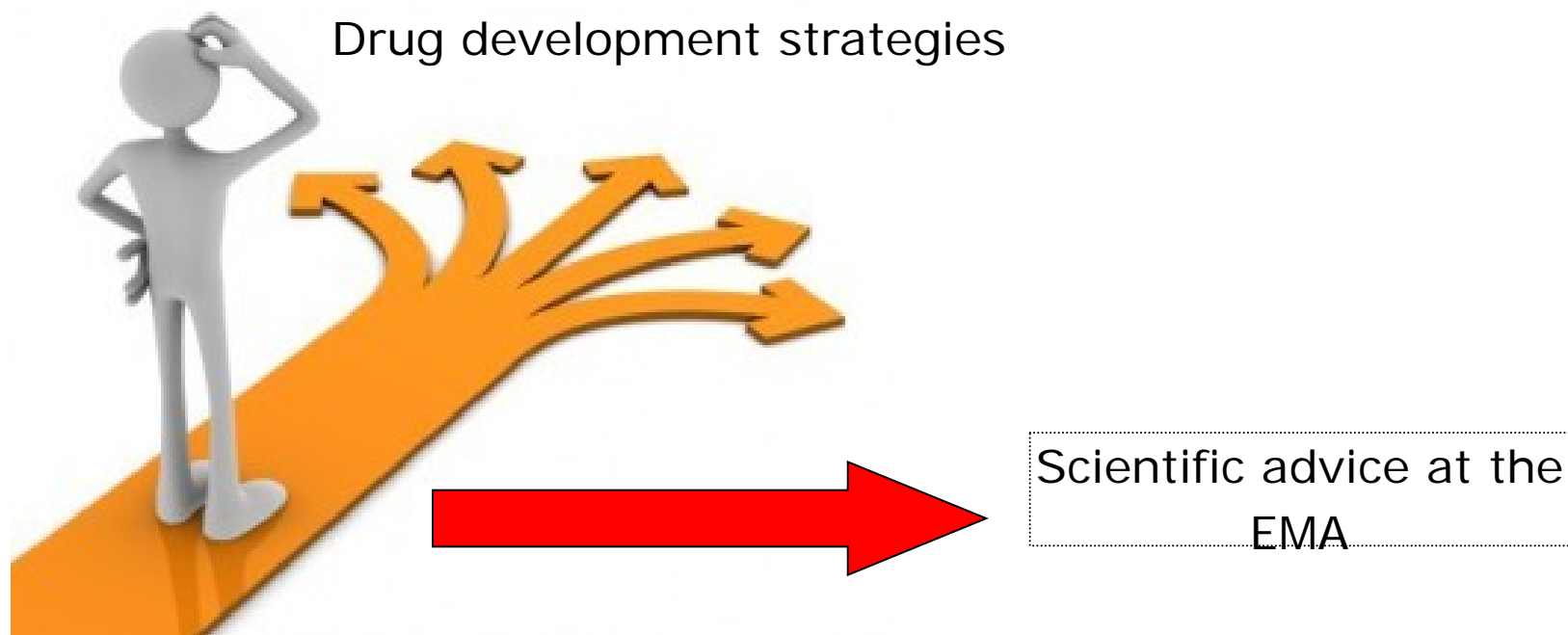
Dr Jane Moseley, Scientific Administrator, EMA scientific advice

email Jane.moseley@ema.europa.eu Tel +44 (0)20 7523 7149

➤ Planning – **HTA EMA Workshop Nov 26 2013**



Struggling to find the best way forward?





Thank you



Annexed HTA EMA parallel advice procedure



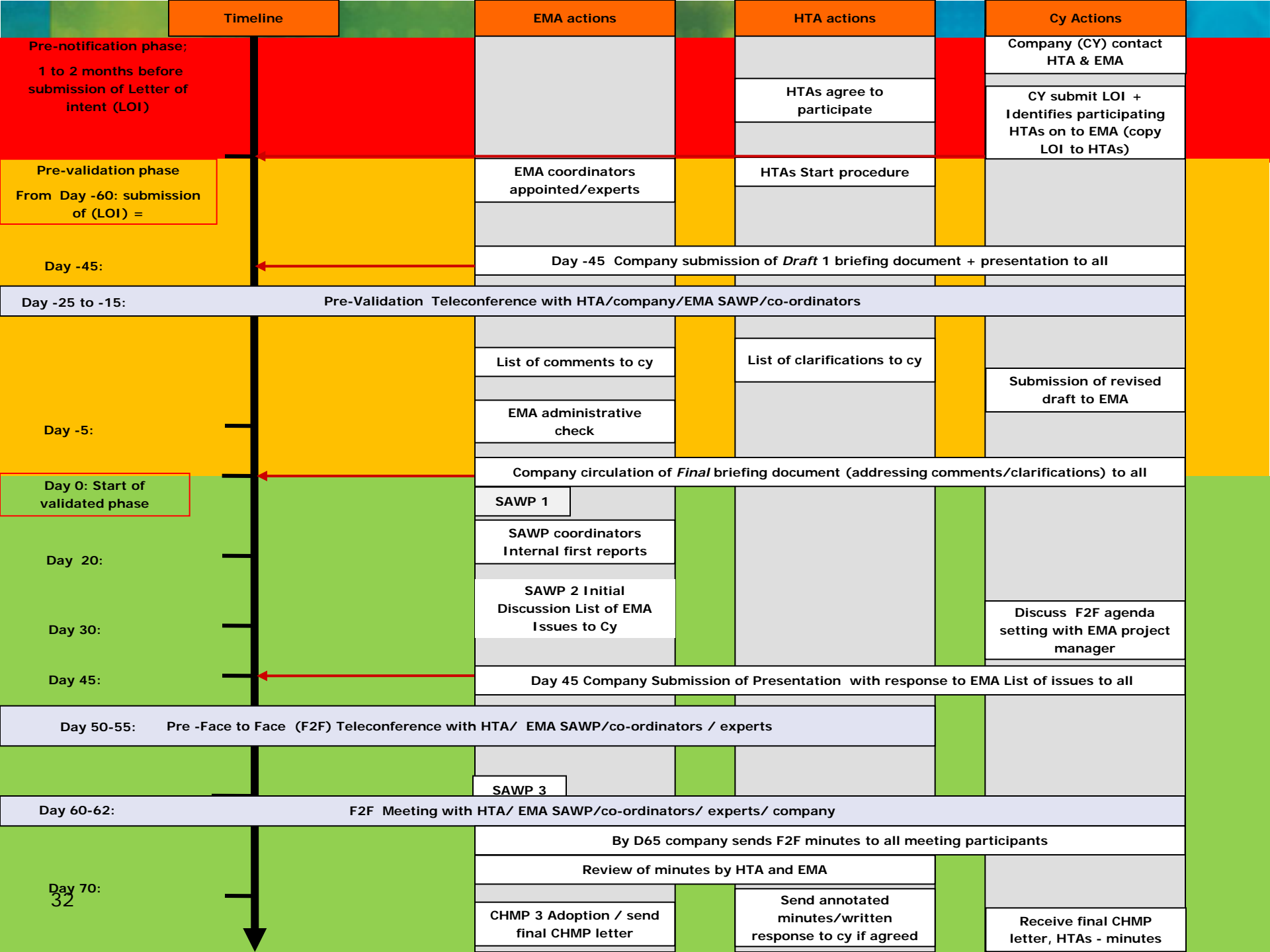
Best practice guide to HTA EMA parallel scientific advice

- Parallel scientific advice with HTAs and the EMA pilot, has a pre-notification phase, a pre validation phase and a meeting phase. The procedure is confidential. As a multi-lateral process, contact between project managers is important.
- Prenotification phase – companies engage early in informal discussions with HTAs and EMA announcing intention for procedure, product and timescale, and which HTA will participate. Ideally all participating HTAs should be engaged before sending a letter of intent (LOI) to the EMA; additional HTAs are able to join the procedure in later phases if they are agreeable. HTAs may also participate as observers only.
- Companies should **prenotify the EMA well in advance of sending in the LOI if possible**; to advise EMA of the impending procedure and if any advice is needed on contacting specific HTAs. EMA can brief participants on the expected process. Contact details of the HTAs can be provided.



Prevalidation Phase

- Prevalidation phase- It is preferable to have one principal point of company contact (with a back up); for both HTAs and the EMA. The letter of intent should be sent to EMA together with the contact details of any participating HTAs. The company can send a copy of the LOI to the HTAs.
- The EMA and HTA project managers should be kept up to date with any changes/developments. E.g. new HTAs/contact changes
- At an early stage, HTA and EMA may consider the clinical experts required for participation in the procedure /face to face meeting. Two Co-ordinators who are members of the EMA Scientific Advice Working Party (SAWP), from national regulatory agencies are appointed to lead their respective assessment teams for the EMA.
- Project managers (EMA and HTAs will consult early) on a draft timetable (EMA can provide first draft) to be agreed for key dates in the parallel procedure. Email and phone contact details of all participants are needed.
- Meeting requests can be sent by EMA to HTAs and other regulatory participants, and be communicated with the company





Prevalidation Phase

- The first draft of the briefing book should be sent to the EMA and participating HTAs within 2 weeks of sending in the LOI. EMA uses Eudralink- a secure system for sending /receiving (large) documents between parties in its in house procedure. The company should clarify with HTAs on their preferred method of sending and receiving documents. Additional Eudralink accounts can be easily set up for interested parties.
- **A prevalidation teleconference (TC) will take place approximately 2-3 weeks after the briefing book has been received by all parties ; involving the EMA* , HTA and company.** * EMA participants could include Scientific advice working party (SAWP) secretariat/co-ordinators/experts. EMA can arrange this TC upon receipt of the LOI.
- The company circulates a briefing presentation with numbered slides covering briefly the background, the questions and company positions, to all participants at least 48 hours before the TC including a list of company participants.



Prevalidation Phase

- **The aim of the prevalidation TC is to discuss the scope, wording and clarity of the questions, and whether the material provided in the briefing package is sufficient to answer the questions posed.** EMA will send their comments on the package in writing within 2 days. Reviewing the choice of questions, such as questions on population, comparator etc at an early stage is considered important as the procedure will not be able to expand to add new questions at a later date.
- HTAs may send comments on the package/seek clarifications individually to the company after the pre validationTC according to their usual practice.



Meeting Phase

- The company sends a revised briefing draft, addressing the EMA comments and HTA points of clarification in the agreed time frame - approximately 10 days. EMA will conduct an administrative check to ensure the briefing pack is fit for purpose i.e. that all annexes and references are included and that the questions were amended according to the prevalidation TC. The company circulates the final briefing package to the EMA contacts, and to the HTAs in the manner agreed.
- In the EMA in house process, the scientific advice working party (SAWP) discusses the first reports (preliminary views) at the SAWP 2 meeting and generates a List Of Issues by the end of SAWP 2 which is sent to the company. The company can send this to the HTAs.
- The company is advised to contact the EMA project manager to discuss the format of the Face to Face meeting.
- The Company should send the presentation for the face to face meeting within 2 weeks of receipt of the list of issues - to the EMA and to the HTAs, together with any written responses if these are requested.



Meeting Phase

- The presentation can include the very brief introduction, rationale and status of the program; all the briefing document questions + key points of the company – with tables and figures. The issues raised by the EMA can be intercalated into the presentation with the relevant question but this can be discussed with the EMA scientific administrator. The introduction, rationale and status of the program section should be very brief to maximise the time for the questions and discussion. It is usual to pause after each question OR issue for discussion.
- Once sent to the meeting participants, according to the agreed timelines, the presentation should not be substantially amended by the company.
- The EMA will arrange a preparatory TC with the HTAs; this will be arranged to take place after the company sends the responses to the list of issues/presentation to review respective preliminary positions.
- The Face to Face meeting will normally have 2 co-chairs- one from EMA* and one from the HTAs. Regarding the choice of HTA chair, this will rotate amongst the HTAs, or be agreed between the HTAs, on a case by case basis.



Meeting Phase

- The Meeting time is **approximately 4 hours** including a short break. The company can prepare the agenda allocating time according to priorities, sending this with the presentation and list of company attendees. Hard copies are not required. The EMA will circulate a final list of regulatory participants 2 days in advance of the face to face meeting. The meeting is hosted at EMA premises.
- The inclusion of patient representatives in the Face to face meeting will be on a case by case basis; briefing of chairs, and patients regarding the purpose and role of the meeting and of patient representation is essential. Additional time or facilities required by patients should be considered in these cases.
- The company is expected to send minutes of the Face to face meeting within 5 days to all participants who will review these.
- The EMA final advice letter is CHMP advice only. HTA feedback is provided directly to companies according to HTA normal practice or by annotating the company minutes.



Meeting Phase

- There is some flexibility in arranging timelines; timelines will be agreed with all parties in advance, it is advisable to adhere to suggested timeframes to ensure the optimum time is available to assessors and reviewers of documents.
- Document version control and numbering is essential to ensure all parties have the appropriate document at the correct time.



Example of Draft Timetable

EMA HTA parallel advice

Company circulates the draft briefing package xxx date to all parties

Cy circulates Prevalidation TC presentation Start of Business to all parties -2 days before next TC

Prevalidation TC inc HTA/Company/EMA xxx time and date

Cy circulates Final briefing package to EMA xxx date for administrative check

Cy circulates Final briefing package xxx date to all parties

EMA discussion (internal) xxx date SAWP and sends list of issues to company xxx date

Cy circulates face to face presentation, and list of cy attendees to all parties xxx date

Pre face to face TC EMA with HTA (not incl company) xxx time and date

EMA send list of attendees for face to face meeting xxx time and date

Face to face xxx time and date : all parties.

Company circulates minutes after 5 days to all parties

HTAs send comments on minutes/written responses

CHMP letter xxx date