EMA Perspective on PRO Instrument Qualification and Harmonization

Maria Isaac, Spiros Vamvakas, Mira Pavlovic

Scientific Advice Section

Presented at:

FIRST ANNUAL
PATIENT-REPORTED OUTCOMES (PRO) CONSORTIUM WORKSHOP

March 23, 2010 – Bethesda, MD
EMA committees

**CHMP**
(Committee for Human Medicinal Products)
Chair: Dr. E. Abadie – Vice Chair: Dr. T. Salmonson

**COMP**
(Committee for Orphan Medicinal Products)
Chair: Dr. K. Westermark – Vice Chair: Mrs. B. Byskov Holm

**HMPC**
(Committee for Herbal Medicinal Products)
Chair: Dr. K. Keller - Vice-Chair: Dr. I. Chinou

**PDCO**
(Paediatric Committee)
Chair: Dr. D. Brasseur - Vice-Chair: Dr. G. Pons

**CAT**
(Committee for Advanced Therapy Medicinal Products)
Chair: Dr. C. Schneider - Vice-Chair: Prof. P. Salmikangas
Scientific Advice Working Party

• standing WP of the CHMP
  ▪ only WP specifically addressed in the legislation, Regulation EC 726/2004
  ▪ thorough peer-review from CHMP members, ad hoc CHMP discussions of difficult issues
  ▪ final advice letter signed by CHMP chair

• multidisciplinary expert group
  ▪ 28 members put together by expertise, not by Member State, selected based on complementary scientific competence
  ▪ 3 COMP, 1 CAT, 1 PDCO
  ▪ 16 are from NCAs, and 12 from academic centers
  ▪ SA Section of the EMA secretariat support: 10 medical doctors and pharmacists and 7 secretaries and administrative assistants

• network external experts
  ▪ involvement: average 7/procedure, mainly background academia & regulatory agencies
  ▪ nomination and conflict of interest declaration

• interaction with PDCO and patient organizations
  protocol assistance for orphan drugs for rare diseases, the SAWP secretariat contacts the Patients' and Consumers' Working Party (PCWP)
SA/PA procedure

• optional/voluntary procedure
  ▪ upon Company’s request (unlike e.g. FDA EoP2 meeting)
  ▪ not binding for the Agency & Company, but strong commitment from the CHMP is achieved

• procedure 40 days (written) or 70 days (DM)
  – face-to-face discussion meetings (DM) for aprox. 50% requests
  – pre-submission meeting optional

• fee-related activity €€€
  – fee waiver for orphan products (PA) and paediatric-only
  – fee reduction SMEs (10% full fee)

• scope: product-specific advice (generally), prospective, no data pre-assessment
FAQs scope

- **Quality/CMC**
  - comparability, stability, etc.

- **Non-clinical**
  - *in vivo* pharmacology for innovative products with complex MoA
  - animal models for products with human specific targets, animal models mimicking the human disease, surrogate molecules
  - carcinogenicity and reprotoxicity waivers, etc.
  - juveniles studies in paediatric drug development

- **Clinical**
  - PK/PD, dose-finding, interactions
  - exploratory & pivotal trials: study endpoints, population, comparator, blinding, statistics (interim A, adaptive/seamless design), safety DB
Other SAWP activities

• **Product-related**

• **Qualification of Novel Methodologies (BMs) and CHMP Opinion**

• **Workshops** EFPIA-SAWP
  – 2005 & 2006 Biomarkers
  – 2007 Adaptive designs
  – 2008 Modeling and Simulation in Paediatric Drug Development
  – 2008 Pharmacogenomics
  – 2010 Alzheimer’s disease

• **Broad advice**
  – PROs, manufacturing, etc.
Scientific Advice and Protocol Assistance

* Protocol Assistance = Scientific Advice for Orphan Medicinal Products
Qualification procedure
Guidance document

London, 22 January 2009
Doc. Ref: EMEA/CHMP/SAWP/72894/2008 Corr¹

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<th><strong>COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)</strong></th>
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<td><strong>QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT: GUIDANCE TO APPLICANTS</strong></td>
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<th><strong>DRAFT AGREED BY SAWP</strong></th>
<th>27 February 2008</th>
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<td><strong>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</strong></td>
<td>24 April 2008</td>
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<td><strong>END OF CONSULTATION (DEADLINE FOR COMMENTS)</strong></td>
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<th><strong>KEYWORDS</strong></th>
<th><strong>EMEA. CHMP. Novel methodology. Qualification. Scientific Advice.</strong></th>
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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
- input CT design
- **surrogate endpoint**

**Drug utilisation**
- optimise target population
- guide treatment regimen
New regulatory procedure

- **CHMP Qualification Opinion** (*binding*) on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data, not specific to one product

- **CHMP Qualification Advice** on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted
New regulatory procedure

OBJECTIVES

• SAWP/CHMP early involvement in the design of the strategy towards qualification of novel methodologies

• SAWP/CHMP commitment to evaluate the data obtained from the agreed studies and to provide a Qualification Opinion regarding the use of the method in R&D

• Goal: speed up drug development, contribute to public health
Scope

- Focus on acceptability of specific use of the proposed technology/BM developed for a **specific intended use** in the context of pharmaceutical R&D.
- Based on the assessment of submitted data by a specialised BM Qualification team (BMQT), peer review and public consultation.
- **Output:** CHMP Qualification Advice and scientific assessment (public document).
Applicants

- Consortia, Networks
- Public/private partnerships
- Learned societies
- Pharmaceutical industry

**Input:** Protocols, study reports, raw data etc to establish the use of a defined biomarker for a specific purpose in drug development.

**Fee** i.e. 75.500 €, follow-up 37.700 €

- SMEs 90% fee reduction
- Free for paediatrics and orphans
Qualification procedure flow

- Day -30: Letter of Intent
- Day 0: Start of procedure
- Preparatory meeting
- Day 30: SAWP 1
- Day 60: SAWP 2, QT mtg
- Day 70: SAWP 3
- Day 90:

  - Submission of draft dossier
    - EMEA validation
    - Appointment of Coordinator and QT
    - Draft report
    - Discussion of draft report
    - List of Questions and draft report to Applicant
    - Meeting with Applicant
    - Revised draft report

  - Day 120: SAWP 4
  - Day 130: CHMP 1
  - Day 160: CHMP 2
  - Day 220: CHMP 4

- Discussion of revised report
- Submission of draft Scientific Advice
- Adoption of Scientific Advice

- Public consultation
- Day 130

PRO consortium
Qualification team

Experts

- multidisciplinary, min 4

Coordinator
(SAWP or CHMP)

project manager
(EMA)

therapeutic areas

statistics

core context for the intended use: e.g. non-clinical safety testing, translational research

technology supporting the development of the novel methodology: e.g. proteomics, genomics, ultrasound, MRI imaging
Experience to date

• 6 procedures started
• after 10 procedures: evaluation of process planned
• 2 CHMP Qualification Opinion on nephrotoxicity BM
• 2 CHMP Qualification Advice
• applicants are encouraged to apply in parallel to the EMA and FDA (confidentiality agreement), who communicate during the assessment and meet with the Applicant together.
Harmonizing PRO Measurement Standards: EMEA Regulatory Perspective
PRO and drug evaluation process

- In 2003, EMEA decides to draft a guideline on HRQL/PRO evaluation in registration trials
- AIM: to define the place and give recommendation for use of PRO in drug evaluation process
- PRO scope considered too large (umbrella term):
  - “Simple” patient-assessed measures
    - Single item (pain)
    - Multi-item, single concept (HAQ)
  - “Intermediate” patient-assessed measures
    - Multi-item, multi-concept (ALD) or isolated domains of HRQL
  - “Broad” multidimensional measures (such as HRQL)
  - Health status, adherence/satisfaction with treatment
PRO and drug evaluation process

- Simple patient-assessed measures: core symptoms of a disease assessed by patient himself
  - well established primary and secondary efficacy endpoints in registration trials, no specific regulatory requirements needed
- Scope:
  - narrowed to include only HRQL as a specific type/subset of PRO
  - defines the place of HRQL in the context of drug approval
  - no specific recommendation is given for development and validation of HRQL measures in clinical trials²
  - no specific recommendation on “intermediate” measures

EMEA paper on HRQL³
Basic recommendations

• Efficacy and safety of a medicinal product in the given condition are the basis of approval

• HRQL claim
  • goes beyond efficacy and safety assessments (HRQL are never primary endpoints)
  • is optional
  • should be supported by data collected by instruments validated for use in the corresponding condition
  • Both generic or disease specific questionnaires are acceptable
  • Choose questionnaire which is adapted to explore the domains relevant for the disease and its treatment

• 3. CHMP reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. EMEA/CHMP/EWP/139391/2004
Global or specific HRQL claims

• Global claim (product “improves HRQL”):
  • All (most) HRQL domains are known/measured
  • clinically relevant improvements are demonstrated in all/most HRQL domains

• Specific HRQL claim (product “improves physical functioning”), based on the subset (one or two) of domains of HRQL, is acceptable if:
  • Whole HRQL instrument is adequately developed and validated before the trial
  • Subset of domains of interest pre-specified

• In all cases a full disclosure of complete results should be provided (section 5.1 of the SmPC)
When the HRQL claim may be granted

- Based on the strength of evidence and the relevance of the finding
  - Rationale for HRQL assessment in the context of the disease/medicinal product
  - Choice of the HRQL questionnaire justified
  - Objectives of HRQL assessment and hypothesis of HRQL changes defined
  - Evidence of validation of HRQL questionnaire
  - Adequate study design: *comparative blinded* data, predefined statistical analysis plan
  - Relevance of the observed changes
Study design for HRQL assessment

- Randomised, preferably double-blind, comparative trials (placebo, active comparator)
- Disease:
  - chronic non-life threatening conditions
  - Chronic diseases with acute exacerbations (asthma, rheumatoid arthritis)
  - Severe life threatening diseases (cancer)
- Trial duration:
  - long-term trials (3 - 6 months or more)
  - Short-term trials (e.g. 1 month) are discouraged (assess improvement of daily living due to treatment efficacy)
Study design for HRQL assessment (2)

• Medicinal product has no MA:
  • HRQL may be studied simultaneously to the efficacy/safety of the medicinal product in pivotal (phase III) trials
  • HRQL may be the part of a co-primary endpoint or key secondary endpoint
  • Study should be powered for both endpoints
• Medicinal product has obtained MA (or efficacy and safety of the test drug have already been shown):
  • Active comparator trials: should incorporate both efficacy and HRQL change endpoints
Statistical analysis plan

- Multiplicity
  - of endpoints: hierarchical testing
  - of domains: correction of p-values, hierarchical testing
  - global test procedures: not encouraged
- Missing data
- Timing of assessment
- Sample size/power and expected difference, MID
  - studies frequently overpowered for MID
- Randomisation, blinding
- Study duration
- Interpretation of results
- Bias
What happened after 2006 (EMEA NfG published)

- Several scientific advice requests with the HRQL related claims
- Improved comprehension of the HRQL development and assessment both by regulators and industry
- However, everything is not resolved
- Recent EMEA scientific advice examples
  - Y: add-on to PPI for symptomatic GERD
  - Z: broad advice on COPD
What happened after 2006
Scientific advice Y

- Z + PPI vs PPI in symptomatic GERD patients
- Primary endpoint: responders (symptoms)
- Secondary endpoint:
  - two domains of QL (food/drink and sleep), pre-specified, validation ongoing, 4-week study
- Full HRQL assessment planned in a 6-month trial
- SAWP discussion:
  - Accept ?: food/drink and sleep are important/disturbed in GERD patients, may help illustrating the observed efficacy on symptoms
  - Refuse ?: only 2 domains of HRQL assessed, validation ongoing, trial too short
  - SmPC wording
What happened after 2006
Scientific advice Z

• Ongoing broad advice on PRO in COPD
• Co-development of new PRO (EXACT-PRO and IMI Proactive consortia)
  – EXACT-PRO: outcome measure to evaluate effects of treatment on acute exacerbations of COPD
  – IMI Pro: 5-year project, PRO to capture dimensions of physical activity of daily life in COPD patients
• Discussions on methodology used to validate two PRO scales in development:
  – Conceptual framework (for functional performance)
  – Content validity (for both scales)
  – Responder definitions
EMEA regulatory perspective?

- EMEA/EWP guidelines revised every 5 years or when needed
- « Simple » PRO (symptoms) will stay out of scope (not problematic)
- The EMEA reflection paper still valid for the HRQL-related claims
- Should we broaden the scope of the reflection paper?
  - Conceptual framework, content validity, ability to detect change, « intermediate PRO measures » to support claims
- We may well rely upon the FDA guideline
EMEA regulatory perspective?

- Harmonizing FDA and EMEA regulatory requirements
- « Endpoint model » is not really new:
  - Clear definition of all endpoints, hierarchy and expected claims are always required for all applications
  - EMEA guidelines recommend primary and secondary endpoints in most therapeutic fields
  - New PRO as primary endpoint: acceptance on case by case basis (will depend on the type of PRO), clear and detailed justification needed in all cases
  - New PRO as secondary endpoint: acceptable, define claim and relation to other endpoints
PRO in drug evaluation process

Conclusion

• If you ask for a « PRO » claim for your product

  • Specify well the type of PRO (simple patient-assessed efficacy measure, HRQL, specific HRQL domains) (“endpoint model”) and the type of claim to avoid misunderstandings
  • Define the most appropriate PRO and the best instrument to measure it in the given context
  • Design blinded comparative randomised trial
  • Always incorporate efficacy measures in HRQL trials
  • Always display all results

IT MAY WORK
Links

EMEA guidance for companies requesting SA or PA

Qualification of novel methodologies for drug developments

Scientific guidelines
  •  http://www.emea.europa.eu/htms/human/humanguidelines/backgroun
d.htm