



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



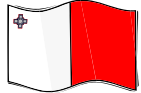
SAWP



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)

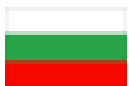
Chair: Dr. D. Basseur - Vice-Chair: Dr. G. Pons



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)

SAWP areas of expertise



PRECLINICAL
Pharmacology
Toxicology
Juvenile studies

MANUFACTURING/CMC
Biotechnology

Qualification of Novel Methodologies

METHODOLOGY

Clinical Trials/Statistics

THERAPEUTIC AREAS

Oncology Psychiatry
 Immunology
Diabetes Cardiology
Endocrinology Neurology
Dermatology Ophthalmology

Clinical Pharmacology
Pharmacokinetics

PAEDIATRICS

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 approx. 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

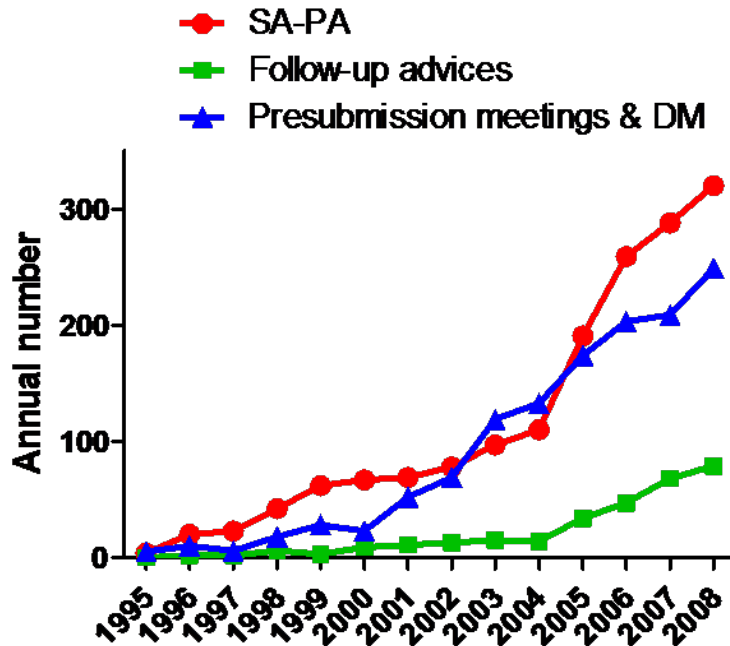
- **Quality/CMC**
 - comparability, stability, etc.
- **Non-clinical**
 - *in vivo* pharmacology for innovative products with complex MoA
 - animal models for products with human specific targets, animal models mimicking the human disease, surrogate molecules
 - carcinogenicity and reprotoxicity waivers, 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**



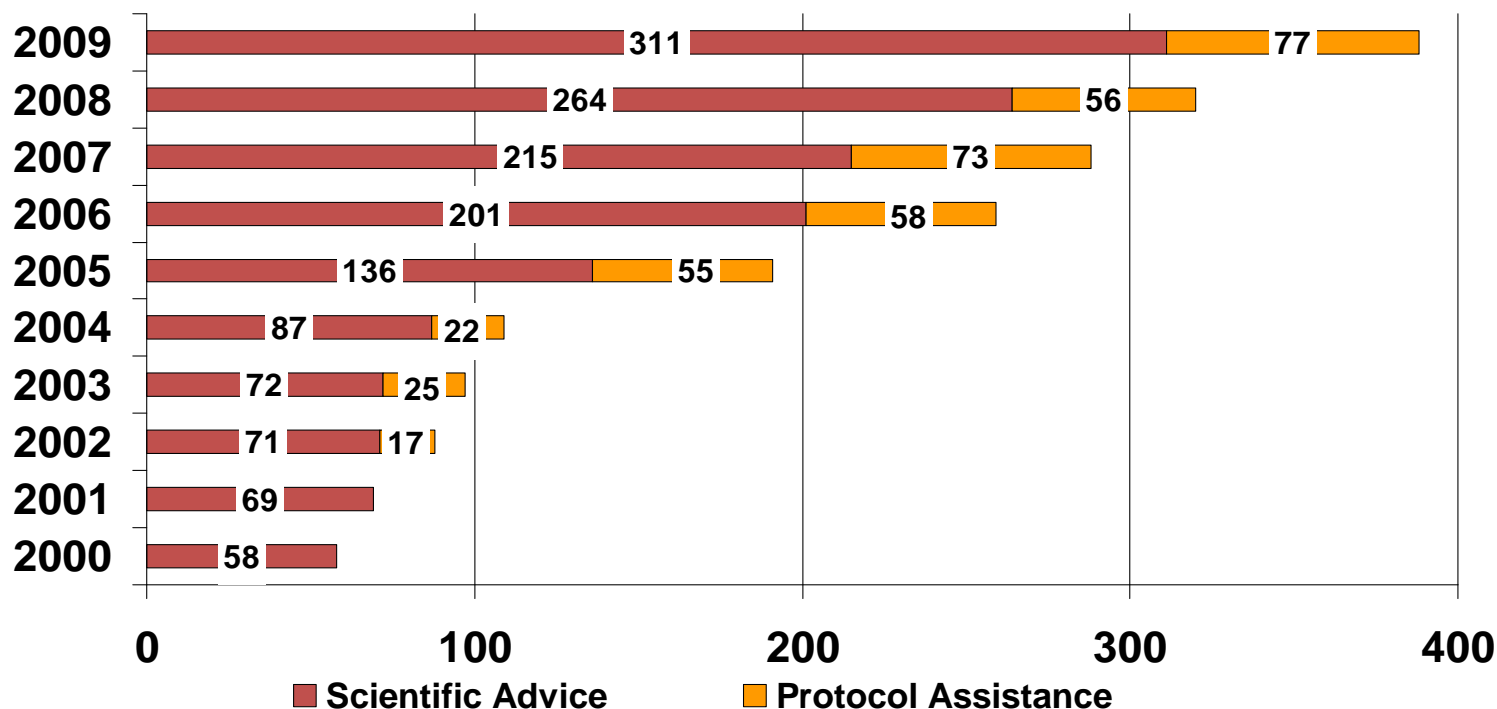
- **Workshops EFPIA-SAWP**

- 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

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT:
GUIDANCE TO APPLICANTS**

DRAFT AGREED BY SAWP	27 February 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 April 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 June 2008
FINAL AGREED BY CHMP	22 January 2009

KEYWORDS	<i>EMEA. CHMP. Novel methodology. Qualification. Scientific Advice.</i>
-----------------	---

Qualification of Novel Methodologies



Preclinical development

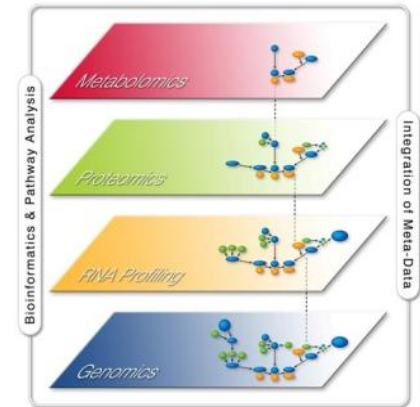
- pharmacological screening
- mechanism of action
- predict activity/safety
- PK/PD modelling
- toxicogenomics

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

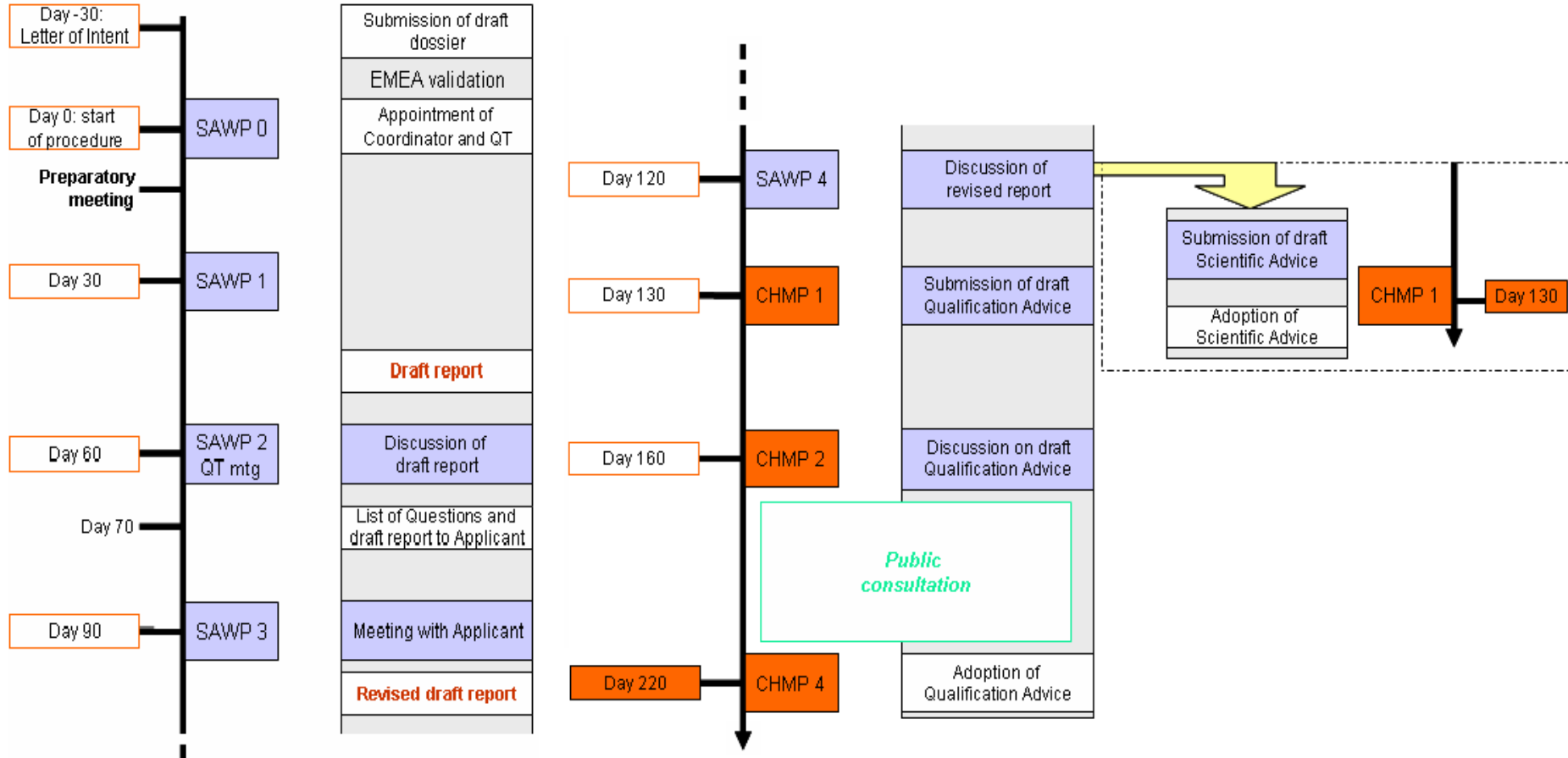
Input: Protocols, study reports, raw data etc to establish the use of a defined biomarker for a specific purpose in drug development.

Fee i.e. 75.500 €, follow-up 37.700 €

SMEs 90% fee reduction

Free for paediatrics and orphans

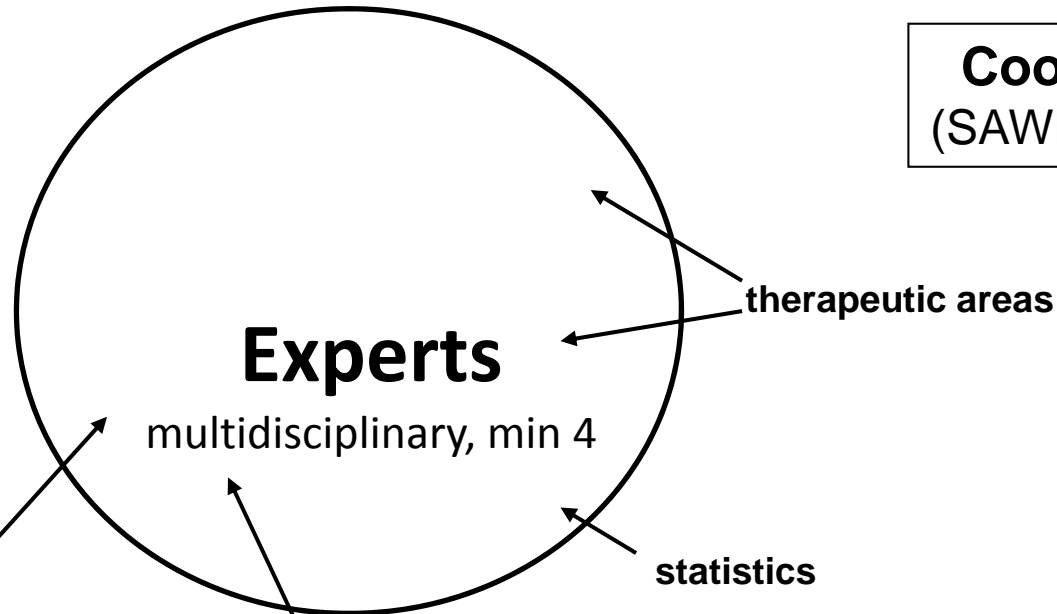
Qualification procedure flow



Qualification team



Coordinator
(SAWP or CHMP)



Experts

multidisciplinary, min 4

therapeutic areas

statistics

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

project manager
(EMA)

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
- 2. FDA Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims.

EMA 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. EMA/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



EMA guidance for companies requesting SA or PA

- <http://www.emea.europa.eu/pdfs/human/sciadvise/426001en.pdf>

Qualification of novel methodologies for drug developments

- <http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf>

Scientific guidelines

- <http://www.emea.europa.eu/htms/human/humanguidelines/background.htm>