Poster no. PMC21

Patient-Reported Outcomes as Mentioned in Product Development Guidance

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Background

- Regulatory agencies are paying increasing attention to the use of patient-reported outcomes (PRO) data in product approval and labeling claims.
- Recently imposed standards related to the development and validation of PRO measures, as well as the level of documentation required to support these measures, have made it much more challenging to secure favorable reviews by the Food and Drug Administration (FDA).
- Some PRO measures frequently used to support product approvals and/or labeling claims in the past are no longer considered adequate (or "fit") for either of these purposes.
- Some disease areas and/or regulatory bodies necessitate the use of PRO data to substantiate product efficacy for securing approval, leaving sponsors in a tenuous position until new PRO measures meeting regulatory guidelines can be developed.

Objectives

- Identify final product development guidance documents available from the European Medicines Agency (EMA) or the FDA for clinical/medical research indicating PROs as a mandatory component of efficacy
- Determine whether a hierarchy of PRO endpoints is specified within each guidance document
- Characterize the type of PRO (e.g., signs/symptoms) referenced in the final guidance document

Methods

- Final product development guidance documents were accessed from the Web sites of the EMA[1] and the FDA[2] in October-November 2009.
- EMA guidance documents in the following categories were excluded: Clinical Pharmacology and Pharmacokinetics, Blood and Blood Forming Organs, Blood Products (including biotech alternatives), and Herbals.
- FDA guidance review was limited to documents in the Clinical/Medical category.
- Only final EMA and FDA guidance documents were reviewed.
- The following information, when available, was collected from each identified guidance document:
  - Guidance number
  - Name
  - Issue date
  - Disease area
  - Body system classification
  - PRO requirement
  - PRO endpoint hierarchy: primary, nonprimary, primary and nonprimary, exploratory
  - Summary of the PRO language included in the guidance
- PRO statements then were characterized as follows:
  - Signs/symptoms (yes/no)
  - Function/feeling (yes/no)
  - Health-related quality of life (HRQL) (yes/no)
  - Patient global rating (yes/no)

Results

- Of the 134 final guidance documents reviewed (81 from the EMA and 53 from the FDA), 53 specified the inclusion of PROs as primary or nonprimary endpoints (EMA: n = 39; FDA: n = 14).
- One additional EMA guidance (for human immunodeficiency virus [HIV]) recommended inclusion of PROs as an exploratory endpoint.

Results

EMA Results

- Roughly half of the EMA guidance documents (49%) included recommendations or statements regarding PROs in clinical investigations of medicinal products.
- PROs were included in adopted guidance documents dating back to 1991, and half of the identified guidance documents predated the FDA's draft guidance on the use of PROs (i.e., were issued before February 2006) (**Table 1**).
- Among the 39 guidance documents, PROs were indicated as primary endpoints (n = 5), nonprimary endpoints (n = 22; of which 4 were secondary and exploratory), or primary and nonprimary endpoints (n = 12).
- Therapeutic areas in which PROs were indicated as primary endpoints included incontinence, juvenile arthritis, menopause, nociceptive pain, and sleep (**Table 2**).
- **Table 3** presents some of the specific PRO measures mentioned in EMA guidance documents.
- The majority of PRO statements referred to measures of signs and symptoms, followed by HRQL measures such as the SF-36 Health Survey (SF-36), the Dermatology Life Quality Index, and the Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC).

Table 1. EMA Guidance Documents That Mention PROs (N = 39)

	Title	Disease	Date Issued
1	Clinical Investigation of Hypnotic Medicinal Products	Sleep	September 1991
2	Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD)	Chronic obstructive pulmonary disease	May 1999
3	Clinical Investigation of Medicinal Products in the Treatment of Cardiac Failure	Cardiac failure	December 1999
4	Points to Consider on Clinical Investigation of Medicinal Products for the Treatment of Amyotrophic Lateral Sclerosis	Amyotrophic lateral sclerosis	October 2000
5	Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders	Epilepsy	November 2000
6	Points to Consider on Clinical Investigation of Medicinal Products for the Treatment of Acute Stroke	Stroke	September 2001
7	Clinical Investigation of Medicinal Products in the Treatment of Peripheral Arterial Occlusive Disease	Peripheral arterial disease	April 2002
8	Clinical Investigation of Medicinal Products in the Treatment of Asthma	Asthma	November 2002
9	Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain	Nociceptive pain	November 2002
10	Clinical Investigation of Medicinal Products in the Treatment of Urinary Incontinence in Women	Incontinence	December 2002
11	Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome	Irritable bowel syndrome	March 2003
12	Points to Consider on Clinical Investigation of Medicinal Products Other Than NSAIDs for Treatment of Rheumatoid Arthritis	Rheumatoid arthritis	December 2003
13	Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure—Addendum on Acute Cardiac Failure	Cardiac failure	July 2004
14	Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-conjunctivitis	Rhino-conjunctivitis	October 2004
15	Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis	Psoriasis	November 2004
16	Clinical investigation of Medicinal Products Indicated for Generalised Anxiety Disorder	Generalized anxiety disorder	January 2005
17	Clinical investigation of Medicinal Products for the Treatment of Obsessive Compulsive Disorder	Obsessive compulsive disorder	January 2005
18	Clinical investigation of Medicinal Products Indicated for Panic Disorder	Panic disorder	January 20005
19	Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women	Menopause	October 2005
20	Evaluation of Anticancer Medicinal Products in Man	Antineoplastic	December 2005
21	Clinical Investigation of Medicinal Products Indicated for the Treatment of Social Anxiety	Social anxiety	January 2006
22	Clinical Investigation of Anti-anginal Medicinal Products in Stable Angina Pectoris	Angina	June 2006
23	Clinical Investigation of Medicinal Products for the Treatment of Sepsis	Sepsis	June 2006
24	Clinical investigation of Medicinal Products in the Treatment of Patients with Acute Respiratory Distress Syndrome	Acute respiratory distress	September 2006
25	Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis	Juvenile arthritis	October 2006
26	Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis	Multiple sclerosis	November 2006
27	Non-Clinical and Clinical Development of Medicinal Products for the Treatment of Nausea and Vomiting Associated With Cancer Chemotherapy	Chemotherapy-induced nausea and vomiting	December 2006
28	Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis	Psoriatic arthritis	December 2006
29	Clinical Investigation of Medicinal Products for Treatment of Migraine	Migraine	January 2007
30	Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain	Neuropathic pain	January 2007
31	Guideline on Clinical Trials With Haematopoietic Growth Factors for the Prophylaxis of Infection Following Myelosuppressive or Myeloablative Therapy	Infection prophylaxis following treatment	March 2007
32	Clinical Evaluation of Medicinal Products Used in Weight Control	Weight control	November 2007
33	Clinical Investigation of Medicinal Products for the Management of Crohn's Disease	Crohn's disease	July 2008
34	Development of Medicinal Products for the Treatment of Post-Traumatic Stress Disorder (PTSD)	Post-traumatic stress disorder	July 2008
35	Clinical Evaluation of Medicinal Products Used in Weight Control (CPMP/EWP/281/96 Rev. 1)—Addendum on Weight Control in Children	Pediatric weight control	September 2008
36	Development of New Medicinal Products for the Treatment of Smoking	Smoking cessation	December 2008
37	Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in Children and Adolescents	Asthma and chronic obstructive pulmonary disease	January 2009
38	Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis	Ankylosing spondylitis	April 2009
39	Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis	Osteoarthritis	January 2010[a]

[a] Revision approved in January 2010 to previously adopted guidance.

Table 2. Therapeutic Area Summary by Endpoint Hierarchy for EMA Guidances Require PROs

Primary (n = 5)	Nonprimary (n = 22[a])	Primary and Nonprimary (n = 12)
Incontinence	Acute respiratory distress	Asthma
Juvenile arthritis	Amyotrophic lateral sclerosis	Ankylosing spondylitis
Menopause	Angina	Chronic obstructive pulmonary disease
Nociceptive pain	Antineoplastic[b]	Epilepsy
Sleep	Asthma and chronic obstructive pulmonary disease	Irritable bowel syndrome
	Cardiac failure (n = 2)	Migraine
	Chemotherapy-induced nausea and vomiting	Neuropathic pain
	Crohn's disease	Osteoarthritis
	Generalized anxiety disorder[b]	Peripheral arterial occlusive disease
	Infection prophylaxis following treatment	Psoriatic arthritis
	Multiple sclerosis	Rheumatoid arthritis
	Obsessive compulsive disorder	Smoking cessation
	Panic disorder[b]	
	Pediatric weight control	
	Psoriasis	
	Post-traumatic stress disorder	
	Rhino-conjunctivitis	
	Sepsis	
	Social anxiety[b]	
	Stroke	
	Weight control	

[a] Includes 18 secondary and 4 that are secondary and/or exploratory.
[b] Secondary and/or exploratory.

Table 3. PRO Measures Mentioned in Some EMA Guidance Documents for Human Medicinal Products

Endpoint Hierarchy	Therapeutic Area (Guidance No.)	PRO Mentioned
Primary endpoint		
	Incontinence (10)	The overall outcome of treatment as perceived by the patient should be recorded by simple scales; examples include: • Likert scale (e.g., "My condition [e.g., urinary incontinence/problems] causes me no problems, very minor problems, minor problems, moderate problems, severe problems, very severe problems") • Treatment benefit (e.g., "My condition has been cured, improved, not changed, worsened during treatment") • Visual analog scale (VAS) with anchors (e.g., "My urinary problems cause me no problems and my urinary problems cause me intolerable problems")
	Juvenile arthritis (25)	• JRA 30 (reflects signs and symptoms) • Parent or patient (if appropriate in age) global assessment of overall well-being (parent/patient global) VAS; anchoring words very well, very poor • Functional ability (Childhood Health Assessment Questionnaire [CHAQ], with different versions in different countries) • Relief of pain
	Menopause (19)	Frequency of moderate to severe hot flushes
	Nociceptive pain (9)	"From regulatory point of view, no specific choice for rating scale is made"
	Sleep (1)	Sleep onset latency, sleep continuity, sleep duration, feeling of restorative sleep, and improved daytime function can be assessed via sleep lab or patient self-report
Nonprimary endpoint		
	Cardiac failure (3)	Minnesota Living with Heart Failure Questionnaire
	Crohn's disease (33)	• Inflammatory Bowel Disease Questionnaire (IBDQ) • EuroQol-5D (EQ-5D) • SF-36
	Psoriasis (15)	• Psoriasis area and severity index (PASI) (patient-reported) • Dermatology Life Quality Index (DLQI) • Dermatology Quality of Life Scales (DQOLS) • Psoriasis Disability Index (PDI) • Psoriasis Life Stress Inventory (PLSI)
	Sepsis (23)	SF-36
Primary and nonprimary endpoint		
	Ankylosing spondylitis (38)	Pain (pain at night due to AS; pain [without time restraints] due to AS): • VAS • Numeric rating scale (NRS) • Refer to a recent past period (e.g., the past week or the past 48 hours) Physical function: • Bath Ankylosing Spondylitis Functional Index (BASI) Dougados Functional Index (DFI) Complementary endpoints: • "…asking the patients to inform on his/her global status during a recent past period (for example last week)," • "Quality of life may be assessed either using some specific questionnaires (e.g. ASQoL) or general instruments (e.g. SF-36)."
	Osteoarthritis (39)	• WOMAC • Lequesne Index for osteoarthritis in hip or knee
	Smoking cessation (36)	Withdrawal: • Wisconsin Smoking Withdrawal Scale • Minnesota Nicotine Withdrawal Scale • Cigarette Withdrawal Scale Craving: • Brief Questionnaire of Smoking Urges
	Rheumatoid arthritis (12)	Primary or secondary: • Patient's global assessment of disease activity (VAS) • Pain score (patient's assessment of pain VAS or Likert scale) • Physical function (assessed by patient, e.g., Health Assessment Questionnaire [HAQ]; Arthritis Impact Measure Scales [AIMS] [function and quality of life]) Supportive: • Emotional and social function (AIMS-1) • Quality of life (RA-specific, e.g., AIMS; SF-36, or generic tests)

FDA Results

- Only one quarter (26%) of the FDA guidance documents included recommendations or statements regarding PROs in clinical investigations of medicinal products.
- PROs were included in guidance documents dating back to 1977, and almost all (79%) of the identified guidance documents predated the FDA draft guidance on the use of PROs (i.e., were issued before February 2006) (**Table 4**).
- Among the FDA guidance documents, PROs were indicated as primary endpoints (n = 6) and nonprimary endpoints (n = 8) (**Table 5**).
- **Table 6** presents the specific PRO measures mentioned within some of the FDA guidance documents.

Table 4. FDA Guidance Documents That Mention PROs (N = 14)

	Title	Disease	Date Issued
1	Guidelines for the Clinical Evaluation of Antianxiety Drugs	Anxiety	September 1977
2	Guidelines for the Clinical Evaluation of Antidepressant Drugs	Depression	September 1977
3	Guidelines for the Clinical Evaluation of Hypnotic Drugs	Insomnia	September 1977
4	Guidelines for the Clinical Evaluation of General Anesthetics	Anesthesia	May 1982
5	Guidelines for the Clinical Evaluation of Local Anesthetics	Anesthesia	May 1982
6	Clinical Development Programs—MDI and DPI Drug Products	Respiratory	September 1994
7	Oncologic Drugs Advisory Committee Discussion on FDA Requirements for Approval of New Drugs for Treatment of Colon and Rectal Cancer (I)	Oncology	March 1998
8	Guidelines for the Clinical Evaluation of Psychoactive Drugs in Infants and Children	Psychiatric disorders	March 1998
9	Guidance for Industry Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)	Rheumatoid arthritis	February 1999
10	FDA Requirements for Approval of Drugs to Treat Non-Small Cell Lung Cancer	Non-small cell lung cancer	January 2001
11	Guidance for Industry: Cancer Drug and Biological Products Clinical Data in Marketing Applications	Oncology	October 2001
12	Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds Developing Products for Treatment	Cutaneous wound treatment	June 2006
13	Guidance for Industry Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children	Allergic rhinitis/asthma	March 2007
14	Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics	Oncology	May 2007

Table 5. Therapeutic Area Summary for FDA Guidance Documents Requiring or Suggesting PROs

PROs Required (n = 6)	PROs Suggested (n = 8)
Allergic rhinitis/asthma	Anxiety
Local anesthesia	General anesthesia
Insomnia	Cutaneous wound treatment
Oncology	Depression
Rheumatoid arthritis	Non-small cell lung cancer
Respiratory	Oncology (n = 2)
	Psychiatric disorders

Table 6. PRO Measures Mentioned in Some FDA Disease-Specific Guidance Documents

Endpoint Heirarchy[a]	Therapeutic Area (Guidance No.)	PRO Mentioned
Primary		
	Allergic rhinitis/asthma (13)	…asthma symptom scores, and use of rescue medication should be recorded in daily diaries. For allergic rhinitis studies, efficacy assessments should include nasal symptom scores and use of rescue medication recorded in patient diaries.
	Local anesthesia (5)	Pain relief
	Insomnia (3)	Subjective postsleep questionnaire (include time to sleep onset, total sleep time, number of nighttime and early morning awakenings, hangover effects, and sleep quality)
	Oncology (14)	For the improvement of signs and symptoms or QOL assessments to be used as primary endpoints to support cancer drug approval, the FDA should be able to distinguish between improvement in tumor symptoms and lack of drug toxicity
	Rheumatoid arthritis (9)	• Reduction in the signs and symptoms of rheumatoid arthritis (signs and symptoms and patient global) • Prevention of disability: – Health Assessment Questionnaire (HAQ) – Arthritis Impact Measure Scales (AIMS) – Adequately validated measures for use as the primary outcome measure • HRQL: – Since the full effect of RA on a patient is not captured without the use of more general HRQL measures, a validated measure such as the SF-36 should also be collected and patients should not worsen on these measures over the duration of the trial.
	Respiratory (6)	Should include ongoing measurements (e.g., diary symptom scores)

[a] Endpoint hierarchy understood based on context within guidance document.

Categories of PRO Statements in EMA and FDA Guidance Documents

- The majority of PRO statements referred to measures of signs and symptoms, followed by measures of functioning and feeling (**Table 7**).

Table 7. Categories of PRO Statements in Guidance Documents

	EMA[a] (n = 39)		FDA (n = 14)	
Signs/symptoms	23	59%	12	86%
Function/feeling	18	46%	8	57%
Health-related quality of life	18	46%	3	21%
Patient global rating	8	21%	4	29%

[a] PRO statement categories are not mutually exclusive.
[b] If multiple endpoints (e.g., primary and nonprimary) were required or suggested, then only the characterization of the highest endpoint in the hierarchy is summarized.

Limitations

- Only adopted EMA guidance documents were reviewed.
- Only final FDA guidance documents were reviewed.
- FDA guidance documents can exist in draft form for years; these drafts may include references to PROs.

Conclusions

- PRO data in many disease areas are viewed by regulatory agencies as supportive evidence of a primary endpoint; in some instances, a PRO may represent a primary endpoint.
- PRO data are essential in the support of product submissions to regulatory stakeholders, especially within the EMA.
- The majority of references to PROs within product development guidance documents continue to be oriented toward the assessment of signs and symptoms.

References

1. European Medicines Agency (EMA). Scientific guidelines for human medicinal products. Available at: http://www.ema.europa.eu/htms/human/humanguidelines/efficacy.htm. Accessed November 2009.
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