# Use of Patient Reported Outcomes to Support FDA Approval Decisions

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Societal Benefits of Medicines: Session 4
Recognition of PROs in Approval and Labelling of Medicines

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DIA EuroMeeting -- Lisbon, Portugal March 7-10, 2005

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PRO data in 30% of labels for new products

PRO assessments are used in clinical trials to

- Describe patient populations
- Characterize disease severity
- Determine eligibility for trials
- Evaluate treatment effects
  - Record otherwise unknowable information
  - Corroborate other endpoints
  - Help evaluate tradeoff between benefit & risk of tx

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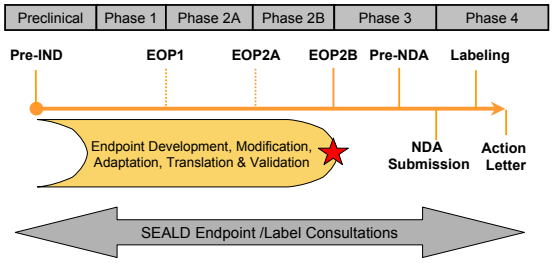
## Patient Reported Outcomes and Streamlining the Critical Path

"For many therapeutics, effectiveness criteria are best defined by the practitioners and patients who use the products. Much work needs to be done on clinical trial designs and patient-driven outcome measures to ensure that endpoints in new therapeutic areas accurately reflect patient needs and values. Community (health professional and patient) consensus on appropriate outcome measures and therapeutic claims can lay a clear development path for new therapeutics, especially when there is international regulatory harmonization."





## Critical Path Milestones for PRO Endpoint Discussions








## Study Endpoint and Label Development (SEALD) Team

SEALD team oversees labeling development and study endpoint quality initiatives for all Review Divisions in CDER Office of New Drugs (OND)

SEALD Team works closely with CBER and CDRH on cross-cutting policy initiatives for labeling development and study endpoints

SEALD Team Members:

**Laurie B. Burke**, R.Ph., M.P.H., Director
**Jane A. Scott**, Ph.D., Study Endpoints Reviewer
**Jeanne M. Delasko**, R.N., M.S., Label Initiatives Specialist
**William F. Pierce**, Pharm.D., Label Initiatives Specialist
**Raquel A. Peat**, M.S., M.P.H., Regulatory Project Officer

## Study Endpoint and Label Development (SEALD) Team

SEALD Team responsibilities include:

- lead OND initiatives on endpoint development, validation, interpretation, and representation in labeling and advertising, including policy development for PROs
- lead OND labeling development initiatives including policy development and implementation of the pending Physician Labeling Rule (PLR) and Structured Product Labeling (SPL).
- develop tools for implementation of endpoint and labeling initiatives including Target Package Profile (TPP), pharmacologic classification terminology standards and standards for OND labeling development processes.
- coordinate with national, international, industry and academic groups on issues related to study endpoints and medical product labeling.





## Draft Guidance on PROs

1. FDA has developed a draft guidance for industry "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims" that will be published for public comment when it completes the review and clearance process.
2. EMEA's Committee for Medical Products in Human Use published "Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products" last year.





## EMEA and FDA Guidance Discussions

FDA and EMEA shared draft versions of their guidance documents and discussed the documents in a meeting prior to publication of the EMEA guidance. Based on that meeting, FDA & EMEA agreed that:

- **both guidance documents describe expectations for adequate measurement of endpoints reported by patients that are used to support medical product claims**
- **the guidance documents differ primarily in their focus**
  **EMEA: only HRQL**
  **FDA: all PRO endpoints**
- **PRO is not just another name for HRQL; HRQL is a multidimensional concept that is measured using PROs, but PROs include many other measurement concepts**

PRO issues consulted to SEALD Team 2004

1. Defining a measurement concept that represents the primary clinical benefit of treatment AND defines the diagnosis or indication for treatment

| |
|---|
| **Acute exacerbations of chronic bronchitis (AECB)** |
| **Chronic obstructive pulmonary disease (COPD)** |
| **HIV-associated adipose redistribution syndrome (HARS)** |
| **Chronic spinal cord injury** |
| **Premature ejaculation** |
| **Fatigue due to anemia in elderly** |
| **Fatigue due to anemia with hepatitis C** |
| **Female sexual dysfunction** |
| **Male sexual dysfunction** |





PRO issues consulted to SEALD Team 2004

2. Defining a new measurement concept within a well-defined condition (secondary endpoint)

| |
|---|
| Patient-perceived impact of insomnia |
| Fatigue, overall health status with anemia |
| Vitality, well-being, physical function with diabetes |
| Reduction in opioid consumption with pain treatment |





PRO issues consulted to SEALD Team 2004

3. Global item (clinician or patient-reported) to support general claims

| | |
|---|---|
| Dyspepsia | Relief of symptoms, treatment satisfaction |
| IBS | Adequate relief or global improvement |
| Xerostomia secondary to radiation | Relief of dry mouth symptoms |
| CHF | Global clinical status |
| Breast cancer w/brain mets | Time to functional independence |

## PRO issues consulted to SEALD Team 2004

| | | |
|---|---|---|
| 4. Evaluate a responder definition | Cystic fibrosis<br>Cancer | Respiratory symptoms; physical functioning<br>Time to symptom progression or return of symptoms |
| 5. Define and interpret a minimum important difference between group means | Female sexual dysfunction<br>Chronic cough | Satisfying sexual events<br>HRQL, reduced clinical burden of cough |
| 6. Evaluating pediatric PRO development and validation | Cystic fibrosis<br>GERD<br>Viral warts | Respiratory symptoms, physical functioning<br>Symptoms<br>HRQL |



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## PRO issues consulted to SEALD Team 2004

| | | |
|---|---|---|
| 7. Electronic PRO data capture validation | low back pain;<br>IBS & dyspepsia<br>Glioblastoma multiforme | Time to pain relief<br>Symptom relief<br>Symptoms (using IVRS) |
| 8. Patients must recall experience over an extended time (>24-48 hours) | COPD<br>Various cancers<br>Sleep<br>Rapid ejaculation<br>Stroke | Dyspnea<br>Fatigue, pain, function,<br>Sleep quality<br>Control of ejaculation<br>Stroke recovery |
| 9. Interpretation of HRQL results when not all domains respond to treatment | Irritable bowel syndrome;<br>Postmenopausal women with breast cancer | "HRQL" replaced with individual symptoms or symptom domains |



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## PRO issues consulted to SEALD Team 2004

| | | |
|---|---|---|
| 10. Visual analog scale with no anchoring marks | Xerostomia, Sjogrens | Relief of dry mouth symptoms |
| 11. Inappropriate use of single items from a multi-item scale | NSCLC | Dyspnea, cough, pain |
| 12. Multiple endpoints without link to study objectives or statistical analysis plan | Type 2 diabetes | HRQL assessment battery |

## Common Concerns Noted in SEALD Endpoint Reviews

1. The concept to be measured is too general in nature to define clearly or measure well.
2. The content validation and development do not adequately assess the appropriateness for the intended population.
3. The measure is created "just in time" for phase 3, so there's little information on responsiveness and interpretation of changes observed with the measure.
4. Measurement of pain and other somatic symptoms in young children is very challenging.





## Common Concerns Noted in SEALD Endpoint Reviews

5. Patient reported symptom instruments are created by clinicians but do not reflect the symptoms that patients see as most troubling and most likely to prompt them to visit their doctor (e.g., chronic respiratory illnesses that have exacerbations).
6. Documentation of development/validation studies (what was done, decisions made, item reduction, samples studied, etc.) is insufficient.





## Conclusions

1. Adequate measurement of endpoints is critical for product labelling and advertising claims
2. FDA sees patient reported data as one of many acceptable sources of information for evaluating new products
3. FDA does not equate PRO and Quality of Life
4. Adequately developed and validated PROs are appropriate endpoints to support labelling and advertising claims if the measurement concept adds value to what is known about the treatment effects

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## Linking Desired Claims to PRO Endpoint Measures