



RTI HEALTH SOLUTIONS®

Date

Patient Reported Outcomes

Presented by: Ari Gnanasakthy
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9th Feb 2015

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Engaging with payers and physicians to support market access

The Goal of Development Program

- Provide added benefit for patients in terms of how they live their lives
 - Improved survival
 - Improved function in daily lives
 - Decreased symptoms

- Too much regulatory focus → possibility of missed opportunities





Patrick D. Aging in Motion. March 28, 2014.

PRO data can make all the difference



Hemoglobin A1c levels are not particularly meaningful to patients more interested in heading off hypoglycemia events. Panel votes to approve . . . and view that a hypoglycemia benefit was not shown.



Sue Sutter, Afrezza review shows need for patient driven endpoints in diabetes, The Pink Sheet, 1 April 2014

PRO data can make all the difference



“It was a secondary endpoint, but in our mind this is why we gave the application full approval. One could quibble about the importance of reduction in spleen size, but with reduction in all the symptoms, full approval was warranted”



Erin McCallister & Steve Usdin, A PROfessional trial, BIO Century, Dec. 5 2011

What is a Patient-Reported Outcome?

- A measurement of any aspect of a patient's health status that comes directly from the patient without interpretation from anyone else
 - Can range from symptom frequency, duration, or severity to more complex issues of health-related quality of life, activities of daily living, etc.
 - Can be assessed through direct self-report or interview administration
 - Measured through individual items, subscales, or full questionnaires administered via electronic (e.g. handheld diary, IVRS, tablet) or paper/pencil format

Source: FDA Guidance, 2009. <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>.

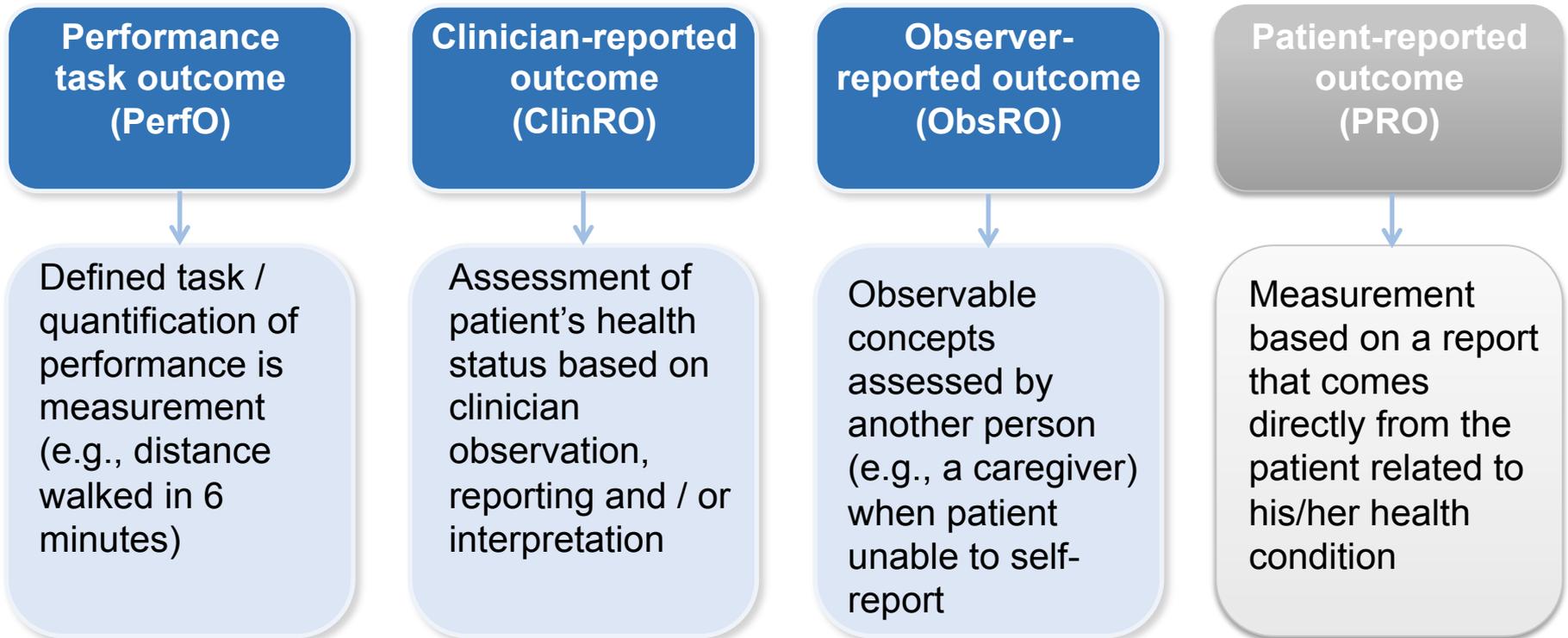
Value of Patient-Reported Outcomes (PRO)

- Some treatment effects known only to patient
- Physiologic endpoints may not be the best predictors of treatment benefit
 - Sometimes poor correlations between objective and PRO measures (i.e., FEV1 and asthma symptoms; exercise capacity and activities of daily living) suggest we are capturing unique information
- Translate the patient's voice into scientific and commercial messages
- Better quantify how products benefit patients
- Compete on the basis of something other than price alone
- Improve medical outcomes from the patient's point of view

PROs and Related Measures

Clinical outcome assessments (COAs) measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions

FDA <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm>



Patient-Reported Outcomes Allow a Holistic View of Treatment Effects

Assessing disease activity and treatment outcomes

Physiological

- Biomarkers
- Lab values & tests
- Functional tests
- Blood tests
- Biopsies
- Tolerance tests
- Vital signs

Clinician

- Signs
- Physical examination
- Visual inspection
- Palpation
- Auscultation
- Clinical impression

Patient

- Experience
- Symptoms
- Activity tolerance
- Cognitive function
- Physical function
- Psych distress
- Rx satisfaction

Caregiver

- Experience
- Symptoms
- Activity limitations
- Cognitive function
- Physical function
- Psych distress
- Burden

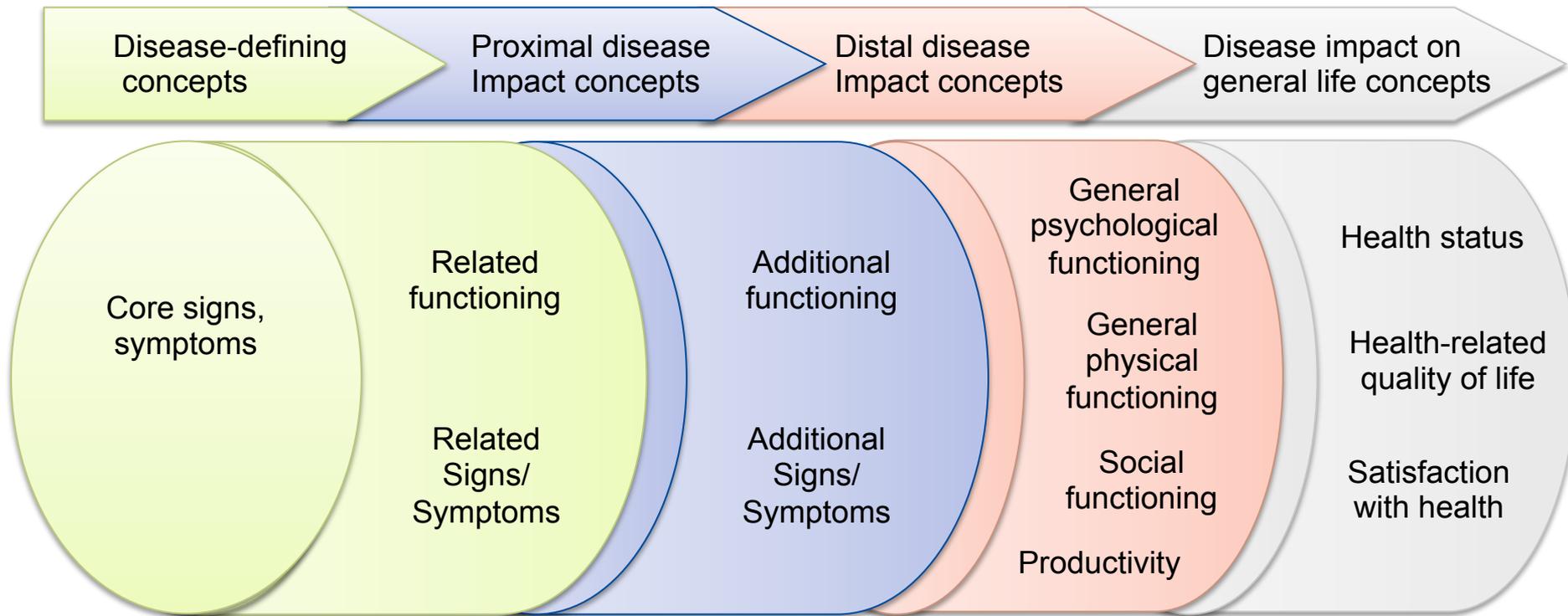
“ Subjectivity ”

Common Types of Patient-Reported Outcome Measures

Type of PRO Measure	Example Coverage/Domains	PRO Measures
Symptoms	<ul style="list-style-type: none"> • Pain • Fatigue • Wheezing • Depression 	0 – 10 numeric rating scale Fatigue Severity Scale Asthma Symptom Diary Beck Depression Inventory
Functioning	<ul style="list-style-type: none"> • Emotional functioning • Productivity • Activities of daily living 	Hospital Anxiety and Depression Scale Work Productivity and Activity Impairment Questionnaire Katz ADL
Health status	<ul style="list-style-type: none"> • Multiple domains of functioning 	SF-36 Sheehan Disability Scale
Health-related quality of life	<ul style="list-style-type: none"> • Impact of health on a patient's subjective sense of well-being 	Cystic Fibrosis QoL Questionnaire
Treatment satisfaction	<ul style="list-style-type: none"> • Satisfaction with medication 	Treatment Satisfaction Questionnaire for Medication
Utility	<ul style="list-style-type: none"> • Health status for the purpose of computing QALYs 	EQ-5D

Patient-Reported Concepts of Interest

Proximal to Distal Impacts on Treatment Benefit



Two General Types of Patient-Reported Outcome Measures

- Generic PRO measures
 - Designed to be used by any population
 - Intended to cover a broad aspect of the concept being measured
 - Can be used to compare one population to another or to compare scores in a specific population to normative scores

- Disease-specific PRO measures
 - Designed to assess concerns that are most important for a given population
 - May be more sensitive and therefore more likely to detect differences and changes in scores when they occur in response to interventions

Example of Each Questionnaire Type

Your Health in General

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully, and mark an **X** in the one box that best describes your answer. *Thank you for completing this survey!*

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

SF-36v2™ Health Survey © 1996, 2000 by QualityMetric Incorporated and Medical Outcomes Trust – All Rights Reserved
SF-36 is a registered trademark of Medical Outcomes Trust
(SF-36v2 Standard, US Version 2.0)

Generic


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PROTOCOL NAME OR NO TRIAL CODE	ID	Center No. _____ Subject No. _____	Visit # _____
		Subject's initials _____ 1. 2. fam. _____	
		Visit Date _____ day month year	

Patient Reported Indices of Multiple Sclerosis (PRIMUS) - Activities

Please read this carefully. This booklet asks about your experience of having MS. Please follow carefully the instructions for each section and choose the response that best applies to you.

Please describe your ability to do each of the 15 activities listed below **during the last week - without the use of aids (for example: cane, walker, wheelchair) or assistance.**

Please mark only one box for each activity.

Were you able to ...	Able to do on own without difficulty	Able to do on own with difficulty	Unable to do on own
1. ... do light jobs around the house or garden	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. ... do heavy jobs around the house or garden	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. ... get out of bed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. ... get dressed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. ... rise from sitting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. ... stand for a short time	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. ... walk around inside the house (not including using the stairs)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. ... walk short distances outside the house	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. ... walk longer distances	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. ... carry heavy items	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. ... climb a flight of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. ... bathe (includes hand bath, bath or shower)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. ... dry yourself thoroughly after bathing (includes hand bath, bath or shower)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. ... prepare food	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. ... shop for groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

qpl.S063_1 PRIMUS-Act v.II-English/US 1 of 1 © Galen Research 2006

Disease-Specific

Generic vs. Disease-Specific Instruments

Instrument	Advantages	Disadvantages
Generic	<ul style="list-style-type: none"> • Investigators and other key stakeholders (e.g., clinicians) may be familiar with instrument • Competitors may have used instrument in their trials • Can be used to compare one population to another or to compare scores in a specific population to normative scores 	<ul style="list-style-type: none"> • May miss important aspects of experience • More likely to ask questions that are irrelevant to group under study • Potential to alienate respondents • Greater potential for missing data • Generally less sensitive to treatment effects
Disease-specific	<ul style="list-style-type: none"> • Highly relevant to patient group under study • Content more likely to cover all important aspects of patients' experience • Less like to pose irrelevant questions • Respondents feel that their experience is valued • Reduced potential for missing data • Likely to have greater responsiveness 	<ul style="list-style-type: none"> • Where new instruments are needed, they may be time consuming and costly to develop • Key stakeholders may be unfamiliar with new instruments

What is a Label Claim?

- Statement or implication of treatment benefit
 - Evidence that the treatment has a positive impact on a concept of interest
 - How a patient feels or *functions* in daily life
 - How long a patient *survives*
 - May relate to safety or efficacy

Cough Suppression

Heroin was commercially developed by Bayer Pharmaceutical and was marketed by Bayer and other companies (c. 1900) for several medicinal uses including cough suppression.

THE NEW YORK MEDICAL JOURNAL 39

BAYER PHARMACEUTICAL PRODUCTS

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PROTARGOL
The anti-erythematous

EUROPHEN
The sedative solution

CREOSOTE CARB
The cough suppressant

QUINALGEN
The anti-rheumatic

PIPERAZINE
The sedative

HEROIN-HYDROCHL.
The effective for coughs

GUAIACOL CARB
The analgesic and antipyretic

HEROIN
The sedative for coughs

LYCETOL
The uric acid solvent

FERRO-SOMATOSE
The iron and potassium salt

SOMATOSE
The iron and potassium salt

PHENACETIN
The analgesic

HEMICRANIN
The specific for leishman

SULFONAL
The uric acid solvent

SYCOSE
The uric acid solvent

TRIONAL
The uric acid solvent

SALOPHEN
The anti-rheumatic and antineuralgic

FARBENFABRIKEN OF ELBERFELD CO.

40 STONE STREET, NEW YORK.

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 (Registered March 1885.) See other side.

Dr. Batty's
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ASTHMA CIGARETTES
 (ESTD 1893)

Travel Tip-



Wherever you go, carry **PHILLIPS' TABLETS**

"ON THE SPOT" RELIEF FROM UPSET STOMACH



Wherever you go, upset stomach, gas, heartburn or other symptoms of acid indigestion are liable to cause distress. So for on-the-spot relief carry delightfully flavored Phillips' Tablets with you. Phillips' Tablets will make you feel better—almost instantly—because they contain one of the world's fastest anti-acids. Pack several pocket-size tins—as well as a bottle of 75 or 200 tablets—in your suitcase!

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NO DIET - NO BARS
 NO EXERCISE!
FAT
 the ENEMY that is shortening Your Life
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HOW? with **SANITIZED TAPE WORMS**
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"Pull the Cords"

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Double
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The only mechanism producing a concentrated, continuous massage of the chin and neck, dispelling flabbiness of the neck and throat, restoring a rounded contour to thin, scrawny necks and faces, bringing a natural, healthy color to the cheeks, erasing lines and wrinkles. Price only \$10. What better investment could be made? Sent postpaid immediately.

Free Booklet
 —giving valuable information on how to treat double chin and enhance facial beauty will be sent on request. Write at once to

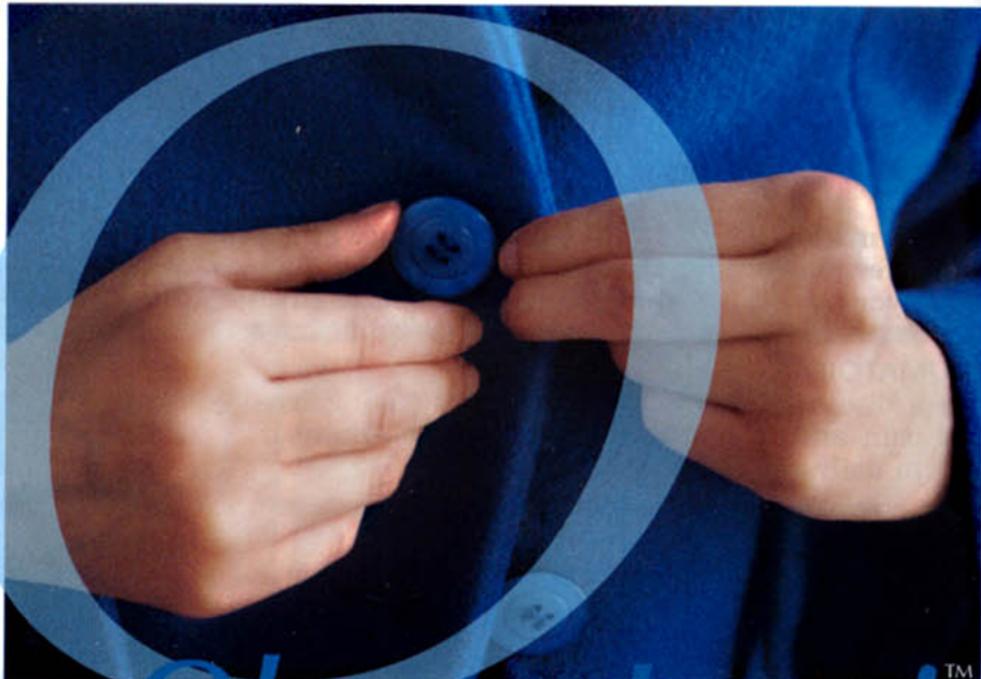
Prof. Eugene Mack
 507 Fifth Ave. Suite 1004 New York



Can you open this?



Fasten this?



Oh, yes I can! TM

Still having trouble with everyday things?

Maybe it's time for a change in treatment.

ORENCIA is an RA treatment that works differently. It's a prescription medication used to treat adults with moderate to severe RA who have not been helped enough by other medications for RA. It's been shown to:

- Relieve the pain, swelling, and fatigue of RA*
- Control the advance of joint damage*
- Help improve physical and emotional health-related quality of life*

Vyvanse: Now approved for adults with ADHD.

This is what successful
ADHD management
could look like.

Fran's ADHD symptoms weren't controlled during her day. She had trouble focusing and finishing her work.

In a clinical study of adults with ADHD, once daily Vyvanse significantly improved symptoms of inattention (e.g. lack of focus), hyperactivity, and impulsivity within one week.

Ask your doctor about Vyvanse.
1-866-630-1283, www.vyvanse.com

FOR ADULTS WITH ADHD

Vyvanse[™] 
lisdexamfetamine
dimesylate capsules

IMPORTANT SAFETY INFORMATION

Vyvanse is indicated for the treatment of ADHD. Efficacy based on two controlled trials in children aged 6 to 12 and one controlled trial in adults.

Tell the doctor about any heart conditions, including structural abnormalities, that you, your child, or a family member, may have. Inform the doctor immediately if you or your child develops symptoms that suggest heart problems, such as chest pain or fainting.

Vyvanse should not be taken if you or your child has advanced disease of the blood vessels (arteriosclerosis); symptomatic heart disease; moderate to severe high blood pressure; overactive thyroid gland (hyperthyroidism); known allergy or unusual reactions to drugs called sympathomimetic amines (for example, pseudoephedrine); seizures; glaucoma; a history of problems with alcohol or drugs; agitated states; taken a monoamine oxidase inhibitor (MAOI) within the last 14 days.

Tell the doctor before taking Vyvanse if you or your child is being treated for or has symptoms of depression (sadness, worthlessness, or hopelessness) or bipolar disorder; has abnormal thought or visions, hears abnormal sounds, or

has been diagnosed with psychosis; has had seizures or abnormal EEGs; has or has had high blood pressure; exhibits aggressive behavior or hostility. Tell the doctor immediately if you or your child develops any of these conditions or symptoms while taking Vyvanse.

Abuse of amphetamines may lead to dependence. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events. These events have also been reported rarely with amphetamine use.

Vyvanse was generally well tolerated in clinical studies. The most common side effects reported in studies of Vyvanse were: children - decreased appetite, difficulty falling asleep, stomachache, and irritability; adult - decreased appetite, difficulty falling asleep, and dry mouth.

Aggression, new abnormal thoughts/behaviors, mania, growth suppression, worsening of motion or verbal tics, and Tourette's syndrome have been associated with use of drugs of this type. Tell the doctor if you or your child has blurred vision while taking Vyvanse.

Shire, your ADHD Support Company[™] © 2008 Shire US Inc. LDX2998 08/08

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Please see Patient Brief Summary of Full Prescribing Information on the following page.

Fran's ADHD symptoms weren't controlled during her day. She had trouble focusing and finishing her work.

In a clinical study of adults with ADHD, once daily Vyvanse significantly improved symptoms of inattention (e.g. lack of focus), hyperactivity, and impulsivity within one week.

What Constitutes a Label Claim in the US?

- May appear in any section of a product's FDA-approved labeling
 - Typically appears in the Indication or Clinical Studies section of the product label
 - May appear in product advertising
- Requires substantial evidence by regulation

PROs appearing in the label can be used for promotion

Guidance for the industry

- Draft PRO Guidance: published December 2006
- Final FDA PRO Guidance: published December 2009
- Guidance developed by the SEALD group within the Office of New Drugs (OND) at FDA
- SEALD serves as an advisory group to all reviewing divisions

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

Regulatory challenges

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A Review of Patient-Reported Outcome Labels in the United States: 2006 to 2010

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¹Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; ²RTI Health Solutions, Durham, NC, USA

ABSTRACT

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Reasons for Rejection of Patient-Reported Outcome Label Claims: A Compilation Based on a Review of Patient-Reported Outcome Use among New Molecular Entities and Biologic License Applications, 2006–2010

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¹RTI Health Solutions, Research Triangle Park, NC, USA; ²Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

ABSTRACT

Objectives: Previous analyses of patient-reported outcome (PRO) label claims concentrated only on successful label claims. The goal of this research was to explore the reasons why PRO label claims were denied and to compile regulatory feedback regarding the use of PROs in clinical trials. **Methods:** By using the Food and Drug Administration's Drug Approval Report Web page, all new molecular entities and biologic license applications assessed between January 2006 and December 2010 were reviewed. **Results:** Of 698 PRO label claims, 200 (28.7%) were denied. The most common reasons for denial were: (1) lack of fit for purpose, issues of study design, data quality or interpretation, statistical issues, administrative issues, and lack of demonstrated treatment benefit. **Conclusions:** Based on drug approval packages, nearly half (45%) of new molecular entity/biologic license application products in the years 2006 to 2010 included PROs in the clinical trials supporting their approval, yet this rate is not reflective of the rate of PRO label claims granted. Under the current regulatory environment, the rate of PRO label claims granted is 69%.

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Available online at www.sciencedirect.com
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 journal homepage: www.elsevier.com/locate/jval



Patient-Reported Outcomes

Assessment of PRO Label Claims Granted by the FDA as Compared to the EMA (2006–2010)

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ABSTRACT

Background: The US Food and Drug Administration (FDA) provides formal guidance for the use of patient-reported outcomes (PROs) in drug labeling claims, whereas the European Medicines Agency (EMA) does not. EMA-granted claims were more likely to include higher order concepts. Few (~12%) were granted the same label claims. Despite this, the majority of PRO label claims granted by the FDA and EMA were for the same label claims.

Four important takeaways . . .

- Sign and symptoms are the most likely candidates for PRO labels
- PRO labels are more likely for primary endpoints
- There are noticeable differences between the FDA and EMA
- Regulatory agencies are not the sole guardians of patients' voice

Patient reported outcomes

- Enable sponsors to understand what matters to the patient
- Enables stakeholders to evaluate new technologies in a holistic manner



That's all Folks!