Are patient-reported outcome (PRO) measures used in the evaluation of orphan drugs?

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BACKGROUND AND OBJECTIVES

- In its report published in February 2016, the IRDiRC concluded that the use of patient-reported outcome (PRO) measures is a necessity in clinical research on rare diseases because they measure the real benefits of the treatment from the patient's point of view.

- The objective of our study was to evaluate the extent to which PROs were used in the evaluation of orphan drugs authorized by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

METHODS

- On July 24, 2017, the websites of the FDA and the EMA were searched to retrieve all products approved with an orphan designation from 01/01/2002 to 30/06/2017 included. The year 2002 was chosen as a started point as it coincided with the date of the first approval of an orphan medicine by the EMA.
- The FDA Orphan Drug Product designation database was explored using the above dates as search criteria and limiting the results to only approved products. (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/). An excel file was downloaded with all the results.
- The Human Medicine section of the EMA website (http://www.ema.europa.eu/ema/) was browsed by type of approvals, selecting orphan medicines among the six possible choices (i.e., additional monitoring, generics, biosimilars, conditional approvals, exceptional circumstances and orphan medicines). An excel file was downloaded with all the results.
- The label (FDA) and the summary of product characteristics (SmPC - EMA) of all products were analyzed to find any mention of PRO used and found relevant by the agencies. If needed, the corresponding medical reviews (MR - FDA) or assessment reports (AR - EMA) were reviewed to clarify endpoint positioning and the name of the measure used.

RESULTS

Number of designations

- FDA: The search retrieved 410 orphan drug product designations, representing 298 different products (i.e., distinct NDAs and BLAs).
- EMA: The search retrieved 101 products including medicines with different indications and designations (n=119).
- The review of both datasets showed that EMA had 42 designations not included in the FDA dataset, leading to a single data set of 452 distinct designations.
- As it was decided not to review the products indicated for oncology purpose, a total of 194 designations were excluded, leaving 258 designations to review.

PRO labeling

- The review of the 258 designations revealed that only 45 designations included PRO claims in their labeling, i.e., 17.4% of the total (non oncology products). These 45 designations represented 42 different products of which 10 were common to both agencies.
- When PRO results were mentioned in the label, the measures were primarily focused on symptoms (e.g., dyspnea, fatigue, pain), rarely on functioning or health-related quality of life (HRQL). See Table 1 for all results. In few cases (e.g., CAPS, cystic fibrosis, acromegaly), measures were specific and developed for the rare condition).

CONCLUSIONS

- This review shows that the patient's perspective in the evaluation of orphan drugs is not fully implemented.
- The few mentions of PROs in FDA labels and EMA SmPCs are generally limited to study-specific symptom scale and legacy, generic instruments. Measures capturing the specific benefits of orphan drugs on functioning and HRQL are lacking.
- The high number of rare diseases, the small number of patients for each pathology, the lack of information on the natural history of certain diseases, or the association with significant disability and cognitive impairments, make the development of specific PRO measures an arduous task.
- One strategy to enhance the use of PRO measures in clinical research might be a wider use of measures of a specific function. A systematic codification of existing instruments measuring function, based on widely recognized categorizations such as ICF and Orphanet indexing, could be of great value to support cost-effective patient-centered clinical research in rare diseases.

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Table 1. EMA and FDA Orphan Products with PRO labeling (by alphabetical order of trade name)

# by Agency	INN	Trade Name	Approved Indication	Marketing Approval Date (YYYY/MM/DD)	Marketing Approval Holder	Type of PRO supporting label/SmPC	Name of PRO measure(s) used*	Primary endpoint	Secondary endpoint	Exploratory endpoint
EMEA/H/C/002737	riociguat	Adempas	Pulmonary arterial hypertension (PAH)	2014/03/27	Bayer	Symptoms (dyspnoea)	Borg CR 10 Dyspnea Scale*		✓	
NDA 021498	nitazoxanide	Alinia	Treatment of diarrhea caused by Cryptosporidium parvum in adults and adolescents	2005/06/16	Romark Laboratories	Symptoms (diarrhea)	Diary to record symptoms and diarrhea stools (categorized as watery or soft)	✓		
NDA 021498	nitazoxanide	Alinia	Treatment of diarrhea caused by Giardia lamblia in adults and adolescents	2005/06/16	Romark Laboratories	Symptoms (diarrhea)	Diary to record symptoms and diarrhea stools (categorized as watery or soft)	✓		
BLA 125444	coagulation factor IX (recombinant), Fc fusion protein	Alprolix	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)	2014/03/28	Bioverativ Therapeutics	Symptoms (bleeding episodes) Hemostatic effect	Diary to record bleeding episodes 4-point bleeding response scale	✓	✓	
EMEA/H/C/004142	eftrenonacog alfa	Alprolix	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)	2016/05/12	Swedish Orphan Biovitrum	Symptoms (bleeding episodes)	Diary to record bleeding episodes	✓		
NDA 022250	dalfampridine	Ampyra	Treatment to improve walking in patients with multiple sclerosis	2010/01/22	Acorda Therapeutics	Physical functioning (walking ability)	Multiple Sclerosis Walking Scale (MSWS-12)*		✓	
BLA 125249	rilonacept	Arcalyst	Treatment of Cryopyrin-Assisted Periodic Syndromes (CAPS)	2008/02/27	Regeneron Pharmaceuticals	CAPS Symptoms (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue)	Daily Health Assessment Form (DHAF)	✓		
EMEA/H/C/001047	rilonacept	Rilonacept Regeneron (previously Arcalyst)	Treatment of Cryopyrin-Assisted Periodic Syndromes (CAPS)	2009/10/23	Regeneron UK	CAPS symptoms (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue) Disease activity (flares) - Patient's global assessment of disease activity Daily Activities - Patients' assessment of the degree of limitation of their daily activities	Daily Health Assessment Form (DHAF)	✓ ✓ ✓	✓	
NDA 208082	d6-tetrabenazine, deutetrabenazine	Austedo	Treatment of chorea associated with Huntington's disease	2017/04/03	Teva Branded Pharmaceutical	Symptoms (patient global impression of change of overall Huntington's disease symptoms)	A patient-rated global impression of change* assessed how patients rated their overall Huntington's disease symptoms		✓	
NDA 050814	aztreonam	Cayston	To improve respiratory symptoms in cystic fibrosis (CF) patients with Pseudomonas aeruginosa	2010/02/22	Gilead Sciences	Symptoms (respiratory)	Questionnaire that asks patients to report on symptoms like cough, wheezing, and sputum production*	✓	✓	
EMEA/H/C/000996	aztreonam	Cayston	To improve respiratory symptoms in cystic fibrosis (CF) patients with Pseudomonas aeruginosa	2009/09/21	Gilead Sciences	Symptoms (respiratory)	Respiratory domain of the Cystic Fibrosis Questionnaire – Revised (CFQ-R)*	✓	✓	
BLA 125267	c1-esterase inhibitor (human)	Cinryze	Routine prophylaxis against angioedema attacks in patients with Hereditary Angioedema (HAE)	2008/10/10	Shire	Symptoms (HAE attacks: number, severity, duration)	Patients recorded all angioedema symptoms daily, severity and duration	✓ (number)	✓ (severity, duration)	
BLA 125506	human factor X	Coagadex	Treatment of patients with hereditary Factor X Deficiency	2015/10/20	Bio Products Laboratory	Symptom (hemostatic effect on bleeding episodes)	Bleed-specific ordinal rating scale of excellent, good, poor and un-assessable*		✓	
EMEA/H/C/003855	human coagulation factor X	Coagadex	Treatment of patients with hereditary Factor X Deficiency	2016/03/16	Bio Products Laboratory	Symptoms (hemostatic effect on bleeding episodes)	Bleed-specific ordinal rating scale of excellent, good, poor and un-assessable*		✓	
NDA 020610	balsalazide disodium	Colazal	Treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.	2006/12/20	Salix Pharmaceuticals	Symptoms (rectal bleeding, stool frequency)	Diary to record rectal bleeding, stool frequency	✓		
BLA 125385	factor XIII concentrate (human)	Corifact	For the routine prophylactic treatment of congenital factor XIII deficiency	2011/02/17	CSL Behring LLC	Symptoms (bleeding episodes)	Diary to record bleeding episodes	✓		
NDA 203952	levodopa and carbidopa	Duopa	Treatment of motor flucuations in patients with advanced Parkinson's disease	2015/01/09	AbbVie	Symptoms (off and on time)	Patient's Parkinson's Disease Diary	✓ (OFF)	✓ (ON)	
BLA 125487	antihemophilic factor (recombinant), Fc fusion protein	Eloctate	Treatment of adults and children with Hemophilia A (congenital Factor VIII deficiency) for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes	2014/06/06	Bioverativ Therapeutics	Symptoms (bleeding episodes) Hemostatic effect	Diary to record bleeding episodes A 4-point rating scale of excellent, good, moderate, and no response*	✓	✓	
BLA 101447	anti-inhibitor coagulant complex	Feiba	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and B patients with inhibitors	2013/12/16	Baxalta US	Symptoms (bleeding) Hemostatic effect	Diary to record bleeding episodes Pre-specified four-point scale of excellent, good, moderate, or none*	✓	✓	
NDA 022150	icatibant	Firazyr	Treatment of acute attacks of hereditary angioedema in adults 18 years of age and older	2011/08/25	Shire	Symptoms (HAE symptoms)	3-item composite visual analog score (VAS), comprised of averaged assessments of skin swelling, skin pain, and abdominal pain*	✓		
EMEA/H/C/000899	icatibant	Firazyr	Treatment of acute attacks of hereditary angioedema in adults 18 years of age and older	2008/07/11	Shire	Symptoms (HAE symptoms)	3-item composite visual analog score (VAS), comprised of averaged assessments of skin swelling, skin pain, and abdominal pain*	✓		
EMEA/H/C/004059	migalast	Galafold	Long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease	2016/05/26	Amicus Therapeutics	Symptoms (gastro-intestinal)	Gastrointestinal Symptoms Rating Scale (GSRS)*		✓	
BLA 125105	immune globulin infusion (human)	Gammagard Liquid	Maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN)	2012/06/22	Baxalta US	Physical function	Patients' assessment of physical functioning was measured by visual analog scale (VAS)*		✓	
NDA 022544	gabapentin	Gralise	For the management of postherpetic neuralgia	2011/01/28	Depomed	Symptoms (pain)	Daily electronic diary using an 11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst possible pain)*	✓		
BLA 125606	c1-esterase-inhibitor, human, pasteurized	Haegarda	For routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients	2017/06/22	CSL Behring	Symptoms (HAE attacks) Rescue medication	Diary to record HAE attacks and rescue medication	✓ (symptoms)	✓ (symptoms and rescue)	
BLA 125606	c1-esterase-inhibitor, human, pasteurized	Haegarda	Treatment of acute attacks of hereditary angioedema	2009/10/08	CSL Behring	Symptoms (HAE attacks) Rescue medication	Diary to record HAE attacks and rescue medication	✓ (symptoms)	✓ (symptoms and rescue)	
NDA 205677	tasimelteon	Hetlioz	Treatment of non-24-hour sleep-wake disorder	2017/01/31	Vanda Pharmaceuticals	Symptoms (duration, timing of nighttime sleep and daytime naps)	Duration and timing of nighttime sleep and daytime naps via patient-recorded diaries	✓		
EMEA/H/C/003870	tasimelteon	Hetlioz	Treatment of non-24-hour sleep-wake disorder	2015/07/03	Vanda Pharmaceuticals	Symptoms [sleep duration - Night-time Total Sleep Time (nTST), Day time Total Sleep Duration (dTSD)] and Global Functioning	Non-24 Clinical Response Scale (N24CRS)*	✓		
NDA 022399	gabapentin enacarbil	Horizant	Management of postherpetic neuralgia in adults	2012/06/06	Arbor Pharmaceuticals	Symptoms (pain intensity)	11-point PI-Numerical Rating Scale (0=no pain, 10=pain as bad as you can imagine)*	✓		
BLA 125582	recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)	Idelvion	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)	2016/03/04	CSL Behring	Symptoms (bleeding episodes)	Diary to record bleeding episodes	✓	✓	
EMEA/H/C/003955	albutrepenonacog alfa	Idelvion	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)	2016/05/11	CSL Behring	Symptoms (bleeding episodes)	Diary to record bleeding episodes	✓	✓	
BLA 125277	ecallantide	Kalbitor	Treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older	2014/03/28	Dyax	Symptoms (HAE Attacks)	Treatment Outcome Score (TOS)* Mean Symptom Complex Severity (MSCS)*	✓ TOS (E3) ✓ MCS (E4)	✓ TOS (E4) ✓ MCS (E3)	
BLA 125277	ecallantide	Kalbitor	Treatment of acute attacks of hereditary angioedema in patients 16 years of age and older	2009/12/01	Dyax	Symptoms (HAE Attacks)	Treatment Outcome Score (TOS)* Mean Symptom Complex Severity (MSCS)*	✓ TOS (E3) ✓ MCS (E4)	✓ TOS (E4) ✓ MCS (E3)	
NDA 203188	ivacaftor	Kalydeco	Treatment of cystic fibrosis (CF) in patients age 6 years and older	2012/01/31	Vertex Pharmaceuticals	Symptoms (respiratory)	Cystic Fibrosis Questionnaire-Revised (CFQ-R)		✓	
EMEA/H/C/002494	ivacaftor	Kalydeco	Treatment of cystic fibrosis (CF) in patients age 6 years and older	2012/07/23	Vertex Pharmaceuticals	Symptoms (respiratory)	Cystic Fibrosis Questionnaire-Revised (CFQ-R)*		✓	
NDA 011366	dichlorphenamide	Keveyis	Treatment of primary hyperkalemic periodic paralysis, primary hypokalemic period paralysis, and related variants	2015/08/07	Strongbridge	Symptoms (muscle weakness)	Self-reported attacks of muscle weakness per week*	✓		
BLA 103950	anakinra	Kineret	Treatment of neonatal-onset multisystem inflammatory disease (NOMID)	2012/12/21	Swedish Orphan Biovitrum	Symptoms (NOMID symptoms)	Disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache*	✓		
NDA 203202	droxidopa	Northera	Treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy	2014/02/18	Lundbeck	Symptoms (orthostatic hypotension)	OHSA item 1 from the OHQ (dizziness, lightheadedness, or feeling like you might black out)*	✓		
EMEA/H/C/003821	nintedanib	Ofev	Treatment of Idiopathic Pulmonary Fibrosis (IPF)	2015/01/15	Boehringer Ingelheim	Health-related quality of life (HRQL)	St George's Respiratory Questionnaire (SGRQ)		✓	
EMEA/H/C/002697	macitentan	Opsumit	Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III	2013/12/20	Actelion Registration	Health-related quality of life (HRQL)	SF-36			✓
NDA 206038	lumacaftor/ivacaftor	Orkambi	Treatment of cystic fibrosis in patients age 12 years and older who are homozygous for F508del mutation in the CFTR gene	2015/07/02	Vertex Pharmaceuticals	Symptoms (respiratory)	Cystic Fibrosis Questionnaire-Revised (CFQ-R)*		✓	
NDA 022395	capsaicin	Qutenza	Management of neuropathic pain associated with postherpetic neuralgia	2009/11/16	Acorda Therapeutics	Symptoms (pain intensity)	Patients recorded their pain daily in a diary using an 11-point Numerical Pain Rating Scale (NPRS) ranging from 0 (no pain) to 10 (worst possible pain)*	✓		
NDA 021272	treprostinil	Remodulin	Treatment of pulmonary arterial hypertension.	2002/05/21	United Therapeutics	Symptoms (shortness of breath)	Borg CR 10 Dyspnea Scale*		✓	
BLA 125446	coagulation factor IX (recombinant)	Rixubis	Adults with Hemophilia B for routine prophylaxis to prevent or reduce the frequency of bleeding episodes.	2013/06/26	Baxalta US	Symptoms (bleeding) Hemostatic effect	Diary to record bleeding episodes Four point scale of excellent to poor	✓		
BLA 125495	c1-esterase inhibitor (recombinant)	Ruconest	Treatment of acute attacks of hereditary angioedema (HAE) in adult and adolescent patients	2014/07/16	Pharming Group	Symptoms (HAE Attacks)	Study 1: Treatment Effect Questionnaire (TEQ)*: the TEQ required patients to assess the severity of their attack symptoms at each affected anatomic location, using a seven-point scale ("much worse" to "much better" [TEQ Question 1]), and whether their symptoms had begun to decrease notably since receiving since receiving the study medication ("yes" or "no" [TEQ Question 2]) Studies 2 & 3: Patients scored their symptoms using a visual analog scale (VAS) ranging from 0-100mm	✓		
EMEA/H/C/002548	afamelanotide	Scenesse	Prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)	2014/12/22	Clinuvel UK	Symptoms (sunlight exposure without pain)	Patient diary cards. The diaries used in this study more distinctly capture the quantity of time spent in direct sunlight, by having the subjects record time outdoors as direct sunlight exposure or time in shade, for each 15 minute block of time spent outdoors.	✓		
EMEA/H/C/002052	pasireotide	Signifor	Signifor is indicated for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue	2012/04/24	Novartis Europharm	Health-related quality of life (HRQL)	Acromegaly Quality of Life questionnaire (AcroQoL)*		✓	
NDA 203255	pasireotide	Signifor LAR	Treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option	2014/12/15	Novartis Pharmaceuticals	Symptoms (acromegaly symptoms)	Not specified in FDA review. However, same study as EMA. EMA AR specifies: *The investigator asked the patient to score the following symptoms of acromegaly: headache, fatigue, perspiration, paresthesias, osteoarthralgia according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe)*		✓	
BLA 125166	eculizumab	Soliris	Treatment of paroxysmal nocturnal hemoglobinuria to reduce hemolysis	2007/03/16	Alexion Pharmaceuticals.	Symptoms (fatigue) Health-related quality of life (HRQL)	Functional Assessment of Chronic Illness Therapy-Fatigue and Fatigue Scale (FACIT-F and FACIT-Fatigue) EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30)		✓	✓
EMEA/H/C/000791	eculizumab	Soliris	Soliris is indicated in adults and children for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH)	2007/06/20	Alexion Europe	Symptoms (fatigue) Health-related quality of life (HRQL)	Functional Assessment of Chronic Illness Therapy-Fatigue and Fatigue Scale (FACIT-F and FACIT-Fatigue)* EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30)		✓	✓
EMEA/H/C/002155	tobramycin	Tobi Podhaler	Tobi Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in adults and children aged 6 years and older with cystic fibrosis	2011/07/20	Novartis Europharm	Treatment satisfaction	Treatment Satisfaction Questionnaire for Medication (TSQM)		✓	
BLA 125398	coagulation factor XIII A-subunit (recombinant)	Tretten	Routine prophylaxis of bleeding in patients with congenital Factor XIII A-subunit deficiency	2013/12/23	Novo Nordisk	Symptoms (bleeding episodes)	Diary to record bleeding episodes	✓		
BLA 12533	collagenase clostridium histolyticum	Xiaflex	Treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy	2013/12/06	Auxilium Pharmaceuticals.	Symptoms bother	Peyronie's Disease Questionnaire (PDQ) bother domain	✓		
NDA 021196	oxybate	Xyrem	Treatment of excessive daytime sleepiness in patients with narcolepsy	2005/11/18	Rare Disease Therapeutics.	Symptoms (excessive daytime sleepiness)	Epworth Sleepiness Scale (ESS)*	✓		
NDA 021196	oxybate	Xyrem	Treatment of cataplexy associated with narcolepsy	2002/07/17	Rare Disease Therapeutics	Symptoms (cataplexy attacks)	Diary to record cataplexy attacks.	✓		

The blue background indicate products approved by both agencies and with a PRO claim in their label or SmPC.
*Measures with an asterix (*) are clearly mentioned as such in the label or the SmPC. For the other products, names of the measures were retrieved from the assessment reports or medical reviews.