Regulatory considerations for rare disease drug development – A global perspective

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Rare diseases and need for Orphan drug designation

+ Estimated 6000-8000 rare diseases worldwide
+ Manufacturers needed incentive such tax credit, market exclusivity to offset cost of developing drugs for small population
+ US introduced orphan drug act in 1983
+ Amended Pharmaceutical Affairs Law in Japan -1993
+ Orphan drug program of Australia – 1998 Part 3B of therapeutic Goods Regulation 1990 ; introduced reform of orphan drug program in 2017
+ Regulation (EC) No 141/2000 for EU -2000
+ Canada proposed orphan drug program in 2012

Definition - Orphan Drug (US, EU)

+ "A drug or biologic intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug".

-- FDA Office of Orphan Products Development (OOPD)

+ "A medicine for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs"

-- European Medicines Agency

Proposed definition – Health Canada

+ Definitions would include a definition of the term "orphan drug" to mean a drug that meets the following criteria:
+ a. The drug is intended for the diagnosis, treatment, mitigation or prevention of a life-threatening, seriously debilitating, or serious and chronic disease or condition affecting not more than five in 10 thousand persons in Canada; and

+ b. The drug is not currently authorized by the Minister or if currently authorized, it will provide a potentially substantial benefit for the patient distinguishable from the existing therapy.

--Initial Draft Discussion Document for A Canadian Orphan Drug Regulatory Framework 2012

Update to Health Canada orphan drug framework

+ Health Canada says it has launched a new regulatory review of drugs and devices focused on improving access to drugs. "Many elements initially proposed as part of an orphan drug regulatory framework are now being considered more broadly for all drugs as part of this initiative"

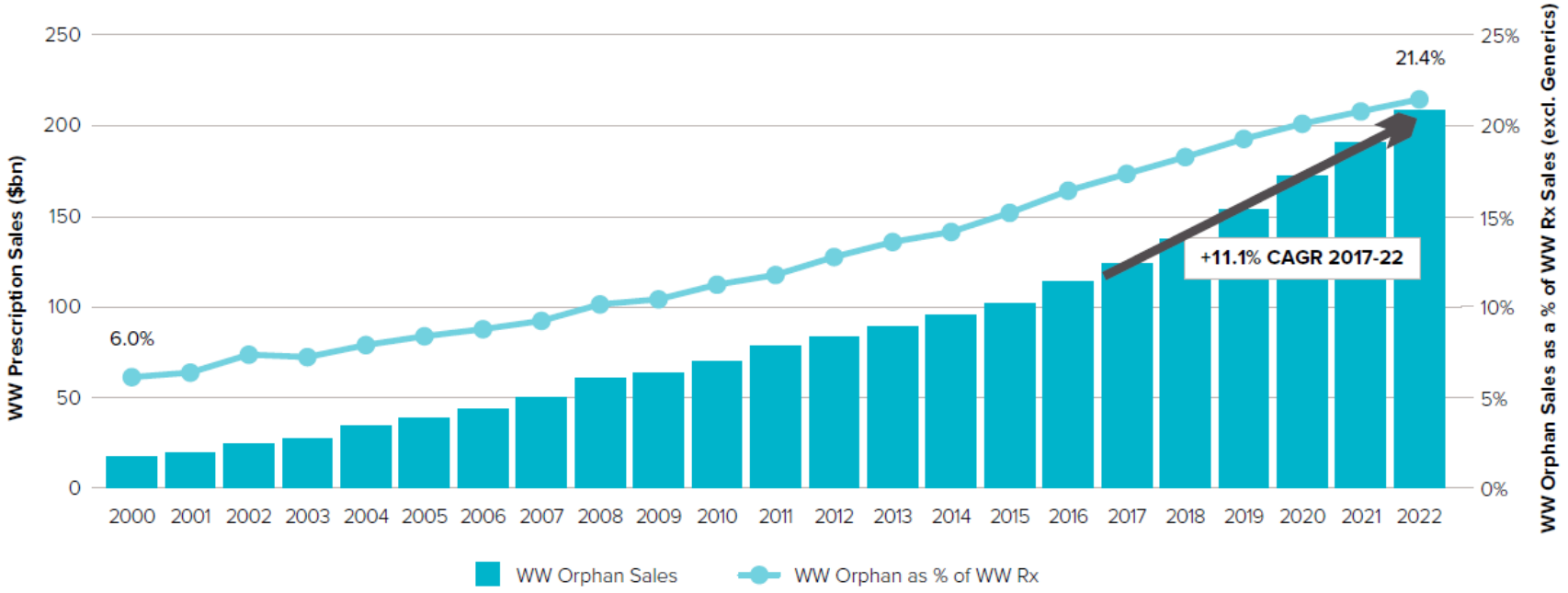
+ Matthew Herder, Director of the Health Law Institute at Dalhousie University, said the change in plans for an orphan drug framework is "a nice example of Health Canada maybe paying attention to the evidence."

http://nationalpost.com/news/politics/health-canada-gives-kiss-of-death-to-planned-policy-for-rare-disease-drugs

Future of orphan drugs

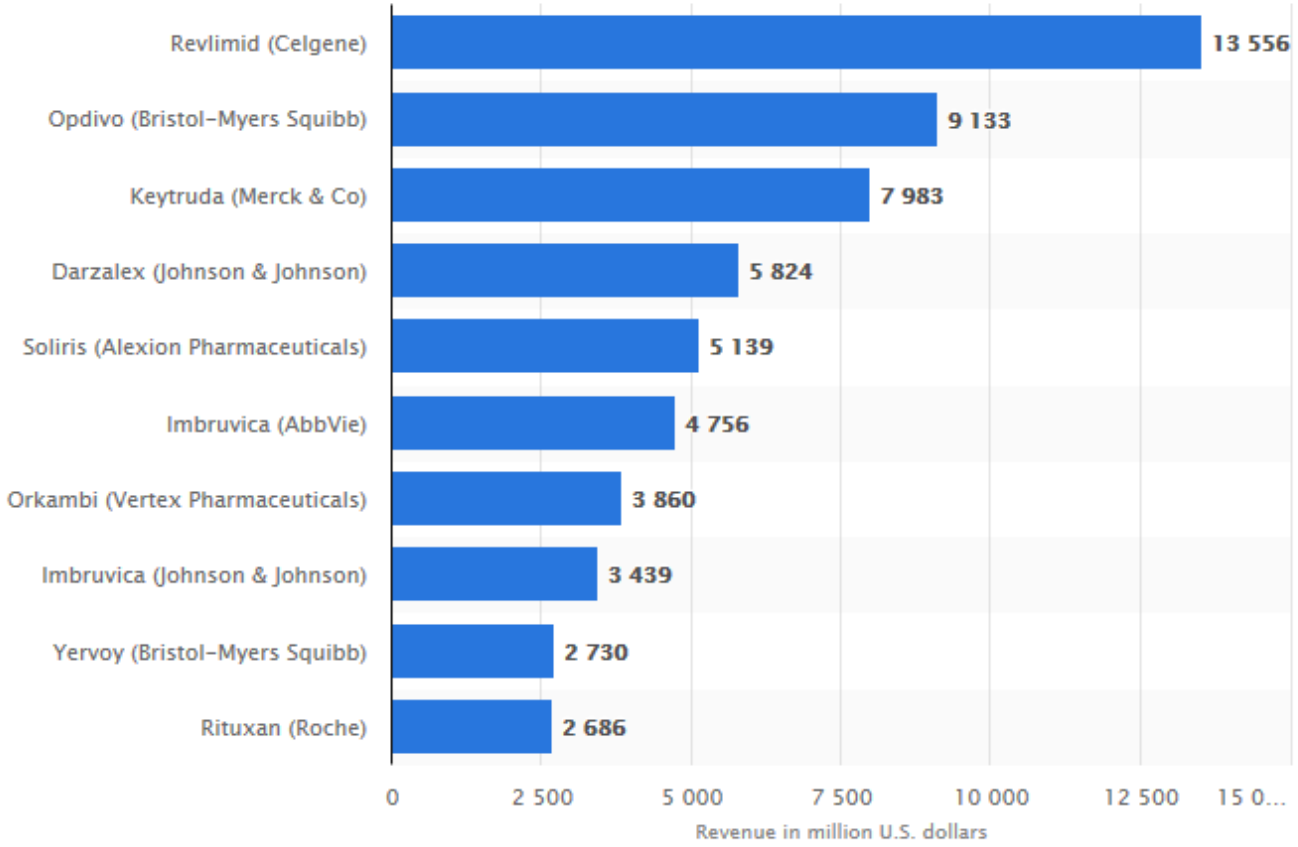
Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2000-2022)

Source: EvaluatePharma® February 2017



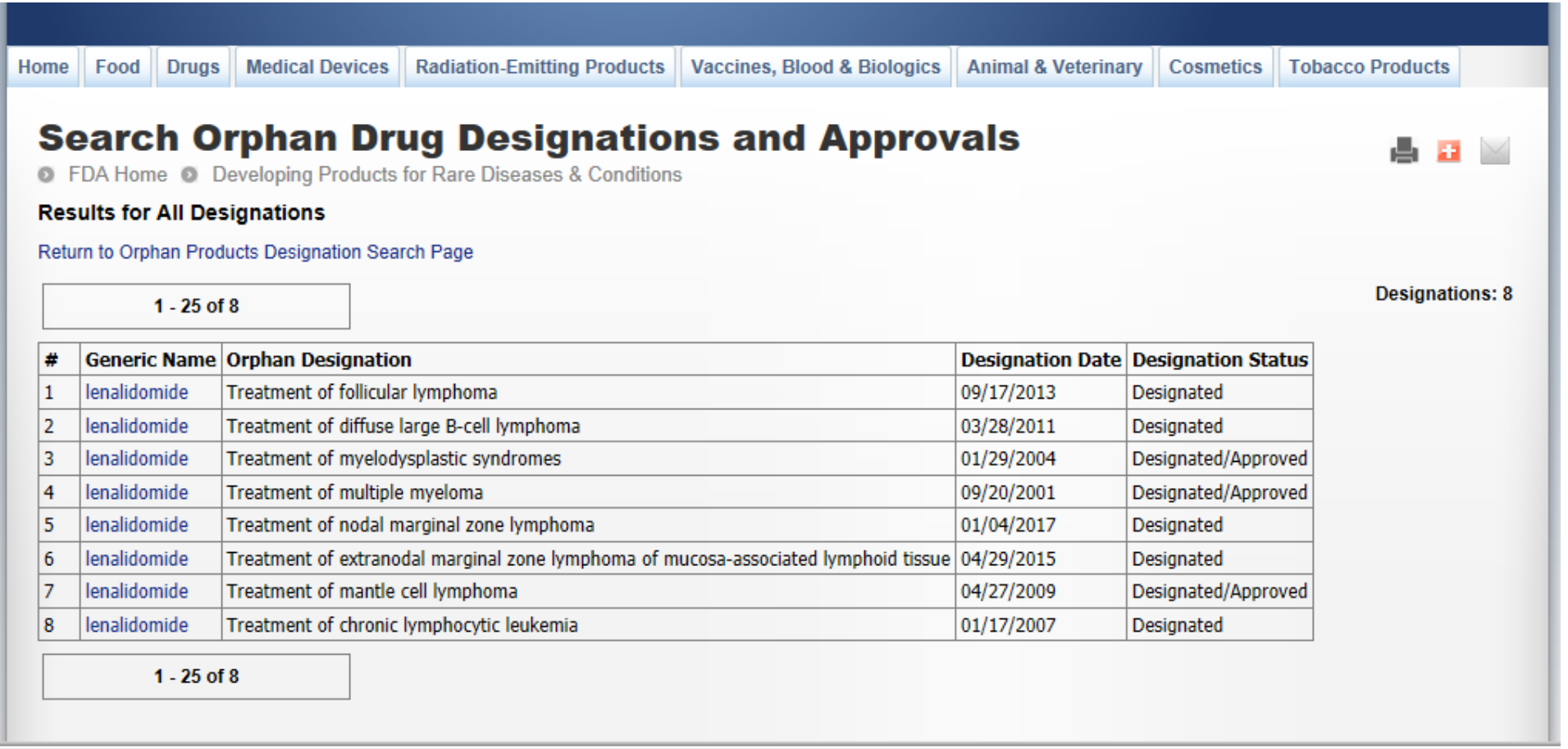
EvaluatePharma®Orphan DrugReport 2017

Projected top 10 orphan drugs worldwide by revenue in 2022 (in million US dollars)



EvaluatePharma®Orphan DrugReport 2017

Celgene's Revlimid (lenalidomide) orphan designations



Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Search Orphan Drug Designations and Approvals

FDA Home › Developing Products for Rare Diseases & Conditions

Results for All Designations

Return to Orphan Products Designation Search Page

1 - 25 of 8

Designations: 8

#	Generic Name	Orphan Designation	Designation Date	Designation Status
1	lenalidomide	Treatment of follicular lymphoma	09/17/2013	Designated
2	lenalidomide	Treatment of diffuse large B-cell lymphoma	03/28/2011	Designated
3	lenalidomide	Treatment of myelodysplastic syndromes	01/29/2004	Designated/Approved
4	lenalidomide	Treatment of multiple myeloma	09/20/2001	Designated/Approved
5	lenalidomide	Treatment of nodal marginal zone lymphoma	01/04/2017	Designated
6	lenalidomide	Treatment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	04/29/2015	Designated
7	lenalidomide	Treatment of mantle cell lymphoma	04/27/2009	Designated/Approved
8	lenalidomide	Treatment of chronic lymphocytic leukemia	01/17/2007	Designated

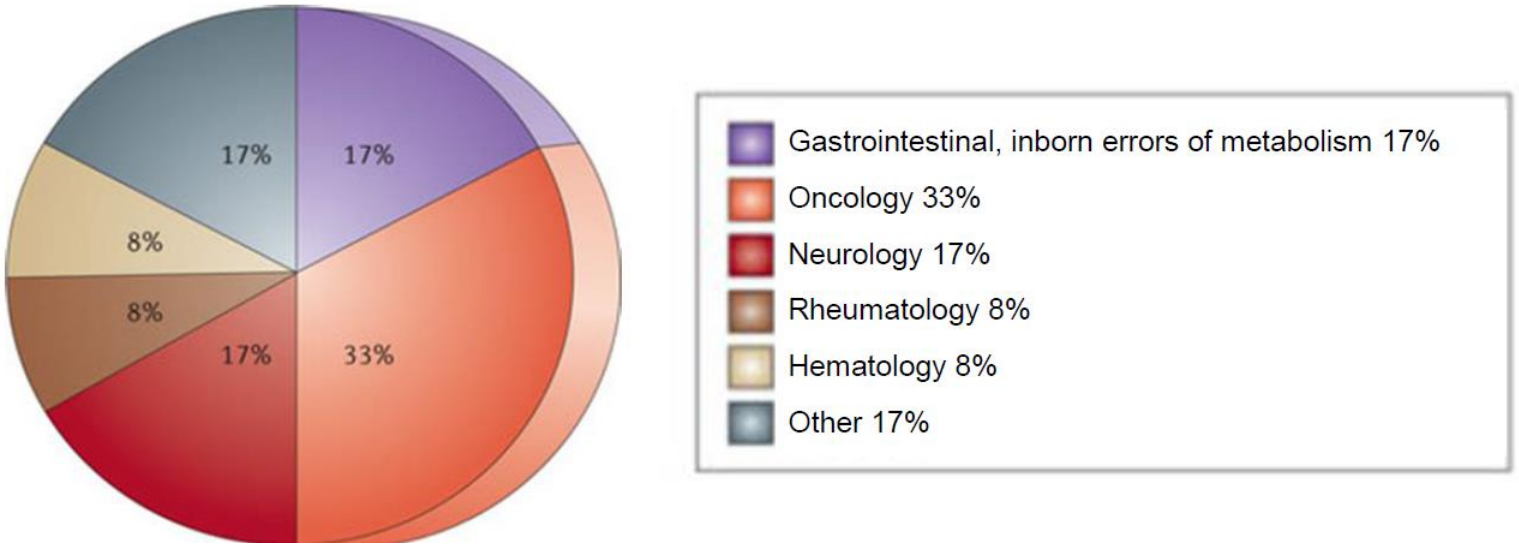
1 - 25 of 8

US ODD for Projected top 10 Orphan drugs by 2022

Drug	Pharmacological class	FDA ODD designations
Revlimid(Celgene) lenalidomide	Immunomodulator	8
Opdivo (BMS) Nivolumab	Anti-programmed death-1 (PD-1) MAb	6
Keytruda (Merck) Pembrolizumab	Anti-programmed death-1 (PD-1) MAb	10
Darzalex (J&J) Daratumumab	Anti-CD38 MAb	1
Soliris(Alexion) Eculizumab	Anti-complement factor C5 MAb	6
Imbruvica (AbbVie) Ibrutinib	Bruton's tyrosine kinase (BTK) inhibitor	9
Orkambi (Vertex) Lumacaftor/ivacaftor	Cystic fibrosis transmembrane conductance regulator (CFTR) corrector	1
Imbruvica (J&J) Ibrutinib	Bruton's tyrosine kinase (BTK) inhibitor	9
Yervoy (BMS) Ipilimumab	Anti-cytotoxic T lymphocyte associated protein 4 (CTLA4) MAb	1
Rituxan (Roche) Rituximab	Anti-CD20 MAb	7

Majority of orphan drug approvals for oncology

Figure 2: US Orphan Drug Approvals by Therapeutic Area (2006 to 2011)



CADTH ENVIRONMENTAL SCAN Drugs for Rare Diseases: Evolving Trends in Regulatory and Health Technology Assessment Perspectives. Product Line: Environmental Scan, Version: 2.0, Issue Number: 42, Publication Date: October 2013 (Updated February 2016)

Where we are with rare diseases - reality

- 80% of rare diseases are genetic in origin, and thus are present throughout a person's life, even if symptoms do not immediately appear
- Approximately 50% of the people affected by rare diseases are children
- 30% of children with rare disease will not live to see their 5th birthday
- Rare diseases are responsible for 35% of deaths in the first year of life
- The prevalence distribution of rare diseases is skewed – 80% of all rare disease patients are affected by approximately 350 rare diseases
- According to the Kakkis EveryLife Foundation, 95% of rare diseases have not one single FDA approved drug treatment
- During the first 25 years of the Orphan Drug Act (passed in 1983), only 326 new drugs were approved by the FDA and brought to market for all rare disease patients combined
- According to the National Institutes of Health Office of Rare Disease Research, approximately 6% of the inquiries made to the Genetic and Rare Disease Information Center (GARD) are in reference to an undiagnosed disease
- Approximately 50% of rare diseases do not have a disease specific foundation supporting or researching their rare disease

https://globalgenes.org/rare-diseases-facts-statistics/

Orphan drug –prevalence criteria

US	EU	Japan	Australia
<200,000 patients (<6.37 in 10,000, based on US population of 314m)	<5 in 10,000 (<250,000 patients, based on EU population of 514m)	<50,000 patients (<4 in 10,000 based on Japan population of 128m)	the condition affects fewer than 5 in 10,000 individuals in Australia when the application is made

Incentives to orphan drug makers - exclusivity

US	EU	Japan	Australia
7 year market exclusivity following authorization	10-year period after the marketing authorization of an orphan medicine when similar medicines for the same indication cannot be placed on the market	10-year market exclusivity (re-assessment) from generic competition.	5 –year exclusivity; TGA will not approve registration of another drug or another product containing the same active drug for the same indication for five years unless clinical superiority has been demonstrated.

Protocol assistance, fee reduction and tax advantage

US	EU	Japan	Australia
50% Tax Credit on R&D Cost, R&D Grants for Phase I to Phase III Clinical Trials, protocol assistance and Waivers of drug approval application fees and annual FDA product fees	Protocol assistance Fee reductions Centralised procedure for marketing authorisation Individual Member State incentives	Financial subsidies for up to 50% of expenses for clinical and non-clinical research, 15% tax credits on research costs excluding financial subsidies and up to a 14% reduction in corporate tax, priority review and fast-track approval, free protocol assistance and user fee waivers	Non-financial incentives include pre-licensing access and Regulatory Assistance; waiver of application and evaluation fees for registration of the product for the treatment of the designated rare disease.

Application and review timeline

US	EU	Japan	Australia
Office of Orphan Products Development	Committee for Orphan Medicinal Products (COMP)	Evaluation and Licensing Division (ELD) of the Ministry of Labor and Welfare (MHLW)	Office of Medicines Authorization, TGA
Review cycle typically 90 days	Maximum of 90-day procedure	Not specified	TGA will assess designation application and make a decision as quickly as possible

Orphan Drug Designation in the US: 21 CFR 316.20 Content and format of a request for orphan-drug designation

+ (a) A sponsor that submits a request for orphan-drug designation of a drug for a specified rare disease or condition shall submit each request in the form and containing the information required in paragraph (b) of this section. A sponsor may request orphan-drug designation of a previously unapproved drug, or of a new use for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same drug as an already approved drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. More than one sponsor may receive orphan-drug designation of the same drug for the same rare disease or condition, but each sponsor seeking orphan-drug designation must file a complete request for designation as provided in paragraph (b) of this section.

21 CFR 316.20 Content and format of a request for orphan-drug designation

+ (b) A sponsor shall submit two copies of a completed, dated, and signed request for designation that contains the following:

+ (1) A statement that the sponsor requests orphan-drug designation for a rare disease or condition, which shall be identified with specificity.

+ (2) The name and address of the sponsor; the name of the sponsor's primary contact person and/or resident agent including title, address, telephone number, and email address; the generic and trade name, if any, of the drug, or, if neither is available, the chemical name or a meaningful descriptive name of the drug; and the name and address of the source of the drug if it is not manufactured by the sponsor.

+ (3) A description of the rare disease or condition for which the drug is being or will be investigated, the proposed use of the drug, and the reasons why such therapy is needed.

21 CFR 316.20 Content and format of a request for orphan-drug designation

+ (4) A description of the drug, to include the identity of the active moiety if it is a drug composed of small molecules, or of the principal molecular structural features if it is composed of macromolecules; its physical and chemical properties, if these characteristics can be determined; and a discussion of the scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition, including all relevant data from in vitro laboratory studies, preclinical efficacy studies conducted in an animal model for the human disease or condition, and clinical experience with the drug in the rare disease or condition that are available to the sponsor, whether positive, negative, or inconclusive. Animal toxicology studies are generally not relevant to a request for orphan-drug designation. Copies of pertinent unpublished and published papers are also required.

+ (5) Where the sponsor of a drug that is otherwise the same drug as an already approved drug seeks orphan-drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug.

21 CFR 316.20 Content and format of a request for orphan-drug designation

+ (6) Where a sponsor requests orphan-drug designation for a drug for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people ("orphan subset"), a demonstration that, due to one or more properties of the drug, the remaining persons with such disease or condition would not be appropriate candidates for use of the drug.

+ (7) A summary of the regulatory status and marketing history of the drug in the United States and in foreign countries, e.g., IND and marketing application status and dispositions, what uses are under investigation and in what countries; for what indication is the drug approved in foreign countries; what adverse regulatory actions have been taken against the drug in any country.

21 CFR 316.20 Content and format of a request for orphan-drug designation

+ (8) Documentation, with appended authoritative references, to demonstrate that:

  (i) The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in §316.21(b), or

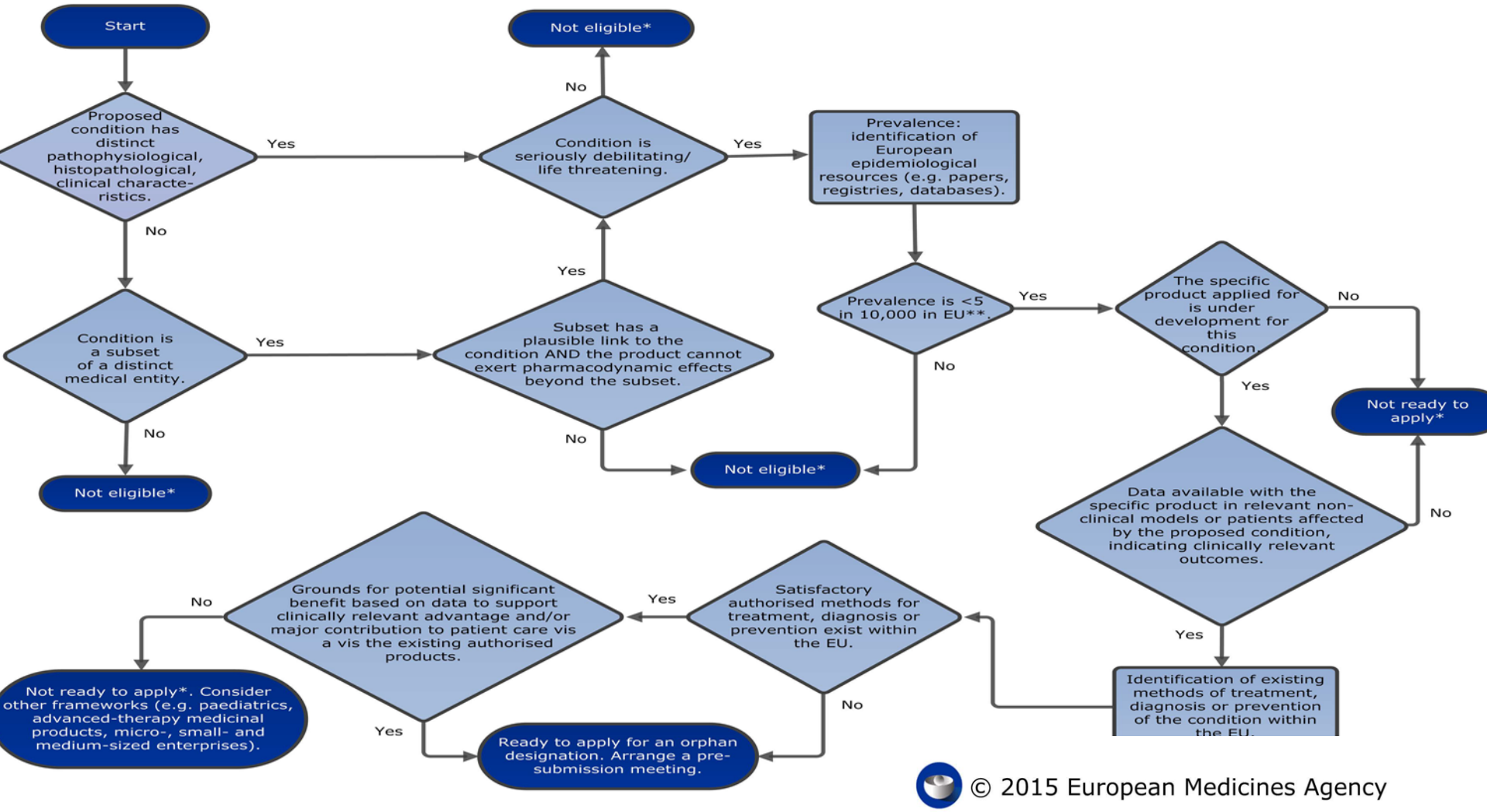
  (ii) For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in §316.21(c).

+ (c) Any of the information previously provided by the sponsor to FDA under subpart B of this part may be referenced by specific page or location if it duplicates information required elsewhere in this section.

Common application to request ODD to FDA and EMA

+ https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048361.pdf

EMA sponsor's guide to an orphan designation



Orphan drug process - Japan

+ **MHLW (Ministry of Health, Labour, and Welfare)**

  Review and designation of orphan drugs/medical devices

  Review and approval of orphan drugs/medical devices

  Pre-designation consultation for orphan drugs/medical devices

  Payment for the operational cost of the National Institute of Biomedical Innovation (NIBIO)

+ **PMDA (Pharmaceuticals and Medical Devices Agency)**

  Priority scientific consultation for clinical trials and dossiers for marketing authorization of orphan drugs/medical devices

+ **National Institute of Biomedical Innovation (NIBIO)**

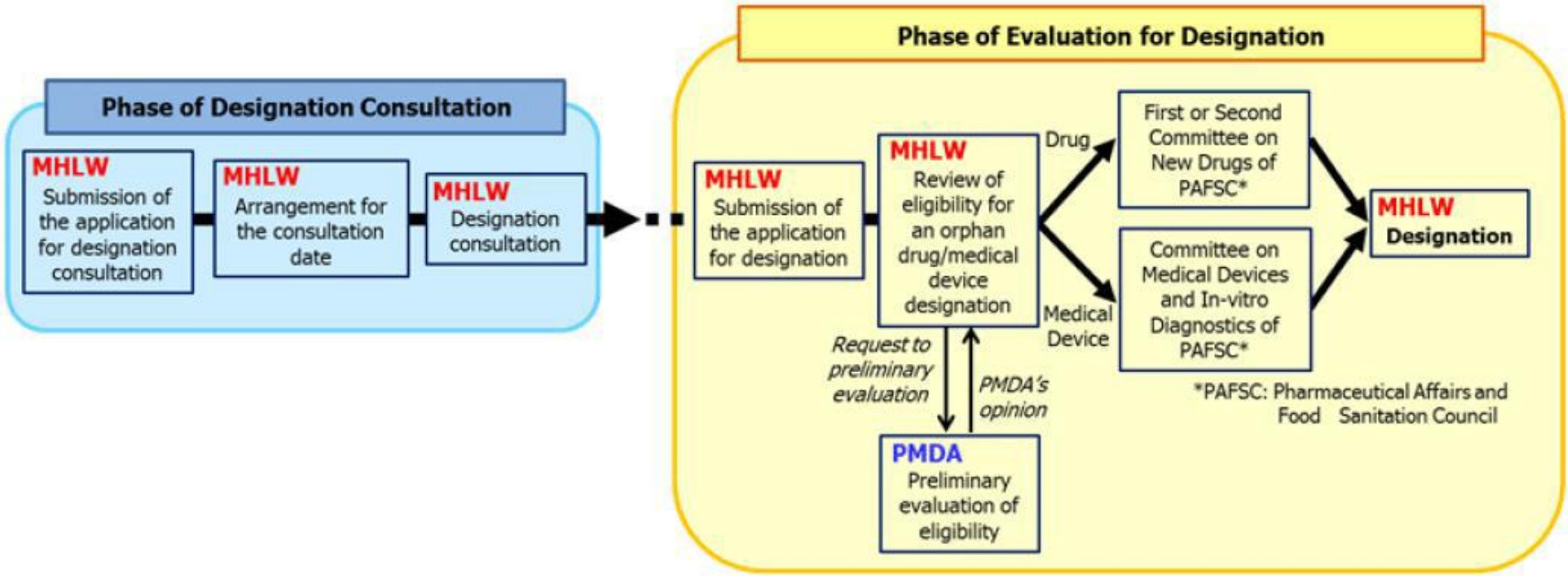
  Subsidy payment to the applicant

  Accreditation for research expenses to be used by the applicant

  Provision of guidance and consultation to the applicant

Drug approval system of Japan APEC Harmonization Center, December 2015

Orphan drug designation process in Japan



Drug approval system of Japan APEC Harmonization Center, December 2015

TGA step-by step guidance for ODD
Version 1.0, June 2017

1. Arranging a pre-submission meeting/early notification

You can make this notification informally by sending an email (one month in advance) to AET.Application.Entry.Team@health.gov.au, including details of the planned:

· designation/s to be sought

· the active ingredient

· the sponsor's name

· the proposed indication for designation.

2. Verifying your access to TGA Business Services (TBS)

TGA business portal requires TGA client ID number, password access to our TGA Business Services portal and Submitter access to the TBS portal

3. Submitting your designation application

At least 3 months prior to submission of registration

Eligibility: Orphan Drug designation may be granted for:

a previously unregistered medicine

an already registered medicine with a new 'orphan' indication

a new dosage form medicine.

Meet eligibility criteria

TGA- Orphan drug eligibility criteria

Application type	Standard orphan drug	New dosage form medicine
1. Serious Condition	the indication is the treatment, prevention or diagnosis of a life-threatening or seriously debilitating condition[1] in a particular class of patients (the relevant patient class)	the indication is the treatment, prevention or diagnosis of a life-threatening or seriously debilitating condition
2. Medical Plausibility	it is not medically plausible that the medicine could effectively treat, prevent or diagnose the condition in another class of patients that is not covered by the relevant patient class	-
3. Orphan drug prevalence threshold OR lack of financial viability	at least one of the following applies: i.if the medicine is intended to treat the condition – the condition affects fewer than 5 in 10,000 individuals in Australia when the application is made; ii.if the medicine is intended to prevent or diagnose the condition the medicine, if it were included in the Register, would not be likely to be supplied to more than 5 in 10,000 individuals in Australia during each year that it is included in the Register; iii.it is not likely to be financially viable for the sponsor to market the medicine in Australia unless each fee referred to in paragraph 45(12)(c) of the Therapeutic Goods regulations were waived in relation to the medicine	it is not likely that it would be financially viable for the sponsor to market the medicine in Australia unless each fee referred to in paragraph 45(12)(c) of the Therapeutic Goods Regulations 1990 were waived in relation to the medicine
4. Comparison with existing therapeutic goods	either: i.no therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register; or ii.if one or more therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register-the medicine provides a significant benefit in relation to the efficacy or safety of the treatment, prevention or diagnosis of the condition, or a major contribution to patient care, compared to those goods.	either: i.no therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register; or ii.if one or more therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register-the medicine provides a significant benefit in relation to the efficacy or safety of the treatment, prevention or diagnosis of the condition, or a major contribution to patient care, compared to those goods.

TGA step-by step guidance for ODD
Version 1.0, June 2017

4. TGA assessment of the designation application

Meets all administrative requirement, review to meet eligibility criteria, request for additional information

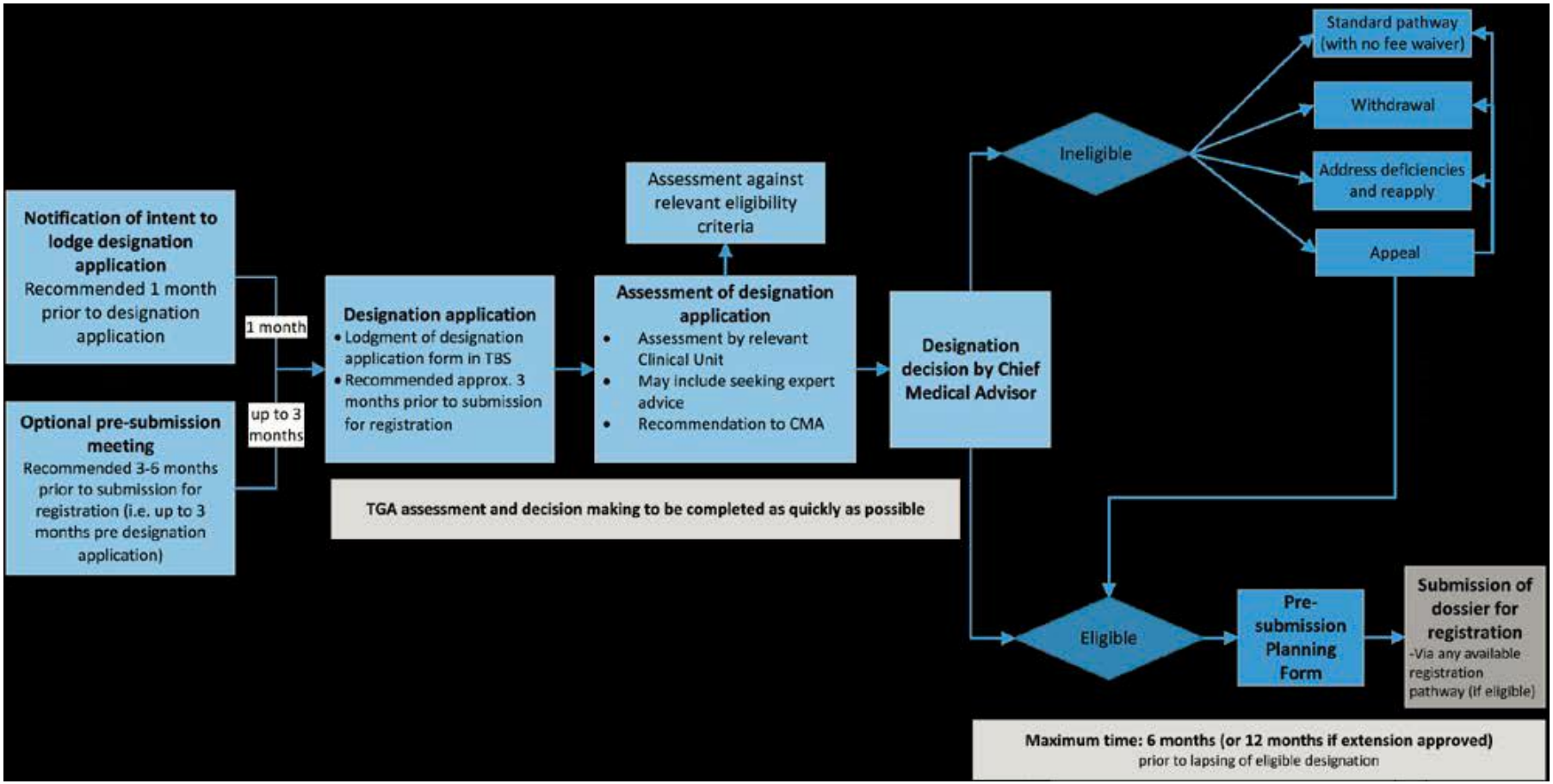
5. Notifying sponsors of the designation decision

+ details of designation(s) eligible/ineligible and the relevant indication
+ a statement of reasons for designation decisions (for ineligible decisions only)
+ the date on which the designation (if approved) lapses (six months after the date of the designation decision)
+ Details of your appeal rights.
+ Publication of designation will include: the name of the medicine, the sponsor's name, the eligible Orphan drug indication, the dosage form, designation decision date and lapsing date, designation status (i.e. active or lapsed – valid for six months to be eligible for orphan drug fee waiver at the time of registration).

6. Submitting your application for registration

Through standard or priority review; with active designation. Apply for request of designation extension with evidence, or re-apply for new orphan designation if lapsed.

TGA process for Orphan drug designation



Recap – requirements for EMA, FDA and Japan

US
Application form and
Sponsor statement
Name and address of sponsor
Description of rare disease or condition with indication
Discussion of scientific rationale including all supportive data
Description of clinical superiority, if relevant
Justification of a valid subset, if relevant
Summary of regulatory and development history
Documentation of prevalence of < 200,000 in the USA or evidence that there is no reasonable expectation that the costs of research and development can be recovered by the sales

Europe
Application form and
A1. Details of the condition
A2. The proposed orphan indication
A3. Medical plausibility
A4. Justification of severity (life-threatening or debilitating)
B1-2. Prevalence of the condition
C. Return on investment
D1. Existing methods of treatment
D2. Justification why methods not satisfactory
D3. Justification of significant benefit
E1. Summary of development
E2. Current regulatory status
F. Bibliography

Japan
Application form and
Data on the number of patients with objective statistical data for whom the drug will be indicated
Data on medical needs
Data on the disease including aetiology and symptoms
Data on the current status such as availability of similar drug and treatment
Data on the theoretical rationale for the use of the drugs
Related data in a draft dossier of application for marketing authorisation, which is available at the time of application for orphan drug
Development plan (data on the possibility of development), including outline of the development plan, current development status, expected test items, duration of the study and necessary expenses
Preparation of summary of the orphan drug

Daniel J O'Connor BSc MB ChB MSc PhD MFPM (2013) Orphan drug designation – Europe, the USA and Japan, Expert Opinion on Orphan Drugs, 1:4, 255-259

Reality check on orphan drug process

+ Drugs For Rare Diseases Have Become Uncommonly Rich Monopolies
+ Many orphan medicines, originally developed to treat diseases affecting fewer than 200,000 people, come with astronomical price tags.
+ More than 70 orphan drugs were repurposed mass use drugs which received orphan drug designations
+ High Prices For Orphan Drugs Strain Families And Insurers
+ Loop hole in orphan drug process allowing sponsors to avoid obligation to test products in pediatric populations due to orphan designations granted for pediatric subsets of common diseases

https://www.npr.org/sections/health-shots/2017/01/17/509507035/high-prices-for-orphan-drugs-strain-families-and-insurers

https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies

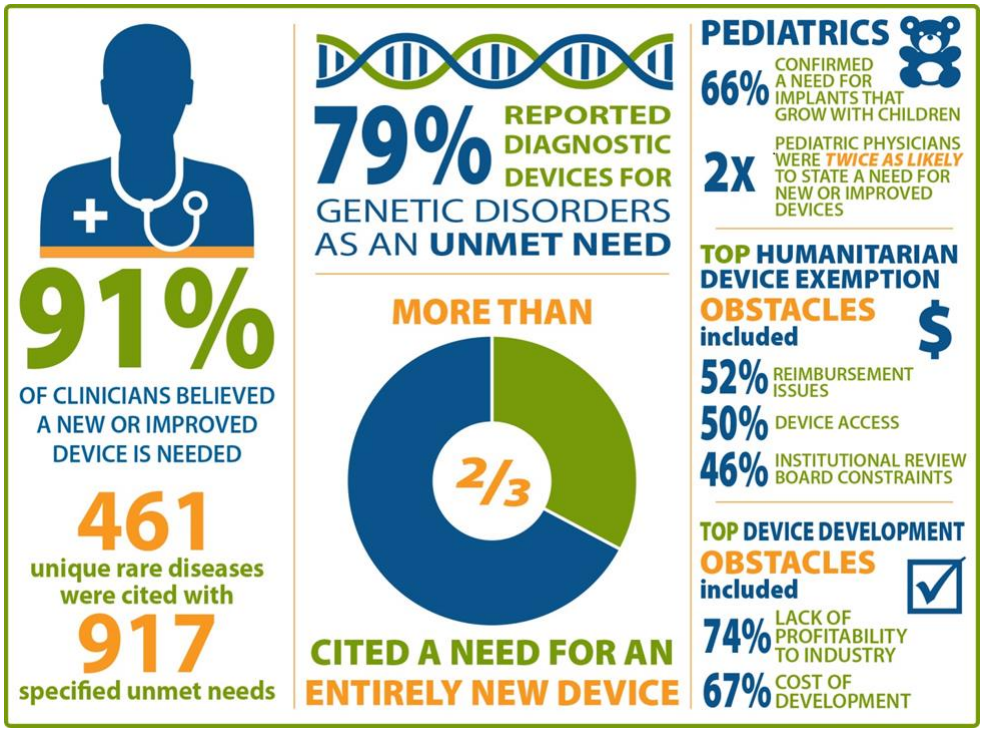
https://blogs.fda.gov/fdavoice/index.php/2017/09/fda-is-advancing-the-goals-of-the-orphan-drug-act/

Future for Orphan drugs in the US

+ The FDA Reauthorization Act of 2017 (FDARA) introduced in May 2017 and passed as public law No. 115-52 on 18 August 2017 introduces in Section 607 the new requirement to demonstrate clinical superiority to receive orphan exclusivity for a drug that is otherwise the same as another drug designated as orphan drug under Section 526 of the Food Drug and Cosmetics Act (FDC Act) and is intended to treat the same condition. As mentioned above, initially this requirement included in the Orphan Drugs Act only applied at the time of orphan drug designation. The FDARA now requires the clinical superiority designation at the time of approval to obtain the orphan drug exclusivity benefit. A summary of the superiority determination will be published. The rules apply prospectively from enactment of the FDARA and remain unchanged for any determinations under Section 526 and 527 under the FDC Act prior to enactment.

2018 FDA/NCATS Report on Unmet Medical Device Needs for Patients with Rare Diseases

+ The **survey results** from National Institutes of Health's (NIH) National Center for Advancing Translational Sciences (NCATS), clearly document that patients with rare diseases face numerous unmet needs regarding diagnostic and therapeutic devices for the pediatric and adult population. **This survey demonstrates the need for innovative medical devices to care for children and adults with rare diseases. FDA and NIH continue to support and seek opportunities to accelerate device development for rare disease patients.** The figure below illustrates some of overall findings from the survey.



Taking New Steps to Meet the Challenges of Rare Diseases — FDA Marks the 11th Rare Disease Day

Posted on February 26, 2018 by FDA Voice

By: Scott Gottlieb, M.D.

- In June 2017, FDA's Orphan Drug Designation Modernization Plan was announced.
- to create a more efficient, scientifically advanced, predictable, and modern approach to the approval of safe and effective treatments for rare diseases.
- Elimination backlog of orphan drug designation requests.
- 90-day timetable for processing new designation requests.
- FDA Orphan Products Council to further address scientific and regulatory challenges pertaining to orphan products.

FDA's on-going commitment to products for rare disease

- Pilot program for efficient designation requests -Fillable application form, on-line tutorial for sponsors
- Memorandum of Understanding with the National Organization for Rare Disorders to conduct outreach with agency's new Patient Affairs Staff on ways to enhance the incorporation of patient experience into regulatory discussions
- Public workshop Wednesday, May 9, 2018 9 a.m. to 5 p.m., register by April 25, 2018 at 5 p.m. Eastern Time. https://www.eventbrite.com/e/tissue-agnostic-therapies-regulatory-considerations-for-orphan-drug-designation-public-workshop-registration-42244255706
- A new website for all information on orphan drug products development

  https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/Events/ucm593077.htm

References

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+ https://blogs.fda.gov/fdavoice/index.php/2017/09/fda-is-advancing-the-goals-of-the-orphan-drug-act/
+ Orphan drug designation: a step-by-step guide for prescription medicines V1.0 June 2017, published by TGA
+ Current Status and Challenges of Development for Orphan Drugs in Japan. Akiko Nitta, MPharm, Reviewer Office of Standards and Guidelines Development Pharmaceuticals and Medical Devices Agency (PMDA), 2012

Thank you!

Questions and Comments?