WHITE PAPER

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# RARE DISEASE

## FDA Designations for Rare Disease Products: A Complete Guide

**OVERVIEW**

The U.S. Food and Drug Administration (FDA) offers sponsors a variety of special designation programs to incentivize them to develop and deliver therapies to treat unmet patient needs, such as Fast Track Designation, Breakthrough Therapy Designation, and Qualified Infectious Disease Product Designation.

Many diseases and conditions affect such small numbers of people that a drug or biological product developed to treat these patients generates relatively little return on investment for development costs.

## Comparing orphan drug, rare pediatric disease, and humanitarian use device designations

In this paper, we will highlight those designation programs available specifically for products with rare disease indications: Orphan Drug Designation (ODD), Rare Pediatric Disease Designation (RPDD), and Humanitarian Use Device (HUD) designation. We will detail the criteria for, timeline and maintenance for, and benefits of each designation, and the paper will conclude with a chart comparing and contrasting all three programs.

## Orphan drug designation

Many diseases and conditions affect such small numbers of people that a drug or biological product developed to treat these patients generates relatively little return on investment for development costs. Companies developing such products can expect to incur a financial loss, and, as a result, the pharmaceutical industry has neglected many rare diseases.

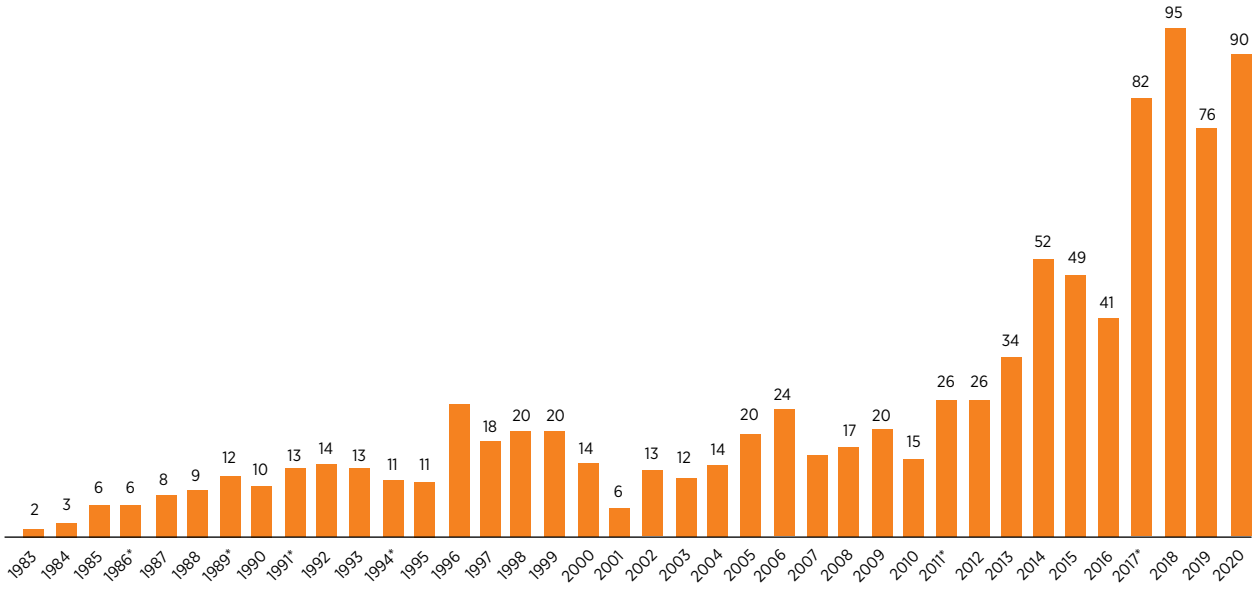
To incentivize pharmaceutical companies to address the unmet needs of patients with rare diseases, the Orphan Drug Act of 1983 was passed. This act established the ODD program and has since been amended several times to add clarity and additional incentives. Since the passage of the Orphan Drug Act, the number orphan indications approved in the U.S. has risen dramatically.

## Criteria

There are three major criteria for obtaining ODD for a drug or biological product:

1. The product must be intended for use in a rare disease or condition.
2. Adequate documentation or prevalence data must demonstrate that the intended condition is rare.
3. There must be a scientific rationale establishing a medically plausible basis for the use of the product for the rare condition.

A key point to remember is that ODD applies to both the active moiety and the condition, but not necessarily the product formulation. It is also worth noting that esters, salts, and other noncovalent derivatives of a given active moiety are generally considered the same drug when it comes to ODD.




*Includes a withdrawn designation approval.
Source: FDA's Orphan Drug Designations and Approvals Database

Figure 1. FDA approvals of orphan products

### Definition of a rare disease or condition

The Orphan Drug Act defines a rare disease or condition as one (a) which affects less than 200,000 persons in the U.S. or (b) for which there is no reasonable expectation that the cost of developing a drug and making it available in the U.S. will be recovered from sales in the U.S. The second criterion is rarely used by sponsors due to the difficulty of proving unprofitability.

Sometimes, a product intended for use in a subset of an otherwise non-rare disease or condition (known as an "orphan subset") qualifies for ODD, provided the product cannot be used to treat the broader disease or condition due to some property of the drug – toxicity in some subsets but not others, for instance.

### Scientific rationale

The content and format requirements for an ODD request are listed in 21 CFR 316.20. In addition to general information about the drug and rare condition for which the ODD is being requested, the sponsor must provide:

*[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.*

**Is your disease/condition of interest rare?**
Useful prevalence and incidence statistics sources

- NORD
- Orphanet
- GARD
- SEER Cancer Statistics
- Patient advocate group websites
- Published literature

For an ODD request for a previously unapproved drug, extensive clinical data are generally not necessary, and sometimes nonclinical proof-of-concept data may be sufficient to demonstrate a medically plausible basis for use of the drug for the indication. However, if another sponsor has already obtained ODD for the same drug and condition and a marketing application has been approved, the new sponsor has the added requirement of providing a plausible hypothesis as to why the proposed drug may be clinically superior to the first already marketed drug in order to obtain ODD.

## Timeline and maintenance

ODD requests are submitted to the FDA's Office of Orphan Products Development (OOPD) at any time during drug development prior to new drug application (NDA) or biologics license application (BLA) submission for the desired orphan drug and condition. Since an ODD request is not submitted as an amendment to an investigational new drug (IND), a sponsor does not need to have an open IND – or even intend to open an IND – in order to request ODD.

In its 2017 Orphan Drug Modernization Plan, the FDA committed to a goal of responding to all new ODD requests within 90 days of their receipt.

Once ODD is granted, the sponsor is required to submit orphan annual reports – which are different from an IND Annual Report – every year until the marketing application is approved.

## Benefits

A sponsor may be eligible for the following benefits and incentives for a product with ODD:

- **Pre-approval:**
  - Potential Pediatric Research Equity Act (PREA) requirements exemption (Note: This exemption may not apply for certain molecularly targeted anticancer agents.)
  - Marketing application user fee waiver
  - Tax credits and research grants for qualified clinical testing expenses
  - FDA protocol assistance
- **Post-approval:** Seven years of orphan drug market exclusivity (Note: This benefit may not be available if the active moiety is already approved or if clinical superiority is not supported with data.)

The indication associated with the eventual NDA or BLA must be for the same disease or condition be narrower, for these benefits to apply. For example, if a sponsor obtains ODD for Drug A for Condition 1 but files an NDA for Drug A with an indication for Condition 2, the user fee waiver and market exclusivity do not apply. Likewise, if the NDA is approved for indications in both Condition 1 and Condition 2, the market exclusivity only applies to Condition 1. However, since the NDA includes an indication not covered by the ODD, the user fee still applies.

### PREA requirements exemption

PREA requires NDAs and BLAs – or application supplements – for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment, unless the applicant has obtained a waiver or deferral.

While some products granted ODD are exempt from PREA requirements for pediatric studies, not all qualify. Drugs intended for the treatment of an adult cancer that are directed at a molecular target that is substantially relevant to the growth or progression of a pediatric cancer are not eligible for the exemption. The FDA has molecular target lists to assist sponsors, and they can also coordinate with the FDA's Oncology Center of Excellence (OCE) and relevant review divisions to discuss PREA requirements for such products.

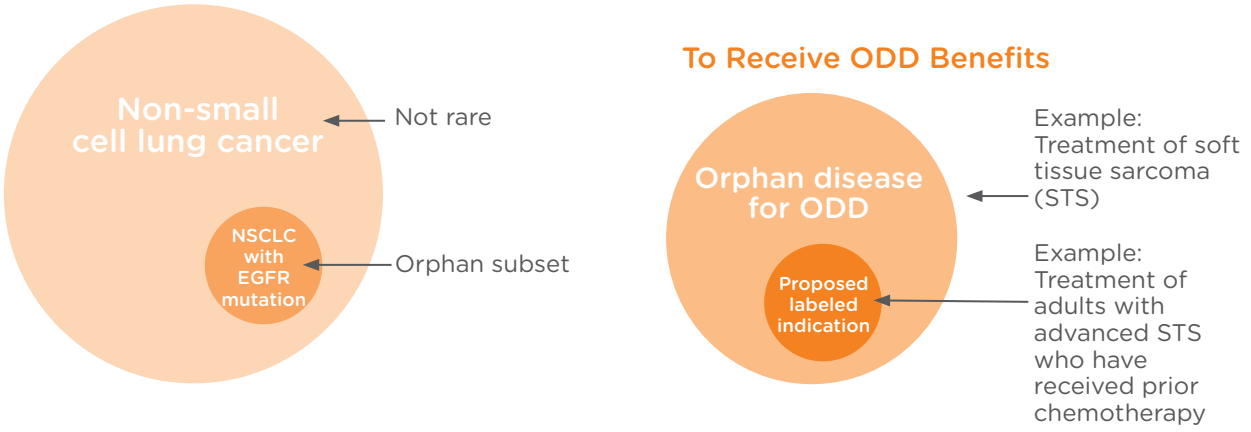



Figure 2. Orphan disease examples

**ODD requests typically include information about:**

- Sponsor
- Proposed product, including regulatory history
- Intended disease/condition, including prevalence/incidence data
- Scientific rationale for use of the product in the rare disease/condition
- Additional information, if applicable, e.g., orphan subset, clinical superiority, or justification of no cost recovery
- ODD requests can be submitted to the OOPD at any time prior to NDA or BLA submission
- The FDA's goal is to respond to ODD requests within 90 days of receipt

## Financial incentives

Under Section 736(a)(1)(F) of the FD&C Act, an NDA or BLA for a product to be used in a rare disease or condition granted ODD is not subject to an application fee. The annual program fee may also be waived if certain conditions are met. In addition, sponsors of products with ODD may be eligible for a 25 percent federal tax credit for qualified clinical testing expenses for studies conducted in the U.S. Sponsors may also be eligible for research grants from the OOPD to support clinical studies.

## Protocol assistance

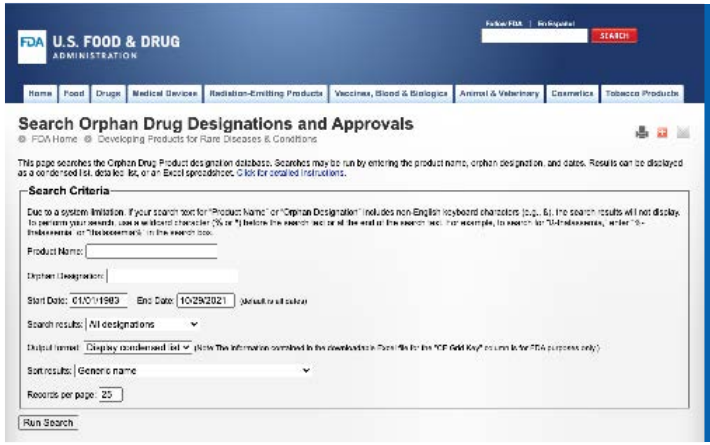
Though there are mechanisms through which the FDA provides feedback on protocols for products without ODD, the FD&C Act provides formal protocol assistance regarding nonclinical and clinical investigations that must be conducted to support development of a product with ODD.

## Orphan market exclusivity

One of the most significant benefits of obtaining ODD is the seven-year orphan drug market exclusivity following approval of an NDA or BLA. This market exclusivity prevents the FDA from approving another product with the same active moiety for the same disease or condition, unless the second product is demonstrated to be clinically superior to the first.

There are three ways a sponsor can move forward when confronted with the market exclusivity of another sponsor's orphan product:

- Wait for the market exclusivity to expire
- Develop the same drug for a different indication
- Demonstrate that the new product is clinically superior to the already approved product (In this case, the FDA considers the clinically superior product to be a different drug even if the active moiety is the same.)




### FDA Orphan Drug Designations and Approvals Database

Unlike RPDDs, ODDs are listed on a public FDA database, which is searchable and filterable by product name, orphan designation, designation date, and more. For some sponsors, the public availability of the database may have an impact on commercial outlooks, or competitive intelligence concerns may come into play. Therefore, it is important to consider how the public listing of an ODD approval will affect a program before submitting a request to the FDA.

**RPDD requests generally include information about:**

- Sponsor
- Proposed product
- Intended disease/condition, including prevalence/incidence data
- Mechanism of action/supportive data suggesting efficacy in the rare pediatric disease
- RPDD requests can be submitted to the OOPD at any time prior to NDA or BLA submission, but it is preferred that it be submitted concurrently with the ODD or FTD request
- A response, designation letter or deficiency letter, is expected within 60 days, unless the request is not submitted concurrently with the ODD or FTD

## Rare Pediatric Disease Designation

The RPDD program was established with a similar rationale as the ODD program, with a focus on pediatric patients with rare diseases and unmet needs. Its purpose is to stimulate the development of new drugs for rare pediatric diseases by offering additional incentives for obtaining FDA approval of such products beyond the incentives offered by the ODD program.

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 added Section 529 to the FD&C Act, establishing the RPDD program and its associated priority review vouchers. In 2016, the Advancing Hope Act provided additional clarifications and definitions for the RPDD program, and the 21st Century Cures Act extended the sunset provisions for the program.

### Criteria

#### Criteria to obtain the designation

A rare pediatric disease is one that is serious or life-threatening in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including neonates, infants, children, and adolescents. It must also be a rare disease or condition as described in the FD&C Act, with a prevalence of less than 200,000 people in the U.S.

As with ODD, there are three major criteria that a drug or biological product must meet to obtain RPDD:

1. The drug must be intended for the prevention or treatment of a rare pediatric disease.

2. Adequate documentation or prevalence data must demonstrate that the intended pediatric disease or condition is rare.

3. There must be supportive data suggesting that the drug may be effective in the rare pediatric disease or condition.

The FDA expects a lesser level of supportive data suggesting the drug may be effective in the disease for RPDD requests than it does for ODD requests. Per the FDA's guidance on RPDD:

*In vitro data supporting the mechanism of action of the drug in the disease or in a related disease may suffice for rare pediatric disease designation, whereas that level of data would not generally suffice for orphan-drug designation.*

For RPDD, the FDA expects a lesser level of supportive data suggesting the drug may be effective in the disease for RPDD requests than it does for ODD requests.

### Criteria to obtain the benefit

The FDA may award the sponsor of an RPDD product that receives NDA or BLA approval a priority review voucher (PRV), which can be either redeemed to expedite the review of subsequent NDA or BLA for another product* or sold to another sponsor for use in the same manner. For a sponsor to receive a PRV upon approval of a rare pediatric disease product application – a marketing application for a drug with RPDD – the NDA or BLA must be a human drug application that meets several criteria:

- The application must be for a drug or biological product that is for the prevention or treatment of a rare pediatric disease and that contains no active ingredient – including any ester or salt of the active ingredient – that has been previously approved in any other application under relevant sections of the FD&C Act and the Public Health Service Act (PHS Act)
- The FDA must deem the application eligible for priority review (i.e., the product treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness)
- The application must be submitted under Section 505(b)(1) or 505(b)(2) of the FD&C
- The application must rely on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population
- The original rare pediatric disease product application must not seek approval for an adult indication
- The application must be approved after Sept. 30, 2016, the date the Advancing Hope Act of 2016 was enacted

**Note that redeeming a PRV does not guarantee approval for the product receiving priority review.*

## Timeline and maintenance

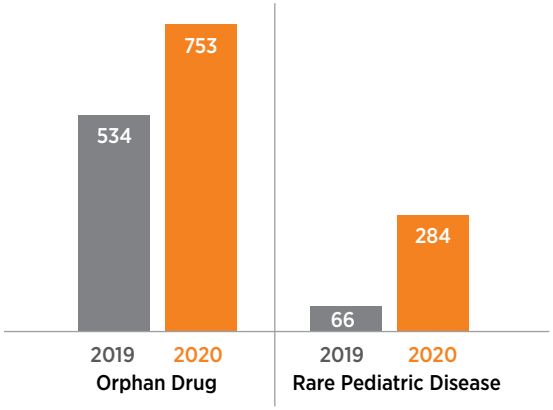
Sponsors should request RPDD at the same time as or within two weeks of submitting a request for ODD or Fast Track Designation (FTD). ODD requests can be submitted to the OOPD any time prior to submission of an NDA or BLA, and FTD requests can be submitted to the appropriate review division as early as the time of original IND submission or any time thereafter up until the Pre-NDA or Pre-BLA meeting. Regardless of submission timing, each RPDD request should be a separate proposal submitted to the OOPD.

If a sponsor submits a timely request for RPDD, the FDA should make a decision on the request no later than 60 days after submission. It is worth noting that, while the FDA is willing to accept RPDD requests submitted at a different time from the ODD or FTD request, the 60-day response deadline does not apply to these requests. It is also important to note that RPDDs are not listed on any public FDA database – unlike ODDs, which are public information. Sponsors may still choose to disclose the granting of RPDD for their products via press releases or other means.

While there are no apparent requirements for maintaining a RPDD prior to NDA or BLA submission, the FDA can revoke the PRV if the product is not marketed in the U.S. within one year of approval. The sponsor must also submit a report to the FDA no later than five years after its approval that addresses specific questions regarding the first four post-approval years. This report should contain several pieces of information:

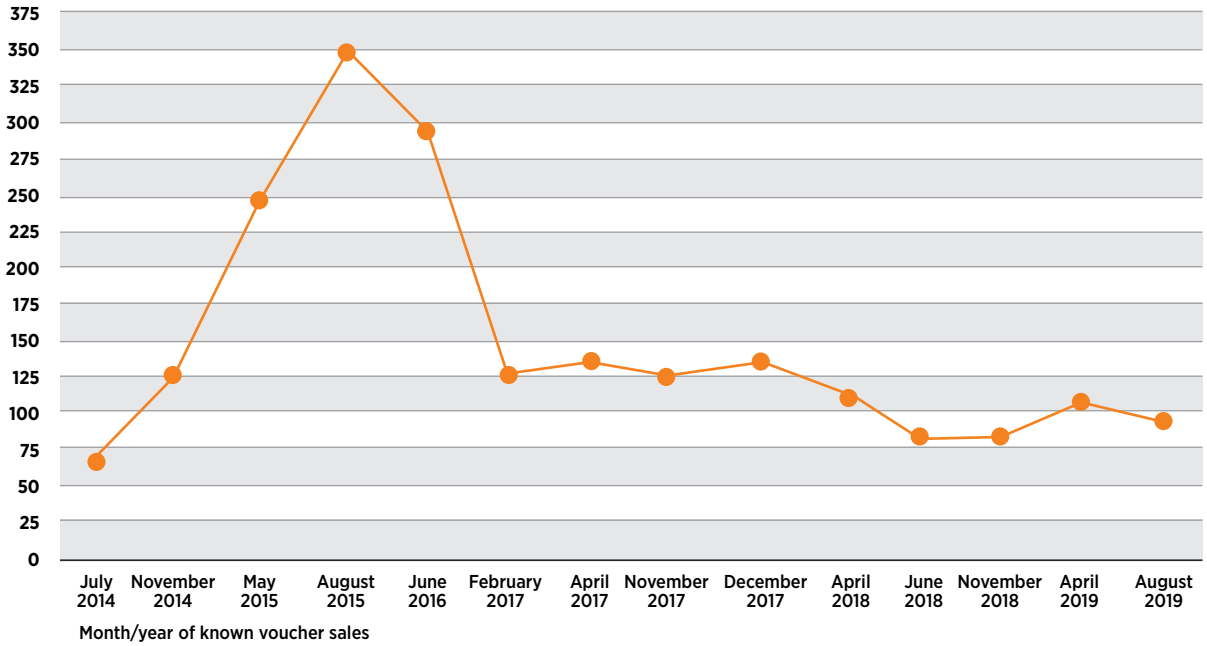
- The estimated population in the U.S. with the rare disease or condition for which the product was approved (both the overall population and the population aged 0 through 18 years)
- The estimated demand in the U.S. for the product
- The actual amount of product distributed in the U.S.

Figure 3. ODD and RPDD requests




Source: Rare Disease Day 2021: FDA Shows Sustained Support of Rare Disease Product Development During the Public Health Emergency

Figure 4. Sales prices of priority review vouchers (dollars in millions)




Source: GAO analysis of publicly available information on priority voucher sales

## Benefit

The benefit of RPDD is a sponsor's eligibility to receive a PRV, though the sponsor can receive additional benefits through another incentive program like ODD. Under Section 529 of the FD&C Act, the FDA may award a PRV upon approval of an RPDD product, provided the sponsor requests the PRV in the original NDA or BLA.

As noted above, the PRV can be either redeemed by the sponsor of the RPDD product to expedite the review of a subsequent NDA or BLA for another product or sold to another sponsor for use in the same manner. According to available sales information, PRVs have been sold for prices ranging from $80 million to $130 million since February of 2017.

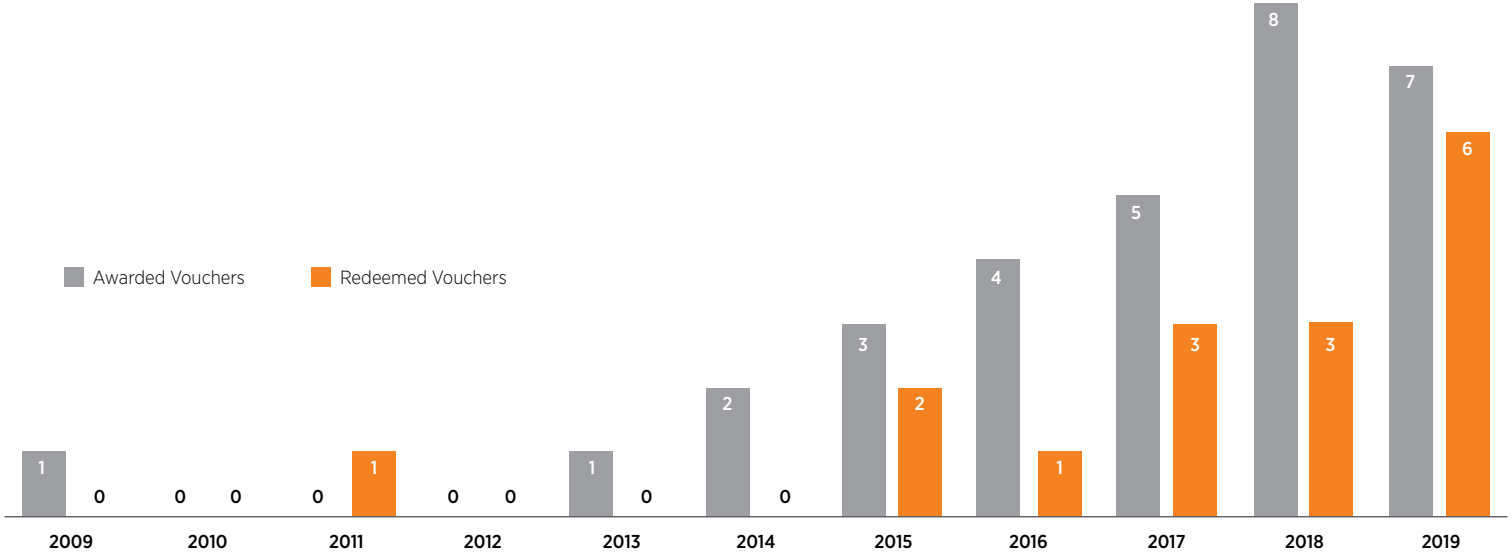
A major caveat to keep in mind for RPDD is the program's sunset provisions, as the program has a termination date unless it is extended.

Per the FDA's website:

*On December 27, 2020, the Rare Pediatric Disease Priority Review Voucher Program was extended. Under the current statutory sunset provisions, after September 30, 2024, FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024. After September 30, 2026, FDA may not award any rare pediatric disease priority review vouchers.*

It is also important to note that there is a user fee associated with redeeming a PRV, in addition to the other user fees required for marketing applications. For FY 2021, the fee for redeeming a PRV is $1,360,879.

Figure 5. Priority review vouchers awarded and redeemed (fiscal years 2009-2019)




## Humanitarian use device designation

The HUD designation program is designed for medical devices and is similar in may ways to the ODD program for drugs and biological products. The HUD designation program provides an incentive for sponsors developing medical devices to be used in the treatment or diagnosis of diseases affecting small populations. Established in 1990 with the passage of the Safe Medical Devices Act, the program creates an alternative pathway for market approval of medical devices that may help people with rare diseases or conditions. It was updated as part of the 21st Century Cures Act and is codified in 21 CFR §814 Subpart H.

### Criteria

#### Criteria to obtain the designation

To obtain HUD classification, a device must meet several criteria:

1. It must be intended to benefit patients in the treatment or diagnosis of a rare disease or condition that affects or is manifested in 8,000 or fewer people in the U.S. per year or is a rare subset of a non-rare disease or condition.
2. Adequate documentation or prevalence data demonstrating that the intended disease or condition is rare must be provided.
3. There must be scientific rationale supporting use of the device in the rare disease or condition.

According to the FDA guidance document on HUD designation:

*The scientific rationale supporting use of the device for the rare disease or condition, or orphan subset of a nonrare disease or condition (see Section III.C) in the HUD request should contain all relevant nonclinical, clinical, and/or proof-of-principle data pertaining to the device as applicable – whether positive, negative, or inconclusive. It should be noted that the nonclinical information on whether a device has been verified and validated against the proposed device design specifications is reviewed in the HDE marketing application and not in the HUD request.*

For the HUD designation program, a request is submitted to the OOPD and can be submitted at any time prior to submission of an HDE or other device marketing application. The FDA should respond to the request within 45 days. There are no apparent requirements for maintaining HUD designation prior to submission of an HDE or other device marketing application.

### Criteria to obtain the benefit

After obtaining HUD designation for a medical device, a sponsor can apply for a Humanitarian Device Exemption (HDE), a type of marketing application. The FDA may grant an HDE if the device meets the following criteria:

1. The device will not expose patients to an unreasonable or significant risk of illness or injury

2. The probable benefit to health from use of the device outweighs the risk of injury or illness from its use, when considered with the probable risks and benefits of currently available devices or alternative forms of treatment

3. The device would not be available to a person with the disease or condition in question without the HDE

4. No comparable device, other than another one approved under an HDE or Investigational Device Exemption (IDE), is available to treat or diagnose the disease or condition

5. The device is designed to treat or diagnose a disease or condition that affects not more than 8,000 individuals in the U.S. on an annual basis

## Timeline and maintenance

A request for HUD designation is submitted to the OOPD and can be submitted at any time prior to submission of an HDE or other device marketing application. The FDA should respond to the request within 45 days.

There are no apparent requirements for maintaining HUD designation prior to submission of an HDE or other device marketing application. The sponsor of an approved HDE application is subject to post-approval requirements – such as limitations regarding selling the device for profit – and must submit periodic reports in accordance with the approval order. In addition, the HDE holder is responsible for ensuring that the HUD is administered only in facilities having oversight by an Institutional Review Board (IRB).

## Benefit

Once a medical device is designated as an HUD, the device is eligible for an HDE marketing application. An HDE application is similar in both form and content to a Premarket Approval application (PMA) but is exempt from PMA effectiveness requirements as described in Sections 514 and 515 of the FD&C Act. FDA approval of an HDE application authorizes the sponsor to market the device in accordance with the approved labeling and indication(s) for use.*

**Note: An HUD designation and the subsequent submission of an HDE application do not guarantee FDA approval.*

**HUD requests typically include information about:**

- Sponsor
- Proposed device, and how it is relevant to the intended disease
- Intended disease/condition, including prevalence/ incidence data
- Scientific rationale for use of the product in the rare disease/condition
- Additional information as needed, e.g., rare subset
- HUD requests can be submitted to the OOPD at any time prior to HDE or PMA submission.
- A response, designation letter, info request, or disapproval letter, is expected within 45 days

Figure 6. Comparing the FDA's rare disease designations

| | Orphan Drug Designation | Rare Pediatric Disease Designation | Humanitarian Use Device Designation |
|---|---|---|---|
| **Where is the regulation found?** | 21 Code of Federal Regulations (CFR) §316; Orphan Drug Act | Section 529 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)/21 United States Code (USC) §360ff | 21 CFR §814 Subpart H |
| **What type of products qualify?** | Drugs and biological products | Drugs and biological products | Medical devices |
| **What are the major criteria?** | ▪ The product must be intended for use in a rare disease or condition<br>▪ The disease or condition must affect fewer than 200,000 people in the U.S.<br>▪ There must be strong scientific rationale supporting the use of the product in the proposed indication | ▪ The product must be intended for the prevention or treatment of a rare disease that is serious or life threatening and primarily affects patients 0-18 years old<br>▪ The disease or condition must affect fewer than 200,000 people in the U.S.<br>▪ Supportive data must suggest that the product may be effective in the indication (with a lower bar than for ODD)<br>▪ Additional criteria for the marketing application must be met to obtain the benefits | ▪ The device must be intended to benefit patients in the treatment or diagnosis of a rare disease or condition<br>▪ The disease or condition must affect or be manifested in no more than 8,000 individuals in the U.S. per year<br>▪ There must be scientific rationale supporting the use of the device in the proposed indication |
| **When can a sponsor submit the request?** | Any time prior to NDA or BLA submission | Preferably concurrent with the ODD or FTD request, but any time prior to NDA or BLA filing | Any time prior to submission of the HDE or other device marketing application |
| **To which FDA office or division is the request submitted?** | Office of Orphan Products Development | Office of Orphan Products Development | Office of Orphan Products Development |
| **How long does it take for the FDA to respond to the request?*** | 90 days | 60 days (This does not apply if the request is submitted later than the ODD or FTD request.) | 45 days |

*The timelines provided are goals for the FDA but may not be strictly enforced.

Figure 6, continued. Comparing the FDA's rare disease designations

| | Orphan Drug Designation | Rare Pediatric Disease Designation | Humanitarian Use Device Designation |
|---|---|---|---|
| **What are the benefits?** | **Pre-approval benefits**<br>▪ Potential PREA requirements exemption<br>▪ Waiver of user fee for NDA or BLA<br>▪ Tax credits and grants<br>▪ Protocol assistance<br><br>**Post-approval benefits**<br>Seven years of orphan drug market exclusivity upon NDA or BLA approval<br><br>Note: This benefit may not be available if the active moiety is already approved. | **Pre-approval benefits**<br>No significant preapproval benefits<br><br>**Post-approval benefits**<br>Receipt of a PRV for use on another product or application:<br>▪ The voucher is received upon NDA or BLA approval of the RPDD product<br>▪ PRVs can be used to expedite the review of another NDA or BLA from the 10-month standard review time to the 6-month priority review time<br>▪ The PRV can be either used by the sponsor who initially received it or sold to another sponsor | **Pre-approval benefits**<br>Eligibility for an HDE application<br><br>Note that the HDE application has its own separate benefits, but HUD designation is required to submit an HDE:<br>▪ Exemption from the effectiveness requirements in Sections 514 & 515 of the FD&C Act<br>▪ Shorter review time compared to a PMA application (75 days instead of 180 days)<br>▪ No user fees (marketing application submission fee)<br>**Post-approval benefits**<br>If approved via HDE, no user fees (marketing application maintenance/ periodic reporting fee) |
| **Are there any required activities for maintaining it?** | An annual report must be submitted (distinct from an IND annual report) | No, but a post-marketing five-year report is required after approval | No, but post-approval requirements exist, including post-marketing reporting to both the FDA and the IRB and IRB approval for use of HUDs in the clinical care of patients at a facility |
| **Can the designation be rescinded later in product development?** | Yes, if the product no longer meets the designation-specific qualifying criteria | Yes, if the product no longer meets the designation-specific qualifying criteria (The FDA may also revoke the PRV if the product is not marketed in the U.S. within one year of approval) | Yes, if the product no longer meets the designation-specific qualifying criteria |
| **Can it be obtained in conjunction with other rare disease designations?** | Yes, sponsors can request both ODD and RPDD for the same product | Yes, sponsors can request both ODD and RPDD for the same product | No, since the program is intended for medical devices and not drugs or biological products, it is highly unlikely that it could be obtained for the same product as ODD or RPDD |

## About the Author

Marissa Berry, Ph.D., RAC, has several years of experience in pharmaceutical research and development, global regulatory strategy, and regulatory operations/submissions. A Manager of Regulatory Strategy at Camargo (now Premier Consulting), she has experience applying for and managing orphan drug designations in both the U.S. and the EU and with the U.S. FDA's expedited programs. She also has earned the Regulatory Affairs Certification (RAC) professional credential through the Regulatory Affairs Professional Society (RAPS). Dr. Berry earned her Ph.D. in Pharmacology from the University of North Carolina in 2017.

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8. The Regulatory Affairs Professionals Society - Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers
9. Humanitarian Use Device (HUD) Designations: Guidance for Industry
10. Humanitarian Device Exemption (HDE) Program: Guidance for Industry


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Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.


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