Frequently Asked Questions (FAQ)

Does the contact person's signature need to be on the cover letter? Do you need an original signature? Can a signature page be sent separately?

- An original signature of an individual associated with the sponsor is required on one copy of the orphan designation application.
- The original signature does not have to be the contact person. For example, the sponsor's CEO may sign the application cover letter but the individual listed as the contact person is the head of regulatory affairs.
- OOPD requires that the original signature page be submitted with the application.

Can we submit the designation electronically? What is required? If so, how?

- An electronic Orphan designation application can be submitted on a single CD-ROM disk with a signed cover letter.

What information concerning approved designations is publicly available?

- Public available information (sponsor's name, address and contact information, name of drug, orphan designated use and date of designation) on orphan designated products are posted on the **OOPD website. (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm)**
- After the designated Orphan product receives NDA or BLA marketing approval additional information about the drug and application including a copy of the written designation review, may be released through the **Freedom of Information Act (FOIA). (http://www.fda.gov/RegulatoryInformation/FOI/default.htm)**

What is the review process like once application is received in OOPD? How is a designation application reviewed in OOPD? Please describe the review process for a designation application.

- Following receipt of the Orphan designation application, the OOPD review process is as follows: The application is assigned a designation application number and logged into OOPD database and an acknowledgement letter is sent to the sponsor. The assigned OOPD reviewer completes the review of the application by preparing a review. The review is forwarded to the OOPD Team Leader for a second level review and concurrence. The review is forwarded for a 3rd level review by the OOPD Office Director. Following the OOPD Director's concurrence, a designation letter, a letter requesting additional information, or a denial letter is prepared for the Director's signature and the letter is issued to the sponsor.

Are the written reviews conducted by OOPD staff publicly available?

- Once the designated orphan product achieves FDA marketing approval under an NDA or BLA, a copy of the written designation review can be requested through the **Freedom of Information Act (FOIA). (http://www.fda.gov/RegulatoryInformation/FOI/HowtoMakeaFOIARequest/default.htm)**

The regulations say that the sponsor is required to submit all relevant data about their drug, why doesn't the sponsor have to submit animal toxicology data for orphan designation?

- In order to designate a product as an orphan drug, the scientific rationale portion of the designation application must include enough information to establish a medically plausible basis for expecting the drug to be effective in the rare disease. This is best supported by clinical trials of the drug in the rare disease or condition
- However, in absence of human data, the application for orphan drug designation may be satisfactorily supported with compelling preclinical data that uses the active moiety or principal molecular structure of the proposed orphan drug in a relevant animal model for the rare human disease. Animal toxicology data, which describes the safety of the drug in animals, does not provide efficacy data, so is not useful in supporting the scientific rationale section of the orphan drug designation.

Common application (EMEA & FDA). What are the prevalence differences? How do you complete the form? When is it necessary to use? What are main advantages and disadvantages? Will one approval/denial affect the other? Can a sponsor submit a designation request simultaneously to the EMEA and FDA from this workshop? Â How does the OOPD form differ from the EU designation application?

- **Common EMEA application (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048361.pdf)**.
- A sponsor can choose to use this application or use the content and format in the regulations (21 CFR 316.20).
- However, the common form includes items on pages 6 to 8 that are specific to EMEA. If a sponsor is going to apply for orphan drug designation to both the EMEA and FDA, the sponsor may want to consider using the common form.
- EMEA requirements are slightly different Guidance for filing an orphan drug designation application with the EMA may be found on the **EMEA webpage (http://www.ema.europa.eu/ema/)**.

(For international sponsors). What is needed from a US sponsor/contact? What are they responsible for? If the sponsor is from a foreign country, is a US agent required in order to file a designation application?

- A foreign sponsor must have a US resident agent in order to file an application for orphan drug designation.
- A US agent can be anyone residing in the US who is responsible for the paperwork involved with the designation application and if designation is granted to the application, will serve as the contact person. Generally a US sponsor is associated with a regulatory affairs firm or a contact person at a US university.
- OOPD requires that all correspondence related to international sponsors to and from the Office of Orphan Products Development go through the US agent.

What if the sponsor has difficulty finding data on prevalence? What if data is not available? What are the best prevalence estimate resources? What should a sponsor do if the best resource they can find is 10-20 years old (or from other countries only)?

- Besides referenced texts and journals, prevalence data for many rare diseases can be found on the Internet at government and patient support group websites. Copies of all materials documenting how the prevalence estimate was made should be provided in the application. If the reference source is from the Internet, a hard copy of the document should be included as well as the website address. The date each website was accessed should also be provided for all website sources referenced.
- A sponsor is expected to make a good faith effort in finding the most recent prevalence data that refers to a United States population. If only old and or foreign data is available, the sponsor should explain this in the application.
- If data is old, the sponsor should explain why the data is still pertinent and, if from a foreign source, why data with that country's population could also be representative of US population.
- The sponsor should be reminded that the prevalence estimate must be current to reflect the prevalence at the time of submission of the request for orphan drug designation [21CFR 316.21 (b)]. To update this estimate, the sponsor should use US population data available from the **US Census Bureau (http://www.census.gov/)**.
- The **National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program (http://seer.cancer.gov/)** is another resource for determining cancer statistics in the United States.

In the case of a product used for an "acute" condition, should incidence of < 200,000 be used instead of prevalence?

- If a disease is an acute condition (i.e., less than one year duration) incidence may be used as an estimate of the target population.

If a drug is used for transplant to "prevent" rejection (solid organ tumors versus separate kidney & heart transplant indications). If a drug is used for "prevention" of rejection versus for "treatment" of rejection would prevalence or incidence be used in each case?

- If the drug is being used as a preventative, the target population is the number of people to whom the drug will be administered annually.

Is there a general list (besides OP database) of specific conditions considered to have prevalence of <200,000?

- The **NIH Office of Rare Disease Research (ORDR) (http://rarediseases.info.nih.gov/site-search?q=rare%20disease%20list)** provides a Rare Disease list.
- However, the purpose of the list is to distribute general information about rare diseases and on its own does not provide the current prevalence information that would be supportive for an application for orphan drug designation.
- OOPD will not accept the fact that a disease is listed as a rare disease on a website as evidence of prevalence of <200,000.

How does OOPD define what constitutes "Pediatric" patient population for Orphan product designations, given the wide range of pediatric ages across the various Centers at FDA?

Given that OOPD designates products that are subsequently regulated by different Centers across the agency, OOPD will adhere to the pediatric age definitions used by each center as listed below:

- For the purposes of a **drug or biologic** designation, the OOPD will define pediatric as encompassing up to and including age 16. {Source: CDER 21 CFR 201.57 (c)(9)(iv)]; CBER 1996 Guidance for Industry "The Content and Format for Pediatric use Supplements" [59 FR 64242]}
- For purposes of a **HUD** designation, the OOPD will define a pediatric device as one designed for individuals up to the age of 22. [Source: Pediatric Medical Device Safety and Improvement Act of 2007 303 (a) (6) (E) (i)]
- For f**oods or special dietary use** designation, OOPD defines pediatric as persons from birth to less than 12 years old. [Source: 21 CFR 105.3 (e) Foods for Special Dietary Use]
- In cases of **combination products**, the OOPD will follow the age associated with the primary classification of the product as determined by the Office of Combination Products.

If a product with an Active Pharmaceutical Ingredient (API) is already approved for a rare disease indication, but a different formulation is believed to have a greater efficacy for the same rare disease indication, can an orphan designation be requested?

- The public policy objective of the Orphan Drug Act is to further the testing and marketing of products for rare diseases in which no current therapy exists or where the product will significantly improve the existing therapy.
- Â If a product has received marketing approval in the United States for use in the proposed orphan indication, the only way the proposed product can be designated as an orphan drug is if the sponsor provides a reasonable hypothesis that their product is **"clinically superior" to the approved product by means of greater effectiveness, greater safety, or that it provides a major contribution to patient care (MC-to-PC)**.
- Further, if orphan drug designation is ultimately granted, in order for the product to receive orphan drug exclusive approval for this indication, the sponsor must actually demonstrate the superiority claim by showing their product is significantly more effective than the approved product in a clinical trial, is safer in a substantial portion of the target population, or can provide a major contribution to patient care.
- Any claim for clinical superiority could require a head-to-head trial.

What does OOPD need to determine clinical superiority? Explain "major contribution to patient care."

- A claim that a proposed orphan product may be clinically superior to an approved orphan product by a measure of major contribution to patient care **MC-to-PC** is intended to constitute a narrow category and its use is not intended to open the flood gates to FDA approval for every drug in which a minor convenience over and above that attributed to an already approved drug can be demonstrated. Historically, the only situation which FDA has identified as a **MC-to-PC** is the development of an oral dosage form where the first drug was available only as a parenteral form. However, each measure of **MC-to-PC** stands on its own and it could be possible that an oral dosage form is not superior to a parenteral form.
- What **cannot** be used for a **MC-to-PC** hypothesis: cost of therapy (FDA has no authority on drug pricing or any authority to consider it in drug approval), and compliance to therapy (significantly improved compliance needs to be based on a measure of greater safety or efficacy).

Please explain "Orphan Subset." Specific orphan subset questions (need to make case for why drug would be used only for this subset).

- An orphan subset means the use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug.
- An example of an orphan subset is that it might not be appropriate to treat all persons with a non-rare disease or condition with a drug that is highly toxic; those patients who are refractory to, or intolerant of, other less toxic drugs might be reasonable candidates for treatment with the drug and may be considered an appropriate orphan subset for purposes of orphan-drug designation of the highly toxic drug. In addition, other inherent properties of a drug, such as its pharmacologic or biopharmaceutical

characteristics, may provide a reasonable basis upon which to identify a subset of patients to whom it would be appropriate to limit treatment and who thus would qualify as an orphan subset of a non-rare disease or condition. Likewise, characteristics of the drug that have been demonstrated through previous clinical experiences may be used to identify an appropriate orphan subset.

If changes are made to the product formulation (such as solution form instead of emulsion versus intravenous, subcutaneous, intrathecal, intranasal or oral or a different concentration is formulated) after receiving orphan designation and prior to NDA submission - will the approved NDA still qualify for exclusivity?

- Orphan drug designation is conferred to the **active moiety** rather than the product formulation; therefore, changes to the product formulation should not affect orphan drug designation status.
- The first sponsor to bring an active moiety to market receives the benefits of exclusivity if that sponsor has orphan designation. If the sponsor subsequently makes a change in formulation to the original product, which was designated and approved for marketing, we consider the sponsor to still have designation for the active moiety. But the sponsor will **not** receive exclusivity upon approval of the changed formulation unless the sponsor can demonstrate that the changed formulation is clinically superior to the original approved product.