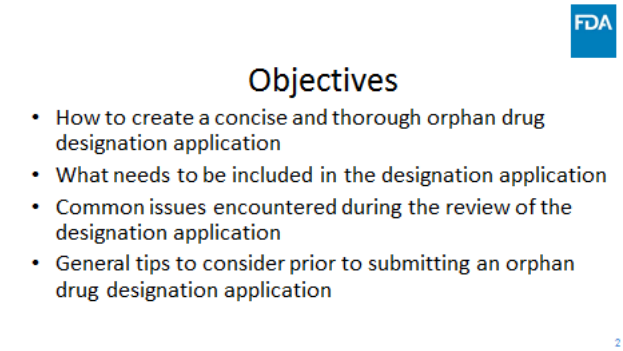
Recommended Tips for Creating an Orphan Drug Designation Application

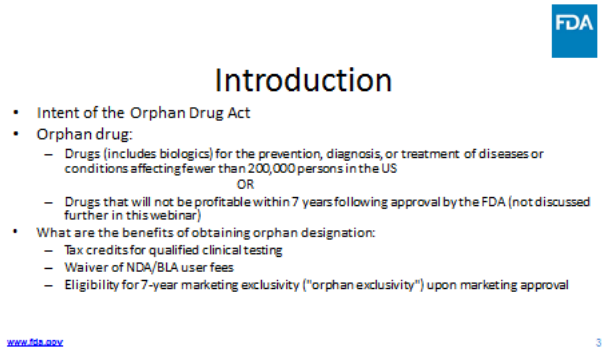
A Webinar by the Office of Orphan Products Development (OOPD)
2018

Slide 1: Welcome to the Office of Orphan Products Development or OOPD's webinar on recommended tips for creating an orphan drug designation application. We hope that you will find this webinar useful when putting together your orphan drug designation application.



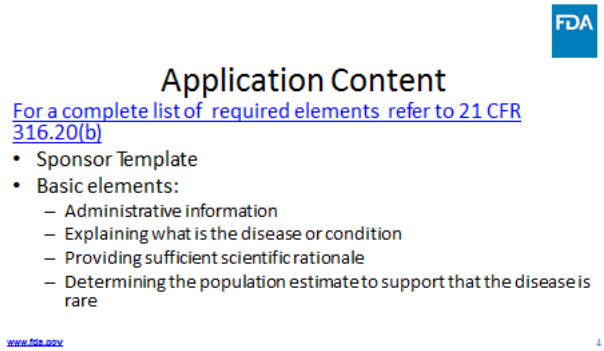
Slide 2: This webinar will cover several objectives.

- First, it will provide you with information on how to create a concise and thorough orphan drug designation application.
- Second, it will address what information should be included in the designation application.
- Third, it will address common application issues found during the designation review process.
- And lastly, it will provide some general tips that should be considered before submitting an orphan drug designation application.



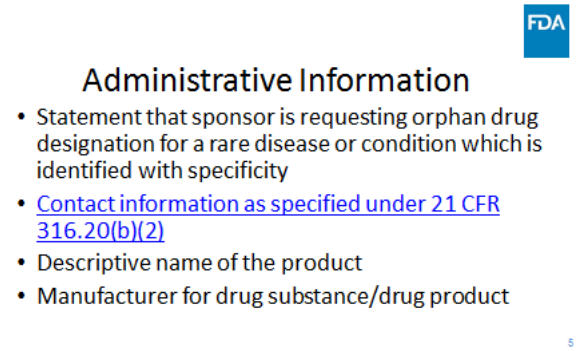
Slide 3: Before putting together an orphan drug designation application, it is important to understand the intention of the Orphan Drug Act.

- The Orphan Drug Act provides incentives that are intended to promote the development of promising drugs and biologics for the prevention, diagnosis, or treatment of rare diseases or conditions and to foster the prompt availability of therapeutically superior drugs.
- For the purposes of this presentation, the term "drug" will refer to both drugs and biologic products.
- Ok. So what is an orphan drug? The term "Orphan drug" has two definitions. The first describes drugs or biologics that are used for the prevention, diagnosis, or treatment of diseases or conditions affecting fewer than 200,000 persons in the US. The second definition describes a drug or biologic that is 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, where the drug will not be profitable within 7 years following FDA approval. The focus of this webinar will only be on the first definition of an orphan drug.
- Now that we've defined orphan drug, let's go over some of the benefits associated with orphan drug designation.
    - A sponsor who holds orphan drug designation may be eligible to receive tax credits for some of their clinical trial costs for qualified clinical testing. These tax credits are administered by the Internal Revenue Service or IRS and not by the FDA.
    - In addition to tax credits, sponsors who hold orphan drug designation may be eligible to receive a waiver of the Prescription Drug User application fee that is collected when a marketing application is submitted. The typical application fee is currently over $2 million dollars.
    - Lastly, a sponsor with orphan drug designation may be eligible for seven years of marketing exclusivity upon product approval. This exclusivity would prohibit FDA from approving the same drug as the orphan designated approved drug for the same use or indication for seven years after the marketing approval. For more information on orphan exclusivity, we refer you to the Code of Federal Regulations, or CFR Title 21 Part 316.31.



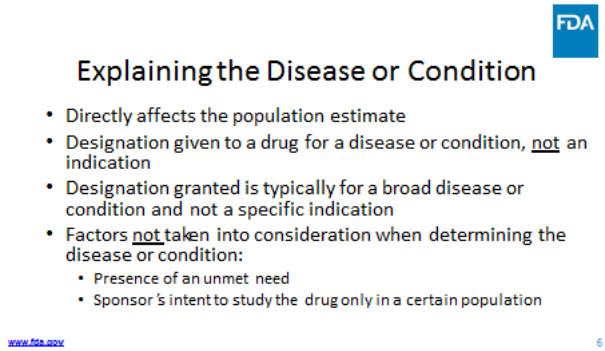
Slide 4: Now that we've established what an orphan drug is, we'll discuss the required content for an orphan drug designation application.

- The complete list of required elements for an orphan drug designation application can be found at 21 CFR 316.20(b). A hyperlink is included on this slide to allow for easy access to that regulation.
- Alternatively, a sponsor wishing to apply for orphan drug designation is encouraged to use the sponsor template form found on our website at www.fda.gov forward slash orphan.
- The basic elements that should be included in each orphan drug designation application include: administrative information; a brief description of the disease or condition that is the subject of the designation application; sufficient scientific rationale to show that the drug that is the subject of the designation application demonstrates promise to treat, diagnose or prevent the disease or condition; and a sufficient population estimate calculation to show that the disease or condition that is the subject of the orphan drug designation application is a rare disease. While there are several required elements that constitute a complete orphan drug designation application, it is important to keep in mind that each required element should be addressed completely yet concisely.
- We will now address each of these elements in more detail.



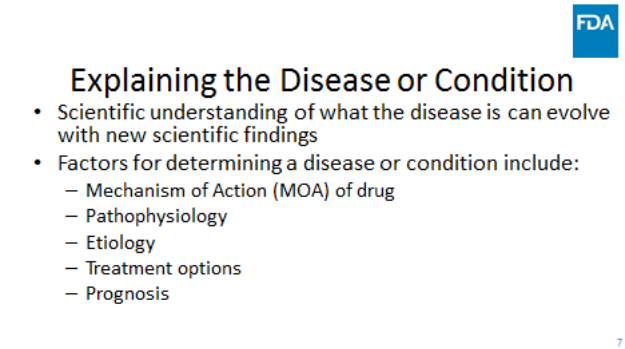
Slide 5: The first basic element that is required in an orphan drug designation application is the administrative information.

- Sponsors must include a statement in their application that they are requesting designation for a rare disease or condition that is identified with specificity. In other words, the sponsor must clearly identify what the disease or condition is that they are requesting designation for in their application.
- Sponsors must also include the required contact information as noted in 21 CFR 316.20(b)(2). A hyperlink is included on this slide to allow for easy access to that regulation.
- Additionally, a descriptive name must be furnished for the product. This may include the chemical name, generic name, or trade name. While company code names may be furnished, a code name by itself is not considered to be an adequate descriptive name for the product.
- Lastly, a sponsor must provide the manufacturer for the drug substance and drug product.



Slide 6: In addition to capturing the appropriate administrative information, a sponsor applying for orphan drug designation must clearly explain what the disease or condition is that their product is addressing.

- Determining the disease or condition is critical to estimating the size of the affected patient population.
- One commonly noted issue seen with designation applications is when a sponsor requests orphan drug designation for a drug for a specific indication. This results in issues when reviewing a designation application because generally orphan drug designation is granted for a drug for a disease or condition and not for a specific indication.
    - For example, we generally will not designate a drug for moderate to severe traumatic brain injury. For orphan drug designation purposes, the disease would be traumatic brain injury. However, if there is some feature of the drug that limits its use to a subset of patients with traumatic brain injury, the sponsor may provide such information and if we accept its validity, we can designate the drug for an orphan subset of traumatic brain injury. The issue of orphan subsets will be discussed in further detail later in this presentation.
- In the majority of cases, the orphan drug designation will cover a broad disease or condition while the marketing application for the drug will be for a specific indication.
- Factors that we do not consider when determining what the disease or condition is, include the presence of an unmet need or a sponsor's desire to restrict the designation use based on their intent to study the drug in only a specific population.

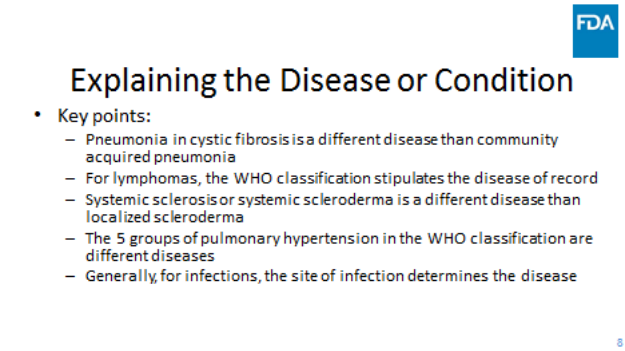


Slide 7: Scientific understanding of certain diseases and conditions may evolve over time. When evaluating whether there should be a change to how the disease is viewed, the OOPD may consult with the National Institutes of Health, the European Medicines Agency, and the appropriate FDA Review Division.

- Because how we view a disease may evolve, simply because a disease or condition has been designated previously does not mean that the designated disease or condition would be an orphan disease or condition in perpetuity for future designation applications.
- Similarly, as scientific understanding of disease changes, we may newly consider a certain disease or condition to be distinct for the purposes of orphan drug designation when the disease was previously subsumed within a broader disease or condition with a larger population estimate.
  - For example, historically OOPD considered lymphoma to be a distinct disease or condition. Over time it evolved into "Hodgkin's disease and non-Hodgkin's lymphoma" which then progressed to "Hodgkin's disease, non-Hodgkin's B-cell lymphoma, non-Hodgkin's T cell lymphoma or non-Hodgkin's null-cell lymphoma." However, B-cell lymphoma and T-cell lymphoma are thought to be agglomerations of distinct disease entities. For designation purposes, we now recognize each lymphoma type as its own disease entity and use the current World Health Organization or WHO classification of lymphomas as stipulating the disease of record.

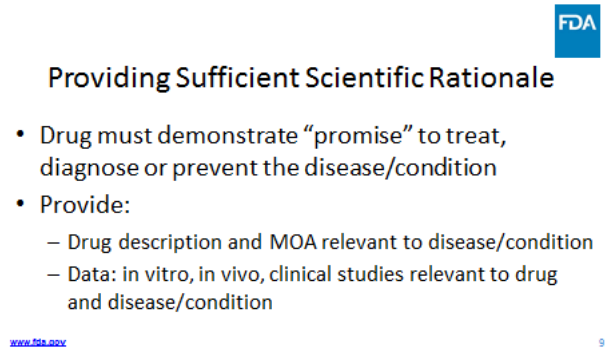
- The second bullet point outlines factors that we take into consideration when trying to determine what the disease or condition is that the drug is treating. These include:
  - The drug's mechanism of action; disease pathophysiology and etiology; available treatment options; and prognosis. Additionally, OOPD may consult with the FDA Review Division, the European Medicines Agency, as well as the National Institutes of Health.
  - Sometimes we encounter situations where a sponsor notes that their drug treats a disease or condition when in fact it treats one symptom or complication of the disease or condition. In these cases, OOPD may consider the relevant disease or condition, for the purposes of orphan drug designation, to be the symptom or complication that the drug is treating. Often times, OOPD considers the mechanism of action of the drug when determining what the appropriate disease is that the drug is treating.
    - For example, for a drug that can treat the lytic bone lesions found in multiple myeloma, if the drug can treat lytic lesions regardless of cause, the appropriate disease or condition for purposes of orphan drug designation may be lytic lesions instead of multiple myeloma.

- Another example is the use of pancreatic enzymes to treat pancreatic insufficiency in cystic fibrosis. Likewise, the appropriate disease or condition for purposes of orphan drug designation may be pancreatic insufficiency regardless of cause, instead of cystic fibrosis.



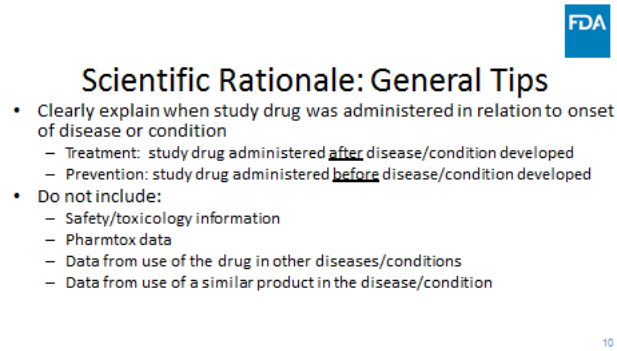
Slide 8: When determining the disease or condition, sponsors are encouraged to keep in mind that the OOPD currently considers:

- Pneumonia in cystic fibrosis to be a different disease or condition than community – acquired pneumonia.
- The current World Health Organization, or WHO, classification of lymphomas as stipulating the diseases of record for lymphomas.
- Systemic sclerosis or systemic scleroderma to be a different disease or condition than localized scleroderma.
- The 5 groups that comprise the WHO classification of pulmonary hypertension to be different diseases or conditions.
- For infections, the site of infection generally determines the disease or condition rather than the microorganism. Exceptions to this approach include malaria and tuberculosis, where the microorganism defines the disease and in these cases, for designation purposes, the disease is defined by the microorganism.



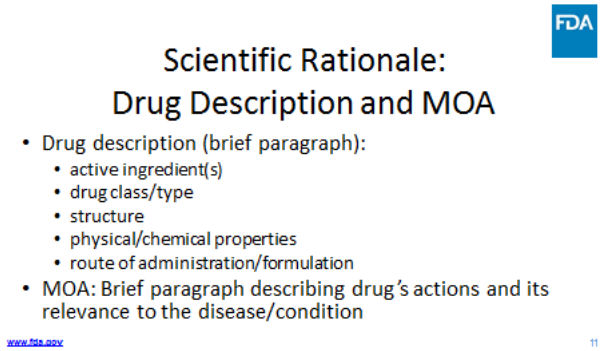
Slide 9: After clearly identifying the disease or condition, the next step is to provide scientific rationale to support the use of the drug in that disease or condition.

- In order for there to be sufficient scientific rationale, the drug must demonstrate promise to treat, diagnose or prevent the disease or condition. In other words, 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. As we will discuss later, this is best supported by clinical studies of the drug in the rare disease or condition.
- In this section, the sponsor is encouraged to provide:
    - A description of the drug along with its proposed mechanism of action relevant to the disease or condition that is the subject of the review.
    - And in vitro, in vivo and clinical study data, if available, if relevant to the drug and the disease or condition noted in the application.
    - Each of these items will be discussed in detail in the following slides.



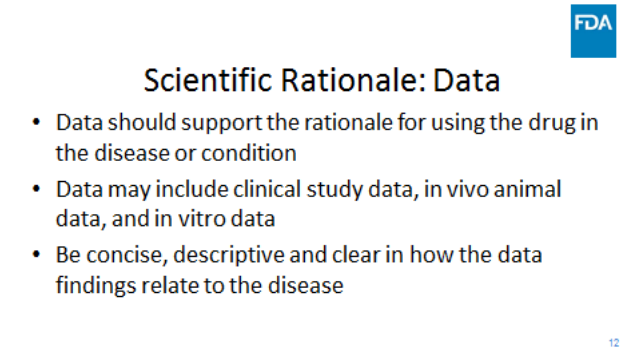
Slide 10: However, prior to discussing the individual data requirements, it is important to keep in mind some general tips:

- First, when discussing the data, please include details on when the study drug was administered in relation to the onset of the disease or condition. Regardless of whether you are submitting human data or data from a relevant animal model of the disease, it is extremely important to clearly describe when the study drug was administered in relation to the onset of the disease or condition. An application for a treatment use should include studies in which the study drug is administered *after* the disease or condition has already developed. In contrast, an application for a preventive use should include studies in which the study drug is administered *before* the disease or condition has developed.
- The next bullet point discusses items that generally should not be included in this section of the application. Because the review is focusing on whether the drug may have promise for effectiveness, a sponsor need not include safety data or toxicology data unless this information is used to limit the use of the drug to a subset of patients or if this information is being used to demonstrate that there is a plausible hypothesis for clinical superiority, which we will discuss later. Similarly, pharmtox data should be excluded as it pertains to safety of the drug in animals and does not provide efficacy data.
- Lastly, data from the use of the study drug in other diseases or conditions as well as data from the use of a similar product in the disease or condition generally should also be excluded from the application. However, such data may be provided if there is no animal model of the disease and if clinical data are unavailable. In this case, the sponsor would have to also provide supportive information to suggest that their product would have a role in the disease or condition that is the subject of the designation application.

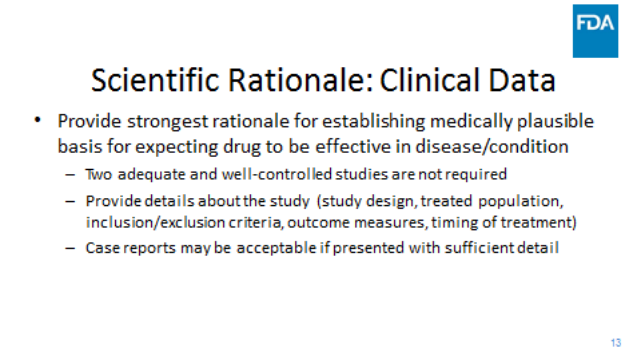


Slide 11: Now that we have covered some general tips, let us move on to the drug description and the mechanism of action section of the scientific rationale.

- The drug description should include a brief paragraph discussing:
    - The active ingredient or ingredients, drug class and/or type, structure, physical and chemical properties, route of administration and the formulation.
- The mechanism of action of the drug should also be limited to a brief paragraph that details the drug's actions in the disease or condition that is the subject of the designation application. This section should clearly tie in how the drug's mechanism of action would have relevance to the disease or condition at hand.

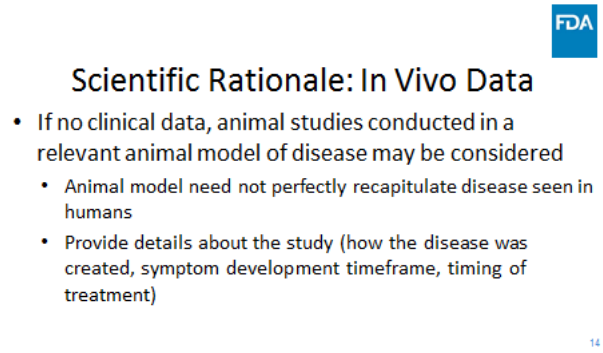


Slide 12: The drug description and mechanism of action section of the scientific rationale should be followed by data that supports the rationale for using the drug in the identified disease or condition. All relevant data from in vitro laboratory studies, preclinical efficacy studies conducted in an animal model for the human disease or condition, and available clinical experience with the drug in the rare disease or condition, whether positive, negative, or inconclusive must be included in this section. If you have clinical data on the drug in the proposed disease, you need not provide a lot of detail with non-clinical or preclinical studies. Try to keep this section as concise yet as descriptive as possible and most of all, be very clear in your findings on how they relate to the disease.



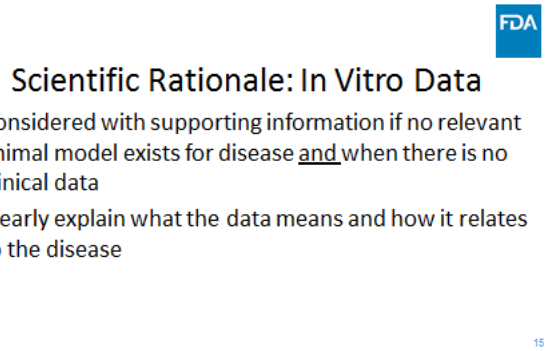
Slide 13: Clinical studies are considered to provide the strongest rationale for establishing a medically plausible basis for expecting the drug to be effective in the identified disease or condition.

- Clinical studies should support the effectiveness of the use of the drug in the proposed setting. Two adequate and well-controlled studies demonstrating statistical significance on a clinically significant endpoint are not required for designation purposes. However, sponsors should provide adequate level of detail regarding the study including the study design, details about the treated patient population such as age, inclusion/exclusion criteria, outcome measures, and treatments administered. Also include the timing of the administration of the treatment with relationship to the development of the disease. Please be sure to explain the study in the application and do not simply provide a reference link to the study.
- Case reports may be included in this section. However, sponsors should provide a sufficient amount of detail about the case report.
- In terms of demonstrating that the drug serves a benefit in the disease or condition, it is worthwhile to note that a common issue encountered with cancer designation requests occurs when a sponsor will simply state that stable disease indicates that the drug is beneficial in that cancer. For the purposes of orphan drug designation, a complete or partial response would be required to indicate that there is a benefit of using the drug in the disease. Stable disease by itself is insufficient to support orphan drug designation.



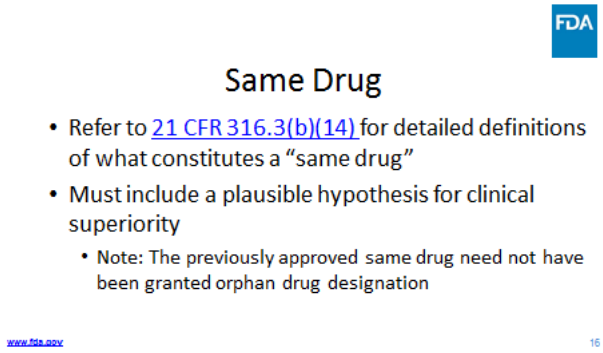
Slide 14: While clinical studies provide strongest rationale for establishing a medically plausible basis for expecting the drug to be effective in the identified disease or condition, if human data is unavailable, we will consider animal data from the use of the drug in a relevant animal model of the disease.

- A relevant animal model needs to exhibit an appropriate pathophysiology for the disease in which to assess the drug therapy. It need not perfectly recapitulate the disease in humans.
- As with clinical data, when providing animal data, it is important to note details of the animal study conducted. For example, information on how the disease is created in the animal model as well as what the symptoms are and when they develop in the model should be clearly explained. Further, there should be information on when treatment is administered in the animal model with relation to when the disease develops. Please be sure to explain the study in the application and do not simply provide a reference link to the study.
- A common deficiency in orphan drug designation applications occurs when a sponsor provides alternative data such as pathogenesis or mechanism of action, or provides in vitro data or data from the use of the drug in an animal model of another disease even though there is a relevant animal model of the proposed disease available.
    - If a sponsor chooses not to use the available animal models of a disease or condition because they believe that the animal models are not appropriate to study the effects of their product, they would have to explain their rationale for why they believe this to be the case.



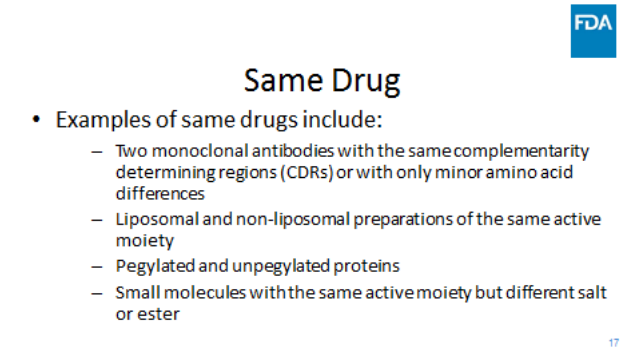
Slide 15: In vitro data along with supporting information such as the mechanism of action of the drug and the pathogenesis of the disease may be provided when there is no relevant animal model of the disease and in the absence of human data.

- When providing in vitro data, the sponsor should clearly explain what the data means and how it relates to the disease or condition that is the subject of the designation application.
- Please note that in vitro data may be provided as additional supportive information in the presence of an animal study and/or human study.
- Please keep in mind that if you use biomarkers for supporting this section, clearly explain how changes in the biomarkers translate into the therapeutic effect.



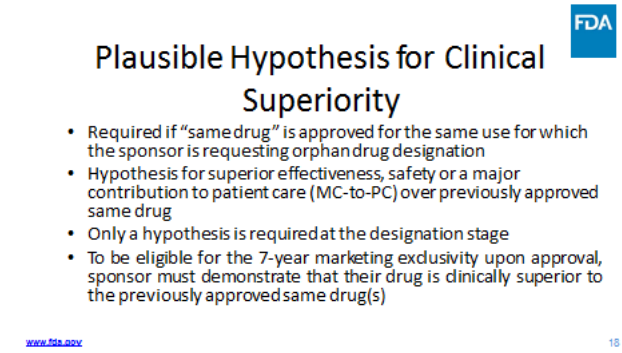
Slide 16: The next few slides are dedicated to what additional information should be provided in the orphan drug designation application in the situation that the same drug is already approved for use in the same disease or condition.

- When determining what constitutes a same drug, sponsors are encouraged to refer to 21 CFR 316.3(b)(14). A hyperlink is included on this slide to allow for easy access to that regulation.
- Same drug as defined in 21 CFR 316.3(b)(14) does not mean identical. Rather it refers to products that contain the same active moiety or principal molecular structural features.
- The same drug issue occurs when a sponsor requests orphan drug designation for a same drug and indication as a previously approved drug. The OOPD views a previously approved drug as any drug with a new drug application or a biologics license application that has been granted marketing approval.
- An 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. If a product has received marketing approval in the United States for use in the proposed orphan indication, the only way another same product can be designated as an orphan drug for the same use is if the sponsor requesting orphan drug designation provides a plausible hypothesis that their product is clinically superior to all approved products (for the same use) by means of greater effectiveness, greater safety, or that it provides a major contribution to patient care. Please be aware that to be considered a same drug, the approved same drug need not have been granted orphan drug designation.
- It is important to note that the sponsor is required to determine whether the same drug has been previously approved for use in the same disease or condition.



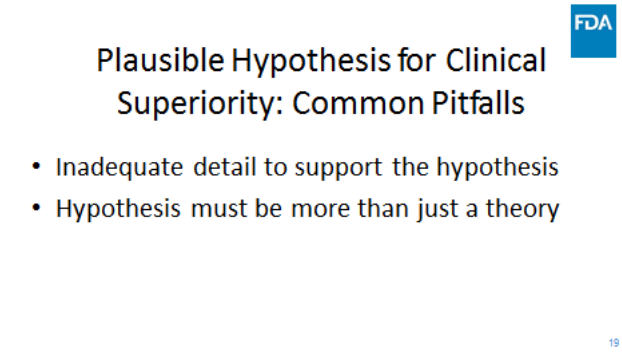
Slide 17: This slide details some examples of what OOPD considers to be same drug products.

- With respect to monoclonal antibodies, the OOPD considers two monoclonal antibodies to be the same if their complementarity determining regions are the same or if there are only minor amino acid differences between the two products.
- The OOPD views liposomal and non-liposomal products to be the same.
- Additionally, the OOPD views pegylated and unpegylated proteins to be the same.
- The OOPD views small molecules with the same active moiety as being the same drug even if they have different salts or esters.



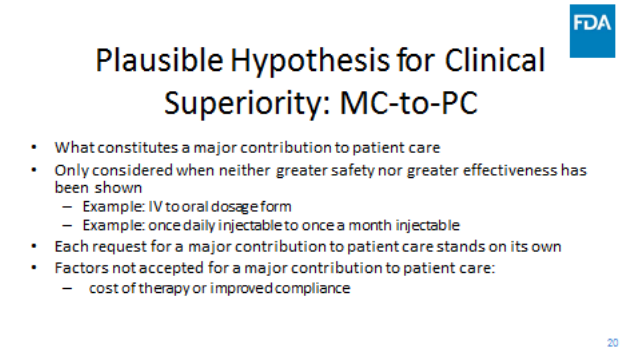
Slide 18: As mentioned earlier, a plausible hypothesis for clinical superiority must be provided if the same drug is approved for the same use for which the sponsor is requesting orphan drug designation.

- This plausible hypothesis for clinical superiority may be based on greater effectiveness, safety or a major contribution to patient care, or MC-to-PC, over the previously approved same drug.
- It is important to realize that only a plausible hypothesis of clinical superiority is needed at the orphan drug designation stage if there is a same drug already approved for the same use. However, in order to be eligible for the 7-year marketing exclusivity upon approval, the sponsor needs to demonstrate that their drug is clinically superior to the previously approved same drug or drugs and this may require head-to-head clinical studies.



Slide 19: Common pitfalls when providing a plausible hypothesis for superior effectiveness or safety include not providing enough detail to support that there could be a plausible hypothesis present.

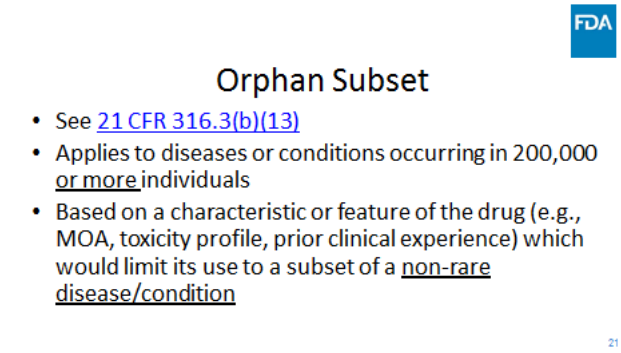
- For example, providing pharmacokinetic data showing a longer half-life or better absorption or changes in plasma concentration with one product over another should be coupled with a detailed explanation as to why such changes would result in a more efficacious or safer product.
- While a plausible hypothesis need not involve head-to-head studies, it must involve more than just a theory.
  - For example, it isn't enough to just state that the drug that is the subject of the orphan drug designation application has a higher bioavailability compared to the approved same drug which could result in a safer product. The sponsor must clearly explain why this increased bioavailability could improve safety. Perhaps improved bioavailability will allow for the use of a lower dosage of a drug that is typically associated with dose-limiting toxicities.
  - If the drug that is the subject of the orphan drug designation application is associated with fewer adverse events, resulting in a possibly safer product, it isn't enough to simply note that the plausible hypothesis is based on a reduction of adverse events. Rather, in addition to this information, the sponsor should provide sufficient support to suggest that there is a reduction in adverse events associated with the product and explain the mechanism behind why there would be a reduction in adverse events.



Slide 20: Now, let's discuss what constitutes a major contribution to patient care, or a MC-to-PC: Determination of clinical superiority based on a MC-to-PC is intended to constitute a narrow category and must be decided on by considering the nature of the disease or condition, the nature of the drug, the nature of the mode of administration, and other factors related to that specific case. The major contribution to patient care argument is made in unusual cases where neither greater safety nor greater effectiveness has been shown. It is not intended to open the flood gates to orphan designation for every drug in which a minor convenience over and above that attributed to an already approved drug can be demonstrated.

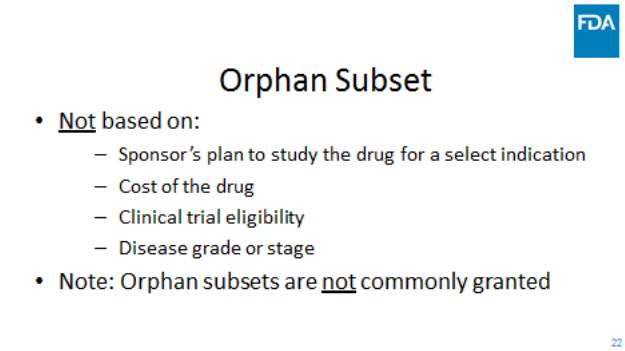
- When determining whether a drug may make a major contribution to patient care, the OOPD may consider in appropriate cases factors such as convenient treatment location, duration of treatment, patient comfort, reduced treatment burden, advances in ease and comfort of drug administration, longer periods between doses, and potential self-administration.
- Historically, the OOPD has accepted the development of an oral dosage form where the same drug is available only as a parenteral form as constituting a major contribution to patient care. Another example is a once daily injectable product that is reformulated into a once a month injectable product. However, in some cases this may not constitute a major contribution to patient care, say if the once a month drug is significantly more painful than the once daily drug. Similarly, an oral dosage form may not be superior to a parenteral dosage form.

- Each request for a major contribution to patient care stands on its own.
- Factors that the OOPD will not accept for a major contribution to patient care claim are the cost of therapy or improved compliance.



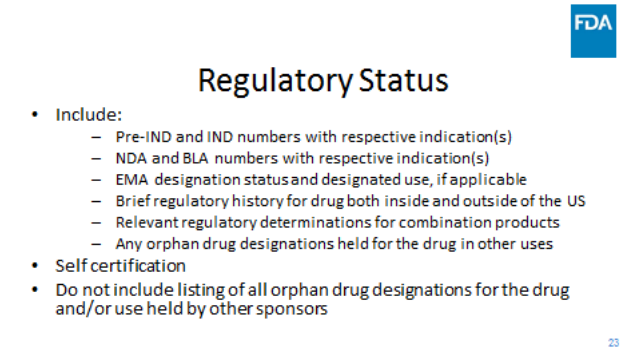
Slide 21: This next slide discusses an orphan subset as noted under 21 CFR 316.3(b)(13). A hyperlink is included on this slide to allow for easy access to that regulation.

- A drug for a disease or condition occurring in 200,000 *or more* individuals may still be eligible for orphan drug designation if the sponsor can demonstrate that the drug is for an "orphan subset" of the non-rare disease or condition.
- An orphan subset of a non-rare disease or condition is defined by some characteristic or feature of the drug such as its mechanism of action, toxicity profile, or prior clinical experience, that would limit its use to a subset of the disease or condition and would make the drug or biologic ineffective or too toxic to use in the complement of the subset of the disease or condition. In other words, the drug may be appropriate for a subset of patients with the non-rare disease or condition, but the 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 or properties of the drug.
    - An example of an orphan subset based on toxicity would be one where it might not be appropriate to treat all persons with a non-rare disease or condition with a drug that is highly toxic. However, 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. Additionally, other inherent properties of a drug including its pharmacologic or biopharmaceutical characteristics, may provide a reasonable basis upon which to identify a subset of patients to whom it should be appropriate to limit treatment and who thus would qualify as an orphan subset of a non-rare disease or condition.
    - An example of an orphan subset based on the drug's mechanism of action would be one where the drug in question is an antibody-specific targeted therapy that could only be used in a subset of patients with the non-rare disease or condition, such as in patients with subtypes of tumors that possess the specific antigen targeted by the drug.
    - An example of an orphan subset based on prior clinical experience with the drug would be one where the drug's activity has been elucidated from clinical studies or clinical literature and shows that the drug has no significant activity in patients outside of a certain orphan subset of the non-rare disease or condition.



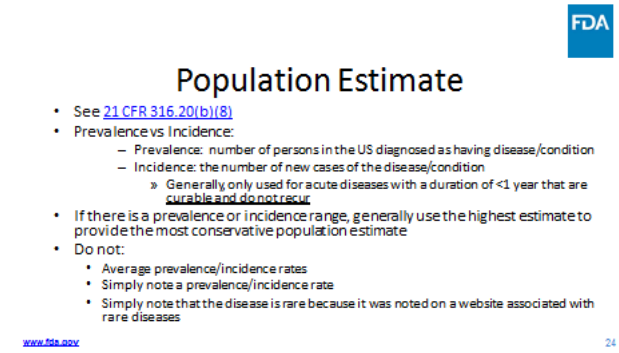
Slide 22: An orphan subset cannot be based on the sponsor's wish to study the drug in a select indication, the cost of the drug, clinical study eligibility, or disease grade.

- Please be aware that requests for orphan subsets are not commonly granted.
- Even if you do not intend to make the case that your product should be limited to an orphan subset, please address this section in your application. Also, when addressing this section in your application, do not simply reiterate your desired indication in this section. Sometimes sponsors will request orphan drug designation for an orphan subset and under this section in their application, they will note that they are requesting designation for the entire orphan subset that they have identified without any additional information to support the request. Sometimes sponsors are not aware that they are even requesting designation for an orphan subset.



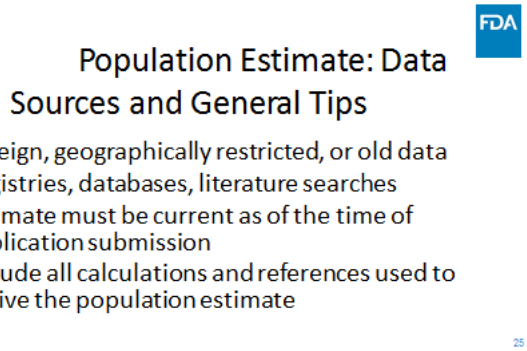
Slide 23: Another part of the orphan drug designation application is the regulatory section. The information provided by sponsors in this section is often times incomplete.

- For this section, sponsors are encouraged to include:
    - Pre-investigational new drug applications or investigational new drug applications or IND numbers with their respective indications being studied even if the indications differ from the orphan drug designation use. If you haven't submitted a US IND, briefly state that you are still in the preclinical stage of development.
    - Sponsors are also encouraged to include new drug applications or NDA or biologics license applications or BLA numbers in this section with their respective indications.
    - If applicable, include the European Medicines Agency or EMA designation status and designated use for the product that is the subject of the orphan drug designation application.
    - Also note a brief regulatory history for the drug both inside and outside of the US. Please include a list of countries where the drug is approved and for what it is approved for.
    - If the product that is the subject of the orphan drug designation application is a combination product, provide any regulatory determinations. For example, for combination products, it is a good idea to first determine whether the product will be reviewed as a drug or biologic or device by the FDA Office of Combination Products or OCP before filing an application for orphan drug designation. Otherwise, the orphan drug review process may be held up as the product's primary mode of action would not have been determined by the FDA OCP. Lastly, please include any orphan drug designations you may hold for the drug in other uses.
- Please also self-certify whether there has been a previously submitted marketing application for the same active moiety for the same rare disease or condition prior to submitting the orphan drug designation application.
- Do not include a listing of all orphan drug designations for the proposed drug and/or use held by other sponsors.



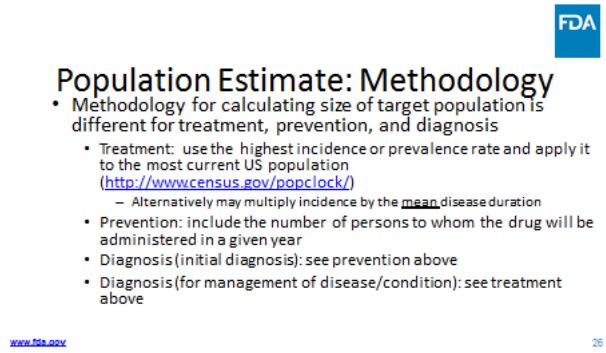
Slide 24: The next few slides discuss the population estimate requirement for an orphan drug designation application as detailed under 21 CFR 316.20(b)(8). A hyperlink is included on this slide to allow for easy access to that regulation.

- The population estimate for a disease or condition may be based on a prevalence figure or incidence figure.
- First, let's review the difference between prevalence and incidence.
    - For the purposes of orphan drug designation, prevalence includes the number of persons in the US who have been diagnosed as having the disease or condition at the time of the submission of the orphan drug designation application.
    - For the purposes of orphan drug designation, incidence includes the annual number of *new* cases of the disease or condition.
        - The OOPD will allow sponsors to use an incidence estimate for acute diseases with a duration of less than one year provided that they are curable and do not recur.
        - Relapsing or remitting diseases such as cancer typically require a prevalence estimate. The National Cancer Institute's Surveillance, Epidemiology and End Results or SEER Program website is OOPD's standard source for cancer statistics in the United States.
- As noted in the third bullet point, in the event that there is a prevalence or incidence range, the OOPD will generally accept the highest figure to estimate the total size of the affected population and encourages sponsors to do the same. This will result in the most conservative population estimate.
- It is important to not average out multiple prevalence or incidence rates but to use the highest rate available. However, the OOPD recognizes that in some cases, the highest rate may not be the most appropriate rate to use. If a sponsor feels that the highest prevalence or incidence rate available is skewed for any reason, they should clearly explain why they feel that this is the case.
- Please do not simply note a prevalence or incidence rate. A sponsor must provide an actual population estimate figure that they accept as being the final population estimate for the disease or condition.
- Further, as noted in the last bullet point, when trying to determine if a disease is a rare disease, it is not sufficient to simply state that a disease is rare because it is found on a rare disease website.



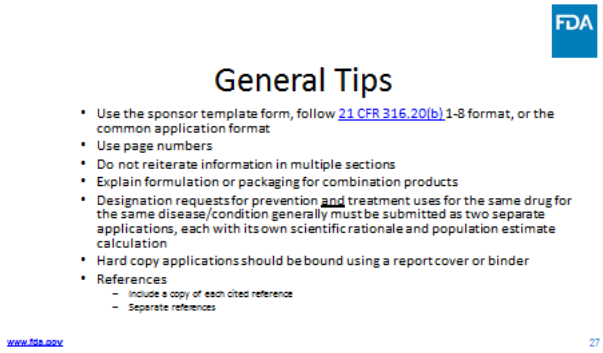
Slide 25: While a sponsor is expected to make a good faith effort in finding the most recent prevalence or incidence data that refers to a United States population, if only foreign data are available, sponsors must clearly explain why they believe that the data are generalizable to the current United States population. Please also clearly explain the limitations of such data. Similarly, if using data from a certain region in the United States, there should be an explanation as to why the data is generalizable to the entire United States population. If only older data is available, the sponsor should explain why the data is still pertinent. In all of these cases, the sponsor should explain in the application efforts made to find the most recent and relevant population estimate data.

- If using multiple different resources such as registries, databases, or literature searches for calculating different population estimates, please clearly indicate what your final accepted population estimate is and provide a strong rationale as to why you have chosen that estimate.
    - Many times sponsors will use ICD-9 or 10 codes to calculate a population estimate. The OOPD believes that there are several limitations to the use of these codes, including miscoding, and generally will not accept the use of claims databases by themselves to support a population estimate for a disease or condition. If such data is being used to support the population estimate, please clearly explain how this data is generalizable to the US population and address the limitations of such data.
- It is important to remember that the final population estimate must be current and must reflect the estimate as of the time of submission of the application for orphan drug designation. To update an estimate, you may refer to the US population data found on the US Census Bureau's US and World Population Clock webpage. This webpage allows you to determine the US population for any given day and year from April 2010 to present.
- Lastly, please be sure to include all calculations and references used to derive the population estimate.



Slide 26: The next slide discusses the different methodologies used for calculating the population estimate for a treatment, preventive or diagnostic use.

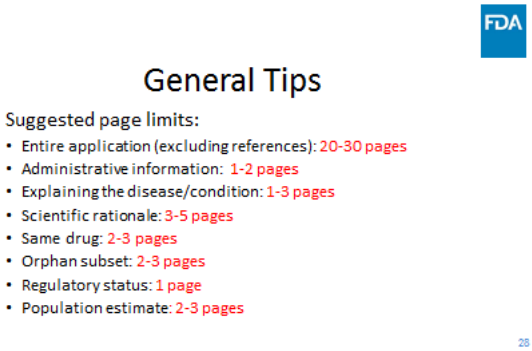
- For a treatment use, the OOPD encourages sponsors to use the highest incidence for a disease with a duration of less than one year, or prevalence rate and apply it to the most current US population which can be found at the Census.gov hyperlink on this slide.
    - If a prevalence rate is unavailable and if the disease is chronic in nature, sponsors may take the incidence and multiply this by the mean disease duration or life expectancy. Often times sponsors will take the incidence of a disease and multiply this by the median disease duration. This is not accepted by the OOPD.
- For a prevention use or if the drug is a vaccine, the sponsors should include the number of persons to whom the drug will be administered annually.
- For a diagnostic product that will be used as an initial diagnostic, the population estimate calculation will follow the prevention methodology above.
- For a diagnostic product that will be used as a diagnostic in the management of a disease or condition, the population estimate calculation will follow the treatment methodology above.



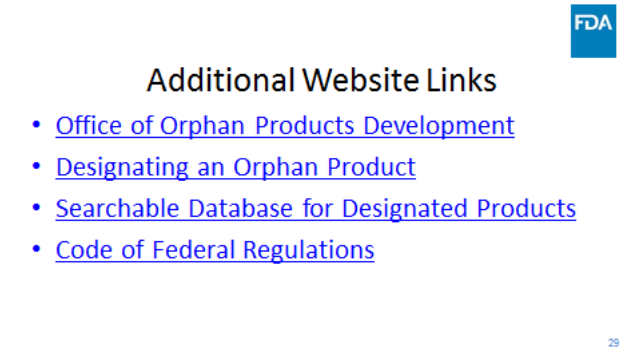
Slide 27: When creating an orphan drug designation application, it is important to consider the following general tips:

- When putting together your application, it is important to ensure that it has been formatted properly. The reviewer of the application needs to be able to walk through your application with ease.
- While we recommend that sponsors use the sponsor template form found on our website, if you choose not to use this form, we recommend that you follow the 21 CFR 316.20(b) 1-8 format which is hyperlinked on this slide or the common EMA and FDA application format. If following the 1-8 format, sponsors are encouraged to number the items in their application 1 through 8 to match the items under 21 CFR 316.20(b). While all eight items will be reviewed, the application will be reviewed most critically under Item 4 discussing the scientific rationale and under Item 8 discussing the population estimate. If you are using the common application format, use the marked appendices to provide all pertinent information.
- Please remember to use page numbers in the application regardless of the format used.
- In order to limit redundancy and the length of the application, it is unnecessary to repeat information in different sections of the application. Rather, please refer the reviewer to the appropriate section if needed.
- If your product is a combination of two or more drugs, please provide information about how you envision marketing the product. For example, will the two drugs be formulated into one dosage form or co-packaged? Please note that the OOPD does not designate drug regimens.
- Generally, if you intend on submitting a designation application for the same drug for the same disease or condition for both a treatment and prevention use, you must submit two separate applications each with its own scientific rationale and population estimate calculation.
- All applications should either be submitted electronically or as a hard copy that is bound using a report cover or binder. No correspondence should arrive loose, or out of the binder or report cover. It helps to label the front of each report cover or binder with the name of the sponsor, drug product, proposed orphan drug use and date of the application.
- Lastly, applications should include a copy of each cited reference.
    - For hard copy applications, separate each reference with tabbed dividers even if you decide to arrange them alphabetically. Colored sheets placed between references are not functional. If you decide to provide an Investigator's Brochure, provide the document behind a tabbed divider labeled "Investigator's Brochure".
    - For electronic applications that do not use the sponsor template form, place references in their own reference folder rather than including them in the same document as the application.

- If you cite sources from the Internet, you should provide a copy of the web document, the website address, as well as the date each website was accessed.
- Keep in mind that more references does not translate into a better application.

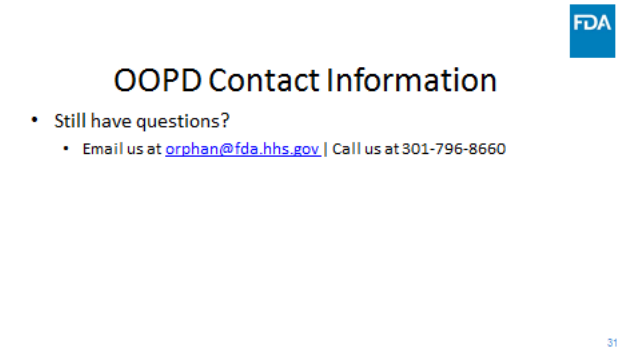


Slide 28: This slide provides some page limit recommendations per each section of the orphan drug designation application. As mentioned in the beginning of this presentation, it is important to keep in mind that each required element should be addressed as concisely yet completely as possible.



Slide 29: This slide provides hyperlinks to websites that may be helpful when thinking about submitting an application for orphan drug designation.

Slide 30: This slide lists Orphan Drug Regulations and Resources that may be of help when putting together an orphan drug designation application.



Slide 31: Lastly, if you have additional questions on orphan drug designations or on any of OOPD's other programs, please email us at orphan@fda.hhs.gov or call our Office at 301-796-8660.

Slide 32: Thank you for listening to our Webinar. We hope you find it useful when putting together your orphan drug designation application.