Standard Operating Procedures and Policies

Orphan Designation Applications

Review of Request for Orphan Drug Designation

SOPP 420 Version #2 Effective Date: November 9, 2010
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CONTENTS

PURPOSE

This SOPP describes the ongoing procedures for performing a review of a request for Orphan Drug Designation. These procedures and policies have been used in the Office of Orphan Products Development (OOPD) since the proposed regulations were published (December 1991). This SOPP serves to document the template used in carrying out these procedures.

HISTORY

This is the second version of this SOPP and it is effective upon date of publication. This version includes two additional appendices (Appendix F and G) and update of Director's concurrence signatory.

POLICY

OOPD was originally established in 1982 and implements the Orphan Drug Act that was signed into law early in 1983. The intent of the law was to provide support for the development of drugs for the diagnosis, prevention, or treatment of rare diseases or conditions. Since its inception, OOPD has assumed numerous roles in an effort to carry out its mission. One method by which OOPD provides incentives for the development of products for the diagnosis, prevention, or treatment of rare diseases is by granting requests for orphan drug designation.

The purpose of this document is to provide a template for a standard review of a request for orphan drug designation. The intent of this template is to provide not only a standard form but a standard process for the review of a request for orphan drug designation. The final goal of this document is to ensure the office continues to provide a consistent and quality review of requests submitted to OOPD for orphan drug designation.

REFERENCES

Appendix A – Template for Review of Request for Orphan Drug Designation
Appendix B – Scientific Rationale Supporting a Request for Orphan Drug Designation
Appendix C – Medically Plausible or Orphan Subsets Supporting a Request for Orphan Drug Designation
Appendix D – Lymphoma as the Subject of a Request for Orphan Drug Designation
Appendix E - Recombinant Products and Orphan Drug Designation
Appendix F - Scleroderma as the Subject of a Request for Orphan Drug Designation
Appendix G - Pulmonary Hypertension as the Subject of a Request for Orphan Drug Designation

PROCEDURES

The following template may be utilized for the review of a request for orphan drug designation. The reviewer must understand the information provided in the review and be able to explain it to others. The order of the elements titled "Population Estimate" and "Scientific Rationale" may be interchanged, at the reviewer's discretion. Headers and/or footers should be included on each page referencing the appropriate designation application file number. The review of the request for orphan drug designation should include page numbers.

Concerning the issue of cutting and pasting, no text is to be directly cut-and-pasted from the sponsor's application. The reviews of requests for orphan status are to include writing of exclusively OOPD genesis, though it is acknowledged that the need to paraphrase the application is inescapable. Where necessary, reviewers may cite references (with page numbers and paragraphs) to the sponsor's application, but should not seek to fulfill a desire for a "stand alone document" by inserting text of origin from the sponsor.

In order to clarify the policy concerning the review of orphan drug designation requests, be advised that one may reference (with page numbers) the sponsor's application. If the text in that portion of the application cited is vital to the review, that text may be included in full in an Appendix that can be referred to in the review. For example "The sponsor estimates the prevalence of Startzman's Disease on page 27 of his application (See Appendix A). The sponsor concludes that the Prevalence of Startzman's Disease is 1." Appendix A, with the vital text, would then be attached after the signature page and references of the review. The review template is in Appendix A.

Prepared by: *Henry Startzman, M.D.*
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Approved by: *Timothy R. Coté, M.D., M.P.H., Director, Office of Orphan Products Development*
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Appendix A

REVIEW OF REQUEST FOR ORPHAN DRUG DESIGNATION

Date Submitted by Sponsor:	mm/dd/yyyy
Date Received by FDA:	mm/dd/yyyy
Date Amendment received:	mm/dd/yyyy (If applicable)
Date Review Completed:	mm/dd/yyyy
Designation Number:	##-####
Trade name:	Name owned by the company and used for Marketing purposes (if available)
Generic name (active ingredient):	Name established by the US Adopted Names (USAN) council (if available) or name of active ingredient
Chemical name:	Description of molecular structure (a sponsor code name for a product is not adequate as the only name supplied by the sponsor for the drug product)
Sponsor:	Name and address of the sponsor
U.S. Resident Agent:	Name, address, and contact information for U.S. resident agent
Manufacturer:	Name and address of manufacturer of drug product and source of drug substance, where applicable
Regulatory Status:	This section should include the marketing history of the product in the United States and foreign countries. One should note if there is an active IND for this product. Any adverse actions taken against this drug should also be included in this section.
Proposed Orphan Designation:	This section should include the drug, the disease or condition, and how the drug is to be used in the disease or condition (prevention, treatment, or diagnosis) that are the subjects of the request for orphan drug designation submitted by the sponsor.

REVIEW OF REQUEST FOR ORPHAN DRUG DESIGNATION
DESIGNATION APPLICATION NUMBER ##-####

Orphan Drug Designation History: History of the drug with respect to orphan designation and history of the disease or condition, where applicable, with regards to orphan designation.

1. Background of Disease or Condition

This section of the review provides the reader as well as the reviewer with a basic knowledge of the disease or condition that is the subject of the request for orphan drug designation. The following elements may provide a working description of the disease or condition:

- Disease History - Rarely required but may provide worthwhile information in a number of diseases or conditions.
- Disease Demographics and Epidemiology - Certainly demographics may be worth discussing, particularly if the disease affects only a portion of the population (age groups, gender, etc.). The more detailed discussion of prevalence should be part of the population estimate later in the review.
- Pathogenesis of the Disease - This should include a discussion of the pathogenesis of the disease relevant to the proposed mechanism of action of the drug product if the mechanism of action of the product is through an accepted pathogenesis of the disease. Pathology may certainly be important. When a disease or condition involves a malignancy, a description of the staging system for that cancer is a valuable part of the description of the disease.
- Disease Presentation - Should include presenting signs and symptoms. May also include results of laboratory tests in the disease state.
- Disease Diagnosis - May include standard method for diagnosing the disease or condition.
- Current Treatment - May include current FDA approved products for the treatment, prevention, or diagnosis of the disease or condition. May also include unapproved products currently used for the intended disease or condition and products intended for the support of patients with the disease or condition.
- Prognosis and Course of Disease

Authoritative sources of information on diseases or conditions include medical textbooks as well as recent review articles on the appropriate disease or condition. If a reviewer has recently written a description of the disease or condition for another review of a request for orphan designation, the reviewer may use that description in the current review. Likewise, a reviewer may use another reviewer's recent description of the disease in question as long as the reviewer identifies that disease description as being excerpted from the designation database. One should remember that the purpose of the "Background of Disease or Condition" is to provide the reader and reviewer basic knowledge of the disease or condition in question. Regardless of the source, the reviewer must understand and be able to explain the review content to others. The reviewer must verify the content of the disease description.

2. Population Estimate

OOPD designates drugs for the treatment, diagnosis, or prevention of rare diseases or conditions. For the purposes of documenting that the number of people affected by the disease or condition for which the drug product is indicated is less than 200,000 persons, the prevalence is defined as the number of persons in the US who have been diagnosed as having the disease or condition at the time of submission of the request for orphan-drug designation. If the drug is a vaccine, diagnostic drug, or preventative drug, the persons to whom the drug will be administered in the US must be fewer than 200,000 per year in order to be eligible for orphan drug designation. In cases where the disease or condition is an acute event of less than one year duration, the FDA has accepted prevalence determinations based on the annual number of affected persons in the US.

A number of sources of prevalence information exist for the sponsor in estimating the prevalence of the disease or condition being reviewed. Acceptable sources of prevalence include recent epidemiological literature from peer-review medical journals, textbooks, or monographs. Prevalence may be obtained from vigorously maintained proprietary or nonproprietary health service databases, pharmaceutical databases, disease registries, or national health surveys. The Surveillance, Epidemiology, and End Results program (SEER) database maintained by the National Cancer Institute has been adopted as OOPD's standard source for cancer prevalence information. It is the policy of OOPD that cancers of different organs represent different diseases. It is the complete prevalence of each of these cancers as listed in the SEER database that constitute the prevalence of the disease when that cancer is the subject of a request for orphan drug designation. When the disease or condition is less well-defined or when reliability of available prevalence information is an issue, multiple data sources should be used to confirm the prevalence. When dated information or that from a foreign source is used to estimate prevalence, the sponsor should provide an explanation why the data is representative of the current US population. United States Census information can be employed to adjust the population to reflect the prevalence at the time of submission of the orphan drug designation request. In the event a search of the medical literature reveals no adequate sources of prevalence of a disease or condition, the sponsor may enlist the statements of three independent experts in the disease in question. These experts must provide an estimate of the prevalence of the disease or condition with a detailed reasoning or method by which they arrived at their aforementioned estimate. All experts contacted must be identified by the sponsor if using this method.

REVIEWER'S COMMENTS: (Italicized) The reviewer comments upon the accuracy of the sponsor's estimate of the prevalence of the disease or condition in terms of the references cited and the method by which the sponsor estimates the prevalence of the target population. Note that when the sponsor submits an acceptable range of estimates for the prevalence of the disease or condition, it is the policy of the Office of Orphan Products Development to accept the largest estimate as the prevalence of the disease or condition. The reviewer should also comment upon any references discovered by the

reviewer that provide estimates of the target population and whether these references support the sponsor's contention that the disease or condition affects fewer than 200,000 people in the United States. Finally, the reviewer should state what he/she accepts as the prevalence of the disease or condition for the purposes of this designation application. Please note that portions of the sponsor's application may be quoted in the reviewer's comments, but the reviewer's comments should reflect OOPD review policy and should contain the reviewer's evaluation of the application being commented upon in the reviewer's own words.

3. Scientific Rationale

Information that can be presented by the sponsor to support the medically plausible basis that a drug is expected to be effective in preventing, diagnosing, or treating a disease or condition can include a description of the pathogenesis of the disease or condition, the proposed mechanism of action of the drug, *in vitro* data, animal data, and human data. The policy of OOPD has been to consider clinical investigations as providing the strongest rationale for establishing a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of the disease or condition. It should be noted that for orphan drug designation purposes, it is only necessary that the clinical data support the effectiveness of the use of the drug in the proposed setting. Two adequate and well controlled clinical studies that demonstrate efficacy on a clinically significant endpoint reaching statistical significance are **not** required to achieve orphan drug designation. In the absence of human data, OOPD will accept animal data in an adequate animal model of the disease or condition to support the expectation that the drug would be effective in the prevention, diagnosis, or treatment of the disease or condition. In the absence of human data and when an animal model of the disease does not exist, OOPD may consider alternatives that include *in vitro* data, a description of the mechanism of action of the product, and the pathogenesis of the disease or condition. It is important that the sponsor provide all pertinent published and/or unpublished information available about the drug and its use in the disease in question, whether positive, negative, or inconclusive. These are the criteria consistently sought by OOPD to establish a medically plausible basis for expecting a drug to be effective in the prevention, diagnosis, or treatment of a disease or condition. For further explanation of the Scientific Rationale, see Appendix B.

REVIEWER'S COMMENTS: The reviewer comments upon the adequacy of the scientific rationale submitted by the sponsor based on their own evaluation and office policy.

One issue often encountered in reviewing a request for orphan drug designation is an instance where a sponsor requests orphan designation for the use of the drug for the treatment, prevention, or diagnosis of a rare subset of a common disease or condition. For explanation of Medically Plausible or Orphan Subsets, see Appendix C.

REVIEWER'S COMMENTS: The reviewer comments upon the sponsor's submitted rationale for the medically plausible subset based on their own evaluation and office policy.

For the OOPD policy on what constitutes the disease or condition when the designation targets lymphoma, see Appendix D.

An issue rarely encountered in a review of a request for orphan drug designation is the case in which a sponsor seeks designation for a same drug as one that has already received marketing approval for the proposed orphan indication. In this case, the sponsor must provide an explanation of why the proposed variation may be clinically superior to the first drug.

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. 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 submitting the request for orphan drug designation 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. A discussion of OOPD policy regarding "same versus different" when dealing with recombinant and tissue-derived products can be found in Appendix E.

REVIEWER'S COMMENTS: The reviewer comments upon the sponsor's submitted hypothesis that the proposed variation is clinically superior based on their own evaluation and office policy.

4. Evaluation and Recommendations

The reviewer should again state the request by the sponsor for the use of the product (product name) for the treatment, prevention, or diagnosis of the disease or condition in question. There are three possible recommendations for an application (see 21 CFR 316.24 and 316.25)

- Denial - It is appropriate to deny orphan designation in certain circumstances. For instance, if a disease in question clearly affects more than 200,000 people in the United States, it is appropriate to deny the request for orphan designation. Similarly, if the scientific rationale proposed by the sponsor is completely irrational, denial is an appropriate recommendation. In these cases, the reviewer outlines the concerns noted with the application and requests that these concerns be conveyed to the sponsor.
- Abeyance - Designation requests that are not granted may be placed in abeyance. In these cases, the reviewer outlines the concerns noted with the application and requests that these concerns be conveyed to the sponsor. The request for orphan designation will be held in abeyance until the sponsor addresses the concerns noted above.

- Designation Granted - The request for orphan designation is granted. In this recommendation, the reviewer should make a comment upon the adequacy of the scientific rationale presented by the sponsor. The adequacy of the prevalence estimate should also be commented upon and the reviewer should state the prevalence of the disease or condition accepted by the reviewer for the purposes of this request for orphan designation. If applicable, the sponsor should comment on the rationale for the medically plausible subset and/or the hypothesis for clinical superiority. Finally, it should be stated that it is recommended that the sponsor be granted orphan designation for the use of (generic name or active ingredient, trade name if available) for the treatment, prevention, or diagnosis of (disease or condition).

Reviewer's Name
Reviewer's Title

Concur: _____ Date:_____

Henry H. Startzman III, M.D.
Director, Orphan Drug Designation Program
Office of Orphan Products Development

Cc:
HF-35 / Designation File # (application number)
HF-35 / Reviewer's Name

Appendix B

Scientific Rationale Supporting a Request for Orphan Drug Designation

PURPOSE

This Appendix describes what constitutes adequate scientific rationale for the use of the drug for the rare disease or condition when applying for orphan drug designation.

BACKGROUND

Per 21 CFR 316.20(b)(4), the content and format of a request for orphan-drug designation should contain "a discussion of the scientific rationale for the use of the drug for the rare disease or condition, including all data from nonclinical laboratory studies, clinical investigations, and other relevant data that are available to the sponsor, whether positive, negative, or inconclusive. Per 21 CFR 316.25(a)(2), the FDA will refuse to grant a request for orphan-drug designation if "there is insufficient information about the drug, or the disease or condition for which it is intended, to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition."

The regulations do not provide further guidance on that which constitutes a medically plausible basis for expecting the drug to be effective. One must keep in mind the spirit of the Orphan Drug Act, which is to promote the development of products for the treatment, diagnosis, or prevention of rare diseases or conditions. As such, it is not in keeping with this spirit that OOPD place too high a bar for the purposes of orphan drug designation (we do not require two adequate and well controlled human studies demonstrating a statistically significant effect on a clinically significant endpoint). On the other hand, there is the need to require some consistent basis for expecting the product to be effective. It would be misleading to the public to grant orphan drug designation to products that had no promise of being effective in the management of a rare disease or condition.

The purpose of this Appendix is to define that which constitutes adequate scientific rationale for the use of a drug or biologic for the treatment, diagnosis, or prevention of a rare disease or condition in an application for orphan drug designation. The final goal of this document is to ensure a consistent and quality review of requests submitted to OOPD for orphan drug designation.

POLICY

OOPD will accept data from clinical investigations as providing the strongest rationale for establishing a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of the disease or condition. It should be noted that for orphan drug designation purposes, it is only necessary that the clinical data support the effectiveness of the use of the drug in the proposed setting. Two adequate and well controlled clinical studies that demonstrate efficacy on a clinically significant endpoint reaching statistical significance are **not** required to achieve orphan drug designation. In

the absence of human data, OOPD will accept animal data using the product in an adequate animal model of the disease or condition to support the expectation that the drug would be effective in the prevention, diagnosis, or treatment of the disease or condition. Therefore, as evidence of a medically plausible basis for expecting the drug to be effective in the rare disease under consideration, OOPD requires sponsors seeking orphan drug designation to provide sufficient information about the drug from in vivo studies in a relevant animal model of the disease or from clinical studies in patients with the rare disease or condition treated with the drug. **Please note, the data must be generated from in vivo studies in a relevant animal model of the disease or from clinical studies in patients with the rare disease or condition in which the animals and/or patients are treated with the active moiety that is the subject of the orphan drug designation request**. In the absence of human data **and when no animal model of the disease exists**, OOPD may consider alternatives that include *in vitro* data, a description of the mechanism of action of the product, and the pathogenesis of the disease or condition. It is important that the sponsor provide all pertinent published and/or unpublished information available about the drug and its use in the disease in question, whether positive, negative, or inconclusive.

These are the criteria consistently sought by OOPD to establish a medically plausible basis for expecting a drug to be effective in the prevention, diagnosis, or treatment of a disease or condition.

Appendix C

Medically Plausible or Orphan Subsets Supporting a Request for Orphan Drug Designation

PURPOSE

The purpose of this Appendix is to provide a definition of a "medically plausible or orphan subset" of a common disease or condition. The final goal of this document is to ensure a consistent and quality review of requests submitted to OOPD for orphan drug designation.

POLICY

In the preamble to the Proposed Rule (Federal Register notice Vol. 56, No. 19/ January 29, 1991 for 21 CFR 316 Orphan Drug Regulations), it is stated with regard to orphan drug designations that "An indication for treatment of a specific disease or condition could involve all patients with that disease or condition or a specified subpopulation of those with the disease or condition." "In diseases or conditions that are common, subsets would qualify for designation only if the subset is medically plausible. For example, a drug might be too toxic for use in treating a disease or condition except in patients refractory to or intolerant of other less toxic treatments; the refractory and intolerant patients might be a reasonable orphan subset. On the other hand, choosing an arbitrary subset (e.g., people with blood pressure over a certain level), simply to qualify a drug as an orphan-drug would be unacceptable."

Any discussion of an orphan-drug designation must include the drug or biologic and the disease or condition that are the subjects of the specified designation. A "Medically Plausible or Orphan Subset" of a more common disease or condition is defined by some characteristic of the drug or biologic that would limit its use to this 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. Examples of such characteristics would include mechanism of action of the drug or biologic or toxicity profile of the drug or biologic. It is the policy of the Office of Orphan Products Development to apply this definition when faced with a request for orphan drug designation that targets a rare subset of a common disease or condition.

Appendix D

Lymphoma as the Subject of a Request for Orphan Drug Designation

PURPOSE

This Appendix describes what constitutes the disease or condition when the subject of a request for orphan drug designation is lymphoma. The purpose of this Appendix is to define that which constitutes the disease or condition when the subject of a request for orphan drug designation is some aspect of lymphoma. The final goal of this document is to ensure a consistent and quality review of requests submitted to OOPD for orphan drug designation.

POLICY

The Office of Orphan Products Development (OOPD) has had considerable discussion regarding how applications for orphan drug designations are considered when the disease involves a lymphoma. At the crux of the issue is the question of "What is the disease?" Historically, OOPD has answered this question in different ways as the times have changed: it began with "lymphoma"; then was "Hodgkin's disease and non-Hodgkin's lymphoma" and subsequently progressed to "Hodgkin's disease, non-Hodgkin's B-cell lymphoma, non-Hodgkin's T-cell lymphoma or non-Hodgkin's null-cell lymphoma". With each iteration of OOPD nosology, sponsors were required to meet the statutory prevalence criteria for the disease terms that were put into effect.

OOPD is now at a juncture where further splitting in the disease entities is well recognized by the medical community, and the terms "B-cell lymphoma" and "T-cell lymphoma" are thought not to be "diseases" but rather to be agglomerations of distinct disease entities. Moreover, patients with such entities as Mantel Cell lymphoma would be denied access to the benefits of the Orphan Drug Act were OOPD to not recognize their disease and rather, hold it to be just one manifestation of "B cell lymphoma", a collection that now surpasses 200,000 individuals in the US. Therefore, OOPD recognizes the current WHO classification of lymphomas as stipulating the diseases of record.

Appendix E

Recombinant Products and Orphan Drug Designation

PURPOSE

This Appendix describes the policy of OOPD in terms of the clinical superiority of recombinant products over tissue-derived products when determinations of "same drug" are being considered. The purpose of this document is clarify the current policy of OOPD when it comes to the determination of "same drug" when dealing with a recombinant product and its relationship to a tissue derived product.

POLICY

The provision of human macromolecules in the treatment of disease has many useful applications, particularly for orphan illnesses such as bleeding diatheses. Such macromolecules have traditionally been derived from human donors. Human-derived therapeutic macromolecules have a long history of infectious disease transmission. However, with each subsequent epidemic of iatrogenic illness, purification and sterilization techniques have improved, and at this time it is generally believed that such processes eliminate the potential for transmission of all know disease agents. Concurrently, biotechnology advances have yielded recombinant products that are devoid of any potential for person-to-person transmission of such agents.

The Office of Orphan Product Development may award orphan product status to a drug that is otherwise the same drug as an already approved drug for the same rare disease or condition if the sponsor can present a plausible hypothesis that its drug may be clinically superior to the approved drug. The Office has frequently been presented with the question of whether or not recombinant products are inherently superior to human-derived products, and Office policy has changed depending on the times. When it first became apparent that HIV was being transmitted via clotting factors obtained from human sources, OOPD regarded recombinant products as inherently superior to factors that originated from human plasma, and the Office granted designations accordingly. However, with improvements in product sterilization this policy was reversed and products from human sources have not been considered inherently superior for at least the last 15 years.

Recently OOPD had the opportunity to review its thinking on this matter, and it has been the subject of an Office-wide discussion group. Of particular concern is the theoretical risk posed by unknown agents that may not be eliminated by current processing practices. Moreover, a review of the current medical literature yielded policy papers from the American Academy of Pediatrics (1) and the US Public Health Service Advisory Committee on Blood Safety (2) that strongly advocate for the development and adoption of recombinant products as superior alternatives to human-derived products. Finally, consultation with CBER's Office of Blood Products gave us to understand that in the conduct of product review for approval, consideration is given to recombinant products for inherent superiority as safer agents.

Appendix E

In consideration of the above facts, OOPD will adopt the policy that products of recombinant origin are inherently superior to those of human origin because they are safer regarding person-to-person transmission of infectious agents. It is recognized that such safety may in fact be only theoretical safety, that is, OOPD would not require evidence of infectious disease transmission with a human-derived product in order to establish the superiority of a corresponding recombinant product. Rather, it is acknowledged that current understanding may not include all potential agents of human disease; accordingly, this epistemological limitation may prevent the institution of processing procedures that render products free from agents not yet discovered. This policy, that recombinant products are inherently superior, is a conservative judgment based on a lengthy history of medical iatrogenesis coincident to the use of human-derived products. But it is acknowledged to be a judgment, and not founded on contemporary data.

1. American Academy of Pediatrics. Red Book Online. Section 2: Recommendations for the care of children in special circumstances; Blood Safety: Reducing the risk of transfusion-transmitted infection. See http://aapredbook.aappublications.org/cgi/content/full/2000/1/2.2

2. US Public Health Service's Advisory Committee on Blood Safety, 1998. Proceedings.

Appendix F

Scleroderma as the Subject of a Request for Orphan Drug Designation

PURPOSE

This Appendix describes what constitutes the disease or condition when the subject of a request for orphan drug designation is systemic sclerosis or localized scleroderma. The purpose of this Appendix is to define that which constitutes the disease or condition when the subject of a request for orphan drug designation is some aspect of scleroderma. The final goal of this document is to ensure a consistent and quality review of requests submitted to the Office of Orphan Products Development (OOPD) for orphan drug designation.

POLICY

Since the passage of the Orphan Drug Act, there have been 18 requests for the treatment of scleroderma, localized scleroderma, or systemic sclerosis. Scleroderma literally means "hard skin." Although it is often referred to as if it were a single disease, the National Institute of Arthritis and Musculoskeletal and Skin Diseases describe scleroderma as a symptom of a group of diseases that involve the abnormal growth of connective tissue, which supports the skin and internal organs. It is sometimes used, therefore, as an umbrella term for these disorders. Scleroderma can be described as localized or systemic.

Localized scleroderma usually affects only the skin on the hands and face and, in some instances, the muscle below. Internal organs are not affected by localized scleroderma and localized scleroderma never progresses to the systemic form of the disease.[1] Often, localized scleroderma improves or resolves spontaneously. However, skin damage can be permanent with severe and disabling consequences.

Systemic scleroderma (systemic sclerosis) may affect large areas of skin and organs such as the heart, lungs, or kidneys. There are two main types of systemic sclerosis: Limited disease (CREST syndrome) and Diffuse disease.

- Limited cutaneous scleroderma typically comes on gradually and affects the skin only in certain areas-fingers, hands, face, lower arms, and legs. Most people with limited disease have Raynaud's phenomenon for years before skin thickening starts. Telangiectasia and calcinosis often follow. Gastrointestinal involvement occurs commonly and some patients have severe lung problems even though the skin thickening remains limited. Patients with limited disease often have all or some of the symptoms called CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyl, and Telangiectasia).
- Diffuse cutaneous scleroderma comes on suddenly. People with diffuse scleroderma experience skin thickening in the hands that spreads quickly over much of the body. Internally this condition is associated with damage to organs such as the heart, lungs, kidneys, and intestines. Patients with diffuse disease suffer the most serious long-term morbidity due to kidney, lung, heart, or intestinal involvement.

Appendix F

OOPD designates drugs and biologics for the treatment, diagnosis, or prevention of rare diseases. Prior to 2009, OOPD designated products for the treatment of systemic sclerosis because the combined prevalence for both localized and systemic sclerosis was under 200,000. In 2009, NIH noted that the prevalence of scleroderma in the United States was 300,000. From that point forward, OOPD has asked sponsors requesting orphan drug designation for the use of their product for the treatment of systemic sclerosis why the product could not be used to treat localized scleroderma and to include that population in their prevalence estimate if there was no reason to exclude them. However, one could make the case that localized scleroderma is a different disease than systemic sclerosis. Localized scleroderma does not progress to systemic sclerosis. Therefore, localized scleroderma could not be considered only a milder form of the disease or part of a continuum of the disease. The prognosis is different for localized disease which may resolve spontaneously and does not carry the systemic ramifications of the systemic disease.

The review division was contacted for their thoughts on the subject. They noted that localized scleroderma does not typically progress to systemic disease and the prognosis is completely different. Therefore, the medical officer believed that there is something different about them. The risk-benefit profile is also completely different. The risk of systemic immunomodulatory or immunosuppressive agents would be difficult to justify to treat localized scleroderma. It was noted that the treatment of the skin manifestations would likely be similar between localized scleroderma and the skin manifestations of systemic sclerosis.

During a monthly telecom with EMA, it was determined that the EMA considers systemic sclerosis to be distinct from localized scleroderma for the purposes of orphan drug designation.

Therefore, due to the characteristics described above, for the purposes of orphan drug designation, OOPD will now consider systemic sclerosis to be a different disease or condition than localized scleroderma. Sponsors requesting orphan drug designation for the use of their products for the treatment of systemic sclerosis will no longer be required to make the case that their product would not be effective in treating localized disease or include the patients with localized disease in their prevalence estimate. This policy went into effect on April 3, 2013.

1 National Institute of Arthritis and Musculoskeletal and Skin Diseases Handout on Health: Scleroderma. www.niams.nih.gov/Health_Info/Scleroderma/default.asp

Appendix G

Pulmonary Hypertension as the Subject of a Request for Orphan Drug Designation

PURPOSE

This Appendix describes what constitutes the disease or condition when the subject of a request for orphan drug designation is pulmonary hypertension. The final goal of this document is to ensure a consistent and quality review of requests submitted to the Office of Orphan Products Development (OOPD) for orphan drug designation.

POLICY

Since the passage of the Orphan Drug Act, as of June 10, 2013, there have been 36 requests for orphan drug designation for the treatment of some segment of the pulmonary hypertension population. Pulmonary hypertension is defined as a resting mean pulmonary artery pressure greater than 25 mmHg. In 1973, the World Health Organization (WHO) was the first to attempt to classify pulmonary hypertension. The groups were intended to classify pulmonary hypertension by etiology and treatment schemes. The WHO classification has undergone modifications in 2003 and 2008. The most current WHO classification of pulmonary hypertension is as follows:

Group 1. Pulmonary arterial hypertension (PAH)

- Idiopathic (IPAH)
- Heritable (HPAH)
  - Bone morphogenetic protein receptor type 2 (BMPR2)
  - Activin receptor-like kinase 1 gene (ALK1), endoglin (with or without haemorrhagic telangiectasia)
  - Unknown
- Drug- and toxin-induced
- Associated with (APAH):
  - Connective tissue diseases
  - Human immunodeficiency virus (HIV) infection
  - Portal hypertension
  - Congenital heart disease (CHD)
  - Schistosomiasis

Appendix G

	○ Chronic haemolytic anaemia • Persistent pulmonary hypertension of the newborn (PPHN)
Group 1'.	Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)
Group 2.	Pulmonary hypertension due to left heart diseases • Systolic dysfunction • Diastolic dysfunction • Valvular disease
Group 3.	Pulmonary hypertension due to lung diseases and/or hypoxemia • Chronic obstructive pulmonary disease (COPD) • Interstitial lung disease (ILD) • Other pulmonary diseases with mixed restrictive and obstructive pattern • Sleep-disordered breathing • Alveolar hypoventilation disorders • Chronic exposure to high altitude • Developmental abnormalities
Group 4.	Chronic thromboembolic pulmonary hypertension (CTEPH)

Appendix G

Group 5.

PH with unclear multifactorial mechanisms

- Haematological disorders: myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

The etiology of the pulmonary hypertension as well as the treatment approaches vary between groups. Group I is known as pulmonary arterial hypertension (PAH). Treatment for PAH includes lifestyle changes, digoxin, diuretics, and FDA approved pharmacotherapy specifically labeled for treatment of PAH (prostacyclin analogs, endothelin receptor antagonists, phosphodiesterase-5 inhibitors). The treatment for pulmonary hypertension falling into groups 2 to 5 involve treating the underlying cause of the pulmonary hypertension with supportive care to slow disease progression. The pharmacotherapy approved for the treatment of PAH is not indicated for use in Groups 2 to 5 due to a lack of evidence of efficacy in current studies.

The Office of Orphan Products Development had previously designated products for the treatment of pulmonary arterial hypertension but it was not clear if PAH was treated as a different disease or condition from the other WHO groups of pulmonary hypertension or if PAH was treated as an orphan subset of pulmonary hypertension. The review division in the Center for Drug Evaluation and Research (CDER) was consulted concerning what constituted the disease or condition when discussing pulmonary hypertension. It was determined that the results of studies of products intended for the treatment of pulmonary hypertension were not generalizable from one WHO classification of pulmonary hypertension to another. The review division noted that the pathologies were different between groups as were the treatments. For these reasons, OOPD is clarifying that for the purposes of orphan drug designation, the five WHO classifications of pulmonary hypertension represent different diseases or conditions. This clarification does not affect prior designations of products for pulmonary arterial hypertension (WHO classification group I). It should also be noted that our European counterparts consider pulmonary arterial hypertension to be a different disease or condition from other WHO classification groups of pulmonary hypertension and have designated for pulmonary arterial hypertension and for chronic thromboembolic pulmonary hypertension (WHO group 4). They opined that it was supportable to consider the 5 groups that comprise the WHO classification of pulmonary hypertension to be different diseases or conditions for the purpose of orphan drug designation.