Guidance for Industry

Sinusitis: Designing Clinical Development Programs of Nonantimicrobial Drugs for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

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I. INTRODUCTION

This guidance is intended to assist the pharmaceutical industry in designing a clinical development program for nonantibiotic drug products[2] for the treatment of sinusitis. Development of antibiotics for the treatment of acute bacterial sinusitis is fairly common and is discussed in the draft guidance for industry *Acute Bacterial Sinusitis — Developing Antimicrobial Drugs for Treatment* (Acute Bacterial Sinusitis guidance).[3] This guidance does not supersede the Acute Bacterial Sinusitis guidance but rather supplements it. However, many of the principles outlined in the Acute Bacterial Sinusitis guidance apply to this guidance. This guidance focuses on the assessment of efficacy in phase 3 clinical studies in sinusitis, but also addresses chemistry, manufacturing, and controls (CMC) issues and pharmacology and toxicology issues because some of the products for sinusitis are developed for nasal delivery, and there are nuances to the nasal route of delivery that should be considered for appropriate clinical study design.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidance documents *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.[4]

[1] This guidance has been prepared by the Division of Pulmonary and Allergy Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] In this guidance, the word *drug* includes of all types of therapeutic agents, such as small and large molecule drugs, and therapeutic biological products, regulated within CDER.

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

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II. BACKGROUND

A. Disease Classification and Terminology

Sinusitis is a disease characterized by inflammation of one or more of the paranasal sinuses. It is one of the most commonly diagnosed diseases in the United States affecting an estimated 16 percent of the adult population annually (Slavin and Spector et al. 2005). Various consensus panels and position papers have classified sinusitis in different ways. The most commonly used classification is based on duration of symptoms (Slavin and Spector et al. 2005; EAACI 2005; Meltzer and Hamilos et al. 2004). Although there are minor variations described in the literature, the general consensus for the classification of sinusitis is as follows:

- Acute — when the duration is less than 4 weeks
- Subacute — when the duration is 4 to 8 weeks
- Chronic — when the duration is longer than 8 weeks
- Recurrent — when three or more episodes of acute sinusitis occur in a year

Acute sinusitis is commonly caused by bacterial invasion of the sinuses following a persistent viral respiratory tract infection. Bacteria commonly associated with acute sinusitis are *Streptococcus pneumonia*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Most sinusitis drug development has consisted of antimicrobial therapies for acute bacterial sinusitis.[5]

Chronic sinusitis is not usually caused by bacterial infection. Most patients with chronic sinusitis have marked inflammation of the sinuses with eosinophils and mixed mononuclear cells, with a relative paucity of neutrophils. This form of sinusitis is often termed chronic hyperplastic eosinophilic sinusitis. Some of these patients have associated nasal polyps, asthma, and aspirin sensitivity (Slavin and Spector et al. 2005). When infectious agents are involved in patients with chronic sinusitis, the agents are usually anaerobic bacteria and less often aerobic bacteria. However, the occurrence of this is rare.

Subacute sinusitis and recurrent sinusitis have an intermediate pathophysiology. Some cases resemble acute sinusitis with a preponderance of bacterial infection and some resemble chronic sinusitis where bacterial infection often is not present.

The term *rhinosinusitis* is often used in the literature, particularly in the European literature, to describe the disease that has been traditionally called sinusitis (EAACI 2005; Meltzer and

[5] See the draft guidance for industry *Acute Bacterial Sinusitis — Developing Antimicrobial Drugs for Treatment.*

Hamilos et al. 2004; Lanza and Kennedy 1997). Proponents of the term rhinosinusitis argue that perennial rhinitis and sinusitis should be lumped into one entity because the two diseases often coexist, mucosa of the nose and sinuses are contiguous, rhinitis typically precedes sinusitis, and sinusitis without rhinitis is rare. Although there are some merits to the argument, for drug development purposes, the FDA considers rhinitis and sinusitis as distinct disease entities. Rhinitis and sinusitis are distinct diseases with differences in pathophysiology, treatment, and risk-benefit assessment for drug development. Lumping the two diseases into one entity may hamper drug development because the symptoms of these two diseases overlap. Furthermore, lumping of the two diseases may lead to inappropriate use of drugs already approved and marketed for one disease but not the other. It should be noted that the term rhinosinusitis is not universally accepted; in particular, recent U.S. literature has adopted the term sinusitis over rhinosinusitis (Slavin and Spector et al. 2005).

B. Current Treatment Options

At present, other than antibiotics, some of which have a labeled indication for acute bacterial sinusitis, the treatment options for sinusitis are limited. Drugs of other classes, such as antihistamines, corticosteroids, alpha-adrenergic decongestants, and mucolytics, are often recommended (Slavin and Spector et al. 2005; EAACI 2005; Meltzer and Hamilos et al. 2004), but none have been specifically approved by the FDA for use in sinusitis, and few have data from controlled clinical studies supporting this use. There is interest within the pharmaceutical industry in the development of new drugs, including drugs other than antibiotics, for the treatment of sinusitis.

III. CLINICAL DEVELOPMENT PROGRAM

This section discusses elements that sponsors should consider as they design a clinical program to demonstrate the efficacy and safety of a drug for sinusitis.

A. General Considerations

1. Types of Drug Products for Sinusitis

Various types of drug products can be developed for sinusitis. The drug product can be a new molecular entity formulated for oral, parenteral, or nasal delivery; a molecular entity that is already approved as an oral or parenteral product with or without a sinusitis indication and is now being studied as a nasal formulation; or an approved nasal drug product that does not have a sinusitis indication. The drug product can be developed as a stand-alone treatment for sinusitis or as an add-on treatment to an approved treatment, such as an add-on treatment to antibiotics for the treatment of acute bacterial sinusitis. The drug product can be a single entity or a combination product. The clinical development program depends on which drug product scenario will be developed.

2. Efficacy Considerations

Since each type of sinusitis has a different pathophysiology, a study conducted in one type of sinusitis (e.g., acute sinusitis) may not be used as evidence to support findings from another type of sinusitis (e.g., chronic sinusitis). In general, then, for acute sinusitis and for chronic sinusitis, we recommend at least two confirmatory studies be conducted to support an efficacy claim. For subacute and recurrent sinusitis, one confirmatory study may be adequate to support an efficacy claim provided efficacy has already been demonstrated for either acute or chronic sinusitis.

3. Safety Considerations

In general, treatment of sinusitis is either repetitive in nature or continuous and prolonged. Therefore, prolonged and long-term data on safety evaluation should be collected. The extent of the safety database should be consistent with the ICH guideline for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment on Non-Life-Threatening Conditions* and the guidance for industry *Premarketing Risk Assessment*. When gathering safety data, other concomitant diseases that patients may have and other concomitant drugs that patients may take should be considered. In cases where efficacy studies are substantially less than one year, separate long-term safety studies should be conducted. Adding a control arm and assessing efficacy over time to rule out long-term effects on the disease characteristics should be considered. In some cases, specific safety hypotheses should be tested, depending on whether safety signals are identified during nonclinical studies or early clinical studies, or based on the class of drug. For drugs formulated for nasal delivery, nasal safety should be assessed in phase 3 studies. Such assessment should include patient reports and physician examination for nasal irritation, nasal ulceration, epistaxis, and nasal septal perforation.

B. Specific Efficacy Trial Considerations

1. Study Design

The nature and design of phase 3 studies depends on the type of drug product that is being studied and the clinical benefit to be demonstrated. In general, studies should be placebo-controlled, double-blind, randomized, and parallel-group in design. We encourage the use of an active comparator in addition to a placebo, especially when comparative efficacy or safety claims are desired, or when there is uncertainty about a novel efficacy assessment methodology and a validation of the methodology is desired. The appropriateness of a placebo control depends on the disease severity of the study subjects and the intent of the study.

The use of a placebo control does not necessarily preclude *usual care* treatments in subjects randomized to placebo. Subjects enrolled in the study should be permitted to use concomitant treatments as needed to manage disease symptoms. Concomitant use of medications that can change nasal symptoms, such as antihistamines, nasal corticosteroids, and nasal decongestants, are discouraged. Use of concomitant treatments should be recorded for each subject throughout the study. An appropriate analysis plan should be defined in the protocol to account for possible imbalance of concomitant treatment use among treatment groups.

Active-controlled studies are viable alternatives to placebo-controlled studies when the intent of the study is to show superiority. When the intent is to show noninferiority to an active comparator and no placebo is planned, many important design issues are raised (e.g., assay sensitivity, the noninferiority margin, knowledge of how the chosen endpoint performs in studies with the active comparator). These issues are discussed in detail in the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*. Before proposing a noninferiority design, there should be a well-defined, reproducible treatment effect for the established comparator such that the effect of that treatment in later studies can be inferred. Alternately, a placebo group could be incorporated into the proposed study to demonstrate that although the active and new treatment are noninferior to one another, the new treatment also has benefits exceeding the placebo effect. Any such proposal should be carefully considered and discussed in depth with the FDA before starting clinical studies using this design. Given the role of symptom assessment in the evaluation of sinusitis, it is important for the assigned treatment to be masked in the study design. Generally, we consider open-labeled studies of sinusitis to be uninformative. Double-dummy designs may be appropriate in comparative studies. In the overall design and conduct of studies, appropriate statistical methodologies should be applied in the handling of missing data, outliers, and other relevant issues as discussed in the guidance for industry *E9 Statistical Principles for Clinical Trials.*

2. Study Population and Entry Criteria

One of the major challenges in designing and conducting clinical studies in sinusitis is that the symptoms that are used in clinical practice to diagnose sinusitis are neither specific nor sensitive. Common symptoms of sinusitis are facial pain or pressure sensation, purulent anterior or posterior nasal discharge or both, nasal congestion, cough, headache, dental pain, olfactory disturbance, ear ache or fullness, and bad breath. However, patients with viral upper respiratory tract infection, allergic rhinitis, or other forms of rhinitis may have symptoms indistinguishable from sinusitis. Patients with migraine or cluster headache may have symptoms that overlap with sinusitis.

Symptoms also can be unreliable, as patients without convincing symptoms of sinusitis may have clear evidence of the disease when examined by an objective assessment such as by imaging. Another complicating factor is that a drug being developed for sinusitis actually may be effective for rhinitis and may even carry a rhinitis indication. This is particularly important for a nasal product, which would have a chance to act on the nasal mucosa. Since it is known that sinusitis patients have accompanying rhinitis, the clinical program should convincingly demonstrate that the efficacy is from improvement of sinusitis and not solely from improvement of rhinitis.

Therefore, clinical studies should not rely on patient-reported subjective symptoms alone. We prefer that some form of objective evidence be included to determine eligibility of patients' entry in clinical studies and for demonstration of efficacy. Objective assessments of sinusitis include imaging techniques such as a computerized tomography (CT) scan or a magnetic resonance imaging (MRI) scan, ultrasonography, microbiological assessment of sinus aspirate, and direct visual examination of the sinus cavity by endoscopic examination when an antral window has been created surgically. However, if a drug will be delivered systemically and is not expected to

reach the nasal cavity or is known not to be effective in rhinitis, objective evidence may not be necessary.

For entry into clinical studies for acute, subacute, or chronic sinusitis, symptoms should be continuously present for at least 10 days, and the diagnosis should be supported by at least one objective assessment, preferably imaging. For entry into recurrent sinusitis studies, an effort should be made to obtain objective evidence from previous sinusitis episodes to ensure that patients with reliable diagnosis of recurrent sinusitis are enrolled in the study. However, because of the historical nature of the diagnostic criteria, we acknowledge that objective assessment may not be reliably available for all patients and for all previous episodes.

3. Dose Selection

The dose or doses and dosing frequency of drugs for phase 3 studies should be selected based on pharmacokinetic considerations and from earlier phase dose-ranging studies using a pharmacodynamic (PD) or clinical efficacy endpoint that is consistent with the expected benefit to be derived from the drug. The endpoint used in dose-ranging studies should be consistent with or known to be predictive of the efficacy endpoint that will be used in phase 3 studies. The dose or doses selected for phase 3 studies should be based on benefit-to-risk assessment. If more than one dose is ultimately intended to be marketed, the clinical program design should produce data that allow for a comparative assessment of efficacy and safety among the doses in addition to the usual comparison of the doses of the new drug to placebo. In circumstances where PD measures are used in phase 2 for dose identification, inclusion of more than one dose level in at least one phase 3 study, even if the goal is to market a single dose, should be considered. This is because even a well-validated PD endpoint may not fully predict efficacy as assessed by a clinical outcome endpoint in larger, longer term phase 3 studies, and usually will not be predictive of safety.

4. Efficacy Endpoints

For phase 3 studies, the primary and secondary efficacy endpoints should be chosen based on the type of sinusitis that is studied, the drug's putative mechanism of action, and the proposed benefit desired to be demonstrated. It is not possible to categorically state in all cases what the primary and secondary efficacy endpoints should be. Suggested primary efficacy endpoints for different types of sinusitis studies are mentioned below.

a. Acute, subacute, or chronic sinusitis

The efficacy endpoint should include patient-reported symptoms and at least one objective measure declared as co-primary, meaning that both measures should statistically demonstrate the desired effect. However, if a drug will be delivered systemically and is not expected to reach the nasal cavity or is known not to be effective in rhinitis, objective measure may not be necessary.

Patient-reported symptoms can include any scientifically supported and logical combination of symptoms that are common in sinusitis. The symptoms combination should be carefully chosen so that they reflect sinusitis rather than other confounding diseases. We prefer a composite score

consisting of the following three symptoms: facial pain or pressure sensation, purulent anterior or posterior nasal discharge or both, and nasal congestion. Each of these symptoms should be scored by subjects daily using a predefined scoring system. Table 1 shows a sample rating system that is commonly used in similar clinical studies. Subjects should be given a clear detailed description of the scoring system. The frequency of scoring should be driven by the dosing interval, but should be at least twice daily, once in the morning and once in the evening, with one or more scorings timed to precede dosing. The symptoms should be scored both as reflective score (evaluation of symptom severity over a predefined period, such as 12 hours) and as instantaneous score (evaluation of symptom severity immediately preceding the time of scoring). Reflective score gives an assessment of consistency of efficacy throughout the dosing interval, and instantaneous score gives an assessment of end of dosing interval efficacy. Either reflective or instantaneous symptom score can be declared as a primary efficacy endpoint.

Table 1. Sample Scoring System

Scale	Symptoms
0	No symptoms
1	Mild symptoms (symptoms clearly present, but minimal awareness, and easily tolerated)
2	Moderate symptoms (definite awareness of symptoms that is bothersome but tolerable)
3	Severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living)

The preferred objective measure for use as an efficacy endpoint is an imaging study of the sinus, such as a CT scan or an MRI scan. In specific situations, other objective measures can also be used, such as microbiological assessment of sinus aspirate for evaluation of an add-on treatment to antibiotics for the treatment of acute bacterial sinusitis, microbiological assessment of sinus aspirate for chronic sinusitis, and direct visual examination of sinus cavity by endoscopic examination when such an exam is technically feasible. The objective measure selected as the efficacy endpoint should be scored by a scientifically justified scoring system. The use of a central independent reader or readers for evaluation of any imaging studies is recommended. The evaluator or evaluators should be blinded to treatment assignments and the timing of the images (i.e., whether the image being evaluated is at study entry or from an efficacy assessment).

When designing studies, a possible difference in the time course of response to treatment for patient-reported symptoms and objective measures should be considered (e.g., patient-reported symptoms may improve quickly, but it may take a longer time for imaging studies to show changes). In such a situation, the duration of treatment and the duration of the study may be different. For example, in acute sinusitis study the objective assessment may be done at some time point after completion of treatment.

b. Recurrent sinusitis

The primary efficacy endpoint should include a clinically meaningful measure of recurrence. Such measure can include time to the first recurrence, number of recurrences in a prespecified time period, severity of recurrences, and duration of recurrences. Any of these measures can be

chosen as the primary efficacy endpoint, but the others should be carefully assessed to ensure that some other measures have not worsened with the treatment. For instance, a delay in the occurrence of a first recurrence would not be meaningful if the end result was more frequent or severe recurrence. Factors for defining a recurrence should be the same as the factors used for the diagnosis of acute sinusitis (i.e., the presence of symptoms for at least 10 days supported by at least one objective assessment).

5. Statistical Considerations

Efficacy should be demonstrated by statistically significant and robust findings, which in acute, subacute, and chronic sinusitis studies could include meaningful improvement in patient-reported subjective symptom scores along with an objective measure; and in recurrent sinusitis studies could include an assessment of recurrence of acute sinusitis. The comprehensive nature of assessment is intended to demonstrate the disease is improved by treatment. Improvement of one aspect of the disease, such as a symptom, would not be adequate for a sinusitis indication, because symptoms of sinusitis are neither specific nor sensitive. Improvement of symptoms alone may not necessarily mean that the disease is better. This position is consistent with a recent decision by the FDA that amended the final monograph for over-the-counter nasal decongestant products to remove the indication "for the temporary relief of nasal congestion associated with sinusitis" and to prohibit the use of the terms *sinusitis* and *associated with sinusitis* on the labeling of these products (FDA, Amendment of Final Monograph for Over-the-Counter Nasal Decongestant Drug Products, 2005). The sinusitis indication was removed because there are no data supporting the efficacy of these drugs in sinusitis, and it was concluded that improvement of nasal congestion symptom may lead to inappropriate care with the patient deferring definitive treatment and ending up with serious complications of untreated disease.

a. Acute, subacute, or chronic sinusitis

Efficacy should be supported by statistically significant findings from both the patient-reported symptom score and an objective measure, eliminating the need for multiplicity correction. For patient-reported symptom score, the active treatment should be compared to placebo or active comparator for improvement from baseline of the composite symptom score averaged over the whole duration of treatment. In certain instances, such as in subacute or chronic sinusitis, improvement from baseline of the composite symptom score measured during the last week of treatment can be used as the primary efficacy endpoint as long as the entire treatment period is also assessed to define efficacy over the duration of treatment. The baseline score should consist of scores over several days, such as days 7 to 10, immediately preceding patient randomization. For the objective measure, the active treatment should be compared to placebo or active comparator for improvement from baseline of the objective efficacy measure scored at the end of treatment or other predefined post-treatment time point.

b. Recurrent sinusitis

Efficacy should be supported by statistically significant findings from a clinically meaningful measure of sinusitis recurrence that is declared as the primary efficacy endpoint along with supportive findings from other measures of sinusitis recurrence. Each episode of acute sinusitis

that constitutes a recurrence should be diagnosed based on subjective and objective factors described above.

6. Routes of Delivery

Drugs for sinusitis are typically formulated for oral, parenteral, or nasal delivery. A drug delivered by oral or parenteral route can reach the sinus cavity or the ostiomeatal complex area through the systemic circulation, whereas a drug delivered by the nasal route can reach these spaces through the nasal cavity. The possible direct access to the sinuses and the ostiomeatal complex area through the nasal cavity makes nasal delivery seem optimal; however intranasal delivery does not ensure that the drug will actually reach the relevant spaces in humans with normal (i.e., not surgically manipulated) nasal anatomy. The narrow opening of the sinuses into the nasal cavity and the ciliary action that is directed away from sinuses toward the nasal cavity can prevent the drug from reaching these spaces. The FDA believes that to be clinically effective the drug should reach the sinus cavity or the ostiomeatal complex area to open up the sinus drainage. However, it is not necessary to demonstrate that the drug reaches the sinus cavity. It is also possible that the drug does not need to reach these spaces in appreciable amounts to be clinically effective. This situation does not apply to sinuses where surgical procedures may have created an opening or even a direct access to the sinuses.

7. Treatment Duration

Treatment duration in a sinusitis study depends on the type of sinusitis that is being studied and the expected benefit that is proposed to be demonstrated. Treatment duration for acute or subacute sinusitis study should be 3 to 4 weeks; treatment duration for chronic sinusitis studies can be longer. Treatment duration for recurrent sinusitis should be 1 year.

8. Combination Drugs

Given the complexity of sinusitis, particularly chronic sinusitis, a single drug may not possess all the necessary pharmacological activities to result in the desired therapeutic effect. Therefore, new drugs can contain a combination of two or more individual drugs. Individual drugs can also be formulated as one combined drug product for convenience. In most situations, individual drugs used in a combination drug were previously evaluated and approved for use in humans, although this may not always be the case.

Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect and the dosing of each component is such that the combination is safe and effective for a significant patient population (21 CFR 300.50, Combination rule). The efficacy of a combination drug product can be supported by comparing the combination drug product to each of its constituents in the same clinical study to demonstrate that the combination drug product provides clinical benefit that is superior to each of its constituents, with or without a placebo. In most situations, use of one set of efficacy endpoints would suffice, where the combination drug product would show efficacy that is statistically significantly better than each of its components. In some situations, where the pharmacological action of the two components are disparate, the efficacy endpoint selected to show superiority of the combination drug product

to one component may be different than the efficacy endpoint selected to show superiority to another component (i.e., two primary efficacy endpoints may be assessed, one for combination drug product AB versus product A and another for combination drug product AB versus product B). In this case, the study would need to show separate superiority on both endpoints to meet the expectations of the Combination rule.

C. Other Considerations

1. Relevant Nonclinical Safety Considerations

The pharmacology and toxicology program for a sinusitis drug product will vary depending on how the drug is developed.

If the drug product is a new molecular entity, the pharmacology and toxicology program should follow the principles outlined in the following guidance documents: the ICH guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*, the ICH guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals*, and the guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*. For calculation of safety margins, systemic as well as local nasal findings should be considered. For a drug product that is developed specifically as a nasal formulation, animal toxicology studies should be conducted with nasal delivery to the animals (e.g., via snout delivery). These studies should include thorough examination of the upper and lower airways, including complete histopathological examination. Safety margins for local effects in the nasal region should be calculated by comparing the total amount of administered drug per surface area of the nasal cavity in animals versus that in humans. To characterize systemic toxicity, additional animal toxicology studies may be appropriate with oral or parenteral dosing if the nasal delivery does not result in adequate systemic exposure. The extent and characteristics of systemic toxicity data that are appropriate for a nasal product may vary depending on the drug's bioavailability via the nasal route and other factors. We recommend that this issue be discussed with the FDA before the toxicology studies are planned.

For a nasal formulation of a drug product that is already approved either as an oral or parenteral formulation and for which complete systemic animal toxicology data are available, the animal toxicology program to support nasal administration can be limited to a single nasal delivery study of up to 6 months duration with examination of the upper airway and lower airway including histopathological examination. Factors influencing the choice of species for a chronic study include the ability to test for toxicity using the clinical dosing apparatus; nasal deposition profile; systemic exposure, metabolism, and pharmacodynamics in test species in relation to humans; and short-term studies by the intranasal route that support testing in a particular species. The systemic toxicity profile for such a drug product should be supported by comparing resulting plasma concentrations from nasal administration to oral or parenteral administration. Prior human use of an oral or parenteral formulation is informative but not adequate to support human nasal administration, because such human use may not have resulted in adequate exposure to the nasal mucosa, and histopathological data from such human use probably would be nonexistent.

For a nasal drug product that is already approved for a nasal indication, separate animal toxicology studies can be avoided provided the human exposures that result from the proposed studies have adequate safety margins for the drug.

Nonclinical studies should also be conducted to qualify all excipients where the intranasal route of administration is novel. Excipients that are generally considered to be safe for human use for oral or parenteral routes are not automatically qualified for use in nasal formulations.

When developing a drug-device combination product, the preclinical information should consider device engineering and biocompatibility information, as well as possible drug-device interactions. When using an accessory delivery unit, development plans should also consider methods to control for accessory delivery unit modifications.

In vitro genetic toxicology studies for a new molecular entity should be conducted before first human dosing. Drugs that are found to be genotoxic should be carefully assessed for putative benefit, and clinical studies with such a compound should include disclosure of the positive finding and its implication in the informed consent. Carcinogenicity studies should be conducted before submission of a marketing application. In some instances, such as with positive genotoxicity findings, carcinogenicity studies can be considered earlier in clinical development. Drugs that are carcinogenic are unlikely to be approved for human use for symptomatic benefit in sinusitis.

2. CMC Considerations

The development of drug products for nasal delivery presents special considerations as discussed in the guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation*. Some aspects of a drug product for nasal delivery that have ramifications for the conduct of clinical studies of sinusitis are discussed below.

a. Nasal drug delivery

Nasal delivery of a drug can be achieved either by a drug product that has a dedicated delivery system or by a drug product that requires an accessory delivery unit.

There are two major types of drug products that have a dedicated delivery system. One type consists of a pressurized canister with a metering valve unit that contains the drug substance, excipients, and propellant (i.e., metered-dose aerosol nasal inhalers (nasal MDIs)). The other type consists of an unpressurized canister or bottle with a metering spray pump unit that contains an aqueous-based formulation derived from the drug substance and excipients (i.e., aqueous nasal sprays). Both nasal MDIs and aqueous nasal sprays can contain a formulation with the drug either in solution or in suspension. These dedicated drug-delivery systems can be provided as prefilled units or as dedicated, reusable, delivery devices with replaceable drug canisters or bottles. In both of these types, the whole product, including the dedicated delivery system, is considered a drug-device combination product as defined in 21 CFR 3.2(e). This combination product is regulated by the Center for Drug Evaluation and Research (CDER) under the new

drug provisions of the Federal Food, Drug, and Cosmetic Act because the *primary mode of action* of the product is attributable to its drug constituent, while the device constituent plays a secondary role in ensuring drug delivery.

Some nasal drug products may require a separately available accessory delivery unit (e.g., a solution to be used in an atomizer). In such situations, the manufacturer of the drug product should ensure that the accessory delivery unit is approved or cleared for marketing through the device regulatory process (e.g., 510(k) process or premarket approval) by the Center for Devices and Radiological Health (CDRH). If the accessory delivery unit is not already approved or cleared for marketing, then it should be approved or cleared at least concurrent with the drug product approval. When the accessory delivery unit is separately available, but the characteristics of the drug product or the delivery unit or both are such that they must be specifically labeled for use with each other, then the two products would be considered a combination product under 21 CFR 3.2(e)(3). In such case, the drug component and the device component should be developed simultaneously and reviewed and marketed as a combination product. Sponsors are encouraged to discuss these types of issues and appropriate marketing applications with the FDA as early in development as feasible.

When developing a drug product for nasal delivery, the aerodynamic characteristics of the formulation generated by the delivery system should be considered to ensure that the drug product will be retained in the nasal cavity and not inhaled into the lung. One important consideration is the aerodynamic-based sizing of the particles or droplets. Particles or droplets that are aerodynamically smaller than the standard 5 micron upper bound of the respirable fragment size can be inhaled. For nasal deposition, the optimal droplet or particle size should be, on the whole, substantially larger than the respirable fragment size.

Nasal products containing the same drug substance but different formulations (e.g., an HFA propellant-based formulation versus an aqueous-based formulation) or nasal products with different delivery systems (e.g., product with a dedicated delivery system versus product with accessory delivery unit) are considered different products. Generally, each of these products should have a complete CMC database and a substantially complete clinical development program to support efficacy and safety of the product.

b. Device changes

The development of any dedicated delivery system or accessory delivery unit should be scrutinized. Careful assessment should be made of any changes implemented during or after the dose-finding and confirmatory clinical studies, because changes to the dedicated delivery system or the accessory delivery unit can have clinical ramifications regarding the applicability of those studies to the to-be-marketed product. Early phase clinical studies usually are conducted using a prototype, which may then undergo design changes because of the information that is gathered during the in vitro and early clinical studies. Depending on the design changes, in vitro and clinical bridging data may be appropriate to link the multiple versions of the device. Changes in the formulation, excipients, formulation flow path within the device, or device components (e.g., dimensions, materials of construction, coatings) that affect the delivery characteristics of drugs are critical and can affect the clinical performance of the product. To avoid having to perform

clinical bridging studies, critical clinical studies, such as definitive dose-finding studies and phase 3 efficacy and safety studies, should be conducted with the to-be-marketed product and device whenever possible. Bridging of nasal products for local action, particularly products that are in a suspension state, can be a substantial undertaking. Some principles that may apply to such a bridging program are outlined in the draft guidance for industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.[6] We recommend that sponsors discuss any planned device changes with the FDA and seek concurrence on their device change plans before implementing those changes.

c. Device performance

If a product has a dedicated delivery system, sponsors are encouraged to develop and implement a plan to evaluate device performance throughout the life of the device. Such a plan should be incorporated into phase 3 studies using the to-be-marketed product. The plan should ask subjects to report devices they perceive to be broken or malfunctioning and to return any such device for evaluation and identification of the problem. Device use and performance also can be evaluated through directed questions defined in the protocols. This helps to generate information regarding the types and frequencies of device malfunction based on data from a large number of devices, and an analysis of the cause may lead to potential improvements to the device itself. In addition, a small number (e.g., 100) of devices that are apparently functioning normally in subjects' hands should be collected near the end of the life of the device and evaluated by in vitro performance testing to ensure ruggedness throughout the product's intended span of use.

For a product that requires an accessory delivery unit, separate device performance evaluation may not be necessary if the device is already approved or cleared for marketing by CDRH and when it is anticipated that using the specific drug product with the device will not affect the device's performance. We recommend that sponsors discuss this issue with the FDA as early in development as feasible.

IV. SUMMARY

Development of novel drug products for sinusitis poses challenges and opportunities. This guidance outlines the FDA's current thinking on the development of various types of drug products for sinusitis. Not all drug products developed for sinusitis will fit into the types described, and the efficacy endpoints discussed in this guidance may not apply to all drug products. We encourage pharmaceutical sponsors to develop clinical programs that fit their particular needs and to discuss their planned approach with the FDA. For novel approaches, where warranted, outside expertise may be sought, including consultation with the Pulmonary — Allergy Drugs Advisory Committee.

[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

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Guidances

Draft guidance for industry *Acute Bacterial Sinusitis — Developing Antimicrobial Drugs for Treatment*. (http://www.fda.gov/cder/guidance/index.htm)

Draft guidance for industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*. (http://www.fda.gov/cder/guidance/index.htm)

Guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*. (http://www.fda.gov/cder/guidance/index.htm)

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