
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DRAFT GUIDANCE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)**

**November 2006
Clinical/Medical**

Guidance for Industry Sinusitis: Designing Clinical Development Programs of Nonantimicrobial Drugs for Treatment

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**U.S. Department of Health and Human Services
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1 **Guidance for Industry¹**
2 **Sinusitis: Designing Clinical Development Programs of**
3 **Nonantimicrobial Drugs for Treatment**
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8 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
9 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
10 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
11 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
12 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
13 the appropriate number listed on the title page of this guidance.
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18 **I. INTRODUCTION**
19

20 This guidance is intended to assist the pharmaceutical industry in designing a clinical
21 development program for nonantibiotic drug products² for the treatment of sinusitis.
22 Development of antibiotics for the treatment of acute bacterial sinusitis is fairly common and is
23 discussed in the draft guidance for industry *Acute Bacterial Sinusitis — Developing*
24 *Antimicrobial Drugs for Treatment* (Acute Bacterial Sinusitis guidance).³ This guidance does
25 not supersede the Acute Bacterial Sinusitis guidance but rather supplements it. However, many
26 of the principles outlined in the Acute Bacterial Sinusitis guidance apply to this guidance. This
27 guidance focuses on the assessment of efficacy in phase 3 clinical studies in sinusitis, but also
28 addresses chemistry, manufacturing, and controls (CMC) issues and pharmacology and
29 toxicology issues because some of the products for sinusitis are developed for nasal delivery, and
30 there are nuances to the nasal route of delivery that should be considered for appropriate clinical
31 study design.
32

33 This guidance does not contain discussion of the general issues of clinical trial design or
34 statistical analysis. Those topics are addressed in the ICH guidance documents *E8 General*
35 *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 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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37 FDA's guidance documents, including this guidance, do not establish legally enforceable
38 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
39 be viewed only as recommendations, unless specific regulatory or statutory requirements are
40 cited. The use of the word *should* in Agency guidances means that something is suggested or
41 recommended, but not required.

42

43

II. BACKGROUND

45

A. Disease Classification and Terminology

47

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

55

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

60

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

65

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

73

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

77

78 The term *rhinosinusitis* is often used in the literature, particularly in the European literature, to
79 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*.

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

B. Current Treatment Options

92
93
94
95 At present, other than antibiotics, some of which have a labeled indication for acute bacterial
96 sinusitis, the treatment options for sinusitis are limited. Drugs of other classes, such as
97 antihistamines, corticosteroids, alpha-adrenergic decongestants, and mucolytics, are often
98 recommended (Slavin and Spector et al. 2005; EAACI 2005; Meltzer and Hamilos et al. 2004),
99 but none have been specifically approved by the FDA for use in sinusitis, and few have data
100 from controlled clinical studies supporting this use. There is interest within the pharmaceutical
101 industry in the development of new drugs, including drugs other than antibiotics, for the
102 treatment of sinusitis.

III. CLINICAL DEVELOPMENT PROGRAM

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

A. General Considerations

1. Types of Drug Products for Sinusitis

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112
113
114 Various types of drug products can be developed for sinusitis. The drug product can be a new
115 molecular entity formulated for oral, parenteral, or nasal delivery; a molecular entity that is
116 already approved as an oral or parenteral product with or without a sinusitis indication and is
117 now being studied as a nasal formulation; or an approved nasal drug product that does not have a
118 sinusitis indication. The drug product can be developed as a stand-alone treatment for sinusitis
119 or as an add-on treatment to an approved treatment, such as an add-on treatment to antibiotics for
120 the treatment of acute bacterial sinusitis. The drug product can be a single entity or a
121 combination product. The clinical development program depends on which drug product
122 scenario will be developed.
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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.

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170
171 Active-controlled studies are viable alternatives to placebo-controlled studies when the intent of
172 the study is to show superiority. When the intent is to show noninferiority to an active
173 comparator and no placebo is planned, many important design issues are raised (e.g., assay
174 sensitivity, the noninferiority margin, knowledge of how the chosen endpoint performs in studies
175 with the active comparator). These issues are discussed in detail in the ICH guidance for
176 industry *E10 Choice of Control Group and Related Issues in Clinical Trials*. Before proposing a
177 noninferiority design, there should be a well-defined, reproducible treatment effect for the
178 established comparator such that the effect of that treatment in later studies can be inferred.
179 Alternately, a placebo group could be incorporated into the proposed study to demonstrate that
180 although the active and new treatment are noninferior to one another, the new treatment also has
181 benefits exceeding the placebo effect. Any such proposal should be carefully considered and
182 discussed in depth with the FDA before starting clinical studies using this design. Given the role
183 of symptom assessment in the evaluation of sinusitis, it is important for the assigned treatment to
184 be masked in the study design. Generally, we consider open-labeled studies of sinusitis to be
185 uninformative. Double-dummy designs may be appropriate in comparative studies. In the
186 overall design and conduct of studies, appropriate statistical methodologies should be applied in
187 the handling of missing data, outliers, and other relevant issues as discussed in the guidance for
188 industry *E9 Statistical Principles for Clinical Trials*.

189 190 2. *Study Population and Entry Criteria*

191
192 One of the major challenges in designing and conducting clinical studies in sinusitis is that the
193 symptoms that are used in clinical practice to diagnose sinusitis are neither specific nor sensitive.
194 Common symptoms of sinusitis are facial pain or pressure sensation, purulent anterior or
195 posterior nasal discharge or both, nasal congestion, cough, headache, dental pain, olfactory
196 disturbance, ear ache or fullness, and bad breath. However, patients with viral upper respiratory
197 tract infection, allergic rhinitis, or other forms of rhinitis may have symptoms indistinguishable
198 from sinusitis. Patients with migraine or cluster headache may have symptoms that overlap with
199 sinusitis.

200
201 Symptoms also can be unreliable, as patients without convincing symptoms of sinusitis may have
202 clear evidence of the disease when examined by an objective assessment such as by imaging.
203 Another complicating factor is that a drug being developed for sinusitis actually may be effective
204 for rhinitis and may even carry a rhinitis indication. This is particularly important for a nasal
205 product, which would have a chance to act on the nasal mucosa. Since it is known that sinusitis
206 patients have accompanying rhinitis, the clinical program should convincingly demonstrate that
207 the efficacy is from improvement of sinusitis and not solely from improvement of rhinitis.

208
209 Therefore, clinical studies should not rely on patient-reported subjective symptoms alone. We
210 prefer that some form of objective evidence be included to determine eligibility of patients' entry
211 in clinical studies and for demonstration of efficacy. Objective assessments of sinusitis include
212 imaging techniques such as a computerized tomography (CT) scan or a magnetic resonance
213 imaging (MRI) scan, ultrasonography, microbiological assessment of sinus aspirate, and direct
214 visual examination of the sinus cavity by endoscopic examination when an antral window has
215 been created surgically. However, if a drug will be delivered systemically and is not expected to

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

218
219 For entry into clinical studies for acute, subacute, or chronic sinusitis, symptoms should be
220 continuously present for at least 10 days, and the diagnosis should be supported by at least one
221 objective assessment, preferably imaging. For entry into recurrent sinusitis studies, an effort
222 should be made to obtain objective evidence from previous sinusitis episodes to ensure that
223 patients with reliable diagnosis of recurrent sinusitis are enrolled in the study. However, because
224 of the historical nature of the diagnostic criteria, we acknowledge that objective assessment may
225 not be reliably available for all patients and for all previous episodes.

226 227 3. *Dose Selection*

228
229 The dose or doses and dosing frequency of drugs for phase 3 studies should be selected based on
230 pharmacokinetic considerations and from earlier phase dose-ranging studies using a
231 pharmacodynamic (PD) or clinical efficacy endpoint that is consistent with the expected benefit
232 to be derived from the drug. The endpoint used in dose-ranging studies should be consistent
233 with or known to be predictive of the efficacy endpoint that will be used in phase 3 studies. The
234 dose or doses selected for phase 3 studies should be based on benefit-to-risk assessment. If more
235 than one dose is ultimately intended to be marketed, the clinical program design should produce
236 data that allow for a comparative assessment of efficacy and safety among the doses in addition
237 to the usual comparison of the doses of the new drug to placebo. In circumstances where PD
238 measures are used in phase 2 for dose identification, inclusion of more than one dose level in at
239 least one phase 3 study, even if the goal is to market a single dose, should be considered. This is
240 because even a well-validated PD endpoint may not fully predict efficacy as assessed by a
241 clinical outcome endpoint in larger, longer term phase 3 studies, and usually will not be
242 predictive of safety.

243 244 4. *Efficacy Endpoints*

245
246 For phase 3 studies, the primary and secondary efficacy endpoints should be chosen based on the
247 type of sinusitis that is studied, the drug's putative mechanism of action, and the proposed
248 benefit desired to be demonstrated. It is not possible to categorically state in all cases what the
249 primary and secondary efficacy endpoints should be. Suggested primary efficacy endpoints for
250 different types of sinusitis studies are mentioned below.

251 252 a. *Acute, subacute, or chronic sinusitis*

253
254 The efficacy endpoint should include patient-reported symptoms and at least one objective
255 measure declared as co-primary, meaning that both measures should statistically demonstrate the
256 desired effect. However, if a drug will be delivered systemically and is not expected to reach the
257 nasal cavity or is known not to be effective in rhinitis, objective measure may not be necessary.

258
259 Patient-reported symptoms can include any scientifically supported and logical combination of
260 symptoms that are common in sinusitis. The symptoms combination should be carefully chosen
261 so that they reflect sinusitis rather than other confounding diseases. We prefer a composite score

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262 consisting of the following three symptoms: facial pain or pressure sensation, purulent anterior or
263 posterior nasal discharge or both, and nasal congestion. Each of these symptoms should be
264 scored by subjects daily using a predefined scoring system. Table 1 shows a sample rating
265 system that is commonly used in similar clinical studies. Subjects should be given a clear
266 detailed description of the scoring system. The frequency of scoring should be driven by the
267 dosing interval, but should be at least twice daily, once in the morning and once in the evening,
268 with one or more scorings timed to precede dosing. The symptoms should be scored both as
269 reflective score (evaluation of symptom severity over a predefined period, such as 12 hours) and
270 as instantaneous score (evaluation of symptom severity immediately preceding the time of
271 scoring). Reflective score gives an assessment of consistency of efficacy throughout the dosing
272 interval, and instantaneous score gives an assessment of end of dosing interval efficacy. Either
273 reflective or instantaneous symptom score can be declared as a primary efficacy endpoint.
274

275 **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)

276
277 The preferred objective measure for use as an efficacy endpoint is an imaging study of the sinus,
278 such as a CT scan or an MRI scan. In specific situations, other objective measures can also be
279 used, such as microbiological assessment of sinus aspirate for evaluation of an add-on treatment
280 to antibiotics for the treatment of acute bacterial sinusitis, microbiological assessment of sinus
281 aspirate for chronic sinusitis, and direct visual examination of sinus cavity by endoscopic
282 examination when such an exam is technically feasible. The objective measure selected as the
283 efficacy endpoint should be scored by a scientifically justified scoring system. The use of a
284 central independent reader or readers for evaluation of any imaging studies is recommended.
285 The evaluator or evaluators should be blinded to treatment assignments and the timing of the
286 images (i.e., whether the image being evaluated is at study entry or from an efficacy assessment).
287

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

294
295 b. Recurrent sinusitis

296
297 The primary efficacy endpoint should include a clinically meaningful measure of recurrence.
298 Such measure can include time to the first recurrence, number of recurrences in a prespecified
299 time period, severity of recurrences, and duration of recurrences. Any of these measures can be

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

306

307 5. *Statistical Considerations*

308

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

325

326 a. Acute, subacute, or chronic sinusitis

327

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

340

341 b. Recurrent sinusitis

342

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

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

348

349 6. *Routes of Delivery*

350

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

365

366 7. *Treatment Duration*

367

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

372

373 8. *Combination Drugs*

374

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

381

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

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

397

C. Other Considerations

399

1. Relevant Nonclinical Safety Considerations

400

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

403

404
405 If the drug product is a new molecular entity, the pharmacology and toxicology program should
406 follow the principles outlined in the following guidance documents: the ICH guidance for
407 industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for*
408 *Pharmaceuticals*, the ICH guidance for industry *S7A Safety Pharmacology Studies for Human*
409 *Pharmaceuticals*, and the guidance for industry *Estimating the Maximum Safe Starting Dose in*
410 *Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*. For calculation of safety
411 margins, systemic as well as local nasal findings should be considered. For a drug product that is
412 developed specifically as a nasal formulation, animal toxicology studies should be conducted
413 with nasal delivery to the animals (e.g., via snout delivery). These studies should include
414 thorough examination of the upper and lower airways, including complete histopathological
415 examination. Safety margins for local effects in the nasal region should be calculated by
416 comparing the total amount of administered drug per surface area of the nasal cavity in animals
417 versus that in humans. To characterize systemic toxicity, additional animal toxicology studies
418 may be appropriate with oral or parenteral dosing if the nasal delivery does not result in adequate
419 systemic exposure. The extent and characteristics of systemic toxicity data that are appropriate
420 for a nasal product may vary depending on the drug's bioavailability via the nasal route and other
421 factors. We recommend that this issue be discussed with the FDA before the toxicology studies
422 are planned.

423

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

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

441
442 Nonclinical studies should also be conducted to qualify all excipients where the intranasal route
443 of administration is novel. Excipients that are generally considered to be safe for human use for
444 oral or parenteral routes are not automatically qualified for use in nasal formulations.

445
446 When developing a drug-device combination product, the preclinical information should
447 consider device engineering and biocompatibility information, as well as possible drug-device
448 interactions. When using an accessory delivery unit, development plans should also consider
449 methods to control for accessory delivery unit modifications.

450
451 In vitro genetic toxicology studies for a new molecular entity should be conducted before first
452 human dosing. Drugs that are found to be genotoxic should be carefully assessed for putative
453 benefit, and clinical studies with such a compound should include disclosure of the positive
454 finding and its implication in the informed consent. Carcinogenicity studies should be conducted
455 before submission of a marketing application. In some instances, such as with positive
456 genotoxicity findings, carcinogenicity studies can be considered earlier in clinical development.
457 Drugs that are carcinogenic are unlikely to be approved for human use for symptomatic benefit
458 in sinusitis.

459 460 2. *CMC Considerations*

461
462 The development of drug products for nasal delivery presents special considerations as discussed
463 in the guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug*
464 *Products — Chemistry, Manufacturing, and Controls Documentation*. Some aspects of a drug
465 product for nasal delivery that have ramifications for the conduct of clinical studies of sinusitis
466 are discussed below.

467 468 a. Nasal drug delivery

469
470 Nasal delivery of a drug can be achieved either by a drug product that has a dedicated delivery
471 system or by a drug product that requires an accessory delivery unit.

472
473 There are two major types of drug products that have a dedicated delivery system. One type
474 consists of a pressurized canister with a metering valve unit that contains the drug substance,
475 excipients, and propellant (i.e., metered-dose aerosol nasal inhalers (nasal MDIs)). The other
476 type consists of an unpressurized canister or bottle with a metering spray pump unit that contains
477 an aqueous-based formulation derived from the drug substance and excipients (i.e., aqueous
478 nasal sprays). Both nasal MDIs and aqueous nasal sprays can contain a formulation with the
479 drug either in solution or in suspension. These dedicated drug-delivery systems can be provided
480 as prefilled units or as dedicated, reusable, delivery devices with replaceable drug canisters or
481 bottles. In both of these types, the whole product, including the dedicated delivery system, is
482 considered a drug-device combination product as defined in 21 CFR 3.2(e). This combination
483 product is regulated by the Center for Drug Evaluation and Research (CDER) under the new

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

487
488 Some nasal drug products may require a separately available accessory delivery unit (e.g., a
489 solution to be used in an atomizer). In such situations, the manufacturer of the drug product
490 should ensure that the accessory delivery unit is approved or cleared for marketing through the
491 device regulatory process (e.g., 510(k) process or premarket approval) by the Center for Devices
492 and Radiological Health (CDRH). If the accessory delivery unit is not already approved or
493 cleared for marketing, then it should be approved or cleared at least concurrent with the drug
494 product approval. When the accessory delivery unit is separately available, but the
495 characteristics of the drug product or the delivery unit or both are such that they must be
496 specifically labeled for use with each other, then the two products would be considered a
497 combination product under 21 CFR 3.2(e)(3). In such case, the drug component and the device
498 component should be developed simultaneously and reviewed and marketed as a combination
499 product. Sponsors are encouraged to discuss these types of issues and appropriate marketing
500 applications with the FDA as early in development as feasible.

501
502 When developing a drug product for nasal delivery, the aerodynamic characteristics of the
503 formulation generated by the delivery system should be considered to ensure that the drug
504 product will be retained in the nasal cavity and not inhaled into the lung. One important
505 consideration is the aerodynamic-based sizing of the particles or droplets. Particles or droplets
506 that are aerodynamically smaller than the standard 5 micron upper bound of the respirable
507 fragment size can be inhaled. For nasal deposition, the optimal droplet or particle size should be,
508 on the whole, substantially larger than the respirable fragment size.

509
510 Nasal products containing the same drug substance but different formulations (e.g., an HFA
511 propellant-based formulation versus an aqueous-based formulation) or nasal products with
512 different delivery systems (e.g., product with a dedicated delivery system versus product with
513 accessory delivery unit) are considered different products. Generally, each of these products
514 should have a complete CMC database and a substantially complete clinical development
515 program to support efficacy and safety of the product.

b. Device changes

516
517
518
519 The development of any dedicated delivery system or accessory delivery unit should be
520 scrutinized. Careful assessment should be made of any changes implemented during or after the
521 dose-finding and confirmatory clinical studies, because changes to the dedicated delivery system
522 or the accessory delivery unit can have clinical ramifications regarding the applicability of those
523 studies to the to-be-marketed product. Early phase clinical studies usually are conducted using a
524 prototype, which may then undergo design changes because of the information that is gathered
525 during the in vitro and early clinical studies. Depending on the design changes, in vitro and
526 clinical bridging data may be appropriate to link the multiple versions of the device. Changes in
527 the formulation, excipients, formulation flow path within the device, or device components (e.g.,
528 dimensions, materials of construction, coatings) that affect the delivery characteristics of drugs
529 are critical and can affect the clinical performance of the product. To avoid having to perform

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

c. Device performance

538
539
540
541 If a product has a dedicated delivery system, sponsors are encouraged to develop and implement
542 a plan to evaluate device performance throughout the life of the device. Such a plan should be
543 incorporated into phase 3 studies using the to-be-marketed product. The plan should ask subjects
544 to report devices they perceive to be broken or malfunctioning and to return any such device for
545 evaluation and identification of the problem. Device use and performance also can be evaluated
546 through directed questions defined in the protocols. This helps to generate information regarding
547 the types and frequencies of device malfunction based on data from a large number of devices,
548 and an analysis of the cause may lead to potential improvements to the device itself. In addition,
549 a small number (e.g., 100) of devices that are apparently functioning normally in subjects' hands
550 should be collected near the end of the life of the device and evaluated by in vitro performance
551 testing to ensure ruggedness throughout the product's intended span of use.

552
553 For a product that requires an accessory delivery unit, separate device performance evaluation
554 may not be necessary if the device is already approved or cleared for marketing by CDRH and
555 when it is anticipated that using the specific drug product with the device will not affect the
556 device's performance. We recommend that sponsors discuss this issue with the FDA as early in
557 development as feasible.

558
559

IV. SUMMARY

560
561
562 Development of novel drug products for sinusitis poses challenges and opportunities. This
563 guidance outlines the FDA's current thinking on the development of various types of drug
564 products for sinusitis. Not all drug products developed for sinusitis will fit into the types
565 described, and the efficacy endpoints discussed in this guidance may not apply to all drug
566 products. We encourage pharmaceutical sponsors to develop clinical programs that fit their
567 particular needs and to discuss their planned approach with the FDA. For novel approaches,
568 where warranted, outside expertise may be sought, including consultation with the Pulmonary —
569 Allergy Drugs Advisory Committee.

570
571

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>)
- Guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation*. (<http://www.fda.gov/cder/guidance/index.htm>)
- Guidance for industry *Premarketing Risk Assessment*. (<http://www.fda.gov/cder/guidance/index.htm>)
- ICH guideline for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*. (<http://www.fda.gov/cder/guidance/index.htm>)
- ICH guidance for industry *E8 General Considerations for Clinical Trials*. (<http://www.fda.gov/cder/guidance/index.htm>)

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- 617 ICH guidance for industry *E9 Statistical Principles for Clinical Trials*.
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- 620 ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*.
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- 623 ICH guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical*
624 *Trials for Pharmaceuticals*. (<http://www.fda.gov/cder/guidance/index.htm>)
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