

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215712Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



PIND 142446

**MEETING REQUEST
WRITTEN RESPONSES**

Perrigo Pharma International Designated Activity Company
Attention: Valerie Gallagher
Vice President Regulatory Affairs, Regulatory Agent
515 Eastern Avenue
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your pre-investigational new drug application (PIND) file for Nasonex (mometasone furoate) nasal spray, 50 mcg per spray.

We also refer to your submission dated February 28, 2020, containing a request for a Type B, pre-NDA meeting. The purpose of the requested meeting was to discuss the integrated summary of safety and efficacy and other data requirements to support the partial prescription to over-the-counter (Rx-to-OTC) switch of Nasonex. Due to the Division's engagement in COVID-19 activities, resources, and workload, FDA and Perrigo came to an agreement for FDA to provide written responses to Perrigo's questions in two parts: FDA's written response only (WRO) dated June 1, 2020 contained FDA's responses to questions 1, 2, 3, 4, 6, 7, 8, 10, 11, 17, 18, 20, and 21. This document contains FDA's written responses to questions 5, 9, 12, 13, 14, 15, 16, 19, 22, 23, 24, and 25.

If you have any questions, call Sherry Stewart, Senior Regulatory Project Manager, at 301-796-9618.

Sincerely,

{See appended electronic signature page}

Nushin Todd, MD, PhD
Acting Deputy Director
Division of Nonprescription Drugs I
Office of Nonprescription Drugs
Center for Drug Evaluation and Research

ENCLOSURE: WRITTEN RESPONSES



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type B – Written Response Only (WRO)

Meeting Category: Pre-NDA

Application Number: PIND 142446

Product Name: Nasonex (mometasone furoate) nasal spray, 50 mcg per spray

Indication: Temporarily relieves these symptoms of hay fever or other respiratory allergies: nasal congestion, runny nose, sneezing, and itchy nose.

Sponsor Name: Perrigo Pharma International Designated Activity Company

Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Perrigo has acquired the right of reference to NDA 20762 for Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg/spray held by Merck Sharp Dohme (MSD) along with the right to pursue a partial prescription to over-the-counter (Rx-to-OTC) switch. Perrigo states that this product will be identical to the approved prescription product, and is proposing the following OTC indication:

Temporarily relieves these symptoms of hay fever or other upper respiratory allergies:

- Nasal congestion
- Runny nose
- Sneezing
- Itchy nose

MSD will retain rights to the prescription product for the two remaining indications:

- Prophylaxis of seasonal allergic rhinitis
- Treatment of nasal polyps

The purpose of the requested meeting was to discuss the integrated summary of safety and efficacy and other data requirements to support the planned 505(b)(1) New Drug

Application (NDA) for the partial Rx-to-OTC switch of Nasonex. As noted above, due to the Division's engagement in COVID-19 activities, FDA worked with Perrigo to come to an agreement to provide written responses to Perrigo's questions in two parts: this document contains the second of the two parts and covers questions 5, 9, 12, 13, 14, 15, 16, 19, 22, 23, 24, and 25; FDA provided written responses to questions 1, 2, 3, 4, 6, 7, 8, 10, 11, 17, 18, 20, and 21 on June 1, 2020.

2.0 DISCUSSION

Question 5 (question 3 in meeting package):

Does FDA agree that the 51 trials Perrigo proposes to exclude from the ISS analysis (ie, the trials for which MSD does not own nor have access to trial-related documents or data, where no subjects were enrolled, and/or where data was corrupted) can, by necessity, be excluded from the summary of trial safety data in this ISS, and that Perrigo's plan to present these trials in tabular form with the information posed in Table B (in Appendix 4), is sufficient?

FDA Response:

The 51 NDA/sNDA trials were reviewed by FDA as part of the original Nasonex NDA for allergic rhinitis in subjects 12 years and older (24 trials) or as part of subsequent Nasonex sNDAs (27 trials in the sNDAs listed below), of which led to labeling updates unless otherwise noted.

- sNDA 20762/S-001 (12 Hour Onset; n=2 trials)
- sNDA 20762/S-004 (Pediatrics down to age 3 years; n=7 trials)
- [REDACTED] (b) (4)
- sNDA 20762/S-011 (Pediatrics down to age 2 years; n=1 trial)
- sNDA 20762/S-023 (Nasal Polyps in subjects 18 years and older; n=4 trials)
- sNDA 20762/S-038 (Nasal Congestion in subjects 2 years and older; n=9 trials)
- sNDA 20762/[REDACTED] (b) (4) /044 [REDACTED] (b) (4)

You previously commented that you intend to submit, as part of the ISS, a high-level narrative summary of the safety issues for Nasonex/MFNS from these 51 trials, including discussion of both common adverse events (AEs) and significant safety issues. We stated that this approach appears reasonable in our Written Responses dated June 1, 2020. We also refer you to the FDA response in the Advice Letter dated March 4, 2020 and to Question 2 in Meeting Minutes dated March 14, 2019, for details of the safety information recommended for inclusion in the ISS. Ultimately, this will be a review issue. As stated previously, you do not need to submit detailed safety data for trials reviewed as part of the initial NDA approval.

Question 9 (question 5 in meeting package):

Does FDA agree that Perrigo's plan to provide a link to the materials available for each of the 89 Nasonex/MFNS trials, including where the study reports are incomplete or almost entirely missing, is sufficient?

FDA Response:

This response addresses only the use of links and is not meant to replace any other advice communicated about the presentation of safety data from these trials.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Appendix 7 (Table E) did not include active hyperlinks. Thus, we could not experience the link to give you a definitive answer. We interpret your proposal to mean, for example that item 38 in the referenced Appendix 7 (Table E) would include a hyperlink to a folder containing the dataset(s) and CSRs and/or other supporting documents. Refer to FDA response to Question 2 (2f.) in Meeting Minutes dated March 14, 2019 noting inclusion of a detailed table of contents with bookmarks that take the reader directly to the table or reference that is in the narrative. Hyperlinks leading to actual materials available within the submission will facilitate efficient review and potentially reduce the need for information requests.

Question 12 (question 6c in meeting package):

Does FDA agree that Perrigo's plan for reviewing and presenting the past 10 years of safety data from the VigiBase is sufficient?

FDA Response:

Yes, you may limit the search of postmarketing datasets to the 10 most recent years and apply a cutoff date for events at 6 months prior to NDA submission.

Your descriptions of postmarketing presentations are limited largely to tables. As with clinical trial safety data, we expect a synthesized discussion of your findings with conclusions. Provide English translations of non-U.S. OTC labeling and include any other presentations, tables, discussion that you believe are critical to evaluation of the safety profile of your proposed NDA switch product when used OTC. This advice applies to all pharmacovigilance datasets.

Refer also to Meeting Minutes dated March 14, 2019 and Written Responses dated June 1, 2020.

Question 13 (question 6d in meeting package):

Does FDA agree that Perrigo's plan for reviewing and presenting the past 10 years of safety data from FAERS is sufficient?

FDA Response:

See FDA response to Question 12.

Question 14 (question 6e in meeting package):

Does FDA agree that Perrigo's plan for reviewing and presenting the past 10 years of safety data from AAPCC/NPDS is sufficient?

FDA Response:

See FDA response to Question 12.

Question 15 (question 6f in meeting package):

Does FDA agree that Perrigo's plan to identify, review, and summarize the past 10 years of Nasonex/MFNS safety data from the medical literature is sufficient?

FDA Response:

Yes, you may limit the search of safety data from the medical and scientific literature to the 10 most recent years and apply a cutoff date for publications at 6 months prior to NDA submission. However, we note that you plan to limit the search to English language articles. We do not

agree with this. If there are non-English publications describing safety findings or adverse events relevant to Nasonex/MFNS, include these publications. You refer also to the use of hyperlinks solely to address limitations in access to clinical trial data. Include hyperlinks to all articles (i.e., do not limit hyperlink use only to clinical trial data).

For literature sources:

- Include a discussion of the strengths and weaknesses of each publication and provide integrated conclusions based on the review.*
- Include a list of references. Ensure that full articles, with English translations if necessary, are available upon request. Alternatively, the full publication may be hyperlinked to the corresponding listing.*
- For critical safety references, include the full hyperlinked publication.*

Refer to Meeting Minutes dated March 14, 2019 and Written Responses dated June 1, 2020 for general discussion of safety data content.

Question 16 (question 7 in meeting package):

Does FDA agree with Perrigo's approach regarding providing MedDRA PTs, SOCs, and verbatim terms reported for AEs in the 16 trials not previously reviewed by FDA, where this information is available?

FDA Response:

On face, your plan is acceptable. Include in the NDA which trials did not include verbatim terms. We may ask for source data to clarify the preferred terms (PTs) and better understand the adverse event data.

Question 19 (question 10 in meeting package):

Does FDA agree with Perrigo's proposal for some trials with datasets to be submitted in SDTM/ADaM format, versus other trials with datasets to be submitted in alternate legacy format, as is detailed above?

FDA Response:

We agree that your plan to include datasets along with a define file, reviewer's guide, and annotated CRF is reasonable. Include datasets with similar documentation for your pooled analyses.

Question 22 (question 13 in meeting package):

Does FDA agree with the approach to pooled data presentation?

FDA Response:

All pooling groups to analyze frequencies by adjusting/stratifying by study, not by crude pooling.^{1, 2}

¹ Chuang-Stein and Beltangady, 2011. Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. Pharm Stat, 10:3-7

² Crowe, Chuang-Stein, et al, 2016. Reporting Adverse Drug Reactions in Product Labels. Therapeutic Innovation & Regulatory Science, 50:455-463.

Question 23 (question 14 in meeting package):

Does FDA agree with the proposed integration strategy?

FDA Response:

We agree with your integration planning. In addition to your frequency tabulations, include by-treatment risk difference comparisons (and their confidence intervals) for these key identified risks: adverse events (AEs) leading to discontinuation, deaths, SAEs, adverse events of special interest (AESIs) and most frequent adverse events occurring in greater frequency in test subjects.

This response is in addition to, and aligned with our comments from Part 1, Written Responses dated June 1, 2020 (Question 21, question 12 in meeting package).

Question 24 (question 15 in meeting package):

Does FDA agree that a medical literature update on animal toxicology is not required?

FDA Response:

No, we do not agree. Consistent with our comments under Question 15 above, submit a review and summary of all relevant nonclinical pharmacology and toxicology literature from the 10 most recent years up through a cutoff publication date of 6 months prior to NDA submission. Include electronic copies (and any necessary English translations) of all literature discussed in your submission.

Question 25 (question 16 in meeting package):

Does FDA agree that the review of these two items, ie, updates from the MSD PV safety data and the medical literature review, both to cover information from the cutoff date in the partial Rx-to-OTC switch NDA submission to one month after that submission, will be sufficient for the 120-Day Safety Update?

FDA Response:

No, we do not agree. Updates to all database (FAERS, WHO, NPDS, MSD PV) and literature searches are to be included in the 120-Day Safety Update. If there are new trial data, include these data as well.

3.0 Additional Comments

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements/ Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h³ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁴. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁵

³ <https://www.fda.gov/media/84223/download>

⁴ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

⁵ <https://www.fda.gov/media/85061/download>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NUSHIN F TODD
11/09/2020 02:58:24 PM



PIND 142446

**MEETING REQUEST
WRITTEN RESPONSES**

Perrigo Pharma International Designated Activity Company
Attention: Valerie Gallagher
Vice President Regulatory Affairs, Regulatory Agent
515 Eastern Avenue
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your pre-investigational new drug application (PIND) file for Nasonex (mometasone furoate) nasal spray, 50 mcg per spray.

We also refer to your submission dated February 28, 2020, containing a request for a Type B, pre-NDA meeting. The purpose of the requested meeting was to discuss the integrated summary of safety and efficacy and other data requirements to support the partial prescription to over-the-counter (Rx-to-OTC) switch of Nasonex. Due to the Division's engagement in COVID-19 activities, our resources and workload necessitated that FDA work with Perrigo to come to an agreement to provide written responses to Perrigo's questions into two parts. This document contains the first of the two parts and covers questions 1, 2, 3, 4, 6, 7, 8, 10, 11, 17, 18, 20, and 21. FDA will provide written responses to questions 5, 9, 12, 13, 14, 15, 16, 19, 22, 23, 24, and 25 at a future date.

If you have any questions, call Sherry Stewart, Senior Regulatory Project Manager, at 301-796-9618.

Sincerely,

{See appended electronic signature page}

Nushin Todd, MD, PhD
Acting Deputy Director
Division of Nonprescription Drugs I
Office of Nonprescription Drugs
Center for Drug Evaluation and Research

ENCLOSURE: WRITTEN RESPONSES



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type B

Meeting Category: Pre-NDA

Application Number: PIND 142446

Product Name: Nasonex (mometasone furoate) nasal spray, 50 mcg per spray

Indication: Temporarily relieves these symptoms of hay fever or other respiratory allergies: nasal congestion, runny nose, sneezing, and itchy nose.

Sponsor Name: Perrigo Pharma International Designated Activity Company

Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Perrigo has acquired the right of reference to NDA 20762 for Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg/spray held by Merck Sharp Dohme (MSD) along with the right to pursue a partial prescription to over-the-counter (Rx-to-OTC) switch. Perrigo states that this product will be identical to the approved prescription product, and is proposing the following OTC indication:

Temporarily relieves these symptoms of hay fever or other upper respiratory allergies:

- Nasal congestion
- Runny nose
- Sneezing
- Itchy nose

MSD will retain rights to the prescription product for the two remaining indications:

- Prophylaxis of seasonal allergic rhinitis
- Treatment of nasal polyps

The purpose of the requested meeting was to discuss the integrated summary of safety and efficacy and other data requirements to support the planned 505(b)(1) New Drug

Application (NDA) for the partial Rx-to-OTC switch of Nasonex. Due to the Division's engagement in COVID-19 activities, resources and workload necessitated that FDA work with Perrigo to come to an agreement to provide written responses to Perrigo's questions into two parts in lieu of a teleconference. This document contains the first of the two parts and covers questions 1, 2, 3, 4, 6, 7, 8, 10, 11, 17, 18, 20, and 21. FDA will provide written responses to questions 5, 9, 12, 13, 14, 15, 16, 19, 22, 23, 24, and 25 at a future date.

2.0 DISCUSSION

Question 1 (question 1a in meeting package):

Perrigo intends to submit, as part of the ISS, a high-level narrative summary of the safety issues for Nasonex/MFNS from these 51 trials, including discussion of both common adverse events (AEs) and significant safety issues. Does the FDA agree with this plan?

FDA Response:

Your approach appears reasonable. See FDA response in the Advice Letter dated March 4, 2020, and to Question 2 in Meeting Minutes dated March 14, 2019, for details of the safety information that we recommended including in the ISS. Ultimately, this will be a review issue.

Refer also to [eCTD Technical Conformance Guide \(Dec 2019\) at https://www.fda.gov/media/93818/download](https://www.fda.gov/media/93818/download) and guidances for industry:¹

- *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document (April 2009) at <https://www.fda.gov/media/75783/download>*
- *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Feb 2020) at <https://www.fda.gov/media/135373/download>*

Question 2 (question 1b in meeting package):

Does FDA agree that, in addition to the narrative summary noted in Q1a, it is acceptable for Perrigo to present information in tabular format summarizing key information for these 51 trials (eg, including trial title, phase, number of subjects, brief trial description, and summary safety conclusions; see Table A in Appendix 3)?

FDA Response:

On face, this approach appears acceptable. However, we may request additional content formatting during review of your marketing application.

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We note your proposal to include events that require an intervention, such as visiting a health care provider, urgent care, or emergency room visit, even if did not result in a hospitalization (Meeting Package dated May 1, 2020, p. 22-23/52). Include this type of information in your marketing application. See FDA response to Question 2 from Meeting Minutes dated March 14, 2019, for details of safety information content.

Question 3 (question 2a in meeting package):

Does FDA agree that Perrigo's proposed approach to analyzing the AEs of special interest and the AEs that led to drug/trial discontinuation and/or which required additional treatment for these 51 trials will be adequate?

FDA Response:

As stated in FDA Advice Letter dated March 4, 2020, a high level, synthesized summary and discussion of the safety of your drug is expected. Include also whether the specific source described adverse events or not, and if so, provide the level of detail. Include significant events as related to an OTC space if such are described. Additional information may be requested during review of the data.

Summarize the "adverse events beyond death and serious adverse events for the OTC setting" described above using graphical methods (in addition to study narrative format), where feasible. Consider which studies are reasonable to summarize together. Consider across comparable studies whether there are patterns that would be of concern when there is no learned intermediary to assist the consumer, such as the pooling groups noted in Table 12 of the Meeting Package and any relevant subgroups which may affect the benefit-risk balance for consumers.

Assuming that means and confidence intervals are available or can be calculated for each treatment and study, construct forest plots for these "adverse events beyond death and serious adverse events for the OTC setting" with frequencies, risk difference (relative to control group) and their confidence intervals for each study. Discuss uncertainty in estimated effects. What level of risk can be ruled out?

Question 4 (question 2b in meeting package):

Based on the feedback from FDA's Pre-IND Meeting Minutes, Perrigo has identified a list of AEs/safety issues and MedDRA terms of special interest (see bulleted list above) for these 51 trials. Does FDA agree with this list and approach?

FDA Response:

The list is reasonable. As noted in the FDA response to Question 2 of Meeting Minutes dated March 14, 2019, include an analysis of your product for the following areas of special interest:

- a. *Local nasal events*
 - i. *Bacterial rhinosinusitis, candidiasis, nasal septal perforation, epistaxis*
- b. *Other*
 - i. *Ocular events, effects on the HPA axis, effects on growth, effects on bone metabolism, effects on glucose metabolism, visual disturbances and central serous chorioretinopathy, relative potency of your steroid, unit to unit, as compared to the active ingredient in other OTC intranasal corticosteroid sprays*

Question 6 (question 4a in meeting package):

Does FDA agree that the planned summary of safety data from the available trial data for the 38 Nasonex/MFNS trials that have not been previously reviewed by FDA is sufficient?

FDA Response:

On face, this approach appears reasonable. However, adequacy of the data will be a review issue and additional information may be requested during the detailed review of the submitted trial data.

Include an explanation for the absence of data from trials conducted by MSD or SP. For efficiency of review, in addition to presentation such as in the corresponding appendix, include a data table (JMP) grouped by similarity in trial design that includes a column identifying whether the adverse events (AEs) were available (yes/no) with columns for SAEs, discontinuations secondary to an AE, and OTC significant AEs. If these are not available, indicate this in the submission. "None" would mean it is reported and there were no events of that nature. Datasets would facilitate efficient review.

See FDA response to Question 3.

Question 7 (question 4b in meeting package):

Given the limited availability of electronic CRFs for the 38 trials not previously reviewed by FDA, does FDA agree with Perrigo not submitting CRFs?

FDA Response:

At this time, we cannot agree or disagree with you. We acknowledge your efforts to obtain case report forms (CRFs) as described in the Meeting Package of May 1, 2020 (p.31/52) and your comments that subject CRFs for 15 of the 38 studies are on microfiche along with noting that there may be lack of complete information on the CRFs of the subject (p. 31/52). Provide an explanation for why you were unable to obtain information related to trials conducted by MSD, SP, or yourself, among this group of 38 trials. Ultimately, this will be a review issue.

Question 8 (question 4c in meeting package):

Does FDA agree with Perrigo's planned approach for showing how safety data were collected for these 38 trials?

FDA Response:

Your approach appears reasonable. See FDA response to Question 3. Consider formatting safety data to facilitate efficient review.

Question 10 (question 6a in meeting package):

Does FDA agree that summaries of AEs by listedness (listed vs. unlisted) and seriousness, similar to what is presented in MSD's annual PAERs for Nasonex, are not necessary because these data are excluded from the E2B(R2) data?

FDA Response:

Given the long marketing history of this product, it will facilitate review to know which events are already in the Rx labeling and the associated level of seriousness (e.g., if events were serious or expedited or would be significant in an OTC space or are on the list of special interests discussed in the FDA response to Question 4 above). Include the U.S. label version to which you are referencing the listedness of the event.

Question 11 (question 6b in meeting package):

Does FDA agree that Perrigo's plan for reviewing and presenting the past 10 years of pharmacovigilance data from MSD is sufficient?

FDA Response:

This approach appears reasonable. In Meeting Minutes dated March 14, 2019, we noted that "you may limit the search of the postmarketing datasets to the 10 most recent years."

Question 17 (question 8 in meeting package):

Does FDA agree that Perrigo's plan for the ISE, including a brief summary of efficacy for the OTC indication with additional information provided in tabular form as proposed in Table F (see Appendix 8) for the 34 NDA/sNDA efficacy trials is sufficient?

FDA Response:

Conclusions of efficacy were determined based on previous trials. We will rely on efficacy from the initial NDA submission.

Due to the large number of studies, construct a forest plot for these groupings: Original Rx NDA, Pediatrics sNDA, Nasal Congestion sNDA (onset of action may be displayed in a forest plot as well, but since there are few trials, the tabular format is fine.) Show in these forest plots each study's respective dose arms with respect to placebo for treatment difference and confidence interval. Include sample sizes on the plot. Discuss uncertainty in estimated effects.

Question 18 (question 9 in meeting package):

Does FDA agree that the proposed list of 16 trials not previously reviewed by FDA for which at least partial datasets will be submitted is adequate to support filing and review of the partial Rx-to-OTC switch NDA submission?

FDA Response:

See FDA response to Question 7.

Question 20 (question 11 in meeting package):

Does FDA agree with Perrigo's proposal of specific files to be submitted for each trial-level data package in Module 5 of the NDA, as is detailed above?

FDA Response:

Your proposal to submit legacy data for trials dated from 1995 to 2012, noncompliant with CDISC data standards, is acceptable. However, we expect data from each of the studies to be submitted in the same format, using same dataset and variable names and variable characteristics (character vs numeric variables, same code lists/variable values across studies). Also include the appropriate documentation to describe the datasets, analogous to ADaM and SDTM documentation.

Question 21 (question 12 in meeting package):

Does FDA agree with the proposed pooling plan?

FDA Response:

Regarding data presentation in the Integrated Summary of Safety (ISS), including those not previously reviewed by FDA and those already reviewed by FDA, we agree with your display formats in Tables 13-18 of the Meeting Package. See also FDA response to Question 3; forest plots for certain adverse events.

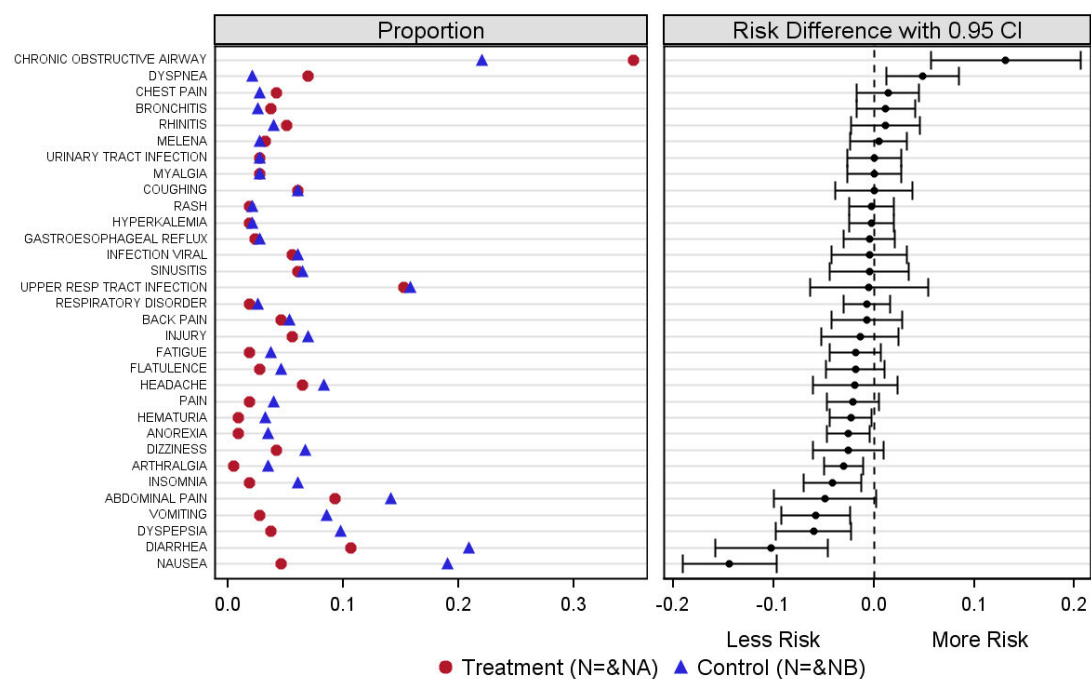
You may construct a forest plot for each of the pooling groups. Note that depending on study design (active or placebo control), you may need more than one forest plot for each pooling group.

Additional comments for pooling:

- *clarify how the 16 Nasonex trials not previously reviewed by FDA fit into your proposed pooling groups*
- *pool safety data by trial design*

We agree with your integration strategy as described in Table 19 in the Meeting Package. In the interest of communicating safety findings accurately and efficiently, use tables and graphs wherever appropriate.

An FDA/Industry/Academia Safety Graphics working group developed well-designed graphs to answer common safety questions. These can be found at <https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome>, including code, to create the graphs of interest. Consider the adverse event graph noted below for most frequent events in each pooling group:



3.0 Additional Comments

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

Because none of the criteria apply at this time to your application, you are exempt from these requirements/ Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h² and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*³. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁴

² <https://www.fda.gov/media/84223/download>

³ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

⁴ <https://www.fda.gov/media/85061/download>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NUSHIN F TODD
06/01/2020 03:20:45 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 142446

MEETING MINUTES

Perrigo R & D Company
US Agent for Perrigo Pharma International Designated Activity Company
Attention: Valerie Gallagher
Vice President Regulatory Affairs
515 Eastern Avenue
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg/spray.

We also refer to the teleconference between representatives of your firm and the FDA on March 14, 2019. The purpose of the meeting was to discuss the requirements for filing an NDA to support the partial Rx-to-OTC switch of Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sherry Stewart, Regulatory Project Manager at (301) 796-9618.

Sincerely,

{See appended electronic signature page}

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Teleconference Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: Thursday, March 14, 2019
9:00 AM to 10:00 AM

Meeting Location: Teleconference

Application Number: PIND 142446

Product Name: Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg/spray

Proposed Indication: Temporarily relieves these symptoms of hay fever or other upper respiratory allergies:

- Nasal congestion
- Runny nose
- Sneezing
- Itchy nose

Sponsor/Applicant Name: Perrigo R & D Company

Meeting Chair: Theresa Michele

Meeting Recorder: Sherry Stewart

FDA ATTENDEES

Division of Nonprescription Drug Products

Theresa Michele, MD, Director

Daniel Brum, PharmD, MBA, BCPS, RAC, Chief, Project Management Staff

Sherry Stewart, PharmD, Regulatory Project Manager

Jenny Kelty, MD, Medical Officer Team Leader

Teresa Podruchny, MD, Medical Officer

Jane Sohn, PhD, Pharmacology/Toxicology Team Leader

Chibueze Ihunnah, PhD, Pharmacology/Toxicology Reviewer

Amanda Pike-McCradden, MAA, Social Science Reviewer

Division of Pulmonary, Allergy, and Rheumatology Products

Stacy Chin, MD, Medical Officer Team Leader

Office of Clinical Pharmacology

Yunzhao Ren, PhD, Pharmacology Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products

Swapan De, PhD, Quality Assessment Lead

Elise Luong, PhD, Chemistry Reviewer

Haritha Mandula, PhD, Biopharmaceutics Team Leader

Suneet Shukla, PhD, Biopharmaceutics Reviewer

SPONSOR ATTENDEES

Perrigo:

Valerie Gallagher, Vice President, Regulatory Affairs

Derick Winkle, Sr. Manager, Regulatory Affairs

Bruce D. Johnson, PhD, Vice President Research & Development

Carlos Paz, Vice President, OTC Pharmaceuticals Research & Development

Isaiah Dahlman, Sr. Director Business Development

Ryan McLaughlin, Switch Lead, Business Development

(b) (4)

Merck Sharp Dohme:

Audrey Wong, Principal Scientist

Frank Mellina, Regulatory Affairs Liaison

1.0 BACKGROUND

Perrigo has acquired right of reference to NDA 20762, held by Merck Sharp Dohme (MSD), along with the right to pursue a prescription (Rx) to Over the Counter (OTC) switch program for Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg/spray for the temporary relief of these symptoms of hay fever or other upper respiratory allergies:

- nasal congestion
- runny nose
- sneezing
- itchy nose

Perrigo plans to submit a 505(b)(1) New Drug Application (NDA) to support the switch. NDA 20762, which will continue to be held by MSD will remain active to support the remaining Rx indications for prophylaxis of seasonal allergic rhinitis and treatment of nasal polyps.

The goal of the meeting is to discuss the requirements for filing the NDA to support the partial Rx-to-OTC switch of Nasonex (mometasone furoate) nasal spray, 50 mcg/spray.

The Sponsor's questions are in **bold** font; FDA's introductory comments and preliminary responses are *italicized*. Discussion that occurred at the meeting is in normal font.

Subsequent to receipt of the preliminary comments, Perrigo indicated that it wished to discuss the preliminary responses to questions 2 and 8.

2.0 DISCUSSION

Question 1

Perrigo proposes that no additional clinical efficacy and safety trials will be required for the approval of the Perrigo OTC NDA since there is extensive clinical testing and marketing experience with Rx Nasonex® Mometasone Furoate Nasal Spray, 50 mcg/spray (see Section 13.1.2 and Appendix 1 in Section 16.1), and Perrigo has acquired right of reference to Rx NDA 20762 held by Merck Sharp Dohme. Does the Agency agree with this approach?

FDA Preliminary Response

This approach appears reasonable. A summary of efficacy and safety data will be required in your NDA submission. See responses to Questions 3 and 4 regarding label comprehension and human factors studies.

Question 2

The safety assessment Perrigo proposes to submit in the OTC NDA will include a review of reported adverse events and serious adverse events from the mometasone furoate clinical trial database and post-marketing pharmacovigilance (PV) data as well as relevant data from the FDA Adverse Event Reporting System (FAERS), World Health Organization (WHO) VigiBase, and National Poison Data System pharmacovigilance databases for signal detection purposes, as well as a review of the relevant published medical scientific literature (see Section 13.1.2.2). Does the Agency agree that these safety data will be sufficient to support the Nasonex® Rx-to-OTC switch NDA? Can the Agency comment on the scope and preferred format of the Integrated Summary of Safety that should be provided in the NDA filing?

FDA Preliminary Response

The proposed data sources appear reasonable. The adequacy of the data to support the Rx-to-OTC switch NDA is a matter for review. We expect that the NDA will include any data or information that are relevant to the safety of this product to support the switch from Rx to OTC marketing status.

Submit the following information in Module 5 of the eCTD:

- 1) *An analysis of your product for the following areas of special interest:*
 - a. *Local nasal events*
 - i. *Bacterial rhinosinusitis*
 - ii. *Candidiasis*
 - iii. *Nasal septal perforation*
 - iv. *Epistaxis*
 - b. *Other*
 - i. *Ocular events*
 - ii. *Effects on the HPA axis*
 - iii. *Effects on growth*
 - iv. *Effects on bone metabolism*
 - v. *Effects on glucose metabolism*
 - vi. *Visual disturbances and central serous chorioretinopathy*
 - vii. *Relative potency of your steroid, unit to unit, as compared to the active ingredient in other OTC intranasal corticosteroid sprays*
- 2) *Clinical trial data: Table 5 of the briefing package indicates there have been multiple trials since the original NDA. The cutoff date for ongoing trials is 6 months before submission of the NDA. Include all studies exposing humans, adult and pediatric, to this NDA product, worldwide, for any indication, that have been conducted since the initial approval of the prescription NDA.*
 - a. *Include an overall table including all clinical trials conducted since approval as one of the summary tables. Include pediatric and adult studies, grouped separately. Include the name and number of the study (which should be the same trial number that is in the datasets), the condition studied (e.g., allergic rhinitis, nasal polyps), the dates of trial conduct and general trial information (e.g., numbers per drug group, number of adverse events, number of serious adverse events, and number of events leading to discontinuation).*
 - b. *In the case of ongoing controlled, blinded trial events, you may submit the events as blinded.*
 - c. *Include MedDRA coding preferred terms and system organ class along with verbatim terms for adverse events.*
 - d. *Organize adverse event data from clinical trials pooled by indication and groups, for example all placebo-controlled trials, all active controlled trials, active and placebo control, open-label studies, open-label extensions performed for seasonal allergic rhinitis, the same groups for trials performed for another indication (per indication). Identify frequently occurring events, serious events, and medically significant events.*
 - e. *Provide brief summaries of the trials. Include a discussion of how safety data were acquired during the trial and what safety parameters were collected. Identify*

- frequently occurring events, serious events, and medically significant events. Do not only reference previously submitted study reports; provide a link to each study report.*
- f. Include a hyperlink to the references in the text (e.g., such as references to summary tables or figures). Include a detailed table of contents with bookmarks that take the reader directly to the table or figure listed in the table of contents.*
 - g. In addition to summary tables that are customary for presentations in an ISS, provide datasets per trial and in an integrated dataset. All adverse events regardless of presumed causality, attribution, or level of severity are to be included in each dataset.*
 - h. In the per trial datasets and in the integrated dataset (ISS dataset), data elements are to include the following, the trial/study number, the site number, the unique subject identifier, the adverse event, whether the event led to discontinuation from the study, whether the event led to discontinuation of the drug, the level of severity of the event, whether it was a serious adverse event, whether the event required treatment, the day of the event relative to dosing, the dose, and the outcome (e.g. resolution, ongoing). Datasets are to be CDISC compliant with only one USUBJID number for each patient in the ADEX dataset, with one row per patient.*
 - i. Submit Case Report Forms for events leading to discontinuation and for serious events. As this is an OTC switch program, submit also Case Report Forms for significant medical events that may not meet a serious criterion but are medically significant regardless of presumed causality.*
- 3) For postmarketing data, the data cutoff date for events is 6 months before the date of the NDA submission. You may limit the search of the postmarketing datasets to the 10 most recent years. Tabulate, summarize, and provide analysis of postmarketing event data by the following:*
- Event year*
 - Subject demographics (age sub-groups, sex, race)*
 - Seriousness and outcome for each case*
 - Relationship to drug exposure*
 - Concomitant medications*
 - Underlying medical conditions*
 - Product-specific characteristics (dose, dosage strength, and duration of use)*
 - Misuse or abuse*
- 4) Provide a list of countries in which the NDA product is marketed as a nonprescription drug, include the date of approval in that country and include the dose of the drug marketed nonprescription in each country. Identify countries that require a pharmacist to dispense the product.*

Discussion: Perrigo inquired about the request for an analysis of relative potency of nasal steroid products. FDA said that the information (e.g., in table format) can guide Perrigo's proposed

labeling related to warnings. FDA recommended that Perrigo include an analysis of comparative potency at maximal dosing permitted in the product labels.

OTC Labeling

Question 3

On the DFL and CIL for the OTC product, Perrigo proposes to use FDA-approved labeling content which is already used on the intranasal corticosteroid products now marketed OTC, except where molecule- or formula-specific information is required and/or where specific changes are supported by MFNS clinical trials (see Section 13.2.1 and Section 13.2.2). Therefore, label comprehension studies should not be required to support approval of the Perrigo NDA to support the switch. Does the Agency agree with this approach?

FDA Preliminary Response

Your approach appears reasonable. Full review of labeling will occur during the NDA review. However, we note that several label statements from your proposed DFL are similar or identical in content to existing labeling, but are under different subheadings within the label (b) (4). We encourage you to mirror existing OTC labeling for nasal corticosteroids as closely as possible, in both content and placement, in order to reduce the need for consumer behavior testing. Ultimately, the labeling needs to be supported by the safety and efficacy findings of your product. Considering that the potency of mometasone furoate is higher than for triamcinolone acetonide, it may be more appropriate to model aspects of your DFL on currently marketed OTC intranasal fluticasone products. If you are proposing DFL changes from approved OTC language, then consumer testing may be necessary to determine if this impacts comprehension.

We have the following comments which will need to be addressed as you further develop the DFL:

(b) (4)

(b) (4)

You will also need to address and provide justification for why your proposed CIL

(b) (4)

(b) (4)

Question 4

On the DFL and CIL for the OTC product, Perrigo proposes to use FDA-approved labeling content which is already used on the intranasal corticosteroid products now being marketed OTC, except where molecule- or formula specific information is required and/or where specific changes are supported by MFNS clinical trials (see Section 13.2.1 and Section 13.2.2) and to use the identical approved Rx Nasonex spray pump/actuator approved in the Merck Sharp Dohme Rx NDA that is substantially the same as the spray pumps/actuators approved by FDA for use on the intranasal corticosteroids currently marketed OTC (see Section 13.2.3). Therefore, a human factors study should not be required to support approval of the Perrigo OTC NDA.

Does the Agency agree with this approach?

FDA Preliminary Response

We have insufficient information to determine if a human factors (HF) validation study would not be required to support approval of your product. We acknowledge your plans that your proposed DFL and CIL would be derived from the Rx Nasonex labeling and currently marketed OTC intranasal corticosteroid products. However, you have not submitted a comprehensive risk analysis. We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, and the potential negative clinical consequences of use errors and task failures.

We acknowledge that you have identified models of similar combination products in the OTC marketplace, and your use-related risk analysis should incorporate applicable information on known use-related problems with those products. You can obtain useful information from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications (see draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development). Additionally, since models of similar combination products exist in the OTC marketplace, it may

be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparators, for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Based on the above information and data, determine whether you need to submit the results of a HF validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. If you determine that a HF validation study does not need to be submitted for your product, submit your risk analysis, comparative analyses, and justification for not submitting the HF validation study to FDA for review under the IND. We will notify you if we concur with your determination.

Submit the requested information to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on HF procedures to follow can be found in:
Applying Human Factors and Usability Engineering to Medical Devices, available online at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to HF for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications can be found online at
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621902.pdf>

Question 5

Perrigo proposes to use the trade name “Nasonex® 24HR Allergy” for the OTC product (see Section 2 above) and believes that a proprietary name review will not be required since “Nasonex” has been previously evaluated and “24HR Allergy” follows a naming convention used for one of the OTC INS products (i.e., Nasacort 24HR Allergy).

Does the Agency agree with this approach (see Section 13.2.5)?

FDA Preliminary Response

No, we do not agree. A Request for Proprietary Name Review will be necessary if you intend to market your product under a proprietary name. We recommend you submit your Request for Proprietary Name Review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft guidance for industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Discussion: Perrigo acknowledged that a Request for Proprietary Name Review will be necessary, and they will initiate the process in the near future.

Bioequivalence

Question 6

Perrigo proposes that no additional bioequivalence studies or characterization testing of the bottles, pumps, actuators, or bottle/pump/actuator combinations will be required to support approval of the Perrigo OTC NDA since Perrigo will be using the exact same qualitative/quantitative formula, manufacturing process, and bottles/pumps/actuators and suppliers approved by FDA for use in the Rx NDA 20762 held by Merck Sharp Dohme. The 19 mL bottle and related pump/actuator approved in the Merck Sharp Dohme Rx NDA will be used for the OTC 120 spray count and the OTC 60 spray count.

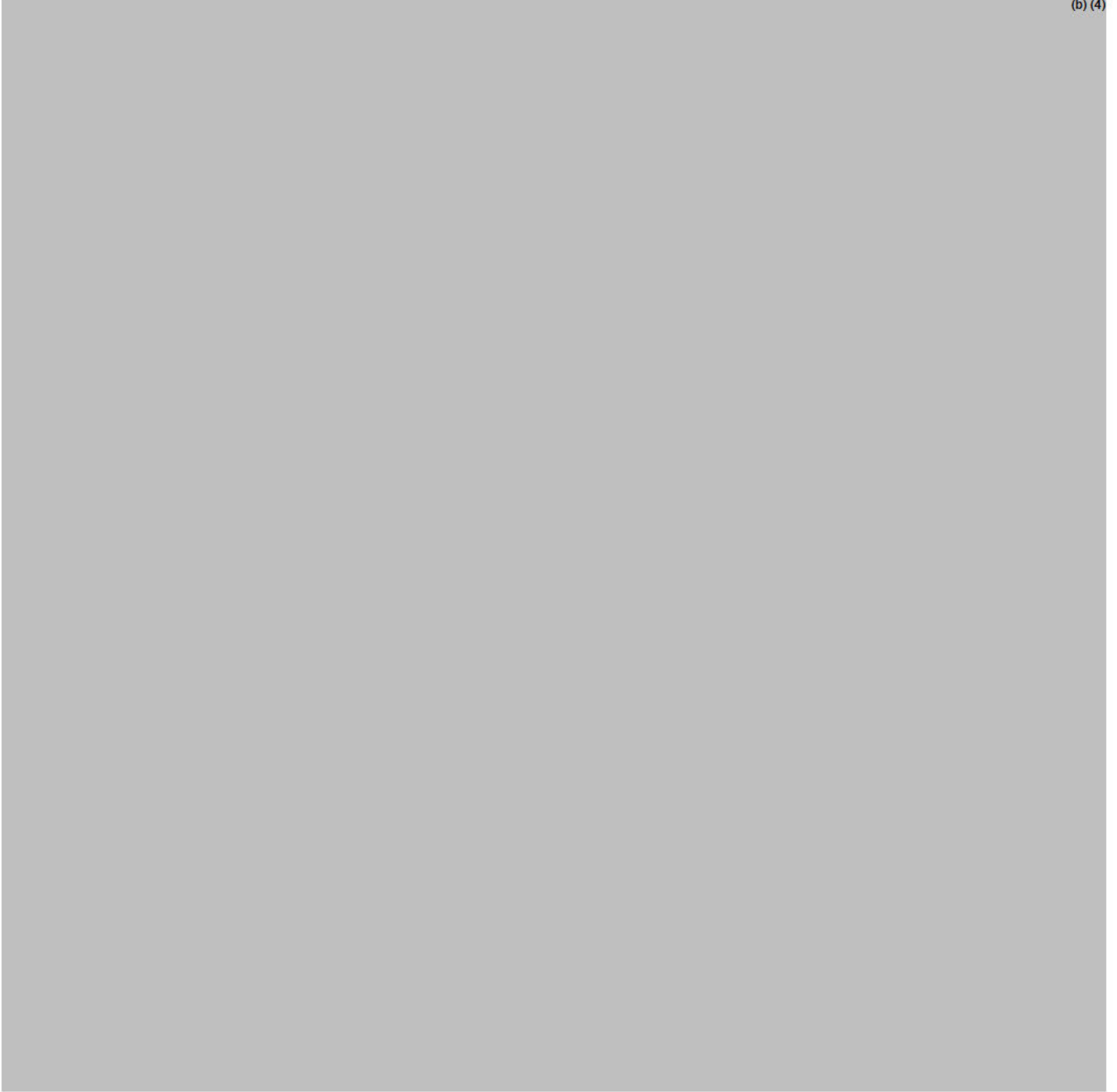
Further, waivers from bioequivalence studies of the Rx formula for OTC use and characterization testing of the Rx bottles/pumps/actuators for OTC use will be submitted in the Perrigo OTC NDA. Perrigo proposes that finished product release testing data, which includes spray pattern, droplet size distribution, and particle size measurement data are adequate to support the waiver requests. This is the same approach used by Merck Sharp Dohme when manufacturing was moved from (b) (4) site to (b) (4) site and approved by FDA (Ref. NDA 20762, Post-Approval Sequence 0042, Approved by FDA 04/13/2012). Does the Agency agree with this proposal (see Section 13.2.3 and Section 13.4)?

FDA Preliminary Response

Your proposal to submit comparative finished product release testing data to support the equivalence of the approved Merck Rx drug product to the Perrigo proposed OTC drug product for the waiver of bioequivalence studies appears reasonable. However, approval of the biowaiver is a review issue and your request will be assessed at the time of the NDA submission based on the totality of the provided data.

Chemistry, Manufacturing, Controls

(b) (4)



2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Regulatory

Question 9

Perrigo proposes that Merck Sharp Dohme would continue marketing prescription Nasonex® under NDA 20762 for the two remaining indications, those related to prophylaxis of SAR and treatment of nasal polyps, while Perrigo would simultaneously market the OTC product under the Perrigo OTC NDA for the OTC INS class indication of:

Temporarily relieves these symptoms of hay fever or other upper respiratory allergies:

- **Nasal congestion**
- **Runny nose**
- **Sneezing**
- **Itchy nose**

Does the FDA agree with this approach (see Section 13.6)?

FDA Preliminary Response

Your approach appears reasonable. However, the final determination as to which indications are appropriate for the OTC use of Nasonex will be determined during review of your application and based upon the supporting data.

We recommend that MSD submit a labeling supplement to remove the OTC indications from the Rx labeling at the same time as Perrigo submits an OTC NDA. The labeling supplement approval would be contingent on the OTC NDA approval.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

5.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts used or distributed at the teleconference.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA M MICHELE
04/12/2019 08:13:58 AM