CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202049Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 28, 2020
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 202049
Product Name and Strength:	Bronchitol (mannitol) inhalation powder, 40 mg
Applicant/Sponsor Name:	Chiesi
OSE RCM #:	2018-2790-1 & 2018-2791-1
DMEPA Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling, and the Healthcare Practitioner (HCP) Instructions for Use (IFU) received on October 26, 2020 for Bronchitol. Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels, carton labeling, and the HCP IFU for Bronchitol (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Barlow, M. HF Study Results & Label and Labeling Review for Bronchitol (NDA 202049). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 22. RCM No.: 2018-2790 & 2018-2791.

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/s/

MATTHEW J BARLOW
10/28/2020 10:23:12 AM

MILLIE B SHAH
10/28/2020 12:19:59 PM

NDA 202049
Mannitol Inhalation Powder
Chiesi USA, Inc.

Dear Dr. Gunto:

We are currently reviewing your NDA submitted on May 1, 2020. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed. Submit revised labeling incorporating the changes noted in the attached document.

In addition, we have the following comments:

A. Healthcare Practitioner Instructions for Use (HCP-IFU)

1. We note that in your submission dated October 20, 2020, the HCP-IFU is in black and white. Amend the HCP-IFU such that the color scheme is the same as when submitted on May 1, 2020.

2. Based on the use errors and subjective feedback related to the tasks of a) waiting 5-15 minutes after instructing the patient to use an inhaled short-acting beta agonist (in Step B) and b) waiting 1 minute and recording new SpO2 and/or FEV1 values (in Steps C through F), we recommend revising the color of the clock images in Steps B-F to increase the prominence of the wait time, as some participants felt that this important information blended in with the rest of the tasks ("other purple information in the QRG") and was easily overlooked.

3. Based on the use errors and subjective feedback related to the task of wait 15 minutes, then monitor SpO2 and FEV1 to confirm recovery to baseline, we recommend adding the following statement to the red "STOP" box" to emphasize the BTT should not be continued or restarted: "DO NOT continue the BTT."

B. General Comments (Container labels & Carton Labeling)

4. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. Consider revising your expiration date to one of the aforementioned formats.

C. Blister Pack labels for the BTT Blister Pack Only

5. Based on the use errors and subjective feedback related to task of administering X number of capsules, we recommend revising the BTT Blister Pack to include boxes around the amount of capsules needed for each of the respective steps (e.g., a box around 1 capsule for Step C, a box around 2 capsules for Step D and so on) and to label each box with the corresponding step, as this may help improve the users' ability to track the amount of capsules that should be administered to the patient for each step of the BTT.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes to the NDA by close of business on October 26, 2020. In addition, please email me a courtesy copy of the revised label.

If you have any questions, please contact Linh Do via email at Ngoc Linh.Do@fda.hhs.gov or phone at 301-348-1896.

NDA 202049
Mannitol Inhalation Powder
Chiesi USA, Inc.

Initiated by: Khalid Puthawala/Bob Lim/ J. Lee	10/22/20
M. Barlow/M. Shah	10/22/20
J. Lee	10/21/20
Cleared: L. Jafari	10/22/20
Finalized: L. Do	10/22/20

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/s/

NGOC - LINH DO
10/22/2020 02:33:06 PM

LABEL AND LABELING AND HUMAN FACTORS VALIDATION STUDY RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 22, 2020
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 202049
Product Name, Dosage Form, and Strength:	Bronchitol (mannitol) inhalation powder, 40 mg per capsule
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Chiesi USA Inc.
FDA Received Date:	May 01, 2020
OSE RCM #:	2018-2790 and 2018-2791
DMEPA Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting):	Jason Flint, MBA, PMP
DMEPA Associate Director of Nomenclature & Labeling:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 202049 for Bronchitol (mannitol) inhalation powder. This is a combination product with a proposed capsule based inhaler constituent part that is intended for the management of cystic fibrosis to improve pulmonary function in patients 18 years and older in conjunction with standard therapies.

1.1 PRODUCT DESCRIPTION

The Bronchitol (mannitol) inhalation powder product user interface consists of an inhaler device and mannitol 40 mg capsules; the contents of the capsules are orally inhaled using the inhaler device. Bronchitol is intended for administration by patients and healthcare providers (HCPs) in the home or healthcare setting.

Prior to prescribing Bronchitol, HCPs must administer the Bronchitol Tolerance Test (BTT) to identify and exclude patients who are hyperresponsive to inhaled mannitol[a]. The BTT requires the HCP to monitor oxygen saturation (SpO2), perform spirometry (FEV1), and to calculate reference values while periodically administering Bronchitol in increasing amounts (e.g., 1 capsule, 2 capsules, 3 capsules, and then 4 capsules).

1.2 REGULATORY HISTORY

We previously reviewed two HF validation study result reports and the proposed labeling during the last submission of NDA 202049[b]. Within our review, we found the HF study results for the patient and caregiver administration of the proposed product user interface acceptable and provided some labeling recommendations, which the Applicant implemented. However, we found the HF study results for the HCP administration of the BTT did not support safe and effective use of the proposed product and recommended the Applicant further revise their proposed product user interface and conduct another HF validation study with the updated BTT user interface. On June 19, 2019, the Applicant received a Complete Response (CR) letter from the Agency due to these deficiencies[c]. On July 23, 2019, the Applicant submitted a HF validation study protocol for the Agency's review, which we provided comments to on September 11, 2019[d]. On May 1, 2020, the Applicant resubmitted their NDA with results from another HF validation study for their BTT user interface, which is the subject of this review.

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[a] Inhaled mannitol, the active ingredient in Bronchitol, may cause severe acute bronchospasm in hyperresponsive patients.

[b] Whaley, E. HF Study Report and Labels and Labeling Review for Bronchitol (NDA 202049). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUNE 18. RCM No.: 2018-2791; 2018-2790.

[c] Do, N-L. Complete Response Letter for Bronchitol (NDA 202049). Silver Spring (MD): FDA, CDER, OSE, DPARP (US); 2019 JUNE 19.

[d] Whaley, E. HF Protocol Review for Bronchitol (IND 070277). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUNE 18. RCM No.: 2019-1564.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The HF validation study included a total of 45 study participants:

- untrained HCPs (n=15) consisting of physicians (i.e., MDs, DOs) and Nurse Practitioners (NPs).
- untrained Respiratory Therapists (RTs) (n=15)
- trained HCPs (n=15) consisting of physicians and RTs

Each participant participated in a simulated use session, simulating performing the BTT with a patient actor. Prior to the simulated use session, each participant was given, on average, 15 minutes to acclimate themselves to the product user interface with the option to review the BTT Quick Reference Guide (QRG), the fact sheet, an instructional video, Prescribing Information (PI), medication information phone line, and a patient chart, similar to what they may see in real-world practice. During the simulated use session, each participant had access to the following materials: simulated clinic office, BTT user interface, spirometer, pulse oximeter, inhaled short-acting beta-agonist bronchodilator, spacers, nose clips, timer, calculator, paper, pen, hand sanitizer, stethoscope, blood pressure cuff, and medications and equipment to manage acute bronchospasm if it were to occur (e.g. bronchodilator, crash cart).

Table 2 below provides a summary of our analyses of use errors/close calls/use difficulties with critical tasks that follow the naturalistic progression of use tasks for the proposed BTT product user interface. Table 3 below provides a summary of our analyses of use errors/close calls/use difficulties with critical tasks related to the inhaler use tasks for the proposed BTT product user interface.

Table 2: HF Study Results for the BTT Tasks

Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Measure baseline SpO2 value [C]	Use Difficulties (n=2; 1 Untrained HCP; 1 Trained HCP) Use Errors (n=3; 1 Untrained HCP, 2 Untrained RTs)	<u>Use Difficulties:</u> -2 participants almost administered the short-acting beta-agonist prior to measuring the baseline values, but then indicated they would measure the baseline values first. This was due to the wait time of 5-15 minutes after having the patient administer the short-acting beta-agonist <u>Use Errors:</u> -3 participants indicated measuring baseline spO2 after instructing the patient actor to use a short-acting beta-agonist.	<u>Use Difficulties:</u> - *Time required for BTT requires change in clinical practice* – HCPs may not have time to wait for extended periods in regular clinical practice and are inclined to shorten wait times or run tasks in parallel to accommodate. - *Study artifact: full variance in clinical practice not represented* – In some facilities, baselines would likely be taken prior to the patient meeting the clinical team member who would perform the BTT, resulting in HCPs expecting to be able to rely on previously recorded values. <u>Use Errors</u>: - *Use of QRG during patient evaluation not consistent with clinical practice – Reliance on QRG inconsistent with*	No mitigation required. If the bronchodilator is administered before the baseline SpO2 and FEV1 values are obtained, the 'baseline' value will be higher than expected and will result in calculation of an 'inflated' STOP value. In this scenario, a decrease in either SpO2 and FEV1 after any dose of Bronchitol will be compared to an 'inflated' STOP value and the patient will be more likely to fail the BTT. This would not introduce patient harm. However, the Applicant proposes to revise the BTT QRG by adding a header to Step A "Pre-assessment calculations," and updating from "baseline" to "Today's baseline."	We note the potential harm associated with the risk of administering a short-acting beta-agonist prior to measuring baseline SpO2 is that non-hyperresponsive patients may appear to not qualify for Bronchitol therapy (i.e., a patient who otherwise would qualify for Bronchitol therapy would appear to fail the BTT). We discussed the Applicant's analysis of the residual risk with our clinical colleagues, and they did not have safety concerns from a clinical perspective, as if the patient fails the BTT, they may be eligible for another tolerance test at a later time. We note the Applicant's proposed revision of specifying baseline as "Today's" baseline and revising the header as "Pre-assessment calculations". Based on our review of the QRG, we also note that there is also a statement "Start here and record values below." with a corresponding arrow pointing to Step A. Based on our heuristic review of the QRG, the subjective feedback

			clinical practice for many HCPs. The BTT requires users to rely on and carefully follow the QRG as a notetaking tool, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice. - *Negative transfer – Similar treatments (e.g. inhaled tobramycin) require administration of bronchodilator*. HCPs may expect to administer the inhaled bronchodilator as a first step as they assume it would help open up the patient's airways so they would better tolerate the BTT (in clinical practice, pulmonary function testing is often performed post-bronchodilator). - *Instructional materials do not sufficiently emphasize importance of bronchodilator sequence* – The QRG and video do not indicate that administering a bronchodilator in		and root cause analysis provided, the implementation of additional labeling mitigations are not likely to further reduce the residual risks. Therefore, we find the residual risk minimized to the extent possible, and we have no further recommendations to address this use error at this time.

			the incorrect sequence (e.g. if done before measuring baseline values or after administering Bronchitol capsules) would invalidate measured values and adversely affect the BTT result. This lack of emphasis may result in HCPs focusing primarily on the Bronchitol dosing steps C, D, E, and F over Steps A and B. - *QRG does not sufficiently emphasize importance of bronchodilator sequence* – The QRG does not indicate that administering a bronchodilator in the incorrect sequence (e.g. if done before measuring baseline values or after administering capsules) would invalidate measured values and the therefore the BTT. - *Study artifact: simulated environment and patient* – Since participants were not in their clinical setting and seeing familiar patients go through their office workflow,		

			they may not have considered all the clinical touchpoints they would typically perform before, during, and after seeing the patient. - *Study artifact: simulation exercise* – If the participant had administered the bronchodilator first in their clinic, they would likely have stopped the BTT, however, the nature of the simulation exercise made the HCP feel the need to complete the BTT for the purposes of the simulation, rather than stopping prematurely based on clinical judgment.		
Measure baseline FEV1 value. [C]	Use Difficulties (n=3; 1 Untrained HCP, 1 Trained HCP, 1 Untrained RT) Use Errors (n=5; 1 Untrained HCP, 4 Untrained RTs)	<u>Use Difficulties:</u> -1 participant initially recorded the baseline FEV1 value as a STOP value. -2 participants almost administered the beta-agonist before measuring baseline FEV1. <u>Use Errors:</u> -4 participants indicated measuring baseline FEV1 after instructing	<u>Use Difficulties:</u> - *Study artifact: communication of values* – Values were transmitted orally to participants following conduct of each test, which may have resulted in confusion. In clinical practice, HCPs would read measured values from the test tool directly.	- Acceptance of the initial measured baseline value as the STOP value, rather than calculating a STOP value would increase the likelihood of the patient failing the BTT. This would not introduce patient harm. - No mitigation required.	We note the potential harm associated with the risk of administering a short-acting beta-agonist prior to measuring baseline FEV1 value, and the risk of recording the baseline FEV1 value as the STOP value is that non-hyperresponsive patients may appear to not qualify for Bronchitol therapy (i.e., a patient who otherwise would qualify for Bronchitol therapy would appear to fail the BTT). We acknowledge that several of the use issues

		the patient actor to use a short-acting beta-agonist -1 participant did not measure a baseline FEV1 but relied on an old percent predicted value from the patient chart.	- *QRG does not sufficiently differentiate baseline and STOP values* – Location of baseline and STOP values are right next to each other and marked as blanks with purple lines underneath which may result in confusion over where to record a value. - *Time required for BTT requires change in clinical practice* – HCPs may not have time to wait for extended periods in regular clinical practice and are inclined to shorten wait times or run tasks in parallel to accommodate. -*Study artifact: full variance in clinical practice not represented* – In some facilities, baselines would likely be taken prior to the patient meeting the clinical team member who would perform the BTT, resulting in HCPs expecting to be able to rely on previously recorded values. <u>Use Errors:</u>	Clinical environment set up to ensure baseline values will be available, ensuring this step would be completed in clinical practice. - No mitigation required. If the bronchodilator is administered before the baseline SpO2 and FEV1 values are obtained, the 'baseline' value will be higher than expected and will result in calculation of an 'inflated' STOP value. In this scenario, a decrease in either SpO2 or FEV1 after any dose of Bronchitol will be compared to an 'inflated' STOP value and the patient will be more likely to fail the BTT. This would not introduce patient harm.	involved the root cause of a study artifact related to the procedures of the participants' actual clinical practice. We discussed the Applicant's analysis of the residual risk with our clinical colleagues, and they did not have safety concerns from a clinical perspective, as if the patient fails the BTT, they may be eligible for another tolerance test at a later time. We note the Applicant's proposed revision of specifying baseline as "Today's" baseline and revising the header as "Pre-assessment calculations". Based on our review of the QRG, we also note that there is also a statement "Start here and record values below." with a corresponding arrow pointing to Step A. Based on our heuristic review of the QRG, the subjective feedback and root cause analysis provided, the implementation of additional labeling mitigations are not likely to further reduce the residual risks. Therefore, we find the residual risk minimized to the extent possible and we have no further recommendations to address this use error at this time.

			- *Study artifact: full variance in clinical practice not represented* – In some facilities, baselines would likely be taken prior to the patient meeting the clinical team member who would perform the BTT, resulting in HCPs expecting to be able to rely on previously recorded values. - *QRG does not sufficiently emphasize importance of bronchodilator sequence* – The QRG does not indicate that administering a bronchodilator in the incorrect sequence (e.g. if done before measuring baseline values or after administering capsules) would invalidate measured values and the therefore the BTT. - *Use of QRG during patient evaluation not consistent with clinical practice* – Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs. Lack of familiarity with the BTT requires users to rely		

			on and carefully follow the QRG, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice. - *Negative transfer* – Similar treatments (e.g. inhaled tobramycin) require administration of bronchodilator. HCPs may expect to administer the inhaled bronchodilator as a first step as they assume it would help open up the patient's airways so they would better tolerate the BTT (in clinical practice, pulmonary function testing is often performed post-bronchodilator). - *Instructional materials do not sufficiently emphasize importance of bronchodilator sequence* – The QRG and video do not indicate that administering a bronchodilator in the incorrect sequence (e.g. if done before measuring		

			baseline values or after administering capsules) would invalidate measured values and therefore the BTT. This lack of emphasis may result in HCPs focusing more on the Bronchitol steps over Steps A and B. -*Study artifact: simulation exercise* – If the participant had administered the bronchodilator first in their clinic, they would likely have stopped the BTT, however, the nature of the simulation exercise made the HCP feel the need to complete the BTT for the purposes of the simulation, rather than stopping prematurely based on clinical judgment.		
Calculate Stop Values [C]	Use Difficulties (n=6; 3 Untrained HCPs, 1 Trained HCP, 2 Untrained RTs) Use Errors (n=5; 1 Trained HCP, 4 Untrained RTs)	<u>Use Difficulties:</u> -1 participant initially confused the baseline SpO2 with the calculated 90-STOP value. -3 participants initially calculated or thought to calculate 90% of FEV1 as the 80- STOP value but then recalculated.	<u>Use Difficulties:</u> - *Use of QRG during patient evaluation not consistent with clinical practice* – Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs. Lack of familiarity with the BTT requires users to rely on	No mitigation required. Acceptance of the initial measured baseline value as the STOP value, rather than calculating a STOP value could result in a patient failing the BTT when they might not have had the STOP value been calculated correctly.	We note the potential harm associated with the risk of confusing baseline values for the STOP values is that non-hyperresponsive patients may appear to not qualify for Bronchitol therapy (i.e., a patient who otherwise would qualify for Bronchitol therapy would appear to fail the BTT). Additionally, we note the potential harm

		-1 participant initially miscalculated the SpO2 90-STOP value but re-calculated it correctly. -1 participant did not initially calculate STOP values. <u>Use Errors:</u> -1 participant did not calculate the STOP values and instead referenced the baseline values for the BTT. -2 participants miscalculated the spirometry 80-STOP value to be higher than it should have been as they had recorded the baseline FEV1 value to be 2.54 L instead of 2.45L. -3 participants did not calculate and/or record one or both STOP values.	and carefully follow the QRG, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice. -*Insufficient link between STOP value and clinical measurement* – The QRG's notation for the STOP values, 90-STOP and 80-STOP, does not sufficiently link with the corresponding clinical measurement of SpO2 and FEV1, which may cause users to confuse the two values. The QRG and instructional video do not sufficiently tie 80% to FEV1 and 90% to SpO2 or explain why the STOP thresholds are unique for each value, which may cause users to confuse the two values. -*Departure from regular clinical practice* – HCPs do not typically calculate STOP values in clinical practice which may result in confusion associated with using them during the BTT.	This would not introduce patient harm. No mitigation required. Values would be recorded directly from the test equipment in clinical practice and would not be subject to error due to mishearing moderator values. Although respiratory therapists or other HCPs may perform the BTT and obtain a result for the individual patient (i.e. pass or fail), the ultimate decision to prescribe Bronchitol would be the responsibility of the CF patient's primary physician after they reviewed all data collected during the BTT. Thus, there is an important degree of redundancy in interpretation of the results of the BTT which mitigates the residual risk. Use errors resulting in incorrect calculation of the STOP values were associated with a root cause analysis finding that transcription and/or calculation errors in the conduct of the BTT represented a departure from	associated with not performing the STOP value calculation or miscalculating could lead to an unindicated patient being prescribed the medication which could lead to bronchospasm, hypoxia, and/or pulmonary compromise. We acknowledge the current mitigations in place, including the blank spaces labeled for the STOP value placement and emphasis on the STOP value placeholders with highlighted boxes. Additionally, we acknowledge the Applicant's revisions to Step A, including adding the tit e "Pre-assessment Calculations" to the top of the Step A box and adding "Today's" baseline to further clarify the meaning of baseline. We discussed the Applicant's analysis of the residual risk with our clinical colleagues, and based on our heuristic review of the QRG, the subjective feedback and root cause analysis provided, we determined that the implementation of additional labeling mitigations are not likely to further reduce the residual risks. Therefore, we find the residual risk minimized to the extent possible and we have no further recommendations to address this use error at this time.

			-*Paper QRG introduces transcription error* – The QRG is a paper-based tool that requires HCPs to accurately input measured values and multipliers into a separate calculating tool and record those values in the QRG, introducing the possibility of transcription and/or calculation error. -*Term "Baseline" insufficiently defined and open to interpretation* – The QRG does not sufficiently specify the need to use a same day baseline value in order to assess a patient's progress through the BTT. This may result in HCPs relying on historical values to determine STOP values. <u>Use Errors:</u> -*Study artifact: communication of values* – Values were transmitted orally to participants following conduct of each test, which may have resulted in confusion. In clinical	regular clinical practice and a lack of familiarity with the QRG. It is not unusual for a new clinical procedure protocol to require experience in order for an HCP to become fully comfortable and proficient. Accordingly, Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation. Although not required, the proposed QRG includes revisions to the box for Step A to add further emphasis for the reader. Due to the narrow scope of these modifications which have been designed to address participant reported root causes identified in the study, it is anticipated that no new risks have been introduced and further validation of the product user interface is not required.	

			practice, HCPs would read measured values from the test tool directly and this may not be an issue. -*Paper QRG introduces transcription error* – The QRG is a paper-based tool and requires HCPs to accurately read and then record measured values from separate measurement devices, introducing the possibility of transcription error. -*QRG does not sufficiently emphasize need to record STOP values* – The box for calculated STOP values was not sufficiently highlighted in the QRG, and the text does not sufficiently emphasize the importance of calculating the values to perform the BTT, which may result in HCPs skipping part or all of this step. -I*nstructional video does not sufficiently emphasize STOP value calculations* – The need to perform calculations is not sufficiently highlighted and		

			STOP value calculations are not actually performed in the instructional video – as the values are already inserted in the QRG. Therefore, HCPs relying on the video to support use may not remember to do this step. -*Departure from regular clinical practice* – HCPs do not typically calculate STOP values in clinical practice and may therefore not understand the relevance for the BTT. -*Use of QRG during patient evaluation not consistent with clinical practice* – Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs. Lack of familiarity with the BTT requires users to rely on and carefully follow the QRG, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice. -*Format of QRG* – The paper-based QRG does not		

			restrict users from continuing if they skip a step in the process. Some HCPs might be accustomed to computer-based programs that provide calculation decision support in their clinical practice. -*QRG does not sufficiently emphasize need to record STOP values* – The box for calculated STOP values was not sufficiently highlighted in the QRG, and the text does not sufficiently emphasize the importance of calculating the values to perform the BTT, which may result in HCPs skipping part or all of this step.		
Instruct Patient to Use an Inhaled Short-Acting Beta-Agonist. Wait 5-15 minutes. [C]	Use Error (n=1; 1 Untrained RT)	-1 participant did not indicate waiting 5-15 minutes after administering Bronchitol. Thought that the wait time here could be further emphasized.	*Study artifact: simulated environment* – The study environment contributes to participant nervousness, resulting in deviation from regular practice during the use assessment. -*QRG does not sufficiently emphasize the need to wai*t – The clock image for waiting is not sufficiently differentiated	No mitigation required. No pattern of performance issues observed.	We note the potential harm associated with the risk of not waiting 5-15 minutes after administering the beta-agonist is that airways are not fully open which could lead to bronchospasm, hypoxia, and pulmonary compromise. We acknowledge that one participant stated they normally wait 10 minutes on average with patients in their practice, but the participant did suggest further emphasizing the wait time on the

			from other purple information in the QRG. Additionally, this step does not require users to fill in a blank or check something off, like other QRG steps, which may cause some users to skip waiting.		QRG. Based on the subjective feedback, root cause analysis, and our review of the QRG, we note that the color of the clock image displaying 5-15 minutes can be revised for increased prominence. See Section 5.2 for our recommendation.
Wait 1 minute. Record new SpO2. [C]	Use Difficulties (n=3; 1 Untrained HCP, 2 Untrained RT) Use Errors (n=5; 1 Untrained HCP, 2 Untrained RTs, 2 Trained HCPs)	<u>Use Difficulties:</u> -2 participants almost forgot to wait 1 minute. -1 participant almost forgot to record the new SpO2 after waiting 1 minute. <u>Use Errors:</u> -4 participants did not wait 1 minute before recording the new SpO2. -1 participant did not record the new SpO2 after waiting 1 minute.	-*QRG does not sufficiently emphasize the need to wait* – The clock image for waiting 1 minute is not sufficiently differentiated from other purple information in the QRG. Additionally, this step does not require users to fill in a blank or check something off, like other QRG steps, which may cause some users to skip waiting for 1 minute (HU01, HU10, RU03, RU09, HT03-RT, HT06-MD). -*Frequency of BTT waiting periods* – Since the BTT requires many distinct waiting periods, users may become impatient or pay less attention to waiting periods as the BTT progresses (HU10). -*Format of QRG* – The paper-based QRG does not	No mitigation required. While not waiting 1 minute before measuring the new SpO2 may lead to continuing the BTT longer than anticipated, there is no unique harm associated with skipping this step, as a hyperresponsive patient would be identified in a subsequent step.	According to the URRA, there is no potential harm associated with the risk of not waiting 1 minute prior to recording the new SpO2, as a hyperresponsive patient would be identified in subsequent steps. We acknowledge the Applicant's current mitigation strategy of the purple highlighted clock with "Wait 1 minute" in the QRG. However, based on the subjective feedback, root cause analysis, and our review of the QRG, we note that the color of the clock image displaying 1 minute can be revised for increased prominence. See Section 5.2 for our recommendation.

			restrict users from continuing if they skip a step in the process, opposed to computer-based programs some users may be familiar with and reliant on to complete testing with patients in their clinical practice (RU03). -*Study artifact: simulated environment* – The study environment contributes to participant nervousness, resulting in deviation from regular practice during the use assessment (RU09). -*Competing focus between inhaler and BTT steps* – Since the BTT requires HCPs to instruct the patient on how to use the inhaler as well as requires following the stepwise BTT steps, some HCPs may become focused on one over the other (HT03-RT). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol		

			required to conduct the BTT, users may be inclined to base their decisions on patient symptoms rather than oxygen saturation and FEV1 values while administering the BTT, as is more common in their current practice (RU10). -Competing focus between using the QRG and assessing the patient – Since the BTT requires a unique approach following the QRG as well as constant monitoring of the patient's response to the medication, some HCPs may focus their attention on the patient and subsequently omit steps (RU10). -*Format of QRG* – The paper-based QRG does not restrict users from continuing if they skip a step in the process, opposed to computer-based programs some users may be familiar with and reliant on to complete testing with patients in their clinical practice (RU15).		

Is new SpO2 more than 90-STOP? (If yes, continue to Step D. If no, stop and do not prescribe BRONCHITOL). [C]	Use Difficulties (n=4; 2 Untrained HCPs, 2 Untrained RTs) Use Errors (n=3; 3 Untrained RTs) 1 Participant Did Not Complete (DNC) this task (Untrained RT)	<u>Use Difficulties:</u> -2 participants made a calculation/almost made a calculation with the new SpO2 but caught themselves and proceeded. -2 participants multiplied the new SpO2 by 0.9 but decided to proceed. <u>Use Errors:</u> -3 participants compared the new SpO2 to the baseline SpO2. 2 of the participants stopped the BTT. 1 of the participants continued the BTT. 1 participant DNC the task due to not recording the SpO2 in the previous task.	-*Insufficient differentiation of QRG Step A3* – The QRG does not sufficiently call out that the calculation associated with the STOP values on Step A3 is unique and does not need to be repeated in the BTT. Additionally, the QRG's notation for the 90-STOP and 80-STOP values is used throughout the BTT and may cause users to recall the calculation they had made in Step A3 in later BTT steps (HU02, HU03, RU05, RU09). -*Repetition of STOP values throughout the BTT* – The 90-STOP and 80-STOP values are used throughout the BTT and may cause users to recall the initial calculation they made on step A3, leading some to make unnecessary calculations later in the BTT (HU02, HU03). -*QRG does not sufficiently emphasize need to record STOP values* – The box for calculated STOP values was not sufficiently	No mitigation required. Calculating a more conservative SpO2 or comparing the new SpO2 to the baseline value could result in an increased likelihood of the patient failing the BTT when they might not have if the correct value comparison had been performed. This would not introduce patient harm. No mitigation required. Making an incorrect comparison between the new SpO2 and baseline value as the STOP value may lead to stopping the BTT prematurely. There is no harm associated.	According to the URRA, there is no potential harm associated with the risk of not comparing the correct values/moving on to the next step as either a hyperresponsive patient would be identified in subsequent steps, or a non-hyperresponsive patient would not prescribed Bronchitol. We acknowledge the current mitigation strategies in place, including a box for the newly taken SpO2 value, a separate box with the question for the HCP "Is the new SpO2 more than 90-STOP," and an algorithm format for the HCP directing them to continue with the test or stop depending on the result. We discussed the Applicant's analysis of the residual risk with our clinical colleagues, and based on our heuristic review of the QRG, the subjective feedback and root cause analysis provided, we determined that the implementation of additional labeling mitigations are not likely to further reduce the residual risks. Therefore, we find the residual risk minimized to the extent possible and we have no further recommendations to address this use error at this time.

			highlighted in the QRG, and the text does not sufficiently emphasize the importance of calculating the values to perform the BTT, which may result in HCPs skipping part or all of this step (RU03). -*Study artifact: simulated environment* – The study environment contributes to participant nervousness, resulting in deviation from regular practice during the use assessment (RU09). -*Study artifact: simulated workstation time* – Although participants were given 15 minutes to use as they chose, this length of time and the arrangement and/or setup of the workstation setup may not have been aligned with or conducive to the way some would expect to spend their time before administering the BTT with a patient for the first time (RU09). -*Insufficient emphasis on STOP value* – The QRG		

			does not provide a clear link for users to compare their newly recorded value to the appropriate STOP value (RU12, RU16). -*Insufficient emphasis on stop values in instructional video* – The instructional video does not include a sufficient description of and emphasis on the importance and use of the STOP values throughout the BTT. Subsequently, some users who rely strictly on this video to prepare for the BTT with a patient may not remember this step (RU16).		
Following steps 3-8 located on the right, instruct patient to inhale contents of 2 capsules, one capsule at a time.	Use Difficulties (n=3; 1 Untrained HCP, 2 Untrained RTs) Use Errors (n=3; 1 Untrained HCP, 2 Untrained RTs)	<u>Use Difficulties:</u> -2 participants almost forgot to instruct the patient actor to inhale the contents of the second capsule. -1 participant instructed the patient actor to inhale the contents of 1 capsule, measured SpO2 and FEV1 then administered the second capsule. <u>Use Errors:</u> -1 participant did not instruct the patient actor to inhale the contents of the second capsule.	-U*se of QRG during patient evaluation not consistent with clinical practice* – Reliance on QRG inconsistent with clinical practice for many HCPs. The BTT requires users to rely on and carefully follow the QRG as a notetaking tool, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice (HU17).	No mitigation required. Although performance issues were observed on this task, all participants ended up administering the tolerance test in an incremental manner, measuring spO2 and FEV1 values between drug administrations. The BTT is designed to provide incremental increases in the amount of Bronchitol given to the patient. The incremental increase in capsules is meant to be convenient and safe for the	We note the potential harm associated with the risk of skipping or missing capsules is an unindicated patient being prescribed the medication, which could lead to bronchospasm, hypoxia, and pulmonary compromise. We acknowledge the Applicant's current mitigation strategies including depicting the number of capsules to administer in each step, and bold text instructing the user of how many capsules to administer for each step. Additionally, we note that based on subjective feedback in the study, the Applicant proposed

		-1 participant instructed the patient actor to inhale the contents of three capsules, reusing their first BTT capsule for each inhalation (e.g. they did not take new capsules out of the blister pack). They referred to the third capsule as "number two." -1 participant instructed the patient actor to inhale the contents of three capsules in total. They determined the first capsule they tried was not working so they disposed of it. Next, they administered their first capsule then started measuring values. Then they realized they had not completed the dose, but then administered 2 additional capsules.	-*Insufficient support for tracking capsules administered* – The blister pack does not assist users in tracking the number of capsules in each increasing dose of medication required for the BTT (HU17). -*Unfamiliar nature of BTT* – The BTT might be unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to the new method and be inclined to base their decisions on patient symptoms while administering the BTT, as they do in their current practice (RU03). -*Insufficient support for tracking capsules administered* – The blister pack does not assist users in tracking the number of capsules in each increasing dose of medication required for	patient, however, the dosing of Bronchitol is to take the ten capsules "one capsule immediately after the other". Therefore, instructing the patient to inhale the contents of more than the indicated number of capsules on a given step in the QRG (while not exceeding 10 capsules) would result in a hyperresponsive patient being identified earlier in the BTT. There is no unique harm associated with earlier detection of hyperresponsiveness.	to include a statement on the QRG instructing users to (b) (4) [redacted] However, per additional subjective feedback, we note that the instructional material does not include information on what the user should do if a capsule is skipped/missed. Therefore, we recommend including this information in the QRG and other instructional materials. Furthermore, per additional subjective feedback we recommend revising the BTT blister pack labeling to aid the tracking of how many capsules have been administered. See Section 5.2 for our recommendations.

			the BTT. The QRG does not explicitly indicate to users to track the number of capsules (i.e. through coloring in the capsules) administered to the patient as they go through the BTT (RU06, RU15). -*Insufficient detail on capsule administration* – The BTT instructional materials do not provide users with sufficient detail regarding how to proceed with the BTT when a capsule is skipped as well as the importance of administering all 10 capsules by the end of the BTT (RU06). -*Study artifact: simulated workstation time* – Although participants were given 15 minutes to use as they chose, this length of time and the arrangement and/or setup of the workstation setup may not have been aligned with or conducive to the way some would expect to spend their time before administering the BTT with		

			a patient for the first time (RU15).		
Wait 1 minute. Record new SpO2 and new FEV1.	Use Difficulties (n=3; 2 Untrained RTs, 1 Trained HCP) Use Errors (n=2; 1 Untrained RT, 1 Trained HCP) 2 participants DNC this task (2 Untrained RTs)	<u>Use Difficulties:</u> -2 participants waited 1 minute after administering each capsule. 1 participant also measured SpO2 and FEV1 after the first capsule. -1 participant waited 1 minute, verbalized the need to check the new SpO2 and new FEV1 values, then was about to continue with 3 capsules before realizing they had not measured the values. <u>Use Errors:</u> -2 participants did not wait 1 minute before recording new SpO2 and FEV1 values.	-*Format of BTT QRG* – The paper-based BTT QRG does not restrict users from continuing if they skip a step in the process, opposed to computer-based programs some users may be familiar with and reliant on to complete testing with patients in their clinical practice (RU03). -*QRG does not sufficiently emphasize the need to wait* – The clock image for waiting 1 minute is not sufficiently differentiated from other purple information in the QRG. Additionally, this step does not require users to fill in a blank or check something off, like other QRG steps, which may cause some users to skip waiting for 1 minute (RU03, HT07-RT). -*Study artifact: simulation exercise* – The role-playing	No mitigation required. While not measuring the new SpO2 and FEV1 may lead to continuing the BTT longer than anticipated, there is no unique harm associated with skipping this step, as a hyperresponsive patient would be identified in a subsequent step. No mitigation required Slow and diligent administration of total dose of Bronchitol during the BTT is not expected to cause harm. No mitigation required. While not waiting 1 minute before measuring the new SpO2 and FEV1 may lead to continuing the BTT longer than anticipated, there is no unique harm associated with skipping this step, as a hyperresponsive patient would be identified in a subsequent step.	We note that according to the URRA, there is no potential harm associated with the risk of not recording the new SpO2 and FEV1, as a hyperresponsive patient would be identified in subsequent steps. We acknowledge the Applicant's current mitigation strategy of the purple highlighted clock with "Wait 1 minute" in the QRG. However, we note some participants overlooked the wait time or misinterpreted how to apply the wait times. Therefore, based on the subjective feedback, root cause analysis, and our review of the QRG, we note that the color of the clock image displaying 1 minute can be revised for increased prominence. See Section 5.2 for our recommendation.

			nature of the simulation exercise may be distracting to participants. Thus, trying to make the scenario feel more realistic may have interfered with the participant's ability to simultaneously focus on performing all aspects of the BTT (HT07-RT). *-Absence of direction on waiting between capsules* – The QRG does not inform users if they need to wait or do not need to wait after administering each capsule in the increasing BTT doses, as it only states to administer "one capsule at a time". Subsequently, users may assume they need to wait 1 minute in between capsules, as they do after the dose is completed (RU10, RU14). *-Insufficient emphasis on sequence of 1-minute wait in instructional video* – The instructional video does not include a sufficient description of when to wait 1 minute (i.e. after the increased dose of capsules) throughout the		

			BTT. Subsequently, some users who rely strictly on this video to prepare for the BTT with a patient may miss this step or misinterpret when to wait 1 minute (RU14). *-Repetitive nature of BTT* – Since the BTT requires repeated instances of measuring SpO2 and FEV1, users may feel like they have already taken the measurements and subsequently skip over measuring new values on a given step (HT13-RT).		
Are both of the following true? New SpO2 is more than 90-STOP? New FEV1 is more than 80-STOP? (If yes to both, continue to Step E. If no to either, stop and do not prescribe BRONCHITOL).	Use Difficulty (n=1; 1 Untrained RT) 2 participants DNC this task (2 Untrained RTs)	-1 participant multiplied the new SpO2 by 0.9 and new FEV1 by 0.8, then proceeded (RU09).	- *Insufficient differentiation of QRG Step A3* – The QRG does not sufficiently call out that the calculation associated with the STOP values on Step A3 is unique and does not need to be repeated in the BTT. Additionally, the QRG's notation for the 90-STOP and 80-STOP values is used throughout the BTT and may cause users to recall the calculation they had made in Step A3 in later BTT steps (RU09).	No mitigation required. Calculating a more conservative SpO2 and/or FEV1 could result in an increased likelihood of the patient failing the BTT when they might not have if the correct value comparison had been performed. This would not introduce patient harm.	We note the potential harm associated with this risk of calculating SpO2 and FEV1 with the newly recorded values is a non-hyperresponsive patient not receiving Bronchitol therapy (i.e., a patient who otherwise would qualify for Bronchitol therapy would appear to fail the BTT). We acknowledge the current mitigation strategies including a box for the newly taken SpO2 value, a separate box with the question for the HCP "Is the new SpO2 more than 90-STOP," and an algorithm format for the HCP directing them to continue with the test or stop depending on the result.

[Critical]			-*Study artifact: simulated environment* – The study environment contributes to participant nervousness, resulting in deviation from regular practice during the use assessment (RU09). -*Study artifact: simulated workstation time* – Although participants were given 15 minutes to use as they chose, this length of time and the arrangement and/or setup of the workstation setup may not have been aligned with or conducive to the way some would expect to spend their time before administering the BTT with a patient for the first time (RU09).		We discussed the Applicant's analysis of the residual risk with our clinical colleagues, and they did not have safety concerns from a clinical perspective, as if the patient fails the BTT, they may be eligible for another tolerance test at a later time. Based on our heuristic review of the QRG, the subjective feedback and root cause analysis provided, we determined that the implementation of additional labeling mitigations are not likely to further reduce the residual risks. Therefore, we find the residual risk minimized to the extent possible and we have no further recommendations to address this use error at this time.
Following steps 3-8 located on the right, instruct patient to inhale contents of 3 capsules, one capsule at a time. [C]	Use Difficulties (n=5; 2 Untrained HCPs, 1 Untrained RT, 2 Trained HCPs) Use Errors (n=1; 1 Untrained RT) 2 participants DNC this task (2 Untrained RTs)	<u>Use Difficulties:</u> -3 participants were initially unsure if they had administered 3 capsules. Each participant counted the used capsules in the blister pack to correctly deduce they had, in fact, administered 3 capsules. -1 participant administered 2 capsules, almost set the timer to wait but then checked the blister	-*Insufficient support for tracking capsules administered* – The blister pack does not assist users in tracking the number of capsules in each increasing dose of medication required for the BTT. The QRG does not explicitly indicate to users to track the number of capsules (i.e.	No mitigation required. The BTT is designed to provide incremental increases in the amount of Bronchitol given to the patient. The incremental increase in capsules is meant to be convenient and safe for the patient, however, the dosing of Bronchitol is to take the ten capsules "one	We note the potential harm associated with the risk of skipping or missing capsules is an unindicated patient being prescribed the medication which could lead to bronchospasm, hypoxia, and pulmonary compromise. We acknowledge all participants self-corrected by counting the number of empty capsules. Additionally, we acknowledge the current

		pack and administered the third capsule. -1 participant administered 1 capsule then was unsure if they had 2 or 3 more capsules to administer. They ultimately realized their mistake and had the patient actor inhale 3 capsules. <u>Use Errors:</u> -1 participant instructed the patient actor to inhale the contents of 4 capsules , reusing their first BTT capsule for each inhalation (e.g. they did not take new capsules out of the blister pack). They referred to the fourth capsule as "the third" and filled in the third capsule on the QRG.	through coloring in the capsules) administered to the patient as they go through the BTT (HU04, HU11, RU06). -*Competing focus between inhaler and BTT steps* – Since the BTT requires HCPs to instruct the patient on how to use the inhaler as well as requires tracking the number of capsules administered, some HCPs may become focused on one over the other (HU04, HT04-RT). -*Study artifact: simulated patient* – The patient actor in the study did not perform tasks that were not specifically articulated by the HCP participant, whereas in clinical practice patients may provide feedback on their comfort level with each step and HCPs may be able to rely on CF patients' regular practice/prior knowledge to support performance (HU04). -*Insufficient support for tracking capsules*	capsule immediately after the other". Therefore, instructing the patient to inhale the contents of more than the indicated number of capsules at a given step in the QRG (while not exceeding 10 capsules) would result in a hyperresponsive patient being identified earlier in the BTT. There is no unique harm associated with earlier detection of hyperresponsiveness. Additionally, a statement was added to the QRG instructing users to color in capsules on the QRG to keep track of how many have been administered.	mitigation strategies in place including depicting the number of capsules to administer in each step, and bold text instructing the user of how many capsules to administer for each step. Additionally, we note that based on subjective feedback in the study, the Applicant proposed to include a statement on the QRG instructing users to "color in capsules on the QRG to keep track of how many have been administered." However, per additional subjective feedback, we note that the instructional material does not include information on what the user should do if a capsule is skipped/missed. Therefore, we recommend including this information in the QRG and other instructional materials. Furthermore, per additional subjective feedback, we recommend revising the BTT blister pack labeling to aid the tracking of how many capsules have been administered. See Section 5.2 for our recommendation.

			administered – The blister pack does not assist users in tracking the number of capsules in each increasing dose of medication required for the BTT (HT04-RT). -*Absence of BTT QRG in Training Kit carton* – Trained HCPs may not know to look for the BTT QRG inside the BTT carton because the Training Kit carton only contains inhaler use instructions and does not include the BTT steps (HT05-NP). -*Insufficient QRG discoverability* – The BTT carton does not allow for sufficient discoverability of the QRG, as there are multiple contents inside the carton that may be removed first and focused on. Thus, some users may only use the PI if they find it before the QRG (HT05-NP). -*Insufficient support for capsule tracking in PI* – The BTT steps for capsule administration in the PI do not sufficiently support		

			users in tracking the number of capsules administered, as there are no check boxes or interaction points on those steps as there are in the QRG (HT05-NP). -*Insufficient support for tracking capsules administered* – The blister pack does not assist users in tracking the number of capsules in each increasing dose of medication required for the BTT. The QRG does not explicitly indicate to users to track the number of capsules (i.e. through coloring in the capsules) administered to the patient as they go through the BTT (RU10). -*Study artifact: simulated patient* – Since the patient actor was not actually inhaling the medication during this study, the capsule that the participant viewed was still full after		

			each inhalation. Therefore, some participants did not deem it necessary to insert new capsules from the blister pack for each inhalation. Thus, this may have impacted their ability to track how many capsules they administered on a given step (RU10).		
Wait 1 minute. Record new SpO2 and new FEV1. [C]	Use Difficulties (n=3; 3 Untrained RTs) Use Errors (n=5; 1 Untrained HCP, 2 Untrained RTs, 2 Trained HCPs) 2 participants DNC (2 Untrained RTs)	<u>Use Difficulties:</u> -1 participant waited 1 minute and measured SpO2 and FEV1 after administering 3 of the 4 capsules (1st, 3rd, and 4th) administered as part of Task E1. -1 participant did not wait 1 minute before recording the new SpO2 and new FEV1. Then they waited 1 minute and measured SpO2 and FEV1 again to make sure the patient actor was okay mentioning they had some chest tightness. -1 participant waited 1 minute and measured SpO2 and FEV1 after administering each capsule. <u>Use Errors:</u> -1 participant waited 1 minute but then stopped the BTT when the patient actor responded they had some chest tightness stating	- *Absence of direction on waiting between capsules* – The QRG does not inform users if they need to wait or do not need to wait after administering each capsule in the increasing BTT doses, as it only states to administer "one capsule at a time". Subsequently, users may assume they need to wait 1 minute in between capsules, as they do after the dose is completed (RU10, RU14). - *Insufficient emphasis on sequence of 1-minute wait in instructional video* – The instructional video does not include a sufficient description of when to wait 1 minute (i.e.	No mitigation required Slow and diligent administration of total dose is not expected to cause harm. Stopping the BTT in response to minor symptoms would only ensure patient safety. Furthermore, there is no harm associated with not prescribing Bronchitol to a potentially indicated patient. While not waiting 1 minute before measuring the new SpO2 and FEV1 may lead to continuing the BTT longer than anticipated, there is no unique harm associated with skipping this step, as a hyperresponsive patient would be	We note the potential harm associated with the risk of not waiting 1 minute before recording new SpO2 and FEV1 is that a hyperresponsive patient would not be identified immediately; however, they may be identified in subsequent steps. Additionally, we note the potential harm associated with stopping the BTT early is a non-hyperresponsive patient not being prescribed Bronchitol (i.e., a patient who otherwise would qualify for Bronchitol therapy would appear to fail the BTT). Furthermore, per the URRA, we note the potential harm associated with the risk of waiting 1 minute between the administration of each capsule would be no patient harm as a hyperresponsive patient would be identified based on dose accumulation.

		"I worry you have some bronchospasm." They did not record new SpO2 and FEV1 values. -2 participants decided to stop the BTT after the patient actor responded they had some chest tightness. They did not wait 1 minute and did not record new SpO2 and FEV1 values. -1 participant waited 1 minute but did not measure/record the new SpO2 and FEV1 values. Instead, they looked back at the values from the previous step D and decided to stop the BTT. This participant had multiplied the FEV1 of 2.1L from Step D by 0.8 and since 1.68 felt low, noted the patient was not tolerating the test and stopped the BTT. They thought to multiply the values because that is what they had done before. -1 participant did not wait or indicate waiting 1 minute before recording the new SpO2 an FEV1 values. The participant said they knew to wait 1 minute but did not verbalize it to the patient actor. Additionally, they thought they had been saying "I would wait 1 minute."	after the increased dose of capsules) throughout the BTT. Subsequently, some users who rely strictly on this video to prepare for the BTT with a patient may miss this step or misinterpret when to wait 1 minute (RU14). - *Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be inclined to base their decisions on patient symptoms rather than oxygen saturation and FEV1 values while administering the BTT, as is more common in their current practice (HU16, RU02, HT08-NP). -*Insufficient detail around clinical symptoms that warrant stopping the BTT* – The QRG does not provide enough context about the level of chest tightness and other symptoms that should lead to stopping the BTT. Thus,	identified in a subsequent step. Stopping the BTT in response to an incorrect decision about the values measured would only ensure patient safety. Furthermore, there is no harm associated with not prescribing Bronchitol to a potentially indicated patient.	We acknowledge the Applicant's current mitigation strategy of the purple highlighted clock with "Wait 1 minute" in the QRG.. However, we note some participants overlooked the wait time or misinterpreted how to apply the wait times. Therefore, based on the subjective feedback, root cause analysis, and our review of the QRG, we note that the color of the clock image displaying 1 minute can be revised for increased prominence. See Section 5.2 for our recommendation.

			HCPs may decide to take a more conservative approach to patient symptoms reported during the BTT and stop before checking values (HU16, RU02, HT08-NP). -*Study artifact: unfamiliar patient* – Since the patient in the study was not an actual patient in the HCPs clinic, participants were unable to rely on their previous understanding and knowledge of the patient's typical symptoms and reactions to previous medications they had tried (HU16). -*Format of BTT QRG* – The paper-based BTT QRG does not restrict users from continuing if they skip a step in the process, opposed to computer-based programs some users may be familiar with and reliant on to complete testing with patients in their clinical practice (RU03). -*QRG does not sufficiently emphasize the need to wait* –		

			The clock image for waiting 1 minute is not sufficiently differentiated from other purple information in the QRG. Additionally, this step does not require users to fill in a blank or check something off, like other QRG steps, which may cause some users to skip waiting for 1 minute (RU03). -*Repetitive nature of BTT* – Since the BTT requires repeated instances of waiting 1 minute, users may feel as though they already waited during a step and in turn skip over waiting again as the BTT progresses (HT01-NP). -*Study artifact: simulation exercise* – The nature of the simulation exercise may have made the HCP feel they did not need to actually wait 1 minute, verbalize they would wait 1 minute during the BTT, or verbalize the waiting period has passed (HT01-NP). - *Insufficient differentiation of QRG Step*		

			A3 – The QRG does not sufficiently call out that the calculation associated with the STOP values on Step A3 is unique and does not need to be repeated in the BTT. Additionally, the QRG's notation for the 90-STOP and 80-STOP values is used throughout the BTT and may cause users to recall the calculation they had made in Step A3 in later BTT steps (RU05).		
Are both of the following true? New SpO2 is more than 90-STOP? New FEV1 is more than 80-STOP? (If yes to both, continue to Step F. If no to either, stop and do not prescribe BRONCHITOL).	Use Difficulty (n=1; 1 Untrained RT) Use Error (n=2; 1 Untrained RT, 1 Trained HCP) 6 participants DNC this task due to stopping the simulated BTT early (1 Untrained HCP, 1 Trained HCP, 4 Untrained RTs)	<u>Use Difficulty:</u> -1 participant multiplied the new SpO2 by 0.9 and new FEV1 by 0.8 but decided to proceed. (RU9) <u>Use Errors:</u> -1 participant decided to stop the BTT after the patient actor responded they had some chest tightness. (HT12MD) -1 participant administered albuterol to the patient actor and continued the BTT. The participant gave the patient actor the bronchodilator because of reported chest tightness. They ultimately decided to proceed based on their clinical judgment (RU3)	-*Insufficient differentiation of QRG Step A3* – The QRG does not sufficiently call out that the calculation associated with the STOP values on Step A3 is unique and does not need to be repeated in the BTT. Additionally, the QRG's notation for the 90-STOP and 80-STOP values is used throughout the BTT and may cause users to recall the calculation they had made in Step A3 in later BTT steps (RU09). -*Study artifact: simulated environment* – The study environment contributes to participant	No mitigation required. Calculating a more conservative SpO2 and/or FEV1 could result in an increased likelihood of the patient failing the BTT when they might not have if the correct value comparison had been performed. This would not introduce patient harm. No mitigation required. Administration of albuterol during the BTT would result in elevated values, and therefore could allow a hyperresponsive patient to be prescribed the medication.	We note the potential harm associated with the risk of administering a bronchodilator to a patient and continuing the BTT is an unindicated patient being prescribed Bronchitol, which may result in a h perresponsive reaction. Additionally, we note the potential harm associated with the risk of calculating the newly acquired SpO2 and FEV1 values is a non-hyperresponsive patient not being prescribed Bronchitol or an unindicated patient being prescribed Bronchitol based on the patient specific values. Furthermore, we note the potential harm associated with the risk of stopping the BTT early due to minor symptoms is the patient would not be prescribed this medication.

			nervousness, resulting in deviation from regular practice during the use assessment (RU09). -*Study artifact: simulated workstation time* – Although participants were given 15 minutes to use as they chose, this length of time and the arrangement and/or setup of the workstation setup may not have been aligned with or conducive to the way some would expect to spend their time before administering the BTT with a patient for the first time (RU09). - *Termination of BTT after using bronchodilator not explicit* – The QRG does not explicitly state that the BTT should not be continued after giving a bronchodilator to the patient (RU03). - *Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol	No pattern of failure observed – this was only observed in one participant (2%). While not required, the QRG to be modified to include that the BTT should be stopped if the patient shows any signs of significant bronchoconstriction requiring treatment with a bronchodilator. No mitigation required. Stopping the BTT in response to minor symptoms would only ensure patient safety. Furthermore, there is no harm associated with not prescribing Bronchitol to a potentially indicated patient.	We acknowledge the current mitigation strategies including a box for the newly taken SpO2 value, a separate box with the question for the HCP "Is the new SpO2 more than 90-STOP," and an algorithm format for the HCP directing them to continue with the test or stop depending on the result. We also note the Applicant's proposed mitigation strategy of adding the statement, "Stop the BTT if the patient shows signs of significant bronchoconstriction requiring treatment with a bronchodilator, such as wheezing or shortness of breath." due to subjective feedback in the study. We discussed the Applicant's analysis of the residual risk with our clinical colleagues, and based on our heuristic review of the QRG, the subjective feedback and root cause analysis provided, we determined that the implementation of additional labeling mitigations are not likely to further reduce the residual risks. Therefore, we find the residual risk minimized to the extent possible and we have no further recommendations to address this use error at this time.

			required to conduct the BTT, users may be inclined to base their decisions on patient symptoms rather than oxygen saturation and FEV1 values while administering the BTT, as is more common in their current practice (HT12-MD). -*Insufficient detail around clinical symptoms that warrant stopping the BTT* – The QRG and training program do not provide enough context about the level of chest tightness and other symptoms that should lead to stopping the BTT. Thus, HCPs may decide to take a more conservative approach to patient symptoms reported during the BTT and stop before checking values (HT12-MD). -*Study artifact: unfamiliar with patient* – Since the patient actor in the study was not an actual patient in the HCPs clinic, participants were unable to rely on their previous understanding and		

			knowledge of the patient's typical symptoms and reactions to previous medications they had tried (HT12-MD).		
Following steps 3-8 located on the right, instruct patient to inhale contents of 4 capsules, one capsule at a time. [C]	Use Difficulty (n=1; 1 Untrained RT) Use Errors (n=2; 2 Untrained RTs) 11 Participants DNC this task (2 Untrained HCPs, 6 Untrained RTs, 3 Trained HCPs)	<u>Use Difficulty:</u> -1 participant instructed the patient actor to inhale the contents of 1 capsule, then set the timer for 1 minute and almost forgot to administer the remaining capsules. They caught their mistake while waiting and administered the last 3 capsules (RU15). <u>Use Errors:</u> -2 participants instructed the patient actor to inhale the contents of 3 capsules in total (RU3, RU4).	-*Insufficient support for tracking capsules administered* – The blister pack does not assist users in tracking the number of capsules in each increasing dose of medication required for the BTT. The QRG does not explicitly indicate to users to track the number of capsules (i.e. through coloring in the capsules) administered to the patient as they go through the BTT (RU03, RU04, RU15). -*Study artifact: simulated workstation time* – Although participants were given 15 minutes to use as they chose, this length of time and the arrangement and/or setup of the workstation setup may not have been aligned with or conducive to the way some would expect to spend their time before administering		We note the potential harm associated with the risk of missing or skipping capsules is an unindicated patient being prescribed Bronchitol, which could lead to bronchospasms, hypoxia, and pulmonary compromise. We acknowledge the Applicant's current mitigation strategies including depicting the number of capsules to administer in each step, and bold text instructing the user of how many capsules to administer for each step. Additionally, we note that based on subjective feedback in the study, the Applicant proposed to include a statement on the QRG instructing users to "color in capsules on the QRG to keep track of how many have been administered." However, per additional subjective feedback, we note that the instructional material does not include information on what the user should do if a capsule is skipped/missed. Therefore, we recommend including this information in the QRG and other instructional materials. Furthermore, per additional

					subjective feedback we recommend revising the BTT blister pack labeling to aid the tracking of how many capsules have been administered. See Section 5.2 for our recommendations.
Wait 1 minute. Record new SpO2 and new FEV1. [C]	Use Difficulty (n=2; 2 Untrained RTs) Use Errors (n=2; 1 Untrained RT, 1 Trained HCP) 10 participants DNC this task (1 Untrained HCP, 6 Untrained RTs, 3 Trained HCPs)	<u>Use Difficulty:</u> -1 participant almost recorded the new SpO2 and FEV1 before waiting 1 minute. They caught their mistake when they saw the timer on the table (RU9). -1 participant waited 1 minute and measured the SpO2 and FEV1 after administering each capsule (RU14) <u>Use Error:</u> - 1 participant did not wait 1 minute before recording the new SpO2 and FEV1 (RU3). -1 participant did not wait or indicate waiting before 1 minute before recording the new SpO2 and FEV1 (HT1-NP).	-*Format of BTT QRG* – The paper-based BTT QRG does not restrict users from continuing if they skip a step in the process, opposed to computer-based programs some users may be familiar with and reliant on to complete testing with patients in their clinical practice (RU03). -*QRG does not sufficiently emphasize the need to wait* – The clock image for waiting 1 minute is not sufficiently differentiated from other purple information in the QRG. Additionally, this step does not require users to fill in a blank or check something off, like other QRG steps, which may cause some users to skip waiting for 1 minute (RU03, RU09).	Given the cumulative doses of Bronchitol administered to that point in the BTT, as well as the fact that some elapsed time was observed, this use error is unlikely to result in harm as the amount of drug inhaled despite not waiting one minute at Step F2 should be sufficient to determine if hyperresponsiveness is present for the majority of patients. Participants generally indicated in their clinic setting, prior to administering a new tolerance test to a CF patient, they have an expectation to have engaged in prior training, discussions with colleagues, and/or at a minimal received a directional email from their Head of Department highlighting required and important task	We note the potential harm associated with the risk of not waiting 1 minute is an unindicated/hyperresponsive patient being prescribed Bronchitol, which could lead to bronchospasms, hypoxia, and pulmonary compromise. We acknowledge the Applicant's current mitigation strategy of the purple highlighted clock with "Wait 1 minute" in the QRG. However, we note some participants overlooked the wait time or misinterpreted how to apply the wait times. Therefore, based on the subjective feedback, root cause analysis, and our review of the QRG, we note that the color of the clock image displaying 1 minute can be revised for increased prominence. See Section 5.2 for our recommendation.

			-*Study artifact: simulated environment* – The study environment contributes to participant nervousness, resulting in deviation from regular practice during the use assessment (RU09). -*Repetitive nature of BTT* – Since the BTT requires repeated instances of waiting 1 minute, users may feel as though they already waited during a step and in turn skip over waiting again as the BTT progresses (HT01-NP). - *Absence of direction on waiting between capsules* – The QRG does not inform users if they need to wait or do not need to wait after administering each capsule in the increasing BTT doses, as it only states to administer "one capsule at a time". Subsequently, users may assume they need to wait 1 minute in between capsules, as they do after the dose is completed (RU14).	for proper tolerance test execution. These expectations are consistent with similar tolerance tests such as the methacholine challenge. The increased familiarity with the BTT over time that these anticipated interactions would provide would likely increase the HCP's confidence in correctly preforming the BTT and further minimize the probability of progressing to collection of final pulmonary measurements prior to waiting 1-minute. Accordingly, Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation.	

			-*Insufficient emphasis on sequence of 1-minute wait in instructional video* – The instructional video does not include a sufficient description of when to wait 1 minute (i.e. after the increased dose of capsules) throughout the BTT. Subsequently, some users who rely strictly on this video to prepare for the BTT with a patient may miss this step or misinterpret when to wait 1 minute (RU14).		
Are both of the following true? New SpO2 is more than 90-STOP? New FEV1 is more than 80-STOP? (If yes to both, BRONCHITOL may be prescribed. If no to either, stop and do not prescribe BRONCHITOL).	Use Errors (n=4; 3 Untrained RTs, 1 Trained HCP) 10 participants DNC this task. (1 Untrained HCP, 6 Untrained RTs, 3 Trained HCPs)	-3 participants decided the patient actor could be a candidate for this medication. 1 participant correctly calculated the STOP values at this step and compared the new FEV1 to the 80-STOP of 1.96 L (RU3). 1 participant multiplied the new SpO2 by 0.9 and new FEV1 by 0.8 (RU9), but the new values seemed fine so that's why he passed the patient actor (RU9). 1 participant compared the new FEV1 value to 1.6 L, which is a cutoff value from their practice (RU14). -1 participant decided the patient actor could be a candidate for this medication. They stated the	-*Format of BTT QRG* – The paper-based BTT QRG does not restrict users from continuing if they skip a step in the process, opposed to computer-based programs some users may be familiar with and reliant on to complete testing with patients in their clinical practice (RU03, RU14). -*Numerous values required for BTT* – Since the BTT requires many instances of measuring SpO2 and FEV1	All 23 healthcare prescribers, whether trained or untrained, concluded correctly in all instances that the patient actor was not a candidate for treatment with Bronchitol. A total of 3 untrained RTs and 1 trained RT incorrectly determined that Bronchitol could be prescribed. It is important to consider that in the actual clinical setting, a RT who performed the BTT and who is not authorized to prescribe medications would provide the BTT results to the patient's primary physician. Healthcare prescribers are	We note the potential harm associated with the risk of the HCP determining the patient is indicated for Bronchitol when they are not is an unindicated/ hyperresponsive patient being prescribed Bronchitol. We acknowledge that the participants that incorrectly concluded that the patient actor was a candidate for this medication were RTs, and not physicians or NPs. However, we disagree with the Applicant's justification that the RT performing the BTT is not authorized to prescribe medications as the patient's primary physician would interpret

[C]		patient actor's numbers looked okay. When probed, the participant attributed not being in a real clinical environment with a real patient as one reason for not picking up that the values fell below the 80-STOP (HT3-RT).	and comparing to STOP values, users may become overwhelmed with values and subsequently pay less attention to them (RU09). -*Insufficient differentiation of QRG Step A3* – The QRG does not sufficiently call out that the calculation associated with the STOP values on Step A3 is unique and does not need to be repeated in the BTT. Additionally, the QRG's notation for the 90-STOP and 80-STOP values is used throughout the BTT and may cause users to recall the calculation they had made in Step A3 in later BTT steps (RU09). -*Study artifact: simulated environment* – The study environment contributes to participant nervousness, resulting in deviation from regular practice during the use assessment (RU09). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/ assessments performed by HCPs. Due to the	the providers who will interpret the BTT and render a prescribing decision in the clinical setting, and the Supplemental Human Factors Validation study supports their ability to make this decision correctly. Accordingly, Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation. While not required, further emphasis of the requirement for calculation of STOP values (per step A3) has been added to the proposed QRG to further support correct performance on this task. Due to the narrow scope of these changes which have been designed to address participant reported root causes identified in the study, it is anticipated that no new risks have been introduced and further validation of the product user interface is not required.	the results of the BTT and decide whether or not to prescribe Bronchitol. Although RTs cannot prescribe Bronchitol, we note that in the real world, they may be conducting the BTT; therefore, if they perform any aspect of the test incorrectly which impacts the FEV1 and SpO2 values, the prescriber will be basing their decision on incorrect/inaccurate information for the patient. Per the Applicant, the participants performed the proper calculations, and therefore, the prescriber would be given the results of the BTT which would show the final SpO2 and FEV1 values being below the STOP values. The prescriber would then make the clinical decision based on these values as to whether they would prescribe Bronchitol. We discussed the Applicant's analysis of the residual risk with our clinical colleagues, and based on our heuristic review of the QRG, the subjective feedback and root cause analysis provided, we determined that the implementation of additional labeling mitigations are not likely to further reduce the residual risks. Therefore, we find the residual risk minimized to the extent possible and we have no

			unfamiliar protocol required to conduct the BTT, users may be inclined to base their decisions on patient symptoms rather than oxygen saturation and FEV1 values while administering the BTT, as is more common in their current practice (RU09, RU14, HT03-RT). -*Notation for 90-STOP* – HCPs may interpret the 90-STOP value to be 90% for all patients. This may be because they have to calculate 90% of the baseline value initially, because 90 is part of the reference name, and/or because the calculated value from Step A3 is not repeated for each decision step in the BTT (RU14). -*Insufficient link between STOP value and new measured value* – STOP values appear at the top of the QRG and are not close in proximity to or visually linked with the new measured values being compared to them (HT03-RT).		further recommendations to address this use error at this time.

			-*Study artifact: simulated patient* – Since the patient actor was not actually inhaling the medication during this study, HCPs were not able to rely on the patient actor's symptoms and status throughout the BTT, whereas in clinical practice HCPs could rely on CF patients' actual reactions throughout the BTT alongside the measured values (HT03-RT).		
Wait 15 minutes, then monitor SpO2 and FEV1 to confirm recovery to baseline. [C]	Use Difficulty (n=2; 1 Untrained HCP, 1 Trained HCP) Use Errors (n=13; 5 Untrained HCPs, 5 Untrained RTs, 3 Trained HCPs) 3 participants DNC this task (2 Untrained RTs, 1 Trained HCP)	<u>Use Difficulty:</u> -1 participant indicated to wait 15 minutes and then measured SpO2 and FEV1 values but was unsure what to do when the values did not match the exact baseline values (HT13-RT). -1 participant initially said they would wait 5 minutes and then check values, but then corrected themselves and said they would wait 15 minutes, and after 15 minutes would measure SpO2 and FEV1 (HU17). <u>Use Errors:</u> -1 participant stated they would wait 5 minutes and then measure SpO2 and FEV1 (HU2).	- *Recovery wait time inconsistent with clinical expectation* – Expecting a shorter patient recovery window after they fail the BTT, HCPs may be inclined to monitor values sooner than 15 minutes (HU02, RU05). -*Study artifact: simulated patient* – Patients who are experiencing hyperresponsive airways may exhibit clinical signs that HCPs would monitor consistent with clinical practice to ensure recovery (HU02).	Not monitoring the patient to ensure recovery could result in a patient experiencing an ongoing hyperresponsive reaction that could include bronchospasm, airway obstruction, decreased oxygenation, hypoxia, etc. As these symptoms would likely be evident in most patients experiencing hyperresponsiveness, there was study limitation associated with the patient actor not displaying any signs of distress due to a hyperresponsive response. In actual clinical practice,	We note the potential harm associated with the risk of not monitoring the patient for return to baseline is an ongoing hyperresponsive reaction. We acknowledge the current mitigation strategies in place including the boxed instructions in the QRG that states when a patient fails the BTT, HCPs are to wait 15 minutes and confirm patient recovery to baseline. We acknowledge the study limitation related to the patient actor not exhibiting clinical symptoms that are likely to be present in a hyperresponsive patient. Thus, we agree with the Applicant that in the real world, a HCP would intervene if a patient

		-2 participants did not wait 15 minutes or measure SpO2 and FEV1. 1 participant asked the patient actor how they were feeling, offered albuterol, and dismissed the patient actor (HU4). 1 participant dismissed the patient actor after they failed the BTT (they did not appear to see the step in the QRG) (HU12). -1 participant waited 15 minutes and remeasured FEV1. They did not remeasure SpO2. They were concerned with FEV1 due to that value being the one that decreased (HU5). -1 participant indicated they would monitor the patient actor for 30 minutes, listening to their lungs and give albuterol if required. They remeasured SpO2 but indicated that they would not necessarily remeasure FEV1 (HU8). -2 participants indicated they would monitor the patient actor for 15 minutes, measure SpO2 and ensure a return to baseline. They did not indicate measuring FEV1 (HT7-RT, HT8-NP). -1 participant dismissed the patient actor and did not indicate performing this step (HT12-MD).	-*Recovery wait time inconsistent with clinical expectation* – Expecting to monitor the patient more closely after they fail the BTT, HCPs may be inclined to check values sooner than 15 minutes, potentially to determine if albuterol should be administered (HU17). - *QRG does not specify action if values do not return to baseline* – The QRG does not indicate what appropriate next steps are for the treatment of patients whose values do not return to baseline after 15 minutes (HT13-RT). - *QRG does not sufficiently emphasize need to remeasure values* – The QRG does not contain fill-in boxes for the remeasured values, does not provide rationale around the importance of measuring both, and does not highlight the importance of relying on values	symptoms consistent with hyperresponsive reaction (i.e. bronchospasm, wheezing, excessive cough, vomiting, chest tightness, shortness of breath) would likely have prompted the HCP to monitor the patient for recovery of oxygenation and FEV1. Such symptoms (if they occur) are usually not severe, are of short duration, and resolve following the inhalation of a bronchodilator medication. Delayed or prolonged adverse responses to Bronchitol following the BTT were not seen in clinical studies and are considered to be unlikely to occur. In a clinical setting, the HCP or other clinical staff would be able to observe the patient for any visible signs of hyperresponsiveness and the patient would be able to report any symptoms, rather than the HCP relying solely on SpO2 and FEV1 values. Due to the nature of the simulation exercise, where HCPs were given the goal of determining whether a	exhibited symptoms despite not remeasuring the SpO2 and FEV1 values. Furthermore, we note that per the Applicant, delayed or prolonged responses to Bronchitol following the BTT were not seen in the clinical study and are unlikely to occur. We also agree with the Applicant that monitoring the patient for recovery would be in accordance with clinical practice. However, we note that one participant in the study would have a patient continue the BTT after giving them a break despite them failing. Therefore, based on this subjective feedback, we recommend adding the statement "DO NOT continue the BTT" in the red box. See Section 5.2 for our recommendation.

		-2 participants did not indicated to wait 15 minutes and did not measure values to confirm recovery to baseline (RU1, RU10). -1 participant indicated they would wait 5-10 minutes and then measure SpO2 and FEV1 values (RU5). -2 participants did not stop. They proceeded with or restarted the BTT after completing this task. 1 participant continued with the BTT after waiting 15 minutes and remeasuring the SpO2 and arrived to this step after seeing values drop on step C3. After waiting 15 minutes and remeasuring SpO2 they proceeded to administer additional capsules with the BTT on Step D (RU3), they remember following the red line down and then following it back up and continuing to Step D. 1 participant waited 15 minutes and measured SpO2 and FEV1 and tried the BTT again from the beginning despite noting that according to the BTT he should not do it again (RU12).	alongside patient symptoms (HU05). -*Next steps following a failed BTT inconsistent with clinical judgment* – HCPs expect patient symptoms rather than measured values to determine next steps following a failed BTT (HU08). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be inclined to base their decisions on patient symptoms rather than oxygen saturation and FEV1 values while administering the BTT, as is more common in their current practice (HU08). -*QRG does not sufficiently emphasize next steps after a failed BTT* – The stop sign signals the end of the BTT but does not sufficiently	patient could be prescribed Bronchitol, several HCPs felt that they had completed the necessary tasks and rendered the correct prescribing decision and therefore completed the simulation, not emphasizing this aspect of their clinical protocol. Moreover, when discussed in the context of the participant root cause analysis, HCPs indicated they would expect to monitor the patient for recovery in accordance with their clinical practices. Additionally, in some clinical environments, the HCP would not be responsible for monitoring the patient after the BTT; instead, the patient would be sent to a waiting room and monitored by other clinical staff. Existing mitigations have minimized the error to the maximum extent possible. These mitigations include providing the instructions for confirming return of FEV1 and SpO2 to baseline in a red STOP box in the QRG. Additionally, the training includes instructions to monitor the patient for 15	

			direct users to next steps to ensure patient recovery. The QRG does not contain fill-in boxes for the remeasured values, does not provide rationale around the importance of measuring both, and does not highlight the importance of relying on values alongside patient symptoms (HT07-RT). -*Unfamiliar nature of BTT* – The BTT might be unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to the new method and be inclined to base their decisions on patient symptoms and status rather than oxygen saturation and spirometry values while administering the BTT, as they do in their current practice (HT07-RT). -*Study artifact: simulation exercise* – The nature of the simulation exercise	minutes and confirm a return to baseline for FEV1 and SpO2. Accordingly, Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation.	

			made the HCP feel the need to only complete certain activities for the purposes of the simulation, rather than continuing their observations of the patient actor based on clinical judgment (HT07-RT). -*Next steps following a failed BTT inconsistent with clinical judgment* – HCPs may be uninclined to perform spirometry as it could result in further bronchospasm when the patient is already symptomatic (HT08-NP). -*QRG does not sufficiently emphasize next steps after a failed BTT*– The stop sign signals the end of the BTT but does not sufficiently direct users to next steps to ensure patient recovery. The QRG does not contain fill-in boxes for the remeasured values, does not provide rationale around the importance of measuring both, and does not highlight the		

			importance of relying on values alongside patient symptoms (HU04, HU12, RU01, RU10, HT12-MD). -*Reliance on self-aware patient* – HCPs expect CF patients to be self-aware about their symptoms and changes in health status including breathing, and therefore may rely on guidance/self-reported symptoms from the patient over measured values (HU04). -*Time required to conduct the BTT requires change in clinic practices* – HCPs do not have time to wait for extended periods in regular clinical practice and are inclined to shorten wait times to accommodate their other responsibilities (HU04). -*Study artifact: simulated patient* – Patients who are experiencing hyperresponsive airways may exhibit clinical signs that HCPs would monitor consistent with clinical practice to ensure recovery (HU04, HU12).		

			-*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be inclined to base their decisions on patient symptoms rather than oxygen saturation and FEV1 values while administering the BTT, as is more common in their current practice (HU12). -*Study artifact: environment* – The simulated environment did not include a non-clinical/non-office room (e.g. a patient waiting room) which may have resulted in participants feeling they could not simulate activities that would occur outside of the clinical or office environments (HU12). -*Next steps following a failed BTT inconsistent with clinical judgment* –		

			HCPs may be uninclined to perform spirometry as it could result in further bronchospasm (RU01). -*Study artifact: simulation exercise* – The nature of the simulation exercise made the HCP feel the need to only complete certain activities for the purposes of the simulation, rather than continuing their observations of the patient based on clinical judgment (RU10). -*Large amount of information communicated through QRG* – Users performing the BTT might forget to complete certain tasks or get lost when progressing through the QRG due to the abundance of steps, text, colors and graphics on the page (HT12-MD). *Unfamiliar nature of BTT* – The BTT might be unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol		

			required to conduct the BTT, users may be getting acclimated to the new method and be inclined to base their decisions on patient symptoms and status rather than oxygen saturation and spirometry values while administering the BTT, as they do in their current practice (RU03, RU12). -*Instructional materials do not sufficiently emphasize inability to continue following failure in BTT* – The QRG and instructional video do not explicitly say not to try the BTT again following patient failure of the BTT in the stop instructions (RU12).		

Table 3: HF Study Results for the Inhaler Tasks

Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Wash & dry Hands [C]	Use Difficulty (n=1; 1 Trained HCP)	<u>Use Difficulty:</u> -1 participant offered the patient actor hand sanitizer if they would	-*Study artifact: simulated patient* – The patient actor in the study did not	In all cases, the HCP participant cleaned their own hands or wore	We note the potential harm associated with the risk of not washing hands is the inhalation of

	Use Errors (n=6; 2 Untrained HCPs, 3 Untrained RTs, 1 Trained HCP)	like to wash their hands. When the patient actor asked if they should, the participant said it was up to the patient actor. The patient actor did handle capsules (HT6-MD). <u>Use Errors:</u> -1 participant did not instruct the patient actor to dry her hands after washing them (HU1). -1 participant did not instruct the patient actor to wash or dry her hands. This participant sanitized their hands initially and wore gloves, but then removed the gloves during the BTT (HU3). -1 participant did not instruct the patient actor to dry her hands after washing them. The patient actor began handling the capsules on the 4th capsule (HT5-NP). -2 participants did not instruct the patient actor to dry her hands after washing them (RU2, RU7). -1 participant did not instruct the patient actor to wash or dry her hands (RU9).	perform tasks that were not specifically articulated by the HCP participant, whereas in clinical practice when an individual is washing their hands they generally also dry them without being told to do so -therefore HCPs can generally rely on CF patients' regular practice/prior knowledge to support performance (HU01, HU03, RU07, RU09, HT05-NP, HT06-MD). -*QRG and instructional video do not sufficiently emphasize the importance of hand washing* – Hand washing is not called out as its own step. Additionally, the impact of improper hand washing and drying is not highlighted in the materials (HU01, HU03, RU02, HT05-NP). -*Deviation from typical clinical workflow* – The BTT may be performed by HCPs who do not typically instruct patients in certain tasks (e.g. hand hygiene). This may result in HCPs	personal protect equipment (PPE). It is notable that given the nature of CF patient interactions and the cleaning protocols utilized in the clinical environment, it is very unlikely that lack of handwashing would result in exposure to microbes. Handwashing is standard in this patient population and the task is not unique to this medication. More importantly, to prevent the spread of germs, clinics that treat CF patients follow rigorous standards for cleaning and the wearing of PPEs by clinic staff. Well established guidelines require special contact precautions for all CF patients regardless of pathogen status including the wearing of mask by patients in common areas of the health care setting, the maintenance of a minimum six-foot distance between CF patients, and auditing the cleaning and disinfection	dirt/dirt-contaminated drug which could lead to microbial pathogen colonization, exacerbation of CF symptoms (more difficulty clearing secretions, trouble with oxygenation). We acknowledge current clinical practice along with the current mitigation strategy including the instruction to have the patients wash and dry their hands under Step B. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no further recommendations at this time.

			skipping steps or forgetting to highlight certain aspects outside of their typical area of care (HT06-MD).	of environmental surfaces. Importantly, guidelines recommend the standards for reducing infection risk with pulmonary function testing which includes hand hygiene (i.e., all health care professionals and people with CF and family members and friends should perfume hand hygiene with alcohol-based hand rub or antimicrobial soap and water when hands should be potentially contaminated with pathogens) and contact precautions (i.e., all health care personnel should implement Contact Precautions [wear a gown and gloves] when caring for all people with CF, regardless of respiratory tract culture results). Clinic personnel interacting with CF patients to conduct the BTT are reasonably expected to be familiar with and adhere to these common	

				safety practices and advice their patients similarly. Accordingly, Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation.	
Twist open inhaler by turning mouthpiece [Critical]	Use Difficulties (n=3; 1 Untrained HCP, 2 Trained HCPs).	-1 participant initially had trouble twisting open the inhaler when explaining the step to the patient actor (HU10). -2 participants initially had trouble twisting open the inhaler, trying to twist it open in the wrong direction (HT07-RT). 1 participant also pressed the buttons to open the inhaler (HT10-DO).	*Misleading small size of the inhaler* – As the inhaler is small, it could give the impression to users that it can be easily opened with little force, meaning they may need to adjust their force level to open it effectively (HU10). -*Insufficient visual distinction of arrow on inhaler* – The arrow on the inhaler is the same color as the rest of the inhaler and therefore blends in with the rest of the inhaler material. Therefore, users might not know what it is indicating about the inhaler or might not see it at all when administering the BTT (HU10, HT07-RT, HT10-DO). -*QRG step 2 does not provide sufficient instruction on*	No mitigation required. All participants were able to twist open the inhaler.	We note the potential harm of the associated risk of not opening the inhaler is user inconvenience or a brief delay in administering Bronchitol. We acknowledge that despite the use difficulties, all participants were able to open the inhaler. Additionally, we acknowledge the current mitigation strategies in place including a task in the QRG with an arrow depicting the direction to twist, along with an arrow on the inhaler device itself. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no further recommendations at this time.

			how to open the inhaler – The direction of rotation is not clearly specified, and the inhaler arrow is not present in the QRG (HT07-RT, HT10-DO). -*Unfamiliar button-piercing mechanism* – Due to the unfamiliar button-piercing design of the BTT inhaler, HCPs might have certain expectations of how the device functions, which could result in initial difficulties in opening and closing the inhaler. These expectations might be due to experience with other devices that have lockout mechanisms which require a two-button press, which may result in users believing the two-button design on the BTT inhaler acts as a locking mechanism for the inhaler. Additionally, the blue buttons are positioned at the bottom of the inhaler, in close range to the point where the mouthpiece opens and closes, therefore users might think		

			they are related to an open/close mechanism to lock the mouthpiece in place (HT10-DO)		
Take 1 capsule out of the package and put it in the chamber. [C]	Use Difficulties (n=2; 1 Untrained RT, 1 Trained HCP). Use Errors (n=2; 2 Untrained HCPs) 3 Untrained HCPs, 9 Untrained RTs, and 3 Trained HCPs DNC this for 1 or more capsules because they stopped the BTT before administering all 10 capsules.	<u>Use Difficulties:</u> -1 participant had difficulty removing one of the capsules from the blister pack (capsule 7) and bent the capsule upon removal. The participant then squeezed the capsule so it would revert back to its intended shape and proceeded with the next inhaler step (HT1-NP). -1 participant had difficulty taking 2 capsules (capsule 1 and 7) out of the blister pack. They removed these capsules by punching the foil, then attempting to reach their fingers in to pull the capsule out. In removing the capsules using this method, this participant bent the 2 capsules upon removal, but was ultimately able to remove them successfully. <u>Use Errors:</u> -2 participants did not insert new capsules into the inhaler chamber for each inhalation. 1 participant went to take a new capsule from the blister pack but got distracted by other steps and ultimately forgot to insert a new capsule from the pack, leaving the previous 1 in the chamber and	-*Material of blister pack and size of capsule holders in pack does not afford sufficient grip for capsule removal* – The material of the blister packs does not afford sufficient grip for users conducting the BTT while wearing personal protective gear, such as gloves. Furthermore, the holder where the capsules are stored in the blister packs might not be large enough for users to reach their fingers in and remove the capsules without causing damage. This could result in compromised dexterity and potentially damaging the capsules upon removal from the pack (RU15). -*Negative transfer* – HCPs might have experience handling blister packs and medication capsules similar to the one	No mitigation required. All participants were able to bend capsule back into shape. Had the capsule remained bent, it would still be able to deliver the dose if pierced successfully. Three participants did not insert a new capsule for a total of 4 capsules during the BTT. All participants sited study artifact as a key root cause as the patient actor was not actually inhaling the medication during the study so the capsule following each inhalation was still full – causing some HCPs to confuse "used" and new capsules, and/or causing others to choose to reuse capsules for the purpose of the simulation. While this is unlikely to occur in clinical practice as capsules will look distinct after being inhaled, even a minor	We note that there is no harm with inserting and administering a bent capsule as if pierced successfully, a full dose would be administered. Additionally, we note that all participants were able to eventually remove the capsule from the blister pack. We note the potential harm associated with the risk of not inserting a new capsule/missing a capsule is an unindicated patient being prescribed this medication which could lead to bronchospasm, hypoxia, and pulmonary compromise. We note that per the Applicant's root cause analysis, some of the use issues were related to study artifact. Additionally, we note the current mitigations in place including the dedicated picture and textual instruction on the QRG regarding administering the capsules. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no further recommendations at this time.

		using that instead (HU3). During another administration (capsule 7) this participant again failed to use a new capsule from the blister pack, and instead picked up a used capsule that was left on the table from a previous inhalation and inserted it into the chamber. Another participant kept their first capsule in the chamber after the first inhalation and continued to use it for the remaining inhalations (HU12).	used for the BTT and might assume certain existing handling practices they use with those packs and capsules would similarly not cause harm to the materials used for the BTT (HT01-NP). -*Study artifact: simulated patien*t – Since the patient actor was not actually inhaling the medication during this study, the capsule that the participant viewed was still full after each simulated inhalation. Therefore, some participants did not deem it necessary to insert new capsules from the blister pack for each inhalation or did not realize they had not inserted a new capsule because there was no change in appearance after inhalation (HU03, HU12, RU10). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due	underdosing associated with one or two capsules would be unlikely to affect an HCP's ability to determine hyperresponsiveness to Bronchitol. In the Bronchitol DPM-CF-303 Phase 3 study, the majority of patients who were hyperresponsive to Bronchitol were identified after inhalation of a total dose of ≤240 mg (6 capsules). Only 6 (1%) of the 486 patients screened for the DPM-CF-303 study required inhalation of the full Bronchitol dose of 400mg (10 capsules) for the demonstration of hyperresponsiveness. Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation.	

			to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to their own training methods while administering the BTT which might result in them skipping certain steps and/or changing how they conduct and/or teach certain steps to the patient (HU03).		
Hold inhaler upright and turn the mouthpiece until it locks in place. [C]	Use Difficulties (n=10; 5 Untrained HCPs, 2 Untrained RTs, 3 Trained HCPs) 14 participants DNC this task for 1 or more capsules because they stopped the BTT before administering all 10 capsules.	-9 participants initially turned the mouthpiece the opposite direction to close the inhaler. Since the mouthpiece would not turn any further, they ultimately turned it the correct way and completed the task (HU03, HU07, HU08, HU10, HU17, RU13, HT05-NP, HT09-RT, HT10-DO). HT10-DO also pushed the blue buttons in and closed the mouthpiece while the buttons were pushed. After the mouthpiece was locked closed, the participant released the buttons.	-*QRG step 4 does not sufficiently emphasize how to close and lock mouthpiece in place* – The image in step 4 on the QRG shows closing the mouthpiece in the direction of an arrow, which could lead users to believe it corresponds with the arrow indicator on the mouthpiece itself. Additionally, the text in step 4 does not indicate the need to turn the mouthpiece the opposite way from how it was opened in order to close it (HU03, HU07, HU08, HU10, HU17, RU13, HT05-NP, HT09-RT, HT10-DO).	No mitigation required. All participants were able close the mouthpiece such that no powder would have been lost during inhalations. No pattern of use error observed – this occurred for one (of 45) participant for one (of 450) capsule. All participants were able to close the mouthpiece and all capsules were pierced following locking of the inhaler such that no powder would have been lost during inhalations.	We note the potential harm associated with the risk of not locking the mouthpiece closed/not keeping the inhaler upright before closing the mouthpiece is not receiving the full contents of the capsule during the BTT, causing an unindicated patient to be prescribed this medication, which could lead to bronchospasm, hypoxia, and pulmonary compromise. We acknowledge that all participants were able to self-correct and understood how to close the inhaler. Additionally, we acknowledge the current mitigation strategy in place including picture in Step 4 with an arrow depicting the direction in which to turn the mouthpiece so it closes. Additionally, we note there is a later step for the user to check the inhaler to see if there is any powder remaining. Therefore, we find the Applicant's conclusion acceptable.

		-1 participant initially attempted to pierce the capsule before fully locking the mouthpiece in place. When the capsule did not pierce properly, the participant realized the mouthpiece was not fully locked, and was able to push further to lock it and complete the task (RU14).	-*Significance of inhaler arrow undefined* – The arrow on the inhaler only provides a directional cue for opening the mouthpiece. Users relying on this cue might incorrectly think the arrow is also an indicator for how to close the inhaler. Additionally, the inhaler further does not include any text to indicate the significance of the arrow (e.g. "Open"). Therefore, users might not know what it is indicating about the inhaler or might not see it at all when administering the BTT (HU07, HU08, HU10, RU13, HT05-NP, HT09-RT, HT10-DO). -*Mouthpiece turns in wrong direction for nearly 360 degrees* – Since the mouthpiece continues to turn to open until it has turned nearly in a full circle, it is not immediately		We find the residual risk has been minimized to the extent possible, and we have no further recommendations at this time.

			apparent to the user that they are turning the wrong way to close, until the mouthpiece stops turning completely. This could delay users' awareness that they are turning the wrong way to close (HU08). -*Insufficient visual distinction of arrow on inhaler* – The arrow on the inhaler is the same color as the rest of the inhaler and therefore blends in with the rest of the inhaler material. Therefore, users might not know what it is indicating about the inhaler or might not see it at all when administering the BTT (HT10-DO). -*Unfamiliar button-piercing mechanism* – Due to the unfamiliar button-piercing design of the BTT inhaler, HCPs might have certain expectations of how the device functions, which		

			could result in initial difficulties in opening and closing the inhaler. These expectations might be due to experience with other devices that have lockout mechanisms which require a two-button press, which may result in users believing the two-button design on the BTT inhaler acts as a locking mechanism for the inhaler. Additionally, the blue buttons are positioned at the bottom of the inhaler, in close range to the point where the mouthpiece opens and closes, therefore users might think they are related to an open/close mechanism to lock the mouthpiece in place (HT10-DO). -*Negative transfer* – Other dry powder inhalers currently on the market might function differently or include different use steps. Some users might have used other inhalers		

			previously and assumed this one worked the same way, leading to use issues (RU14). -*QRG step 4 does not provide sufficient indication of "click" feedback to lock mouthpiece* – The text on step 4 in the QRG does not indicate the feedback (i.e. should hear a "click") users should pay attention to when locking the mouthpiece in place, therefore users might not know how much force is required to properly close and lock the mouthpiece (RU14).		
Push both buttons at the same time. Release both buttons at the same time. [C]	Use Difficulties (n=13;4 Untrained HCPs, 3 Untrained RTs, 6 Trained HCPs) Use Errors (n=11;2 Untrained HCPs, 4 Untrained RTs, 5 Trained HCPs) 2 Untrained HCPs, 9 Untrained RTs, and 3 Trained HCP participants DNC this task for 1 or more	<u>Use Difficulties:</u> -1 participant was confused after piercing the capsule because they expected the capsule to look different and "crushed" after they pushed the buttons in and released. They did this several times. Throughout the participant pierced the capsule correctly each time and eventually moved on to the inhalation steps (HU3). -2 participants initially did not instruct the patient actor to release the buttons after they	-*Study artifact: simulated patient* – As patient actors were using a separate inhaler with an empty capsule to simulate an inhalation, there were instances in which the capsule became dislodged from the chamber during the inhaler transition. As such, if the patient actor kept the buttons	All HCPs performed this task acceptably during at least one of the capsule administrations, demonstrating that they understood the need to push and release the buttons in order to pierce the capsule prior to an inhalation (an improvement over the previous validation where two HCPs believed the buttons needed to	We note the potential harm associated with the risk of not releasing the buttons while inhaling is not receiving the full contents of the capsules during the BTT (since the capsule is not pierced), causing an unindicated patient to be prescribed Bronchitol, which could lead to bronchospasm, hypoxia, and pulmonary compromise. We note that patients should hear a rattling sound when inhaling, which prompted many participants in the study to check the inhaler to confirm that it was pierced correctly. We

	capsules because they stopped the BTT before administering all 10 capsules.	were pressed. When the capsule in the chamber did not rattle upon inhalation, they took the inhaler back to check it, and gave it back to the patient actor to repeat steps 6-7, either with the buttons released or instructing the patient to keep the buttons released (HU4, HU11). HU4 went back to the QRG and reviewed the steps again and realized they had not told the patient to release the buttons. HU11 was instructing the patient actor to "pierce" the capsule for 2 capsules, but not specifically to release the buttons. HU11 ended up pushing and releasing the buttons themselves and giving the inhaler back to the patient. -1 participant started to wait 1 minute after piercing and releasing the buttons, then looked at the QRG to review the instructions and realized they could proceed to the inhalation and that the 1 minute wait was actually for after the inhalation (HU5). -5 participants initially did not instruct the patient actor to release the buttons after they were pressed. When the capsule in the chamber did not rattle upon inhalation they took the inhaler back to the patient actor to repeat steps 6-7, either with buttons	pushed upon inhalation, the capsule could have still rattled, falsely indicting a successful inhalation to the participant, when in reality the capsule would not have rattled (HU04, HU11, RU02, RU06, RU15, HT01-NP, HT10-DO, HT12-MD). -*QRG step 5 does not sufficiently emphasize "release"* *task* – Step 5 in the QRG includes 2 separate tasks ("pierce" and "release") and extends in a linear format across the page. As such, users might read the first part of the step ("pierce") which is positioned close to the step number in purple, and overlook the second part of the step ("release") when going through the inhaler steps with a patient (HU04, HU11, RU06, RU15, HT15-RT). -*Study artifact: simulated patient* – The patient actor in the study did not	stay pressed to deliver the dose appropriately). Errors related to this task were rarely evident when the HCP performed the task themselves. Most of the failures, difficulties and close calls observed on this task were recorded when the HCP instructed the patient actor to handle the capsule and inhaler and can be largely attributed to study artifact; during each inhalation the patient actor only performed actions explicitly stated by the HCP. Often the incorrect performance was remedied when the HCP participant did not hear the capsule "rattle" in the chamber during the inhalation. Additionally, during an actual inhalation, powder is released out of the capsule through the two holes created by the piercing system and is inhaled by the patient through the mouthpiece. A CF patient inhaling Bronchitol	acknowledge the current mitigation strategies in place including the dedicated step 5 along with figures to represent the correct step performance which distinguishes the steps to 'push' then 'release'. Additionally, we note the Applicant's proposed revision of "pierce" to "push" to clarify the term based on subjective feedback from participants. Furthermore, we note several use issues can be attributed to study artifact. Therefore, we find the Applicant's conc usion acceptable. We fine the residual risk has been minimized to the extent possible, and we have no further recommendations at this time.

		released or instructing the patient actor to keep the buttons released (HT1-NP, HT5-NP, HT10-DO, HT12-MD, HT15-RT). -1 participant experienced a close call when they initially did not tell the patient actor to release the buttons before putting their mouth on the mouthpiece to inhale but caught themselves and instructed the patient actor to release the buttons (capsule2) (HT7-RT). -2 participants initially did not instruct the patient actor to release the buttons after they were pressed. When the capsule in the chamber did not rattle upon inhalation, they checked the capsule, determined the patient actor did not inhale all of the medication, and gave it back to the patient actor to repeat steps 6-7 with the buttons released (RU6, RU15). -1 participant almost forgot to pierce one capsule (capsule 2), giving the inhaler to the patient actor with the capsule unpierced then remembering. This participant took the inhaler back to push and release the buttons to pierce the capsule (RU2).	perform tasks that were not specifically articulated by the HCP participant, whereas in clinical practice HCPs could rely on CF patients' regular practice/prior knowledge to support performance (HU04, HU11, RU15, HT01-NP, HT07-RT, HT12-MD, HT15-RT). *-Instructional video and QRG do not sufficiently emphasize connection between releasing buttons and successful inhalation* – The instructional video instructs users to release the buttons during the initial inhalation walkthrough, however, the need to release the buttons is not emphasized further when the patient is inhaling the medication, when users might be still be pushing the buttons. Further, in the inhalation walkthrough of the video, there is no information about releasing the buttons as a	would have additional cues to a successful administration including the taste and feel of the powder as it is inhaled. It is expected that the CF patient would provide some level of feedback to the HCP regarding their experience during the inhalation. This would offer an additional opportunity for the HCP to become aware of any inhaler task issues arising during product administration, especially if no dry powder was detected. Since most HCPs performed this task correctly on most capsules, it is likely that despite a minor underdosing associated with one or more unpierced capsules, a hyperresponsive patient would be identified based on findings among adult CF patients screened for participation in the Bronchitol DPM-CF-303 Phase 3 study. In	

		Use Errors: -2 participants did not instruct the patient actor to release the buttons after they were pressed. In all instances, the capsule still rattled in the chamber, which indicated to the participant that the medication was inhaled (HU4, HU11). -3 participants did not instruct the patient actor to release the buttons after they were pressed. In all instances, the capsule still rattled in the chamber which indicated to the participant that the medication was inhaled (HT1-NP, HT10-DO, HT12-MD). -1 participant did not instruct the patient actor to release the buttons after they were pressed. The capsule did not rattle in the chamber, but the participant continued to the next steps after the inhalation (HT15-RT). -1 participant pushed the buttons and released them, but the capsule had moved out of place in the chamber, and they therefore did not successfully pierce the capsule (capsule 1) (HT2-NP). -3 participants did not instruct the patient actor to release the buttons after they were pressed.	potential troubleshooting technique if the capsule does not rattle in the initial walkthrough. Similarly, step 5 in the QRG instructs users to release the buttons but the QRG does not provide information about how holding the buttons in during inhalation could compromise the quality of the inhalation or about the connection between the rattle sound and releasing the buttons in step 5 or elsewhere (i.e. in step 7 inhalation tasks, in step 7 troubleshooting information, etc.). Due to this lack of information in the instructional materials, users might not fully appreciate the importance of the button release and could not instruct patients to release them during inhalation (HU04, RU06, RU15, HT15-RT). *-Connotation of instruction to "pierce" capsule in QRG*	that study, the majority of patients who were hyperresponsive to Bronchitol were identified after inhalation of a total dose of ≤240 mg (6 capsules) Only 6 (1%) of the 486 patients screened for the DPM-CF-303 study required inhalation of the full Bronchitol dose of 400mg (10 capsules) for the demonstration of hyperresponsiveness. Accordingly, Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation. Although not required, the proposed QRG includes revisions to Step 5 changing the words "Pierce" to "Push". Due to the narrow scope of these modifications which have been designed to address participant reported root causes identified in the study, it is anticipated that no new risks have been introduced and further validation of the product	

		In all instances, the capsule still rattled in the chamber which indicated to the participant that the medication was inhaled (RU2, RU6, RU15). -1 participant did not push the buttons to pierce the capsule at all before instructing the patient actor to exhale fully (capsule 7)(RU10).	*step 5* – The action to "pierce" something might imply different instructions to users (e.g. "push," vs. "push and release"). This might cause some users to simply instruct patients to "pierce" and not mention the need to actually release the buttons upon inhalation (HU11). -*Small size of inhaler* – Since it is possible for patients to wrap their hand fully around the base of the inhaler to hold to inhale, it could be difficult for users to see clearly whether or not the patient released the buttons after pushing them in to pierce the capsule (HU11, RU02, RU06, RU15). -*Study artifact: simulated inhalation* – During this study, the patient actor was not actually inhaling medication and	user interface is not required.	

			was instead using a separate inhaler with an empty capsule, therefore the capsule in the participant's inhaler was still full after each simulated inhalation. In this simulation, if the buttons remained pushed with no release, the participant would not see the effect in the chamber if all the medication was not inhaled. This lack of real-life feedback left participants without a true indicator as to whether the medication was inhaled fully or not (RU02, RU06, RU15). -*Negative transfer* – Other dry powder inhalers currently on the market might function differently or include different use steps. Some users might have used other inhalers previously and assumed this one worked the same way, leading to use issues (RU02, RU06, HT15-RT).		

			-*QRG step 5 does not sufficiently emphasize significance of releasing buttons* – The QRG notes the need to "Release" in step 5, however, it does not explain the significance of releasing the buttons as the step relates to inhalation. The lack of information about why it is important to release the buttons in step 5 of the QRG could result in users overlooking the "Release" step (RU06). -*Use of QRG during patient evaluation not consistent with clinical practice* – Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs. Lack of familiarity with the BTT requires users to rely on and carefully follow the QRG, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical		

			practice (RU15, HT10-DO, HT12-MD). -*Training session instructed to "puncture" capsule on step 5* – The training session incorporated the word "puncture" to describe what the action in step 5 is doing to the capsule in the inhaler chamber. The action to "puncture" something might imply different instructions to users (e.g. "push," vs. "push and release"). This might cause some users to simply instruct patients to "puncture" and not mention the need to actually release the buttons upon inhalation (HT01-NP, HT15-RT). -*Repetitive nature of BTT and "large" number of capsules* – Users performing the BTT might forget to complete certain tasks for certain capsules due to the number of capsules they are required to administer and the repetitive steps		

			(HT05-NP, HT07-RT, HT10-DO, HT12-MD). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to their own training methods while administering the BTT which might result in them skipping certain steps and/or changing how they conduct and/or teach certain steps to the patient (HT10-DO). -*Encouragement of patient to use medication* – In an effort to make patients feel comfortable about the idea of starting a new medication, HCPs might tailor their style of instruction and hesitate to fix certain incorrect steps that they do not deem high priority in an effort to avoid being too critical of patients. HCPs might be more inclined to treat the		

			BTT as a learning curve for the patient so they are more open to trying the medication if they pass the BTT (HT10-DO). -*Reliance on memory from training session* – Users who receive a training session on how to administer the BTT might feel a sense of confidence going into a session with a patient. As a result, users might not reference the QRG inhaler steps during the BTT but instead rely on memory from the training, and as such skip steps or perform steps incorrectly (HT10-DO, HT12-MD). -*Study artifact: simulated patient* – As patient actors were using a separate inhaler with an empty capsule to simulate an inhalation, participants might have experienced		

			confusion when the patient actor switched inhalers. This could have led participants to be uncertain about what about the BTT process was happening due to simulation and what was happening due to a use issue (HT12-MD). -*Study artifact: simulated patient* – The patient actor in the study did not perform tasks that were not specifically articulated by the HCP participant, whereas in clinical practice HCPs could rely on CF patients' regular practice/prior knowledge to support performance (RU02). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to their own training methods while		

			administering the BTT which might result in them skipping certain steps and/or changing how they conduct and/or teach certain steps to the patient (RU02, HT02-NP). -*Repetitive nature of BTT and "large" number of capsules* – Users performing the BTT might forget to complete certain tasks for certain capsules due to the number of capsules they are required to administer and the repetitive steps (RU10). -*Use of QRG during patient evaluation not consistent with clinical practice* – Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs. Lack of familiarity with the BTT requires users to rely on and carefully follow the QRG, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice (RU10).		

			-*QRG step 5 does not provide sufficient information about piercing capsule* – Step 5 in the QRG instructs users to "push both buttons at the same time" and "release both buttons at the same time" but does not provide further information about what these actions are physically doing to the capsule, or what audible feedback the user should expect to hear after a successful "pierce" of the capsule. Therefore, user might not know if they have successfully pierced the capsule and released the medication in the chamber until after the inhalation (HT02-NP). -*QRG step 5 text does not provide instruction about inhaler positioning for piercing capsule* – The QRG does not sufficiently emphasize the need to hold the inhaler steady and upright between		

			closing the mouthpiece and piercing the capsule. As such, users might handle the inhaler in such a way that dislodges the capsule out of the chamber, which would result in unsuccessful piercing of the capsule to release the medication (HT02-NP). *-Inhaler chamber does not secure capsule in place* – Once loaded, the capsule has excess room in the chamber to move around if the inhaler is handled in a rough way. Therefore, the capsule can become dislodged from the chamber which will lead to unsuccessful piercing of the capsule (HT02-NP). *-QRG step 5 does not provide sufficient information about end-state of capsule and powder after piercing* – The QRG does not indicate to users what the act of "piercing" the capsule does to the medication inside the chamber, why it		

			is necessary to push and release the buttons to pierce the capsule, nor what the capsule and powder are intended to look like in the chamber after successfully completing this step. This could result in users not feeling confident that they have completed this step correctly (HU03). *-Linear steps in QRG indicate progression and time –* The BTT steps in the QRG are all depicted linearly and with arrows, and all include waiting 1 minute. Additionally, step 7 in the QRG is shown in a linear format and includes holding breath for 5 seconds after inhalation. Since step 5 is shown in the same format, it is possible users could associate that step with waiting a certain amount of time before proceeding (HU05).		

			-*Large size / dimensions of QRG paper make it difficult to manipulate* – When opened fully, the QRG is larger than a standard patient chart or piece of paper. This might not be able to fit on in a typical clinical setting where HCPs see patients, and users might need to fold the sheet and flip back and forth between the BTT and inhaler steps, or not look at the inhaler steps at all, leading to potential missed steps an use issues (HU05). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to their own training methods while administering the BTT which might result in them skipping certain steps and/or changing how they conduct and/or teach certain steps to the patient (HU05).		

Exhale fully (do not exhale into the inhaler). [C]	Use Difficulties (n=2; 1 Untrained RT, 1 Trained HCP) Use Errors (n=10; 3 Untrained HCPs,4 Untrained RTs, 3 Trained HCPs) 14 participants DNC this task for 1 or more capsules because they stopped the BTT before administering all 10 capsules.	<u>Use Difficulties:</u> -1 participant experienced a close call when they initially did not instruct the patient actor to exhale fully before closing their lips around the mouthpiece on 1 capsule (capsule 7). They caught themselves and told the patient actor to exhale (RU14). -1 participant experienced a close call when they initially did not instruct the patient actor to exhale fully before closing their lips around the mouthpiece on 1 capsule (capsule 5). They caught themselves and told the patient actor to exhale (HT3-RT) <u>Use Errors:</u> -10 participants did not instruct the patient actor to exhale fully before closing their lips around the mouthpiece (HU5, HU7, HU12, RU3, RU9, RU11, RU12, HT-1NP, HT4-RT, HT13-RT). -	-*Instruction priority and focus given to inhalation tasks in step 7 in QRG* – Users following the QRG might choose to focus on following the exact tasks in step 7 when instructing the inhalation process to their patients. The exhalation step (step 6) is linked to the process of using the inhaler, however, since it is not part of step 7 in the QRG, it might be overlooked if users are looking at and following the tasks in step 7 specifically for the inhalation (HU05, HU07, HU12). -*QRG does not sufficiently emphasize step 6* – Since steps 5 and 7 are structured in a linear format with multiple tasks within each step, step 6 might be overlooked by users since the amount of tasks in the surrounding steps make them appear more significant (HU05, HU07, HU12).	No mitigations required. There is no unique harm associated with not exhaling fully before closing lips around the mouthpiece to inhale.	We note, per the Applicant's URRA, there is no potential harm associated with the risk of not having the patient exhale fully prior to inhaling, as the patient would still receive sufficient medication deposition to assess hyperresponsiveness if the patient inhales, taking a deep, steady breath per Step 7. We also note that exhaling prior to inhaling the medication is not a unique task to Bronchitol and is seen with other inhaled products. We acknowledge the current mitigation strategies in place including a dedicated step for this task along with a figure depicting the task (Step 6). Additionally, we note several use issues occurred due to study artifact. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no further recommendations at this time.

			-*Study artifact: simulated patient* – The patient actor in the study did not perform tasks that were not specifically articulated by the HCP participant, whereas in clinical practice HCPs could rely on CF patients' regular practice/prior knowledge to support performance (HU05, RU03, RU09, RU11, RU14, HT01-NP, HT03-RT, HT13-RT). -*Use of QRG during patient evaluation not consistent with clinical practice* – Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs. Lack of familiarity with the BTT requires users to rely on and carefully follow the QRG, which is not how clinicians are used to interacting with patients. Furthermore, HCPs might have existing clinical practices that they rely on with their patients that affect their		

			prioritization and/or instruction of certain inhalation steps in the QRG. As such, users might choose to tailor their instruction based on what works best for a patient's clinical needs (e.g. skipping QRG steps, prioritizing completing certain steps over/before others, etc.) (HU05, RU12). -*Clinical practice inconsistent with use steps in QRG* – HCPs might have existing clinical practices that they rely on with their patients that contradict the explicit inhalation steps in the QRG. As such, they might choose to tailor their instruction based on what works best for a patient's clinical needs (RU03, RU12). -*QRG does not sufficiently emphasize nuances of dry powder inhaler* – Dry powder inhalers follow a different procedure than other common inhalers used to treat CF.		

			The instructional materials for the BTT do not sufficiently emphasize this, which might lead users to skip important steps unique to the dry powder inhalation process because they assume they can follow the same routine practices as other types of inhalers (RU12). -*Negative transfer* – Other inhalers currently on the market might function differently or include different use steps. Some users might have used other inhalers previously and assumed this one worked the same way, leading to use issues (RU12). -*Repetitive nature of BTT and "large" number of capsules* – Users performing the BTT might forget to complete certain tasks for certain capsules due to the number of capsules they are required to administer		

			and the repetitive steps (RU14). -*Study artifact: test environment* – Test environment contributes to participant nervousness, resulting in them deviating from regular practice (RU14). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to their own training methods while administering the BTT which might result in them skipping certain steps and/or changing how they conduct and/or teach certain steps to the patient (HT04-RT).		
Close lips around mouthpiece and take a steady deep breath. Remove inhaler from	Use Difficulties (n=2; 1 Untrained RT, 1 Trained HCP) Use Errors (n=18;5 Untrained HCPs, 10 Untrained RTs, 3 Trained RTs)	<u>Use Difficulties:</u> -1 participant almost did not tell the patient actor to remove the inhaler from their mouth after holding their breath for 5 seconds and before exhaling. They caught themselves and instructed the patient actor to remove before the	-*Use of QRG during patient evaluation not consistent with clinical practice*– Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs.	Holding breath for five seconds before exhaling is considered ideal but is not necessary to achieve sufficient deposition of Bronchitol in the lungs to be able to assess	We note the potential harm associated with the patient not holding their breath for 5 seconds after inhaling is inadequate lung deposition of the drug, causing an unindicated patient to be prescribed this medication, which could lead to bronchospasm, hypoxia, and

mouth. Hold breath for 5 seconds before exhaling (do not exhale into inhaler). [C]	14 participants DNC this task for 1 or more capsules because they stopped the BTT before administering all 10 capsules	patient actor exhaled into the mouthpiece (HT8-NP). -1 participant initially did not instruct the patient actor to hold her breath for 5 seconds at all before exhaling but corrected themselves before the patient actor exhaled (RU11). <u>Use Errors:</u> -11 participants did not instruct the patient actor to remove the inhaler from their mouth before exhaling (HU4, HU11, HU12 HT7-RT, HT9-RT, RU2, RU4, RU6, RU9, RU14, RU15). -7 participants did not instruct the patient actor to hold their breath for 5 seconds before exhaling (HU9, HU12, RU1, RU2, RU3, RU7, HT14-RT).	Lack of familiarity with the BTT requires users to rely on and carefully follow the QRG, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice (HU09, RU01, RU02, RU03). -*QRG step 7 does not sufficiently emphasize holding breath for 5 seconds* – Since step 7 in the QRG involves 3 separate tasks, it is possible users will overlook the 5 second hold at the end and focus more on the inhalation step. Furthermore, patients might be naturally inclined to exhale after the "Remove" task, as they just completed a deep inhale of the medication, and therefore might skip the 5 second hold (HU09, RU01, RU11, HT14-RT).	hyperresponsiveness to inhaled mannitol. While some duration of breath-hold is almost universally recommended in use of orally inhaled medications, the majority of a dry powder dose is estimated to be inhaled even without employing a 5-second breath hold. A recent study examining the significance of breath-hold time in dry powder aerosol drug therapy reported that the lung dose of 6 different powder formulations was enhanced by 11.3% to 26.5% (mean 21.4%) with a 5-second breath-hold compared to no breath-hold (Horvath et al, 2017). The study by Horvath et al. did not evaluate Bronchitol. Bronchitol was designed to deliver a dose of 32.2 mg inhaled mannitol per capsule, which equates to 322 mg of mannitol delivered following administration of	pulmonary compromise. Additionally, we note the potential harm associated with the risk of the patient exhaling into the inhaler is an unindicated patient being prescribed Bronchitol due to moisture in the inhaler resulting in an accumulation of dosage and potential underdose, which could lead to bronchospasm, hypoxia, and pulmonary compromise. We acknowledge that several of the use issues were attributed to study artifact. We note that this task is not a unique task to Bronchitol and is seen with other inhaled products. Additionally, we acknowledge the current mitigation strategies in place including a dedicated picture and textual instruction in the QRG clearly depicting the three steps of inhaling, removing the inhaler, and holding the breath (Step 7). Therefore, we find the Applicant's conclusion acceptable. We fine the residual risk has been minimized to the extent possible, and we have no further recommendations at this time.

			-*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to their own training methods while administering the BTT which might result in them skipping certain steps and/or changing how they conduct and/or teach certain steps to the patient (HU09). -*Lack of training on BTT administration* –Some users might be accustomed to more hands-on training instruction for novel medical devices and tests. Therefore, some users might require additional training beyond watching an instructional video before they believe that they are fully prepared to administer the BTT to a patient (HU09).	10 capsules. By extrapolation, taking the case scenario of a 21.4% decrement (69 mg) in the total delivered dose of Bronchitol during the BTT, if no breath-hold was used on any of the 10 capsules, an estimated total inhaled Bronchitol dose of 253 mg would be expected. While minimal drug dose may be lost if the patient exhales immediately after inhalation, this will not impact the HCPs ability to determine hyperresponsiveness in most patients as the underdosing would be minimal. Among adult CF patients screened for participation in the Bronchitol DPM-CF-303 Phase 3 study, the majority of patients who were hyperresponsive to Bronchitol were identified after inhalation of a cumulative dose of ≤ 240 mg (6 capsules) which equates to an expected delivered dose of 193.2 mg. Only 6 (1%) of the	

			-*Study artifact: simulated patient* – The patient actor in the study did not perform tasks that were not specifically articulated by the HCP participant for the BTT tasks, however the patient actor might have completed other tasks related to a CF patient's regular practice without explicit instruction from the participant earlier in the session (e.g. taking dose of a bronchodilator inhaler). If the patient actor demonstrated that they were capable of doing certain tasks without instruction, participants might have made an assumption they did not need to explicitly instruct the patient actor to complete certain inhaler steps during the BTT administration that they had demonstrated earlier (i.e. steady deep breath, do not exhale into inhaler) (HU12).	486 patients screened for the DPM-CF-303 study required inhalation of the full Bronchitol dose (10 capsules) for the demonstration of hyperresponsiveness. Accordingly, Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation. Inhaling into the inhaler would introduce moisture into the chamber, potentially causing drug product to clump during inhalation from subsequent capsules or the capsule not spin during inhalation, resulting in a potential underdose. However, patients need not receive the full 400 mg dose of Bronchitol during the BTT in order to demonstrate hyperresponsiveness. Only 6 (1%) of the 486 patients screened for the DPM-CF-303 study required inhalation of the full Bronchitol dose of	

			-*Clinical practice inconsistent with use steps in QRG* – HCPs might have existing clinical practices that they rely on with their patients that contradict the explicit inhalation steps in the QRG. As such, they might choose to tailor their instruction based on what works best for a patient's clinical needs (RU01, RU07). -*Large size / dimensions of QRG paper make it difficult to manipulate* – When opened fully, the QRG is larger than a standard patient chart or piece of paper. This might not be able to fit on in a typical clinical setting where HCPs see patients, and users might need to fold the sheet and flip back and forth between the BTT and inhaler steps, or not look at the inhaler steps at all, leading to potential missed steps and use issues (RU02).	400mg (10 capsules) for the demonstration of hyperresponsiveness. Chiesi asserts that the amount of moisture introduced during exhalation would not prevent a hyperresponsive patient from being identified. Incorrect inhaler technique is common, regardless of the type of device prescribed. In the Supplemental Human Factors Validation study, untrained participants experienced this use error more frequently than trained participants. Root cause analysis was most frequently linked to lack of appreciation of nuances of dry powder formulations and negative product transfer from other inhalers. Chiesi has included discussion of proper inhaler best practices as part of the proposed training module to help to reinforce these best practices with HCPs. HCPs who seek further information, the	

			-*Study artifact: simulated patient* – The patient actor in the study did not perform tasks that were not specifically articulated by the HCP participant, whereas in clinical practice HCPs could rely on CF patients' regular practice/prior knowledge to support performance (RU02, RU03, RU11). -*Apparent simplicity of inhaler based on small size and shape* – As this inhaler is small, it could give the impression to HCPs that it will be simple to use. This could lead to HCPs assuming they know how to use it without reading through and/or following the QRG steps (RU03). -*Negative transfer* – Other inhalers currently on the market might function differently or include different use steps. Some users might have used other inhalers previously and	Bronchitol website will contain a "frequently asked questions" section including information on inhalation best practices. Consequently, Chiesi concludes that the level of residual risk is acceptable and given that the use error observed is inherent in all dry powder inhalers, it does not warrant further risk mitigation.	

			assumed this one worked the same way, leading to use issues (RU03, RU07). -*Absence of training inhaler* – Some users might prefer to have, or are used to having, their own "dummy" or training inhaler to demonstrate the steps to the patient as the patient goes through the inhalation process, rather than relying on verbalizing each step for each capsule (HU04). -*Study artifact: simulated patient* – The patient actor in the study did not perform tasks that were not specifically articulated by the HCP participant for the BTT tasks, however the patient actor might have completed other tasks related to a CF patient's regular practice without explicit instruction from the participant earlier in the session (e.g. taking		

			dose of a bronchodilator inhaler). If the patient actor demonstrated that they were capable of doing certain tasks without instruction, participants might have made an assumption they did not need to explicitly instruct the patient actor to complete certain inhaler steps during the BTT administration that they had demonstrated earlier (i.e. steady deep breath, do not exhale into inhaler) (HU04, HU12). *-Lack of training on BTT administration* –Some users might be accustomed to more hands-on training instruction for novel medical devices and tests. Therefore, some users might require additional training beyond watching an instructional video before they believe that they are fully prepared to administer the BTT to a patient (HU11).		

			-*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to their own training methods while administering the BTT which might result in them skipping certain steps and/or changing how they conduct and/or teach certain steps to the patient (HU11, RU04). -*QRG step 7 does not sufficiently emphasize exhaling away from inhaler* – The instruction to exhale away from the inhaler is in the smaller text for "Hold for 5 seconds." As exhaling away is not emphasized as its own task within step 7, users might not realize the importance of not exhaling before holding for 5 seconds, and further of not		

			exhaling into the inhaler (HU11, RU04, RU06). -*Large size / dimensions of QRG paper make it difficult to manipulate* – When opened fully, the QRG is larger than a standard patient chart or piece of paper. This might not be able to fit on in a typical clinical setting where HCPs see patients, and users might need to fold the sheet and flip back and forth between the BTT and inhaler steps, or not look at the inhaler steps at all, leading to potential missed steps and use issues (RU02). -*Study artifact: simulated patient* – The patient actor in the study did not perform tasks that were not specifically articulated by the HCP participant, whereas in clinical practice HCPs could rely on CF patients' regular practice/prior knowledge to support performance (RU02,		

			RU06, RU09, RU14, HT07-RT, HT08-NP). -*Use of QRG during patient evaluation not consistent with clinical practice* – Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs. Lack of familiarity with the BTT requires users to rely on and carefully follow the QRG, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice (RU02, RU15, HT07-RT). -*QRG does not sufficiently emphasize nuances of dry powder inhaler* – Dry powder inhalers follow a different procedure than other common inhalers used to treat CF. The instructional materials for the BTT do not sufficiently emphasize this, which might lead users to skip important steps unique to the dry powder inhalation		

			process because they assume they can follow the same routine practices as other types of inhalers (RU04, RU06, RU15, HT09-RT). -*Negative transfer* – Other inhalers currently on the market might function differently or include different use steps (e.g. MDI inhalers that do not involve dry powder, therefore do not have the same risks associated with use and might incorporate other materials such as spacers to facilitate use). Some users might have used other inhalers previously and assumed this one worked the same way, leading to use issues (RU04, RU06, RU15, HT09-RT). -*Study artifact: test environment* – Test environment contributes to participant nervousness, resulting in them deviating from regular practice (RU14).		

Open inhaler. If powder is left in capsule, repeat steps 6 and 7. [C]	Use Difficulties (n=3;2 Untrained HCPs, 1 Trained HCP) Use Errors (n=20; 7 Untrained HCPs, 7 Untrained RTs, 6 Trained HCPs) 14 participants (9 Untrained RTs, 2 Untrained HCPs, 3 Trained HCPs) DNC this task for 1 or more capsules because they stopped the BTT before administering all 10 capsules.	<u>Use Difficulties:</u> -1 participant set the time for 1 minute (on capsule 1) before checking the capsule to see if the medication was inhaled. They then checked the capsule during the 1 minute wait and before taking the patient actor's SpO2 value (HU7). -1 participant was confused when they checked the capsule after the first inhalation, expecting to see an empty chamber and a broken/crushed capsule. They then had the patient actor repeat steps 6 and 7 since there was still powder left in the chamber (HU10). -1 participant set the timer (on capsule 1) for 1 minute and got the patient's SpO2 before checking the status of the inhaled capsule. When moving on to capsule 2 the participant realized they had not checked after the first inhalation. They then had the patient actor repeat steps 6-7, checked the chamber to make sure the medication was inhaled, waiting another minute, and took the SpO2 value again (HT7-RT). <u>Use Errors:</u> -20 participants moved on to the next step (either	-*Study artifact: simulated inhalation* – Since the patient actor was not actually inhaling the medication during this study, the capsule that the participant viewed was still full after each simulated inhalation. This could have resulted in participants deeming it unnecessary to visually check each capsule after inhalation (HU03, HU04, HU05, HU07, HU17, RU07, HT03-RT, HT06-MD, HT07-RT). -*Repetitive nature of BTT and "large" number of capsules* – Users performing the BTT might forget to complete certain tasks for certain capsules due to the number of capsules they are required to administer and the repetitive steps (HU04, HU07, HU11, RU03, RU07, RU14, RU15, RU16, HT06-MD, HT07-RT).	No mitigation required. There is no unique harm associated with repeating the inhalation tasks due to confusion about what the capsule should look like in the chamber after inhalation. Most HCPs checked to confirm that the capsule was empty of powder at the end of each inhalation. However, a pattern of forgetting to check a capsule was observed, particularly associated with the final capsule of each incremental dosing (e.g. capsule 1, 3, 6, 10). It is unlikely that a minor underdose associated with not checking a subset of capsules would result in failure to detect hyperresponsiveness. Only 6 (1%) of the 486 patients screened for the DPM-CF-303 study required inhalation of the full Bronchitol dose of 400mg	We note the potential harm associated with the risk of not checking for residual powder is an underdose and an unindicated patient potentially being prescribed Bronchitol, which could lead to bronchospasm, hypoxia, and pulmonary compromise. We acknowledge the current mitigation strategies in place including the dedicated step and figure in the QRG (Step 8). Additionally, we note the Applicant's proposed revisions based on participants' subjective feedback including the addition of a statement on the BTT side of the QRG to remind users that they should confirm the powder has been inhaled, along with the revised term "Confirm" for Step 8 in the inhaler steps of the QRG. Furthermore, we note several use issues occurred due to study artifact. Therefore, we find the Applicant's conc usion acceptable. We find the residual risk has been minimized to the extent possible and we have no further recommendations at this time.

		by going to inhaler step 3 for the next capsule or by taking the patient actor's SpO2 and FEV1 values) before opening the inhaler and checking if the capsule was empty and that no powder was left in chamber (HU03 [x1], HU04 [x10], HU05 [x1], HU07 [x2], HU11 [x1], HU12 [x3], HU17 [x1], RU03 [x4], RU06 [x8], RU07 [x1], RU10 [x3], RU14 [x1], RU15 [x1], RU16 [x1], HT01-NP [x3], HT03-RT [x1], HT04-RT [x1], HT06-MD [x2], HT07-RT [x1], HT12-MD [x2]).	- *QRG step 5 does not provide sufficient information about end-state of capsule and powder after piercing* – The QRG does not indicate to users what the act of "piercing" the capsule does to the medication inside the chamber, why it is necessary to push and release the buttons to pierce the capsule, nor what the capsule and powder are intended to look like in the chamber after successfully completing this step. This could result in users not feeling confident that they have completed this step correctly (HU10). - *Study artifact: simulated inhalation* – During this study, the patient actor was not actually inhaling medication and was instead using a separate inhaler with an empty capsule, therefore the capsule in the participant's inhaler	(10 capsules) for the demonstration of hyperresponsiveness. Additionally, in clinical practice there would be additional cues that indicate to a user that the patient did not receive the full dose, such as not hearing the rattling sound (Step 7) and the patient not feeling the sensation or taste of medication as they inhale. These additional cues would provide a further opportunity to identify inhaler task use issues and correct them. In addition, as HCPs became more familiar with the BTT and best practices of DPI inhalation, their familiarity will further support consistent execution of this step. Chiesi concludes that the level of residual risk is acceptable and does not warrant further risk mitigation. Although not required, the proposed QRG includes revisions to the BTT side of the QRG, incorporating	

			was still full after each simulated inhalation. This lack of real-life feedback left participants without a true indicator as to whether the medication was inhaled fully or not (HU10). -*Unfamiliar nature of BTT* – The BTT is unique from other treatments/assessments performed by HCPs. Due to the unfamiliar protocol required to conduct the BTT, users may be getting acclimated to their own training methods while administering the BTT which might result in them skipping certain steps and/or changing how they conduct and/or teach certain steps to the patient (HU04, HU07, RU07, RU15, HU11, HT04-RT). - *QRG does not sufficiently emphasize need to check contents of inhaled capsules that immediately precede BTT steps* – For several capsules in the BTT	checking the capsule to further emphasize the need to complete this step on capsules that precede BTT steps. Additionally, the "(b) (4)" instruction has been changed to "CONFIRM" as this word is deemed to be more directly relate to the action users need to perform. Due to the narrow scope of these modifications which have been designed to address participant reported root causes identified in the study, it is anticipated that no new risks have been introduced and further validation of the product user interface is not required.	

			sequence, after the patient completes an inhalation, users cannot physically proceed to the next step without checking the contents of the capsule that was just inhaled, since they must physically open the mouthpiece to load the next capsule. However, after administering capsules that are "last" in a sequence (e.g. capsules 1, 3, 6, and 10), users are not immediately loading the next capsule after the inhalation. Therefore, the next task for users is not necessarily to discard the used capsule and load the next capsule, but rather to follow the BTT steps and prepare to obtain FEV1 and/or SpO2 values. Since users can physically still continue with the procedure without checking the capsule on these steps (since it is not a requirement for		

			proceeding to the next step in the process), users might skip this inhaler step in the QRG and not check the contents of the capsule until after they check the patient's values and begin the process of loading the next capsule for the next sequence (HU07, HU12, RU07, RU14, RU15, HT01-NP, HT03-RT, HT04-RT, HT06-MD, HT07-RT, HT12-MD). -*Use of QRG during patient evaluation not consistent with clinical practice* – Reliance on a QRG while in the presence of a patient is inconsistent with clinical practice for many HCPs. Lack of familiarity with the BTT requires users to rely on and carefully follow the QRG, which is not how clinicians are used to interacting with patients, resulting in steps being potentially skipped in clinical practice (HU12). - *QRG does not sufficiently emphasize step 8 as*		

			required step in the process – Since step 8 has a box around it in the QRG, it might appear to be separate from the important inhaler steps. Users might overlook this step, thinking it is something for consideration, or an optional step, rather than something the manufacturer is calling more attention to. Furthermore, users might associate checking that the medication is gone with the process for getting values rather than the inhalation steps (HU12, HT06-MD). -*Instructional video and QRG inform users that "Rattle" during inhalation indicates success* – In the instructional materials for the BTT (video and QRG), users are told the "rattle" sound is an indicator of a good inhalation. If users		

			hear the “rattle” vibration during inhalation, they might feel like they do not need to additionally check the inside of the inhaler visually for any powder that might not have been inhaled (RU03, RU06, RU10). -*Clinical practice inconsistent with use steps in QRG* – HCPs might have existing clinical practices that they rely on with their patients that contradict the explicit inhalation steps in the QRG. As such, they might choose to tailor their instruction based on what works best for a patient’s clinical needs (RU06). -*Instruction priority and focus given to waiting 1 minute and getting patient values* – The BTT step that immediately follows step 8 of the QRG (checking that the powder is gone and discarding the capsule) involves waiting for a		

			specific amount of time (1 minute), obtaining SpO2 and FEV1 values from the patient, and possibly monitoring the patient's physical symptoms. These steps require diligence in recording and evaluating and are unique to the BTT and clearly tied to ensuring the patient's well-being. As such, checking the capsule for powder right after inhalation might be perceived as less significant to the user. This could result in the user forgetting to check or leaving this step for after the 1-minute wait and values are completed (RU14, RU15, RU16, HT01-NP, HT04-RT, HT07-RT). -*Study artifact: test environment* – Test environment contributes to participant nervousness, resulting in them deviating from regular practice (RU14, RU16).		

			-*Reliance on memory from training session* – Users who receive a training session on how to administer the BTT might feel a sense of confidence going into a session with a patient. As a result, users might not reference the QRG inhaler steps during the BTT but instead rely on memory from the training, and as such skip steps or perform steps incorrectly (HT12-MD).		

4 LABEL AND LABELING

We evaluated the proposed labels and labeling and identified areas of vulnerability that may lead to medication errors. The Applicant proposed including some BTT instructions in Section 2 of the PI; however, we note that their proposed language did not incorporate all of the graphics and information from the intend-to-market BTT HCP IFU that was evaluated in the human factors validation study. Thus, we were concerned that HCPs may follow the incomplete instructions in Section 2 of the PI, rather than use the QRG that included graphics and spaces allocated to write down SpO2 and FEV1 values, color in the number of capsules administered etc, which may lead to use errors. Therefore, following discussions with the clinical team, we recommended that these instructions be removed from Section 2 of the PI and the Applicant instead include a reference to the BTT HCP IFU document to minimize the risk of HCPs only utilizing the instructions in Section 2. See Section 5.1 for our specific recommendations.

Additionally, based on the Applicant's IR response (b) (4) We do not have any remaining concerns with the Applicant's proposal.

Furthermore, after reviewing the HF validation study results, subjective feedback, and root cause analysis, we propose some recommendations to the BTT blister pack labels and the HCP IFU based on our expert heuristic review to further emphasize important tasks related to the administration of the BTT. See Section 5.2 for our recommendations.

5 CONCLUSION & RECOMMENDATIONS

The HF validation study results demonstrated use issues (i.e., use errors, use difficulties, and close calls) with some critical tasks that may result in harm. We note that the Applicant has proposed additional mitigations following the HF validation study to further promote the safe and effective use of the proposed BTT product user interface. We discussed the results and observed use issues with our clinical colleagues and based on our expert heuristic review, the proposed mitigations from the sponsor as well as our proposed recommendations for the QRG should help to mitigate some of the observed use errors in the study. We acknowledge that some residual risks remain but determined that based on our review of the QRG, the subjective feedback and root cause analysis provided in the human factors validation study, the implementation of additional labeling mitigations are not likely to further reduce the residual risks. However, we do note that some of the subjective feedback received in the study pointed to the fact that "*the paper-based QRG does not restrict users from continuing if they skip a step in the process. Some HCPs might be accustomed to computer-based programs that provide calculation decision support in their clinical practice."* Therefore, the Applicant could consider developing a computerized BTT that helps to facilitate calculations, comparison of SpO2 and FEV1 values, and timing that is associated with the administration of the BTT. However, we note that this may require information and/or data, such as data from a human factors

validation study, to ensure that this aspect of the user interface, if proposed, does not introduce different risks.

Additionally, after discussions with the clinical team, we note that the BTT will be conducted in specialty clinics by specialized healthcare providers for a closely monitored patient population (patients with cystic fibrosis), which may provide additional mitigation strategies. Furthermore, per discussions with our clinical colleagues, we note that despite recent advances in the treatment of cystic fibrosis, the need for additional treatments in the management of this disease remain, which may outweigh the residual risk for this product.

We provide recommendations for the proposed labels and labeling for the Applicant below. Additionally, we provided PI recommendations for the Division, which were communicated to the Applicant on September 4, 2020[e].

5.1 RECOMMENDATIONS FOR DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

A. Prescribing Information

1. Dosage and Administration Section

a. We recommend revising this section to only include a reference to the BTT HCP QRG, instead of including only certain instructions on performing the BTT to minimize the risk of HCPs only utilizing Section 2 instead of the BTT HCP QRG.

5.2 RECOMMENDATIONS FOR CHIESI USA INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. Consider revising your expiration date to one of the aforementioned formats.

B. Blister Pack labels for the BTT Blister Pack Only

1. Based on the use errors and subjective feedback related to task of administering X number of capsules, we recommend revising the BTT Blister Pack to include boxes around the amount of capsules needed for each of the respective steps (e.g., a box around 1 capsules for Step C, a box around 2 capsules for Step D and so on) and to label each box with the corresponding step, as this may help

[e] Do, Ngoc-Linh. Labeling PMR/PMC Discussion Comments for Bronchitol (mannitol) NDA 202049. Silver Spring (MD): FDA, CDER, OND, DPACC (US); 2020 SEPT 04.

improve the users' ability to track the amount of capsules that should be administered to the patient for each step of the BTT.

C. BTT HCP Instructions For Use (formerly known as BTT QRG)
    1. Based on the use errors and subjective feedback related to the tasks of 1) waiting 5-15 minutes after instructing the patient to use an inhaled short-acting beta agonist (in Step B) and 2) waiting 1 minute and recording new SpO2 and/or FEV1 values (in Steps C through F), we recommend revising the color of the clock images in Steps B-F to increase the prominence of the wait time, as some participants felt that this important information blended in with the rest of the tasks ("other purple information in the QRG") and was easily overlooked.
    2. Based on the use errors and subjective feedback related to the task of administering X number of capsules, we recommend revising the HCP IFU to include instructions on how the HCP should proceed if capsules are skipped or missed in a step or multiple steps.
    3. Based on the use errors and subjective feedback related to the task of wait 15 minutes, then monitor SpO2 and FEV1 to confirm recovery to baseline, we recommend adding the following statement to the red "STOP" box" to emphasize the BTT should not be continued or restarted:
    "DO NOT continue the BTT."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bronchitol received on May 1, 2020 from Chiesi USA Inc..

Table 2. Relevant Product Information for Bronchitol	
Initial Approval Date	N/A
Active Ingredient	mannitol
Indication	indicated for the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.
Route of Administration	Oral inhalation
Dosage Form	inhalation powder
Strength	40 mg per capsule
Dose and Frequency	400 mg twice daily The Bronchitol Tolerance Test must be performed by a healthcare provider able to manage acute bronchospasm. The Bronchitol Tolerance Test requires monitoring oxygen saturation (SpO2) and performing spirometry (FEV1) multiple times. SpO2 and FEV1 values recorded throughout the test must be compared to calculated reference values to determine if BRONCHITOL may be prescribed.
How Supplied	supplied in cartons containing 10, 140 or 560 capsules in blister packs co-packaged with 1, 1, and 4 inhalers respectively in a carton
Storage	BRONCHITOL should be stored between 68°F-77°F (20°C-25°C) with excursions permitted between 59°F-86°F (15°C-30°C). [See USP Controlled Room Temperature]. Do not refrigerate. Do not freeze.
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 3, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, bronchitol and mannitol. Our search identified three previous reviews[f,g,h], and we confirmed that our previous recommendations were implemented.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design & Results

- \\CDSESUB1\evsprod\nda202049\0040\m5\53-clin-stud-rep\535-rep-effic-safety-stud\cystic-fibrosis\5354-other-stud-rep\p3235-r-007\p3235-r-007-v1-1.pdf

APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F. APPLICANT RESPONSE TO AGENCY INFORMATION REQUESTS (IR)

- August 4, 2020 response to the Agency's August 3, 2020 IR: \\CDSESUB1\evsprod\nda202049\0042\m1\us\1-11-3-info-amendment-clinical-fda-ir-03aug2020.pdf
- August 24, 2020 response to the Agency's August 21, 2020 IR: \\CDSESUB1\evsprod\nda202049\0043\m1\us\1-11-3-info-amendment-clinical-fda-ir-21aug2020.pdf
- September 21, 2020 response to the Agency's September 17, 2020 IR: \\CDSESUB1\evsprod\nda202049\0045\m1\us\1-11-3-info-amendment-clinical-fda-ir-17sept2020.pdf
- September 25, 2020 response to the Agency's September 24, 2020 IR: \\CDSESUB1\evsprod\nda202049\0047\m1\us\1-11-3-info-amendment-clinical-fda-ir-24sept2020.pdf

[f] Owens, L. Label and Labeling Review for Bronchtiol (NDA 202049). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 FEB 05. RCM No.: 2012-1361.

[g] Whaley, E. HF Study Report & Label and Labeling Review for Bronchitol (NDA 202049). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUNE 18. RCM No.: 2018-2791; 2018-2790.

[h] Whaley, E. HF Protocol Review for Bronchitol (IND 70277). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEPT 11. RCM No.: 2019-1564.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Bronchitol labels and labeling submitted by Chiesi USA Inc..

- Bronchitol container (inhaler) label received on May 1, 2020
- Bronchitol 1-week carton labeling received on May 1, 2020
- Bronchitol 4-week carton labeling received on May 1, 2020
- Bronchitol blister pack labeling received on May 1, 2020
- BTT carton labeling received on May 1, 2020
- BTT Sample Pack carton labeling received on May 1, 2020
- Sample Pack Training Kit carton labeling received on September 25, 2020
- Training Kit blister pack labeling received on May 1, 2020
- Training Kit container (inhaler) label received on May 1, 2020
- BTT QRG (image not shown) received on May 1, 2020
  - \\CDSESUB1\evsprod\nda202049\0040\m1\us\1-14-1-1-btt-qrg.pdf
- Bronchitol QRG (image not shown) received on May 1, 2020
  - \\CDSESUB1\evsprod\nda202049\0040\m1\us\1-14-1-1-qrg.pdf
- Prescribing Information (Image not shown) received on May 1, 2020
  - \\CDSESUB1\evsprod\nda202049\0040\m1\us\1-14-1-3-bronchitol-pi-draft-word-doc.docx

(b) (4)

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[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 18, 2020

To: Ngoc-Linh Do
Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

From: Taylor Burnett, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., RAC
Team Leader
OPDP

Subject: OPDP Labeling Comments for BRONCHITOL® (mannitol) inhalation powder), for oral inhalation use

NDA: 202049

In response to DPACC's consult request dated June 2, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for BRONCHITOL® (mannitol) inhalation powder), for oral inhalation use (Bronchitol).

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DPACC (Ngoc-Linh Do) on September 4, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on September 17, 2020.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 1, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact name of OPDP reviewer at (240) 402-1349 or Taylor.Burnett@fda.hhs.gov.

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 16, 2020
To:	Sally Seymour, MD Director **Division of Pulmonary, Allergy, and Critical Care (DPACC)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)** Taylor Burnett, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	BRONCHITOL (mannitol)
Dosage Form and Route:	inhalation powder, for oral inhalation use
Application Type/Number:	202049
Applicant:	Chiesi USA, Inc.

1 INTRODUCTION

On May 18, 2012, Pharmaxis Ltd submitted for the Agency's review an original New Drug Application (NDA) for inhaled mannitol to be used for the treatment of cystic fibrosis. On March18, 2013, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) issued a Complete Response Letter (CRL). On December 19, 2018, Chiesi Farmaceutici S.p.A. in collaboration with Pharmaxis Ltd resubmitted for approval, BRONCHITOL (mannitol) inhalation powder, for oral inhalation use.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the DPACC on June 2, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for BRONCHITOL (mannitol) inhalation powder, for oral inhalation use.

2 MATERIAL REVIEWED

- Draft BRONCHITOL (mannitol) inhalation powder, for oral inhalation use PPI and IFU received on December 19, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 4, 2020.
- Draft BRONCHITOL (mannitol) inhalation powder, for oral inhalation use Prescribing Information (PI) received on December 19, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 4, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 14, 2013

TO: Angela Ramsey, Regulatory Project Manager
Anthony Durmowicz, M.D., Medical Officer, Team Leader
Kimberly Witzmann, M.D., Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202049

APPLICANT: Pharmaxis Ltd.

DRUG: inhaled dry powder mannitol (Bronchitol)

NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: Standard review

INDICATION: cystic fibrosis

CONSULTATION REQUEST DATE:	July 27, 2012 (signed)
INSPECTION SUMMARY GOAL DATE:	February 18, 2013 (original)
DIVISION ACTION GOAL DATE:	March 18, 2013
PDUFA DATE:	March 18, 2013

I. BACKGROUND:
Dehydration of airway secretions may lead to impaction of mucus plaques on the cilia and failure of mucus transport up through the bronchi. These pathophysiologic changes in cystic fibrosis patients may lead, in part, to the clinical findings and complications seen in the natural history of this autosomal recessive, chronic disease of the exocrine glands. Although the mechanism whereby osmotic agents increase clearance of mucus remains unclear, the osmotic properties of inhaled mannitol may potentially enhance mucociliary clearance from the lungs.

Two adequate and well-controlled clinical studies were submitted in support of the applicant's NDA. Study DPM-CF-302 was the only trial to include U.S. patients and did not meet its targeted efficacy endpoints. Three U.S. sites were selected for clinical site audit. The U.S. sites had the highest number of randomized, DPM-CF-302. Study DPM-CF-301, an international trial, differed in study results, and potentially in study conduct. Two foreign study sites in the U.K. were selected for clinical site audit.

Study DPM-CF-302
DPM-CF-302 (Study 302) was a double blind, randomized, parallel arm, controlled, intervention clinical trial. The purpose of the study was to determine the efficacy and safety of chronic treatment with dry powder mannitol for inhalation compared with control in subjects with cystic fibrosis. The primary objective was to determine whether inhaled mannitol compared to control improved forced expiratory volume in one second (FEV1) by spirometry in subjects with cystic fibrosis. Subjects with cystic fibrosis, age greater than 6 years, and with baseline FEV1 greater than 40% and less than 90% predicted were eligible to participate. Subjects were administered a mannitol tolerance test. Subjects with a negative mannitol tolerance test result were randomized to receive 400 mg inhaled mannitol BID or control for 26 weeks. The primary efficacy outcome of the study was the change in absolute FEV1 from baseline to week 26.

Study DPM-CF-301
DPM-CF-301 (Study 301) was a double blind, randomized, parallel arm, controlled, intervention clinical trial. The purpose of the study was to determine the efficacy and safety of chronic treatment with inhaled dry powder mannitol (IDPM) compared with control, in subjects with cystic fibrosis. The primary objective was to determine the effect of IDPM compared to control on FEV1 by spirometry in patients with cystic fibrosis. Subjects with cystic fibrosis, age greater than 6 years, and with baseline FEV1 greater than 40% and less than 90% predicted were eligible to participate. Screened subjects were randomized to receive 26 weeks of IDPM 400 mg twice a day or matched control. The primary efficacy outcome of the study was the change in absolute FEV1 from baseline to Week 26.

II. RESULTS:

Name of CI City, State	Protocol/Study Site	Insp. Date	Final Classification*
Perry Brown, MD Boise, ID	Protocol 302 Site #10131 n=10 subjects enrolled	October 1-16, 2012	VAI
Peter Fornos, M.D. San Antonio, TX	Protocol 302 Site #10116 9 subjects enrolled	October 16-18, 2012	NAI
David Schaeffer, M.D. Jacksonville, FL	Protocol 302 Site #10125 7 enrolled	September 19-21, 2012	NAI
Chris Upton, M.D. Norwich, UK	Protocol 301 Site #44103 11 subjects enrolled	September 17-21, 2012	VAI
Martin Walshaw, M.D. Liverpool, UK	Protocol 301 Site #44111 15 subjects enrolled	September 24-28, 2012	Preliminary: VAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.
Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed-out, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. Perry S. Brown, M.D./Protocol DPM-CF-302, Site #10131
Boise, ID

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from October 1 to 16, 2012. A total of 10 subjects were screened and enrolled. Eight subjects completed the study.

An audit of 10 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection. Deficiencies with selected relevant clinical examples are outlined below:

i. Deficiencies related to not conducting the study in accordance with the investigational plan.

a. DPM-CF-302 Protocol Section 3.3.7.3 required two flow volume curve printouts for data verification. The 10 subjects had no print-outs of baseline and recovery spirometry flow volume curves. The Wang and Hankinson program for spirometry measurements was also not utilized for the mannitol tolerance test.

   Per the Principal Investigator's response of October 27, 2012, Dr. Perry Brown noted that at the time Study DM-CF-302 was conducted and spirometry values were obtained, there were limitations in spirometry equipment and software available to adequately conduct the mannitol tolerance test (MTT).

b. Per study protocol, a termination visit including all assessments scheduled for Visit 4 was to be performed, no later than 14 days after discontinuation or study withdrawal. Specifically, Subject (b) (6) was terminated at Visit 5, but the Cystic Fibrosis Questionnaire, Health Utilities Index, and urine pregnancy test required at Visit 4 (and termination) were not conducted.

c. Subject (b) (6) serious adverse event requiring hospitalization on (b) (6) was not reported to the Sponsor within 24 hours of notification of occurrence.

d. Subject (b) (6) adverse event on (b) (6) was not reported to the IRB until (b) (6), which was beyond the 10 calendar day required reporting to the IRB following discovery of the event.

e. Subject (b) (6) Visit 4 used the Knudson program for spirometry predictive values rather than the Wang and Hankinson program.

ii. Deficiencies related to adequate and accurate record keeping. Specifically progress notes were not maintained for the following: (a) Subject [redacted]: Screening Visit [redacted], (b) Subject [redacted]: Screening Visit [redacted], Visit 1 [redacted], and Visit 2 [redacted], (c) Subject [redacted]: Screening Visit [redacted] and Visit 1 [redacted], (d) Subject [redacted]: Screening Visit [redacted] and Visit 1 [redacted], and (3) Subject [redacted]: Screening Visit [redacted].

Findings on the Form FDA 483 and other discussion items between the ORA field staff and the clinical study site were discussed at length with the review division medical team. For this Study DPM-CF-302 that did not meet its pre-specified efficacy endpoints, the observations cited above were not considered critical by the DPARP medical team, when assessed in context. OSI defers to DPARP, in regards to impact of these observations (e.g., lack of baseline and recovery spirometry flow volume curve printouts, utilization of the Wang and Hankinson spirometry predictive value protocols for mannitol tolerance tests, lack of reproducible pre-bronchodilator FEV1 and FVC maneuvers for eligibility criteria), on final efficacy determinations.

c. Assessment of data integrity:
Not withstanding the above regulatory deficiencies, the study appears to have been conducted adequately. OSI defers to DPARP, in regards to the impact these observations may have on data reliability and use of data in their decision making process for this application.

Note: Observations noted above are based on preliminary communications with the field investigator and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

2. Peter Fornos, M.D./Protocol DPM-CF-302 Site, #10116
San Antonio, TX

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from October 16 to 18, 2012. A total of 11 subjects were screened and 9 subjects were enrolled. Three subjects completed the study.

An audit of the 11 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations

during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

3. David Schaeffer, M.D./Protocol DPM-CF-302, Site #10125
Jacksonville, FL

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from September 19 to 21, 2012. A total of seven subjects were screened and enrolled. All enrolled subjects completed the study

An audit of the enrolled subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection. The issue of re-consent of the study subjects was discussed by ORA field staff and site management during and at the conclusion of the clinical site audit. Re-consenting with revised versions of the informed consent form was not deemed necessary by the clinical site, Sponsor, and IRB since the content of the informed consent document did not change. The only changes were in the version number and approval date. These minor administrative changes within the documents appeared to pose no risk to the study subjects.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Chris Upton, M.D./Protocol DPM-CF-301, Site #44103
Norwich, UK

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from September 17 to 21, 2012. A total of 13 subjects were screened and 11 subjects were enrolled. Nine subjects completed the study.

An audit of eight subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence with the IRB. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events (SAEs).

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not conducting the study according to investigational plan and not maintaining adequate investigational drug final disposition records. The following regulatory deficiencies are selected relevant examples:

i. For 7 of the 11 enrolled subjects (i.e., Subjects (b) (6)), spirometric lung function measurements were not performed on a dedicated spirometer.
ii. Study diaries for Subjects (b) (6) were not retained with the study records (which did contain pages removed from the subject diaries).
iii. Study personnel became aware of a SAE (pulmonary exacerbation requiring hospitalization) for Subject (b) (6) on (b) (6). A SAE form was not completed until (b) (6) by the Study Coordinator.
iv. Study records did not identify persons to whom pharmacy personnel gave packages of study drug they prepared for dispensing.
v. Dispensing of study drug to subjects did not include confirmation of the enrollment (subject) number on each carton distributed.

Dr. Upton responded adequately to these observations in a letter dated October 3, 2012.

The List of Inspectional Observations was communicated to the DPARP Medical Team who did not consider the above findings as critical. OSI defers to DPARP, in regards to impact of these observations on final efficacy determinations.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

5. Martin Walshaw, M.D./Protocol DPM-CF-301, Site #44111
Liverpool, UK

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from September 24 to 28, 2012. A total of 20 subjects were screened and 15 subjects were enrolled. Twelve subjects completed the study.

An audit of the 12 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence with the IRB. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events (SAEs).

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection. The following regulatory deficiencies are selected relevant examples:

The following regulatory deficiencies are selected relevant examples:

i. Subject (b) (6) spirometry testing was not performed on a dedicated spirometer to record this patient's lung function measures.
ii. Records for drug dispensed at Visit 1 failed to identify the number of capsules or boxes dispensed to subjects by study site nurses.
iii. Inaccurate recordings of study drugs dispensed: (a) Subject (b) (6) nurse dispensing note at Visit 1 recorded 1240 capsules, but pharmacy records indicated that 1120 capsules were dispensed, (b) Subject (b) (6) nurse dispensing note at Visit 1 recorded 1400 capsules, but pharmacy records indicated that 1120 capsules were dispensed, and (c) Subject (b) (6) nurse dispensing note at Visit 1 recorded 1200 capsules, but pharmacy records indicated 1120 capsules were dispensed.

The List of Inspectional Observations was communicated to the DPARP Medical Team who did not consider the above findings as critical or significant.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this NDA, three U.S. clinical investigator sites for Study Protocol DPM-CF-302 and two foreign clinical investigator sites for Study Protocol DPM-CF-301 were inspected in support of this application.

No regulatory deficiencies were observed for the clinical study sites of Peter Fornos, M.D. and David Schaeffer, M.D. and the final classification is NAI (No Action Indicated). Regulatory deficiencies were observed and Form FDA 483, Inspectional Observations were issued for the clinical study sites involving (a) Perry Brown, M.D. for not conducting the study according to the investigational plan and inadequate study record keeping; (b) Chris Upton, M.D. for not conducting the study according to the investigational plan and incomplete records related to study drug dispensed, and (c) Martin Walshaw, M.D. for not conducting the study according to the investigational plan and inadequate record keeping related to study drug disposition records. Preliminary classification of inspections at these sites is VAI (Voluntary Action Indicated).

Based on review of inspectional findings for these clinical investigator sites and discussion with the medical review team (DPARP), the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above are based on the preliminary communications from the field investigators and preliminary review of EIR; an inspection summary addendum will be generated if conclusions change significantly upon final review of the EIRs.

{See appended electronic signature page}

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