Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Formoterol Fumarate; Glycopyrrolate

February 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients:	Formoterol fumarate; Glycopyrrolate
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strength:	0.0048 mg/inh; 0.0090 mg/inh
Recommended Studies:	Two options: (1) six in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints, or (2) five in vitro bioequivalence studies, one comparative characterization study, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

I. Option 1: Six in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints

To demonstrate bioequivalence by this option, the test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the RS product to satisfy no difference in inactive ingredients.

[1] Q1 (qualitative sameness) means that the T formulation uses the same inactive ingredient(s) as the RS formulation.
[2] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T formulation are within ± 5% of those used in the RS formulation.

Six in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for the T and RS products. Use at least three batches each of the T and RS products, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to demonstrate in vitro bioequivalence. The three batches of T product should be manufactured from, at a minimum, three different batches of drug substances, excipients, and device constituent part components. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.

1. Type of study: Single actuation content (SAC)
   Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages[3] of the product using a flow rate of 28.3 L/min or 30 L/min.[4] U.S. Pharmacopeia (USP) <601> Apparatus A or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one.

   Bioequivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929) for additional information regarding PBE analysis procedures.[a]

2. Type of study: Aerodynamic particle size distribution (APSD)
   Design: The APSD test should be performed at the B and E lifestages of the product using a flow rate of 28.3 L/min or 30 L/min. A cascade impactor (CI) apparatus for inhalation aerosols as per USP <601> Table 2 or another appropriate method may be used to determine APSD using a validated assay. The APSD determination of each unit should be performed with a minimum number of inhalations justified by the sensitivity of the validated assay.

   Additional comments: Drug and co-suspending agent deposition on individual sites, including the mouthpiece adapter, the induction port, each stage of the cascade impactor (CI) and the filter, is requested. Mass balance accountability should be reported based on the sum of all deposition sites. For electronic submission of the individual CI data for the T and RS products, please provide a table using the format in the appendix and send them as part of the abbreviated new drug application (ANDA) submission.

   Bioequivalence based on: PBE analysis of impactor-sized mass (ISM) of the drugs.[5] The CI profiles representing drug and co-suspending agent deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric

[3] Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s) following the labeled number of priming actuations, the actuation(s) corresponding to 50 percent of the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.
[4] The selection of flow rate should match that of the flow rate chosen for APSD testing.
[5] ISM is defined as a sum of the drug mass on all stages of the CI plus the terminal filter but excluding the top CI stage because of its lack of a specified upper cutoff size limit.

standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD.

3. Type of study: Spray pattern
Design: The spray pattern test should be performed at the B lifestage of the product and at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the RS actuator mouthpiece.[6] Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.

Additional comments: Spray pattern should be measured quantitatively in terms of ovality ratio and area within the perimeter of the true shape (to include a high proportion, e.g., 95 % of the total pattern) for the automated analysis or ovality ratio and D_{max} for the manual analysis. Ovality ratio is defined as the ratio of D_{max} to D_{min}. D_{max} and D_{min} are the longest and shortest diameters, respectively, that pass through the center of mass or the center of gravity, as appropriate. The number of sprays per spray pattern would preferably be one.

Bioequivalence based on: At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area within the perimeter of the true shape or ovality ratio and D_{max}.

4. Type of study: Plume geometry
Design: The plume geometry test should be performed at B lifestage of the product. The timed-sequence sound-triggered flash photography method, laser light sheet technology, or other suitable method may be used to determine the plume geometry at the appropriate post-actuation delay time.

Additional comments: Plume geometry measurements should be reported at a single delay time while the fully developed plume is still in contact with the actuator mouthpiece. Plume geometry should be measured quantitatively in terms of plume angle and width. The plume angle is based on the conical region of the plume extending from a vertex that occurs at or near the actuator mouthpiece. The plume width is measured at a distance equal to the greater of the two distances selected for characterization of the spray pattern.

Bioequivalence based on: Ratio of the geometric mean of the three batches of T to that of the three batches of RS (based on log transformed data) for both plume angle and width, which should fall within 90% - 111%.

5. Type of study: Priming and repriming
Design: Priming and repriming tests should be based on the emitted dose (ex-actuator) of a single actuation immediately following the specified number of priming or repriming actuations specified in the reference listed drug (RLD) product labeling. The repriming test should be performed following storage for the specified period of non-use after initial

[6] The distance between the actuator orifice and point of spray pattern measurement should be same for T and RS.

use and/or other conditions (e.g., dropping), if the RLD product labeling provides such repriming information.

Additional comments: For the bioequivalence evaluation, the priming and repriming tests should be based on products stored in the valve upright position, with the exception of metered dose inhalers (MDIs) for which the RLD labeling recommends storage in the valve down position. The priming data can be based on the SAC data at the B lifestage.

Bioequivalence based on: PBE analysis of the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified in the RLD product labeling.

6. Type of study: Realistic APSD
Design: The realistic APSD test should be performed at the B lifestage of the product using mouth-throat models of different sizes (e.g., small and large) and breathing profiles (e.g., weak and strong) that are representative of the entire patient population. A CI apparatus for inhalation aerosols as per USP <601> Table 2 or another appropriate method may be used to determine APSD using a validated assay. The APSD determination of each unit should be performed with a minimum number of actuations justified by the sensitivity of the validated assay.

Additional comments: Drug and co-suspending agent deposition on individual sites, including the mouthpiece adapter, the mouth-throat model, the mixing inlet, and each stage of the CI and the filter, is requested. Mass balance accountability should be reported based on the sum of all deposition sites. For electronic submission of the individual CI data for the T and RS products, provide a table using the format in the appendix, and send them as part of the ANDA submission.

Bioequivalence based on: PBE analysis or other appropriate statistical analysis of ISM of the drugs for each mouth-throat model-breathing profile combination. The CI profiles representing drug and co-suspending agent deposition on the individual stages of the CI along with the MMAD, GSD, and FPM should be submitted as supportive evidence for equivalent APSD. If another statistical analysis is used, it should be adequately and scientifically justified considering the purpose of the study. Prospective applicants are encouraged to discuss other statistical analysis designs with FDA via a pre-ANDA meeting request. For additional information, refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

One comparative characterization study:

A comparative physicochemical characterization study of the T product and the RS product should be performed on a minimum of three exhibit batches of the T product and three batches of the RS product. The comparative characterization study should include:

1. Particle morphology of the emitted dose
    a. Imaging comparisons of the deposited particles from the emitted dose at the B lifestage should be determined to assess particle morphology and agglomeration. Description for the sample collection method should be provided.

Two in vivo bioequivalence studies with pharmacokinetic endpoints:

1. Type of Study: Fasting
   Design: Single-dose, two-way crossover
   Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method
   Subjects: Healthy males and non-pregnant, non-lactating females

   Additional comments: (1) The subjects enrolled for in vivo studies should be trained in the use of the inhalation aerosols in a standard fashion prior to each treatment session to assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) Subjects should adhere to the RLD product labeling for administration. (3) A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose.

   Analytes to measure: Formoterol and glycopyrronium in plasma

   Bioequivalence based on: AUC and C_{max} for formoterol and glycopyrronium. The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00% - 125.00%.

2. Type of study: Fasting
   Design: Single-dose, two-way crossover with charcoal block
   Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method.
   Subjects: Healthy males and non-pregnant, non-lactating females

   Additional comments: (1) The subjects enrolled for in vivo studies should be trained in the use of the inhalation aerosols in a standard fashion prior to each treatment session to assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) Subjects should adhere to the RLD product labeling for administration. (3) A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose. (4) Justification for the charcoal dose should be provided in the ANDA submission.

   Analytes to measure: Formoterol and glycopyrronium in plasma

Bioequivalence based on: AUC and C_{max} for formoterol and glycopyrronium. The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00% - 125.00%.

II. Option 2: Five in vitro bioequivalence studies, one comparative characterization study, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

To demonstrate bioequivalence by this option, it is recommended to conduct the in vitro bioequivalence studies #1 through #5, the comparative characterization study, and the in vivo pharmacokinetic bioequivalence study #1 as described in Option 1. In addition, it is recommended to conduct the comparative clinical endpoint bioequivalence study, described below.

One comparative clinical endpoint bioequivalence study:

1. Type of Study: Comparative clinical endpoint bioequivalence study
   Design: This study could be either of crossover or parallel-group design, taking into consideration the patient population and the current standard-of-care treatment for chronic obstructive pulmonary disease (COPD), and should include appropriate justification for the design chosen. The study should be randomized, single-dose, and placebo-controlled, at minimum consisting of a 2-week run-in period followed by a one-day treatment period of the placebo, T, or RS product.
   Strength: 0.0048 mg/inh; 0.0090 mg/inh
   Dose: 0.0096 mg; 0.018 mg, single-dose (i.e., two inhalations)
   Subjects: Males and non-pregnant females with COPD

   Inclusion criteria should, at minimum, include:
   a. Adult (≥ 40 y. o.) male or female subjects of non-child-bearing potential or of child-bearing potential but committed to consistent use of an acceptable method of birth control
   b. Diagnosis of COPD, as defined by American Thoracic Society (ATS) [GOLD criteria]
   c. Post-bronchodilator forced expiratory volume in one second (FEV_1) ≤ 80%
   d. Post-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤ 0.70
   e. Current or former smokers (e.g., with history of ≥ 10 pack-years)
   f. Willingness to give their written informed consent to participate in the study

   Exclusion criteria should, at minimum, include:
   a. Known respiratory disorders other than COPD including, but not limited to the following: alpha-1 antitrypsin deficiency, cystic fibrosis, significant asthma, active bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, pulmonary edema, or interstitial lung disease
   b. Evidence or history of other clinically significant cardiovascular disease or abnormality (such as, but not limited to, congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, stroke,

glaucoma, cardiac dysrhythmia, arrhythmia, long QT syndrome, paroxysmal atrial fibrillation), renal, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological disease or abnormality which, in the opinion of the investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbates during the study

c. Known active tuberculosis
d. History of paradoxical bronchospasm, narrow-angle glaucoma, prostatic hyperplasia, bladder neck obstruction, or severe renal impairment or urinary retention or any other condition, which, in the opinion of the investigator, would contraindicate the use of an anticholinergic or long-acting beta-agonist agent
e. History of allergy or hypersensitivity to anticholinergic/muscarinic receptor antagonist agents, long- or short-acting beta-2 agonists, sympathomimetic amines, lactose/milk proteins, or specific intolerance to aerosolized formoterol fumarate or glycopyrrolate-containing products or known hypersensitivity to any of the proposed ingredients or components of the delivery system
f. Hospitalization for COPD or pneumonia within 12 weeks prior to the initiation of the study
g. Treatment for COPD exacerbation within 12 weeks prior to study
h. Inability to discontinue COPD medications during the run-in and treatment periods
i. Acute (viral or bacterial) upper or lower respiratory tract infection, sinusitis, rhinitis, pharyngitis, urinary tract infection or illness within 6 weeks prior to the initiation of the study
j. Abnormal and significant electrocardiogram (ECG) finding prior to the screening, during the run-in and treatment periods
k. Lung volume reduction surgery within 12 months prior to the initiation of the study
l. Chronic oxygen use for >12 hours/day

Additional comments:

a. The study may enroll all COPD patients who meet the inclusion and exclusion criteria or may be enriched with patients who demonstrate ≥ 15% reversibility to bronchodilator therapy (appropriate justification should be included for the population chosen).
b. A clear list of permitted and restricted medications should be provided, including justification for use (or restriction) of certain classes of respiratory therapies, that considers the current standard-of-care for COPD.
c. All spirometry should be conducted in accordance with ATS standards.
d. The study protocol should list appropriate withholding times prior to spirometry for permitted concomitant medications (e.g., 4 hours for short-acting beta-agonists, 12 or 24 hours for long-acting beta-agonists).
e. The study is recommended to begin with a placebo run-in period (at least 2 weeks in duration; appropriate justification should be included for the duration chosen) to washout any pre-study long-acting anticholinergic or long-acting beta-agonist agents and to establish FEV_1 baseline values.

f. To ensure adequate study sensitivity, the T and RS products should both be statistically superior to placebo ($p < 0.05$) with regard to the bioequivalence study endpoint.
g. The study protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified (e.g., by the use of subject diaries).
h. It is the prospective applicant's responsibility to enroll a sufficient number of subjects for the study to demonstrate bioequivalence of the T to the RS product.
i. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The prospective applicant should clearly explain whether the medication was used prior to baseline visit, during the study or both.
j. All adverse events (AEs) should be reported whether or not they are considered to be related to the treatment. The report of AEs should include, at minimum, date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution.
k. Appropriate pre-defined withdrawal criteria should be described for patients who may require withdrawal during washout period due to COPD exacerbation or inability to tolerate withdrawal of baseline therapy.
l. Subjects who discontinued from the study early should be identified, and the protocol should clearly, prospectively state how missing data will be handled in the statistical analyses and provide appropriate justification for the method chosen. The protocol should also include subject retention strategies and other plans to minimize missing data. If there are missing data, adequate justification should be provided that the missing data do not lead to biased equivalence determination. Detailed information for all subjects who are discontinued from the study should be provided.
m. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[a] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

Bioequivalence study primary endpoint: Area under the serial FEV_1-time curve calculated from time zero to 12 hours (AUC_{0_12h}) on the first day of treatment.

The above bioequivalence study endpoint should be baseline-adjusted (change from baseline). FEV_1 measurements should be performed and interpreted in accordance with ATS guidelines.

On the first day of treatment, serial FEV_1 should be determined at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 11.5, and 12 hours post-dose.

For each treatment group, time to peak bronchodilator response (T_{max}) and FEV_1 values at all measurement times within each evaluation period should be included in the final study report.

Bioequivalence based on: T/R ratio for the primary endpoints. The 90% confidence intervals for the T/R ratio for the primary endpoint should fall within the limits of 80.00% - 125.00%.

Additional information:

Computational model(s) for regional drug delivery:
An optional computational modeling study may be used to support bioequivalence of the T and RS products. The overall purpose of this additional modeling study would be to differentiate the impact of different products (i.e., device and formulation) on regional drug delivery, such that the results may be used to establish biorelevant limits for bioequivalence comparison of key recommended studies from Option 1, including realistic APSD and plume geometry studies. Equivalently, the model may be used to assess the bioequivalence in terms of regional lung deposition by conducting virtual bioequivalence simulations. The specific purpose(s) of the model should be clearly stated in detail within the ANDA submission. To support the stated model purpose(s), the modeling approach may include a regional deposition model that may use either a computational fluid dynamics (CFD) or semi-empirical method to predict central and peripheral region deposition for each active ingredient. Physiologically based pharmacokinetics (PBPK) modeling may be useful as well if drug absorption is not expected to be rapid, such that regional deposition may not be considered as a surrogate for regional lung delivery, where regional deposition inputs may either be provided by model predictions or in vivo experimental data including imaging data.

Each model included in the ANDA submission should sufficiently establish model credibility, which is defined here as the ability of the model to support its identified purpose(s). To demonstrate model credibility, each model submitted within the ANDA submission must be validated, where model validation is defined here as a comparison between predictions and data from in vivo and/or in vitro sources that establishes the real-world accuracy of the model. Regional deposition models, using either a CFD or semi-empirical approach, should be validated using in vivo regional deposition data that may be collected for the purposes of the ANDA submission or used retrospectively from literature sources. If in vivo regional deposition data used for comparison with model predictions are observed using a two-dimensional scheme, a method should be used to convert three-dimensional regional deposition predictions to the two-dimensional scheme by using an appropriate method, such as the method identified by Schroeter et al.[7] However, any in vivo data collected using a method that collects branch-level deposition data would not require dimensional conversion of model predictions. For regional deposition models, the central and peripheral lung regions should be divided as defined by the International Commission on Radiation Protection (ICRP), which stipulates that bronchi extend from the trachea to lung generation 8 and bronchioles extend from generation 9 up to the limit of the alveolar region,[8] where the bronchi and bronchioles may be taken to represent the central and peripheral lung regions, respectively. Any PBPK model used for the ANDA submission should be validated using available in vivo pharmacokinetics data, which may include systemic pharmacokinetic data and, if available, lung tissue pharmacokinetic data. To establish the ability to accurately distinguish between different drug products, model validation should be performed for each model included in the ANDA submission for the RS product and at least one other drug product that is known to produce a different relevant outcome, where relevant outcomes include regional deposition, systemic pharmacokinetics, or lung tissue pharmacokinetics.

[7] Schroeter JD, Pritchard JN, Hwang D, Martonen TB. Airway identification within planar gamma camera images using computer models of lung morphology. Pharmaceutical research. 2005;22:1692-9.
[8] ICRP. Human Respiratory Tract Model for Radiological Protection. New York: Elsevier Science Ltd; 1994.

For any CFD regional deposition model included in the ANDA submission, model verification activities are also needed to establish model credibility. Model verification is defined here as the ability of the numerical computational model to represent the underlying mathematical model. To support model verification for a CFD model included in the ANDA submission, sensitivity studies should be executed to establish computational mesh density, time step size, and the number of particles injected into the system such that these selections do not affect the predicted outcomes. For more details on concepts related to model credibility of CFD models, including model verification, a useful resource is the published risk-based standard American Society of Mechanical Engineers (ASME) V&V 40 *Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices*.[9] However, the ASME V&V 40 standard is not directly applicable to this guidance due to differences between models for medical devices, which are the focus of that standard, and models for pharmaceutical drug-device combination products.

Acceptance criteria for model validation and methods for statistical analysis of virtual bioequivalence studies should be defined prior to testing, and the selected criteria and methods should be justified. Appropriate criteria for model validation may depend on a variety of factors, including model purpose, model type, and variability of available in vivo and/or in vitro data for comparison. For statistical analysis of virtual bioequivalence, if regional deposition or systemic pharmacokinetics are predicted for multiple individuals, an approach such as average bioequivalence may be appropriate. If a virtual bioequivalence study is based on predictions for one representative individual using input data from multiple units and multiple product batches, a population bioequivalence approach may be appropriate. Regardless of the method selected for conducting a virtual bioequivalence study, the model or collection of models should consider intersubject variability with respect to anatomy and physiology, including considerations for lung morphology, inhalation flow rate, disease characteristics, and mucus layer properties.

In order to clarify the FDA's expectations for prospective applicants early in product development, and to assist applicants to submit an ANDA as complete as possible, FDA strongly encourages applicants to discuss their development program for any optional computational modeling study with the FDA via the pre-ANDA meeting pathway. For additional information, refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

Device:
The RLD is presented as an MDI. The device constituent part is the actuator with metering valve.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the T device including:

- Active, metered, multi-dose format
- Number of doses
- Dose indicator/counter

[9] American Society of Mechanical Engineers. Verification and Validation in Computational Modeling of Medical Devices (American Society of Mechanical Engineers, New York, NY, 2018).

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[b]

Document History: Recommended February 2024

Unique Agency Identifier: PSG_208294

[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

APPENDIX

Variable Name	Variable Type	Content	Notes
Product Name	Character	TEST or REF	Identifier for product
LOT Number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
UNIT Number	Numeric	Numeric values	Identifier for unit must be unique for each product (e.g., #1-30 for test and #31-60 for ref).
Stage 1	Numeric	Numeric Values	S1
Stage 2	Numeric	Numeric Values	S2
Stage 3	Numeric	Numeric Values	S3
Stage 4	Numeric	Numeric Values	S4
Stage 5	Numeric	Numeric Values	S5
Stage 6	Numeric	Numeric Values	S6
Stage 7	Numeric	Numeric Values	S7
Stage 8 or Filter	Numeric	Numeric Values	S8
ISM	Numeric	Numeric Values	ISM
MMAD	Numeric	Numeric Values	MMAD
GSD	Numeric	Numeric Values	GSD
FPM	Numeric	Numeric Values	FRM

Example:

PRODUCT	LOT	Unit	S 1	S 2	S 3	S 4	S 5	S 6	S 7	S8 or Filter	ISM	MMAD	GSD	FPM
TEST	1234	1												
		2												
		3												
		4												
		5												
		6												
		7												
		8												
		9												
		10												