CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213260Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

PIND 137915

**MEETING REQUEST-
WRITTEN RESPONSES**

LiQmed Limited
c/o RegCon Solution LLC
Attention: Lauren Ford
President
10525 Vista Sorrento Parkway
Suite 100
San Diego, CA 92121

Dear Ms. Ford:

Please refer to your Pre-Investigational New Drug Application (PIND) file for atorvastatin calcium oral suspension, 20 mg/5 ml (b) (4).

We also refer to your submission dated January 12, 2018, containing a meeting request. The purpose of the requested meeting was to discuss your development plans for atorvastatin calcium oral suspension.

Further reference is made to our Meeting Granted letter dated January 18, 2018, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 5, 2018, background package.

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-IND
Application Number: 137915
Product Name: atorvastatin calcium oral suspension, 20 mg/5 ml (b) (4)
Indications:
-Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without CHD, but with multiple risk factors
-Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors
-Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in adult patients with CHD
-Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
-Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia
-Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH)
-Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy
Sponsor Name: LiQmed Limited
Regulatory Pathway: 505(b)(2)

1.0 BACKGROUND

Th initial approval of atorvastatin occurred in 1996 under the tradename LIPITOR tablets (NDA 020702, Pfizer, USA). Atorvastatin is an HMG-CoA reductase inhibitor.

Utilizing the 505(b)(2) regulatory pathway, LiQmeds Limited proposes to submit a New Drug Application for atorvastatin calcium oral suspension in a ready to use suspension, which is a different dosage form as the innovator product. (b) (4) This liquid atorvastatin product provides an alternative dosage form to tablets/ capsules and is an option in patients where a liquid is preferred over a solid dosage form.

LiQmeds will rely on the FDA's prior determination that atorvastatin calcium is safe and effective for the same indications. LiQmeds proposes that demonstration of bioequivalence between atorvastatin calcium oral suspension and Lipitor is self-evident based on 21 CFR 320.22 (b)(3) and in vitro data included in this package, and is the basis for the scientific bridge to the FDA's findings of clinical safety and efficacy for atorvastatin as reflected in the approved

labeling. Therefore, LiQmeds plans to conduct the following studies to establish a scientific bridge to Lipitor:

(b) (4)

(b) (4)

The purpose of this meeting is to obtain feedback on the regulatory, clinical, nonclinical, and quality development of this product.

2.0 QUESTIONS AND RESPONSES

2.1. Regulatory

Question 1a: *Does the Agency agree that the 505(b)(2) regulatory pathway is appropriate for submission of the proposed Atorvastatin Calcium Oral Suspension, 20 mg/5 ml* (b) (4) *NDA?*

FDA Response to Question 1a: **Overall, your proposal to seek approval of your product via the 505(b)(2) pathway seems reasonable. If you intend to submit a 505(b)(2) application that relies on the FDA's previous findings of safety and effectiveness for one or more listed drugs or on information from the literature that pertains to the listed drug(s), you need to identify each of those listed drug(s). As with all 505(b)(2) applications, you should establish a "bridge" between the active ingredients in your drug product and each of the listed drug(s) upon which you propose to rely to demonstrate that such reliance is scientifically justified. Additionally, you must submit data necessary to support any aspects of the proposed drug product that differ from the listed drug(s) relied upon. If there are differences between your drug product and the listed drug(s), you may be required to qualify the impact these differences have on safety and effectiveness with additional nonclinical and/or clinical studies.**

Question 1b: *Does the Agency agree that LIPITOR (NDA 020702) is the appropriate Listed Drug?*

FDA Response to Question 1b: **The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon, but your proposal to rely on Lipitor (atorvastatin) tablets, NDA 020702, appears reasonable. Refer to the Response to Question 1a.**

Question 2: *Does the Division agree that the proposed full waiver for pediatric subject's age 6 - 17 years is reasonable?*

FDA Response to Question 2: **If you plan to request a waiver for studies in pediatric patients, you should include your request and rationale in your initial Pediatric Study Plan (iPSP). Refer to the section below titled "PREA Requirements."**

2.2. Clinical Pharmacology

Question 3: *Does the Agency agree with the plan to conduct and submit results of the following studies?*

(b) (4)

FDA Response to Question 3: **Yes. Your plan to conduct the above proposed studies is acceptable from a clinical pharmacology perspective. The adequacy of the results will be a review issue. Please also include the bioanalytical method validation report for these studies in your submission. You should use the final to-be-marketed formulation in the above proposed studies.**

Question 4: (b) (4)

FDA Response to Question 4: (b) (4)

The FDA has the following recommendations regarding the dissolution information (method and acceptance criterion/criteria) that should be provided in the submission.

Dissolution Method: Provide in your submission the dissolution method development report supporting the selection of the proposed dissolution test evaluating the proposed drug product. Include the following information in the dissolution method development report:

a. Solubility data of the drug substance over the physiologic pH range.

b. Detailed description of the dissolution method being proposed for the evaluation of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc.). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions associated with each method development study. The dissolution profile should be complete or whenever a plateau is reached (i.e., no increase over 3 consecutive time-points). It is recommended the use of at least twelve dosage units per testing variable and sampling time points (e.g., 10, 15, 20, 30, 45 60, etc. min).

c. Data supporting the discriminating ability of the selected dissolution method. In general, ensure that the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., ± 10-20% change to the specified values or ranges for these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., *f2* values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.

d. A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.

e. Supportive validation data for the dissolution methodology (bench testing) and analytical method used for assaying the dissolution samples (specificity, precision, accuracy, linearity/range, stability, robustness, etc. For general recommendations on method validation, refer to the USP Chapters "The Dissolution Procedure: Development and Validation" <1092> and "Validation of Compendial Methods" USP Chapter <1225>.

f. Complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, % CV at each time point and mean profiles). Report the dissolution data as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim). For the submission of the dissolution data, refer to data presentation below.

<u>Dissolution Acceptance Criterion</u>: For the selection of the dissolution acceptance criterion of the proposed drug product, consider the following:

a. Use the multi-point dissolution data (n=12, appropriate sampling times) from the pivotal clinical/PK drug product-batches and primary registration batches for the

setting of the dissolution acceptance criterion of the proposed drug product (i.e., sampling time points and limits). When applicable, include the dissolution profile data to support in-process dissolution acceptance criteria.

b. Ensure that the in vitro dissolution profile is complete or if incomplete dissolution occurs, where the plateau of drug dissolved is reached (i.e., no increase over 3 consecutive time-points).

c. Base the dissolution acceptance criterion on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12).

d. Select the sampling time point where Q = (b) (4)% dissolution occurs. However, if the drug product is a slow dissolving product, tting of acceptance limits at two or more sampling time points may be adequate. The first time point should include a dissolution range (e.g., (b) (4)) and the second time point should be where Q = (b) (4)% dissolution occurs.

e. Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the eCTD.

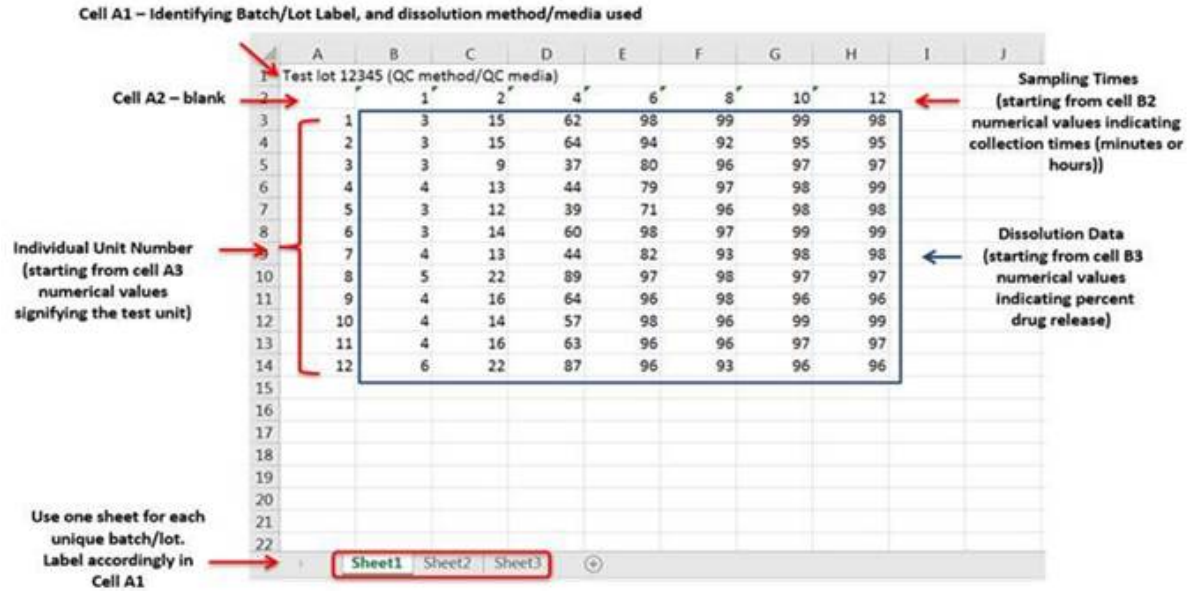
<u>Dissolution Data Presentation</u>: In the dissolution method development report (INDs/NDAs), and/or batch analysis section (NDAs), or In Vitro - in Vivo correlation Study reports and related information section (ANDAs), present detailed experimental dissolution data as follows:

a. In the narrative portion of the dissolution report, include individual vessel data as much as possible, particularly regarding investigation of selection of equipment, media, agitation speed, etc.

b. In addition to the mean dissolution data presented in graphical and tabular formats, submit in the "Batch Analysis" section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel ".xls or .xlsx" format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.

c. Provide in your IND/NDA the dissolution data as described in the example below.

Example - Reporting of individual vessel dissolution data



Follow the instructions provided in "Specifications for File Format Types Using eCTD Specifications" – updated March 2, 2017 (link below).
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf

Dissolution Acceptance Criterion/Criteria Recommendation: Note that the FDA's recommendation on the adequacy of the proposed dissolution acceptance criterion/criteria for the proposed drug product will be made during the review process based on the totality of the provided dissolution data.

2.3. Clinical

Question 5: *Does the Agency agree that if BE is established between Atorvastatin Calcium Oral Suspension,* (b) (4) *and the Listed Drug, LIPITOR) and food effect study is performed no additional clinical efficacy and safety studies will be required to support the submission and approval of the 505(b)(2) NDA?*

FDA Response to Question 5: **Whether additional clinical trials for safety and/or efficacy would be required will depend on our review of your nonclinical and clinical data, as well as our review of your initial Pediatric Study Plan. Refer to the responses to Questions 1a and 2.**

2.4. Nonclinical

Question 6: *Does the Agency agree that the proposed nonclinical pharmacokinetic and toxicity studies, supported by the Agency's previous findings of nonclinical safety of atorvastatin, will be sufficient for NDA submission?*

FDA Response to Question 6: **In general, your proposal to rely on an Orange Book-listed atorvastatin calcium product to support nonclinical safety of the atorvastatin calcium API appears appropriate. However, you must also provide adequate safety justification for any excipients present at higher levels than those listed in the FDA's Inactive Ingredient Database (IID), (e.g., (b) (4) including all ingredients in the flavor), considering the route of exposure and dosing duration. A comparative impurity profile is not required, but all impurities and degradants should be qualified in accordance with ICH Q3A and ICH Q3B, respectively. Any impurities with a structural alert for genotoxicity that exceed the identification thresholds per ICH Q3A and ICH Q3B should be qualified per ICH M7. You should provide adequate safety justification for the levels of leachables from the product container.**

2.5. Quality

Question 7: *Does the Agency agree that the identified Critical Quality Attributes of LQ001 are suitable to guide product development?*

FDA Response to Question 7: **Add the following to the Critical Quality Attributes: identity, viscosity, resuspendability, polymorph, density, bulk uniformity, (b) (4) (b) (4) and microbial limits.**

Additional comment: **In the IND and NDA, provide the qualitative and quantitative composition of the Orange flavor (b) (4) and safety information in support of any ingredient present at a higher level than listed in the FDA's Inactive Ingredients Database for the applicable dosage form and route of administration.**

Question 8: *Is it necessary to include a product administration device with the product as there are several liquid products approved by the FDA which do not include a measuring device as there are measuring devices available commercially that can be used to administer the product to the patient?*

FDA Response to Question 8: **It is not necessary to include a product administration device with the drug product. You should include specific language in the proposed label to address the accuracy of dosing.**

Question 9: (b) (4) *?*

FDA Response to Question 9: **See Response to Question 8.**

3.0 OTHER IMPORTANT INFORAMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study

Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
03/08/2018