CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215320Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124213

MEETING MINUTES

AFT Pharmaceuticals, Ltd.
6574 River Clyde Drive
Highland, MD 20777

Attention: David Zuchero, MS, JD
US Agent for AFT Pharmaceuticals, Ltd.

Dear Mr. Zuchero:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Combogesic IV (acetaminophen and ibuprofen solution for infusion).

We also refer to the telecon between representatives of your firm and the FDA on July 18, 2018. The purpose of the meeting was to discuss the documentation package and adequacy of clinical data required to support submission and approval of a 505(b)(2) NDA.

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

If you have any questions, call me at (240) 402-2476.

Sincerely,

{See appended electronic signature page}

Eva Yuan, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: July 18, 2018, 3 p.m. to 4 p.m. EDT
Phone Arrangements: Dial-in #: 1-800-425-1122, Passcode: 4428520861#

Application Number: IND 124213
Product Name: Combogesic IV (acetaminophen and ibuprofen solution for infusion)

Indication: For the relief of mild to moderate pain (b) (4), where an intravenous route of administration is considered clinically necessary

Sponsor/Applicant Name: AFT Pharmaceuticals

Meeting Chair: Sharon Hertz, MD, Division Director, DAAAP
Meeting Recorder: Eva Yuan, PharmD, Regulatory Health Project Manager, DAAAP

FDA ATTENDEES

Sharon Hertz, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Christina Fang, MD	Clinical Reviewer, DAAAP
Wei Qiu, PhD	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2 (DCP2)
Yun Xu, PhD	Clinical Pharmacology Supervisor, DCP2
Carlic Huynh, PhD	Nonclinical Reviewer, DAAAP
Newton Woo, PhD	Nonclinical Team Lead, DAAAP
Daniel Mellon, PhD	Nonclinical Supervisor, DAAAP
Julia Pinto, PhD	Branch Chief, ONDP, OPQ
David Petullo, MS	Biostatistics Team Lead, Office of Biostatistics
Cameron Johnson, PharmD	Safety Evaluator, DMEPA, OSE
Eva Yuan, PharmD	Regulatory Project Manager, DAAAP

SPONSOR ATTENDEES

Hartley Atikinson, M. Pharm, PhD	Managing Director
John Douglas Wilson, MD CHB, PhD, FRACP, FRCPA	Chief Medical Officer

Ioana Stanescu, Phil.Lic, MSc	Head of Drug Development
Rebecca Playne, PhD	Clinical Scientist
Madeleine Clarke, BA/BSc	Regulatory Affairs Manager – Maxigesic
David Zuchero, MS, JD	Regulatory Affairs Consultant

BACKGROUND

AFT Pharmaceuticals is developing Combogesic IV, an acetaminophen 10 mg/mL and ibuprofen 3 mg/mL solution for infusion, for the treatment of mild to moderate pain (b) (4), where an intravenous route of administration is considered clinically necessary. The Sponsor submitted a Type B Pre-NDA meeting request on March 13, 2018, to discuss the documentation package and adequacy of clinical data required to support submission and approval of a 505(b)(2) NDA.

The questions from the June 5, 2018, meeting package are shown in *italic font*, the Division preliminary responses are shown in **bold font**, the Sponsor's pre-meeting comments received on July 17, 2018, is in Calibri font, and the meeting discussion is in normal font.

FDA sent Preliminary Comments to AFT Pharmaceuticals on July 16, 2018.

DISCUSSION

Chemistry, Manufacturing, and Controls

Question 1: The drug substance and drug product specifications have been provided in sections 10.1.1, 10.1.2 and 10.2.4 of the pre-NDA package. Does the Agency agree with the proposed specifications?

FDA Response:
The proposed release testing appears to be adequate. The drug product release testing should also include loss of volume testing as well as optical rotation determination for ibuprofen. Evaluation of both the drug substance and drug product specifications is deferred to the NDA review, when all the data in its totality will be evaluated.

AFT Pharmaceutical's Pre-Meeting Comments:
The proposed container closure system for Combogesic® IV is a 100 mL, (b) (4) glass vial, closed with a (b) (4) stopper and sealed with aluminium caps. (b) (4) glass vials are generally considered to be an impermeable container. The Sponsor considers loss of volume to be adequately controlled through the following measures:

- During manufacture, (b) (4) testing is performed as an in-process control (b) (4).
- As part of drug product release, extractable volume testing is performed. Acceptance criteria are (b) (4).

- Extractable volume testing is also assessed throughout stability studies; in full-term studies to date, no out of specification results (b) (4) have been observed.

Data collected to date suggests no loss of volume occurs.

Clarification Question: Would the Agency please elaborate on the requirement for loss of volume testing in drug product release testing?

Discussion:
The Sponsor asked for clarification of the term loss of volume. The Division asked whether the extractable volume was equivalent to the loss of volume, and if any evaporation will be picked up by the extractable volume test. The Sponsor confirmed that it is equivalent. The Division clarified that the extractable volume is acceptable in place of the loss of volume. The Division also suggested that the Sponsor may want to consider including a micro test as part of the drug product release testing.

Clinical

Question 2: *Combogesic® IV is indicated for the relief of mild to moderate pain* (b) (4) *, where an intravenous route of administration is considered clinically necessary. The safety and efficacy of Combogesic® IV is supported by a pivotal phase 3 efficacy study (AFT-MXIV-07) conducted in patients undergoing bunionectomy surgery. This study confirmed the superiority of Combogesic® IV over comparable doses of acetaminophen, ibuprofen and placebo. Does the Agency agree with the proposed indication and usage?*

FDA Response:
No, we do not agree. The proposed labeling, including the indication, will be evaluated during the NDA review, and its acceptability will be based on the data submitted. However, we have the following comments:

1. **In addition to treating mild-to-moderate pain, your product may be appropriate as an adjunct to opioid analgesics in treating moderate-to-severe pain, consistent with the approved labeling for intravenous formulations of the individual components.**

2. **We do not agree with the proposed** (b) (4) (b) (4)

[redacted]. **Clarify the indications you plan to seek for your proposed product.**

Discussion: No further discussion.

Post-Meeting Note:

In response to our information request (IR), the Sponsor clarified via an email dated August 16, 2018, that they are seeking the pain indication only.

Question 3: *There is one pivotal study for Combogesic® IV (AFT-MXIV-07). According to Phase 1 pharmacokinetic studies AFT-MXIV-01 and AFT-MXIV-06, AUC_t and AUC_∞ of Combogesic® IV is bioequivalent with Maxigesic® tablets and Combogesic® tablets (NDA 209471), respectively. Consequently, the sponsor intends to submit efficacy and safety data from the pivotal Phase 3 study of Combogesic® tablets (AFT-MX-6) and safety data from studies of Maxigesic® tablets (AFT-MX-1, AFT-MX-3 and AFT-MX-6E). The sponsor also intends to perform an Integrated Summary of Efficacy (ISE) from studies AFT-MXIV-07 and AFT-MX-6 and an Integrated Summary of Safety (ISS) from studies AFT-MXIV-07, AFT-MX-6, AFT-MX-1, AFT-MX-3 and AFT-MX-6E. Safety data will be* [redacted] *appropriate based on the doses, dosing interval and duration of the studies. Does the FDA accept this rationale and approach?*

FDA Response:

No, we do not agree with your plan [redacted]. **Data obtained with Combogesic tablets may be submitted and/or cross-referenced in your Combogesic IV NDA. However, you should clearly describe how the data obtained with Combogesic tablets support your NDA for Combogesic IV.**

An appropriate pooling strategy for your ISS would be to pool data from the two single-dose PD studies and to summarize safety data from single-dose exposures and from 48-hour exposures to the IV formulation separately. Safety data from studies of the oral formulation are not directly supportive of the IV formulation due to the approximately two-fold higher C_{max} achieved for ibuprofen and acetaminophen as well as the much more rapid rise in levels for these two active ingredients as compared to the oral formulation administered at a similar dose.

AFT Pharmaceutical's Pre-Meeting Comments:
AFT accepts the Agency's suggested strategy for pooling the safety data for Combogesic IV.

Clarification Question: Would the Agency please confirm that the "two single-dose PD studies" referred to are the pharmacokinetic studies, AFT-MXIV-01 and AFT-MXIV-06?

Discussion:
The Sponsor asked the Division to clarify whether the pooling strategy for the safety data from the "two single-dose PD studies" is referring to the pharmacokinetic (PK) studies, AFT-MXIV-01 and AFT-MXIV-06. The Division confirmed that we were referring to the two pharmacokinetic studies referenced by the Sponsor.

Question 4: *Does the FDA have a preference as to how the data for the ISE and ISS should be presented? SDTM and ADaM standards, as they currently exist, apply within a single study. There is currently just one document for pooled datasets: ADaM Data Structures for Integration: General Considerations and Model for Integrated ADSL (IADSL) Version 1.0 (Draft) 2015-06-04. We assume that we should start from this document and use best judgement to adapt ADaM for pooled BDS and OCCDs datasets, and also design a customized ADRG.*

a. Does the FDA accept this approach?

b. If not, can the FDA please provide their preferred method of presentation for Integrated Datasets?

FDA Response:
Your approach appears reasonable as long as your customized ADRG includes a well-defined associated user guide.

Discussion: No further discussion.

Regulatory

Question 5: *The Agency has reviewed the proposed proprietary name 'Combogesic' for AFT's tablet formulation (NDA 209471) and has concluded that the name is conditionally acceptable. Is AFT required to submit another proprietary name request to the Office of Surveillance and Epidemiology for the use of 'Combogesic IV' with the IV formulation?*

FDA Response:
Yes, you must submit a new proprietary name request. As you are proposing the addition of a modifier (IV) to the root name (Combogesic), which was found conditionally acceptable for the tablet formulation, you are required to submit a new proprietary name review request.

You may also consider managing both the tablet and injection formulations under one proprietary name (i.e., Combogesic). In this scenario, you are also required to submit a new request for proprietary name review since the application for NDA 209471 is not approved.

If you require information on submitting a request for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- **Guidance for industry: *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf**

- **PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, available at https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf**

Discussion: No further discussion.

Background for Questions 6 to 11:
Previously, AFT agreed with the Agency (under IND 124213) to conduct a pharmacokinetic bridging study to the RLD intravenous single entity products Ofirmev™ (acetaminophen 10 mg/mL; NDA 22,450) and Caldolor™ (ibuprofen 800 mg/8 mL; NDA 22,348) in order to support the submission of a 505(b)(2) NDA. That study (AFT-MXIV-06) has been completed. For commercial reasons, AFT has decided that it cannot refer to these two agreed upon RLDs in its Combogesic® IV NDA otherwise the launch of Combogesic IV would be delayed which given the current clinical and regulatory push to provide alternatives to opioids seems an undesirable

pointAs a result, AFT would like FDA's input and guidance on the following alternative regulatory pathways to support an application to register Combogesic® IV.

AFT has already filed a 505(b)(2) NDA for Combogesic® tablets (acetaminophen 325 mg/ibuprofen 97.5 mg; NDA 209471). FDA issued a Complete Response to that NDA in December 2017 and AFT is currently preparing a response to that letter. As mentioned in Question #3, Phase 1 pharmacokinetic studies AFT-MXIV-01 and AFT-MXIV-06 have demonstrated that the AUC_t and AUC_∞ of Combogesic® IV is bioequivalent with Maxigesic® tablets and Combogesic® tablets, respectively. Consequently, AFT intends to submit efficacy and safety data from the pivotal Phase 3 study of Combogesic® tablets (AFT-MX-6) and safety data from studies of Maxigesic® tablets (AFT-MX-1, AFT-MX-3 and AFT-MX-6E) to support the safety and efficacy of Combogesic® IV, in addition to the pivotal Phase 3 study on the intravenous formulation.

As Combogesic® IV is an alternative route of administration and dose form of the acetaminophen/ibuprofen combination found in Combogesic® tablets, and a pharmacokinetic bridge has been established between them, AFT would like to cross-reference the Combogesic® tablet NDA in a new NDA for Combogesic® IV.

Question 6: Does the information described above, inclusive of the pivotal Phase 3 study for Combogesic® IV, the pivotal Phase 3 study for Combogesic® tablets, and the supportive studies for Maxigesic® tablets, appear to be adequate to support the submission of an NDA for Combogesic® IV that cross-references the Combogesic® tablet NDA 209471, while the latter NDA is still pending?

FDA Response:
You may cross-reference data in NDA 209471 for Combogesic tablets or resubmit it as part of your NDA for Combogesic IV if you believe the data from Combogesic tablets are relevant and supportive. In your NDA, clearly describe how the data obtained with Combogesic tablets support Combogesic IV, keeping in mind the efficacy and safety of Combogesic tablets have not been established as that product is not approved. In this scenario, you would be referencing the Agency's prior findings for Ultracet and Motrin for the purposes of your 505(b)(2) NDA for Combogesic IV regardless of whether Combogesic tablets are approved or not, as those are the products relied upon for the Combogesic tablets application. Therefore, you would need to establish a scientific bridge between Combogesic IV and those reference products to support your Combogesic IV NDA.

Although it would be acceptable to reference the oral products Ultracet and Motrin in support of your NDA for Combogesic IV, additional safety data will be required if the exposures achieved with Combogesic IV exceed those of the individual components with the referenced products (i.e., with regard to C_{max}) administered according to approved labeling. In that situation, safety data using the Combogesic IV formulation in at least 300 patients with multiple-dose exposures and at least 50 of those patients exposed for at least 5 days would be required.

AFT Pharmaceutical's Pre-Meeting Comments:

AFT confirms that, in order to rely on the Agency's previous findings for Ultracet and Motrin, a scientific bridge between Combogesic IV and the oral products will be pursued. AFT seeks clarification on the following aspects of such a study:

- Dr Reddy's ibuprofen tables was previously proposed and agreed upon with the Agency for use in the bridging study for Combogesic tablets (NDA 209471). Given the RLD Motrin (NDA 17463) has been discontinued (not for safety or efficacy reasons), AFT proposes the use of Dr Reddy's IBU™ tablets (ANDA 75,682) in the bridging study for Combogesic IV.

  Clarification Question: Does the Agency agree?

- AFT proposes to conduct a dose-normalised pharmacokinetic study comparing a single dose of Combogesic IV (acetaminophen 1000 mg + ibuprofen 300 mg) with Ultracet® (2 tablets, acetaminophen 325 mg + tramadol HCl 37.5 mg per tablet) and IBU™ (1 tablet, ibuprofen 800 mg per tablet).

  Clarification Question: Does the FDA accept this approach?

- Clarification Question: Would you please confirm that the requirement for "at least 300 patients with multiple dose exposure" refers to the total Combogesic IV safety database to support the NDA?

- Please note that the proposed duration of dosing for Combogesic IV is (b) (4). Clarification Question: Would the Agency clarify the requirement for safety data in subjects exposed to the product for at least 5 days?

Discussion:
The Sponsor asked the Division to confirm whether Dr. Reddy's IBU tablets was acceptable for use in the bridging study for Combogesic IV. The Division responded that the Sponsor can rely on the safety and efficacy findings of the FDA approved product, NDA 017463, even though it is no longer marketed, and use Dr. Reddy's IBU tablets in the comparative bioavailability study, as long as it is a generic drug to the discontinued FDA-approved product. The Division also clarified that the Sponsor will need to address the differences in pharmacokinetic profiles.

The Division noted that the Sponsor may compare the dose-normalized PK, but they must use the absolute PK data for comparison.

The Division also confirmed that at least 300 patients with at least 50 dosed for 5 days with the IV formulation are needed for the total safety database, because of the higher C_{max} and more rapid rise in concentrations with the IV formulation compared to that of the oral formulation.

The Sponsor asked the Division to clarify the recommendation for patients to be exposed for at least 5 days for the safety database. The Division clarified that the range of duration of pain and

hospitalization can vary in the inpatient acute pain setting, so we do not require the efficacy part of the study to last for more than a few days. Safety data may be collected from patients who are on continued need of IV treatment and require longer hospitalizations.

The Division stated that a PK bridging study must be conducted to compare the PK of the Sponsor's proposed product administered as recommended in the final proposed label to the listed drug product administered according to approved labeling. If all products have the same dosing frequency, a single dose will be sufficient. The Division clarified that, if the dosing interval of the of Dr. Reddy's IBU tablets is different than that of the proposed product, the Sponsor could compare PK using a 24-hour dosing frame (e.g., 3 doses for a drug with 8 hour dosing interval and 4 doses for a drug with 6 hour dosing interval). If given at the highest approved doses for both products, a fair comparison can be made between the Combogesic IV and Dr. Reddy's products since it will be a comparison of total daily doses.

Question 7: *If the answer is "no", would it be acceptable to wait until the Combogesic® tablet NDA 209471 is approved and then file a new NDA for Combogesic® IV, cross-referencing the then-approved NDA?*

FDA Response:
Refer to our response to Question 6.

Discussion: No further discussion.

Question 8: *AFT understands that many changes, including change in dosage form and change in indication, are handled in supplements to an approved NDA; but that a change in route of administration typically requires a new NDA. In this instance, could the addition of the intravenous administration dose form be handled as a supplement to the NDA for Combogesic® tablets, if approved?*

FDA Response:
No, the NDA for Combogesic IV could not be submitted as a supplement to the NDA for Combogesic oral tablets due to the differences in route of administration.

Discussion: No further discussion.

Question 9: *If none of the proposals outlined in Questions #6-8 are considered appropriate, would it be acceptable for AFT to submit a 505(b)(2) NDA for Combogesic® IV that relies on FDA's previous findings for the same RLDs cited in the Combogesic® tablet NDA? These RLDs are shown below.*

Table 1: RLDs cited in pending Combogesic® Tablet NDA 209471.

Drug Name	Ingredients	NDA Number	Sponsor
ULTRACET Tablets	acetaminophen 325 mg/ tramadol hydrochloride 37.5 mg	21,123	Janssen Pharmaceuticals
MOTRIN Tablets	ibuprofen 800 mg	17,463	McNeil Consumer

FDA Response:
Refer to our response to Question 6.

Discussion: No further discussion.

Question 10: A pharmacokinetic bridging study to demonstrate the comparability between Combogesic® IV and the RLD products, Ultracet tablets and Motrin tablets, would be conducted for such an application. As Motrin Ibuprofen tablets were discontinued (not for safety or efficacy reasons) and are no longer available, AFT would propose the use of Dr. Reddy's Ibuprofen 800 mg tablets, as was agreed with the Agency for NDA 209471.

Assuming that this bridging study demonstrates pharmacokinetic comparability of the active ingredients in Combogesic® IV with the above mentioned RLDs, would it be acceptable for AFT to rely on FDA's previous findings for these oral products to support an NDA for the intravenous product?

FDA Response:
Refer to our response to Question 6.

Discussion: No further discussion.

Question 11: In the alternative, is the data package described in Table 2 above sufficient to support the filing of a 505(b)(1) NDA for this product. The NDA package would include:

1. *Pharmacokinetic bridging study AFT-MXIV-06 demonstrating the comparative bioavailability of Combogesic® IV with Combogesic® tablets,*

2. *Two adequate and well-controlled clinical studies:*
   a. *AFT-MXIV-07: Maxigesic® IV Phase 3 Bunionectomy Study.*
   b. *AFT-MX-6: Maxigesic® 325 Tablets Phase 3 Acute Dental Pain Study.*

3. *Repeat-dose toxicology studies.*

FDA Response:
No, a 505(b)(1) application must include a complete nonclinical development program that

includes pharmacology studies, safety pharmacology studies, pharmacokinetics (absorption, distribution, metabolism, elimination), repeat-dose toxicology study in two species of at least 14 days duration and the complete battery of genetic toxicology and developmental and reproductive toxicology studies as per ICH M3(R2).

You must also address all aspects of clinical pharmacology, including absorption, distribution, metabolism, elimination (ADME); potential for drug interaction; use in specific populations such as renal impairment and hepatic impairment; and potential for QT prolongation. If you reference literature-based PK data to support your NDA, and do not own or have write of reference to the data, such reference would render your application a 505(b)(2) NDA, and you must demonstrate that the literature data meet the Agency's criteria to support your submission. You must include the raw datasets, bioanalytical method validation report, and in-study bioanalytical performance report to support the submission. You must demonstrate that the product formulation, dosing regimen, and patient population for the study in the literature are the same as your proposed product so that the literature data can apply to your product. If not, you must provide justification that the literature data can be used to support your NDA submission considering any differences.

From a clinical perspective, your proposal for a 505(b)(1) NDA is inadequate. You will need to supply adequate efficacy and safety data from studies of Combogesic IV. If you intend to pursue this pathway, we recommend that you meet with the Division for that specific purpose to define the requirements for a 505(b)(1) NDA for your product.

Discussion: No further discussion.

ADDITIONAL COMMENTS

Nonclinical

1. **Your completed** (b) (4) **toxicology study is not adequate to support filing of your NDA** (b) (4) **At a minimum, a 14-day repeat-dose intravenous toxicology study that mimics the clinical dosing regimen must be submitted at the time of NDA submission.**

AFT Pharmaceutical's Pre-Meeting Comments:
As clarified for question 6, the proposed dosing duration for Combogesic IV is (b) (4)

Clarification Question: Does the FDA agree with this? If not, would you please clarify the appropriate dosing regimen for the recommended 14-day study?

Discussion:
The Division reiterated that a 14-day repeat-dose toxicology study is required to support an NDA submission and clarified that the dosing regimen must be daily with dosing every 6 hours.

2. **Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:**

    a. **You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

    b. **In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14-days duration should be completed.**

        Refer to
        Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*
        http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

        and

        Guidance for industry: *Q3B(R2) Impurities in New Drug Products*
        http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

    c. **Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at,**
    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf.

3. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for**

introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development to mitigate risk.

4. **We note that (b) (4) (b) (4) USP drug substance specification of NMT (b) (4) will be acceptable. Reduce the drug substance specification for (b) (4) to as low as technically feasible and provide adequate safety justification for the proposed specification. Your drug product specifications for these degradants should be based on good manufacturing practices and reduced to as low as technically feasible, if it cannot be reduced to reflect a maximal daily intake of NMT 120 mcg/day for each individual degradant.**

5. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds must be adequately justified for safety from a toxicological perspective.**

6. **Your NDA must adequately address the safety of elemental impurities in accordance with the ICH guidance document: Q3D Elemental Impurities, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM371025.pdf.**

7. **The NDA submission must contain adequate information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Provide justification for the choice of solvents and conditions for the extraction studies (time, temperature, etc). The results of the extraction studies should be used**

to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) must be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you must provide adequate justification that these thresholds are not possible to be met by current analytical methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission must include a detailed discussion of how you established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.

Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.

For all drug products, establish your AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more than 1.5 mcg/day or up to 120 mcg/day pending during of treatment). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect and identify any leachable that is present in the product at 5 mcg/day and higher, unless justified otherwise, to permit an adequate toxicological risk assessment.

For additional guidance on extractables and leachables testing, refer to the following documents:

> **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**
>
> **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**
>
> **FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf**

In your assessment, include a table listing all compounds, including the concentration in ppm, the experimental conditions, and the maximum daily exposure to these compounds based on the maximum daily dose of the product. The extractable/leachable data must be accompanied by an adequate toxicological risk

assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

- **If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.**

- **Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your container closure system.**

- **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.**

8. **Include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product in Module 2 of the NDA submission. Include copies of all referenced citations in the NDA submission in Module 4. Translate all journal articles that are not in English into English.**

9. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.**

AFT Pharmaceutical's Pre-Meeting Comments:
As AFT has agreed to conduct a pharmacokinetic study in humans to establish a bridge between Combogesic IV and the reference listed drugs, AFT considers that an additional pharmacokinetic study in animals to create a bridge is not necessary.

Clarification Question: Does the Agency agree?

Discussion:
The Division noted that the Sponsor must be able to draft labeling that is specific to their product. The Sponsor should review the referenced product labeling and ensure that adequate data exist to inform the exposure margins specific to their product. New nonclinical pharmacokinetic studies may not be required as long as the Sponsor's product labeling is scientifically correct.

10. **We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, conduct a thorough review and integrated analysis of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.**

11. **We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the recommended qualification thresholds or novel excipients that are not justified for safety or if the application lacks adequate safety justification for extractables and leachables.**

ISSUES REQUIRING FURTHER DISCUSSION
No issues require further discussion

ACTION ITEMS

1. The Sponsor will consider relying on the safety and efficacy findings of the FDA-approved product, NDA 017463, even though it is no longer marketed, and use Dr. Reddy's IBU tablets in the comparative bioavailability study, as long as it is the generic drug to the discontinued FDA-approved product.

2. The Sponsor may compare the dose-normalized PK, but they must use the absolute PK data for comparison.

3. The Sponsor will conduct a 14-day repeat-dose toxicology study that will evaluate daily dosing every 6 hours to support their NDA submission.

ATTACHMENTS AND HANDOUTS

No attachments or handouts

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.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized,

and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

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.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

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.

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

/s/

EVA L YUAN
08/29/2018