Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-D-0571: Guidance for Industry: Rheumatoid Arthritis: Developing Drug Products for Treatment

Dear Sir or Madam:

The Combination Products Coalition ("CPC") is pleased to offer its comments on the Draft Guidance for Industry: Rheumatoid Arthritis: Developing Drug Products for Treatment ("Draft Guidance").

By way of background, the CPC is a diverse group of drug, biological product, and medical device manufacturers with substantial experience in the combination products area. Our members range in size from small start-ups to multi-billion dollar manufacturers. These companies all share an intense interest in policy issues affecting combination products. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

One of our principal goals is to work with FDA on such issues in order to advance our common mission of providing the best possible health care for patients. In this regard, the CPC has had frequent dialogue with the Office of Combination Products on regulations, guidance documents, and other policy issues that affect combination products and how best to serve patient needs with respect to such products. For example, we have submitted dozens of written comments, policy documents, proposed guidance documents, and other materials to the agency on these issues for nearly a decade. If you are interested, you can find several of these materials on our website: http://www.combinationproducts.com/.

Below we offer our comments on the Draft Guidance. As the CPC's principal goal is to address issues specific to combination products, our comments are not designed to address all issues with the Draft Guidance. To that end, the CPC offers a general comment that the combination product specific information included in the Draft Guidance appears to be general drug-device combination product guidance and should be included in a separate general guidance document and not included in this RA specific Draft Guidance. In addition to this general comment, the CPC offers specific comments on when pharmacokinetic ("PK") bridging studies

should be required, the requirements for Human Factor ("HF") studies early in development and the "real life" patient handling experience requirements.

I. FDA should consider deleting the general information on drug-device combination products from this Draft Guidance and issuing such information in a separate guidance and/or clarify how such information is specific to drug-device combination products intended for use in the treatment of Rheumatoid Arthritis.

The CPC appreciates that the Draft Guidance addresses combination product specific issues. However, the information provided appears to be general in nature and not specific to combination products intended for use in the treatment of rheumatoid arthritis ("RA"). Including guidance that appears to be broadly applicable to drug-device combination products into a disease specific guidance document has the potential to create inconsistencies in the application of such guidance and is likely to further complicate the combination product development process. Therefore, to the extent the combination product specific information included in the draft guidance is intended to apply to combination products, such information should be extracted from this guidance and included in a separate, more broadly applicable guidance. But, to the extent FDA believes there is a need to expand on existing general guidance and provide additional RA product specific guidance, it should be clear that the guidance is product specific and explain why additional requirements are needed for a subset of products.

In particular, we find it difficult to understand what is unique about combination products intended for use in treatment of RA that would require separate guidance. Particularly, it is not clear how some of the issues associated with patients with RA would not also be associated with patients with other diseases/conditions. Specifically, it fails to explain why the information is specific to RA when there are other diseases/conditions where patients have the same type of impairments as RA patients that would impact the usability of a drug delivery device constituent part. To the extent the information is applicable to patients with similar symptoms, not issuing this information in broader guidance could result in the failure to address the needs of patients who have similar symptoms (hand impairment), subcutaneous tissue characteristics, and usability factors. This consistency is an important consideration since the same or similar drug/biologic constituent parts are used with the same or similar delivery devices for different disease conditions and are in development for those other indications or are already approved by FDA. Therefore, unless FDA can explain why the information is applicable only to RA specific products, such information should be extracted from the Draft Guidance and be issued in a separate broadly applicable guidance document.

As the following sections address the combination product information included in the Draft Guidance, our comments would be applicable regardless of whether FDA agrees that this information should be included in a separate generally applicable guidance document.

II. In general, the additional clinical data requirements suggested by the Draft Guidance are unnecessary to support a change in drug delivery systems unless the change in drug delivery system raises significant new questions about the route of administration or results in a new route of administration.

Unless there is a change to the formulation of the drug constituent part that would require new clinical testing or a change to the device constituent part that would result in a new (i.e., unlabeled) route of administration the data requirements suggested in the draft guidance appear to be overly burdensome. Instead, CPC proposes a stepwise approach to be used to establish the comparability of the investigational and marketed presentations of the product. Each step would be based on the risks to safety and effectiveness presented by the design and/or test results. The need for a PK bridging study should be determined by the novelty of the delivery system or the extent to which the key claims vary from the label. In general, PK studies should not be required if there are no significant differences in the key administration parameters of the two presentations. If key administration parameters are not substantially equivalent (without a change in the route of administration) then a PK study may be necessary. It is only if the design of the system results in a new route of administration, raises significant new risks regarding the safety or effectiveness of the drug product or the PK study does not establish bioequivalence that additional clinical safety or effectiveness data may be required. The specific clinical trial requirements will be product-specific and will be reviewed with the Agency to confirm acceptability.

A. In general, bench testing should be sufficient to bridge from a pre-filled syringe to autoinjector

When bridging from a pre-filled syringe to an autoinjector, the supplement to the application should only need to include in-vitro Design Verification data and the results of Design Validation testing obtained from a summative simulated use HFE/UE study. Not only should this information be sufficient to show comparability, it may be more reliable than comparing clinical responses between, for example, a syringe and an autoinjector. Syringes, when used manually, produce greater variability in key clinical performance parameters (e.g., dose range, PK, safety, efficacy) because of variations in needle insertion depth and angle, and delivery rate. The clinical response using that same syringe assembled in an autoinjector would add precision and repeatability to the injection depth and delivery rate, but that clinical response would already be encompassed in clinical data generated in the studies conducted with the free-hand injected syringe. Additionally, the effect of technique or delivery device precision and repeatability for subcutaneous injections into relatively uniform avascular tissue (biospace) may not be clinically relevant for most drugs, especially those with a wide therapeutic dosing window, a wide safety margin, and a long half-life systemic effect.

Further, FDA should appreciate that there is already significant variability in the subcutaneous administration of drugs and that such variability has not resulted in significantly increased risks or hazards related to the safety and effectiveness of most drugs when used as directed. Specifically, there are thousands of delivery devices (needles, syringes, pen injectors, autoinjectors, needle-free injectors) used to perform millions of subcutaneous injections every day. These products contain needles that vary in length (4-25 mm) and gauge (31- 25 ga). Additionally, syringes for subcutaneous administration vary in barrel diameter and volume

(which impacts delivery time based variations in injection rate that result from these physical differences). Also, the various injection techniques taught to credentialed health care professionals vary in injection angle, pinching techniques and injection site selection, and these techniques are taught to patients who self-administer their drugs as well. However, none of these subcutaneous injection variables have resulted in significant risks or hazards related to the safety and effectiveness of most drugs or significantly impacted the treatment of patients when the devices are used as directed either for professional administration or patient administration. Therefore, FDA should provide its rationale in the final guidance, based on scientific data that demonstrate that using an advanced delivery drug delivery device with improved delivery performance to deliver an RA drug, or for that matter any drug, raises significant new questions of safety and effectiveness for subcutaneously injected RA drugs in comparison to those drugs manually injected with a syringe.

B. If key administration specifications are not substantially equivalent (without a change in the route of administration), the design of the system raises significant new safety or effectiveness risks, or the PK study does not establish bioequivalence, then evidence of clinical comparability may be required.

If the key administration parameters are not equivalent (or fall outside the labeling of the approved presentation) then evidence of clinical comparability may be needed to bridge the existing clinical data to the new delivery system. For most of these changes, bridging data will only require a determination of bioequivalence through Human PK or PD studies comparing the proposed system to the system used in the clinical study. Such PK studies would not require testing across the entire spectrum of body weights and, for device modifications that do not affect injection depth, a representative sample of the target patient population or in normal health volunteers should be sufficient to demonstrate comparability.

Clinical safety and effectiveness data should only be required if the design of the drug delivery system raises significant new safety or effectiveness risks, the PK or PD study does not establish bioequivalence or the delivery system changes the route of administration. In these circumstances the specific clinical trial requirements will be product specific. FDA should provide a rationale justifying any requests for clinical safety and effectiveness data in other circumstances, particularly in those circumstances where PK or PD studies establish bioequivalence.

III. FDA should clarify what constitutes a "real-life use study" and what information captured in such a study cannot be captured in either HF or clinical studies.

FDA should explain what information it is trying to obtain through a "real-life" use study and justify the recommendation of "real-life" patient handling experience studies when transitioning between a pre-filled syringe and an autoinjector. The Draft Guidance states that a transition from a prefilled syringe to an injector delivery system must be supported with clinical data. FDA adds that the data must include a "real-life patient handling experience to assess device performance." CPC may be able to accept the recommendation for PK, PD or clinical studies for drug-device combination products and the need for HF studies for novel delivery devices, but we find it unclear what data cannot be generated in PK, PD, clinical, or HF studies that would require sponsors to perform real-life use studies.

FDA does not define clearly what data such real-life use studies are trying capture or how this information is not already obtained during clinical and HF studies of the combination product. It is our understanding that the purpose of a real-life use study is to establish the safe and effective performance of the delivery device when used by the intended users in the intended environment of use without an analysis of safety or effectiveness. It is also our understanding that it is not an HF study per se, but human factors and/or use errors may be a factor in delivery failures. The draft guidance suggests that "robustness" information can be captured in these studies but it is not clear what this term means and what specific data might be collected in in support of this request.

FDA should not suggest, recommend or require a manufacturer to conduct a real-life use study until FDA issues guidance clearly defining the goals of the study and demonstrating that data collected through clinical testing and HF testing is not sufficient to satisfy these goals. Assuming the goal of the study is to evaluate the performance of the delivery device by the intended users in the intended use environment, such information should generally be available through HF studies, at least with respect to products administered by healthcare professionals. Additionally, such information should be available where the proposed characteristics of use (frequency, user groups, and environment of use) of the device constituent part are similar to existing use of the device constituent part. Therefore, real-life studies should not be necessary for such products.

To the extent such studies are required, there should be no requirement to conduct the evaluation in a blinded fashion, and such a study could be open label.[1] Device use and performance should be evaluated on a small number of users (e.g. 50) representative of the overall user population and covering a very small number of unsupervised uses for each subject (e.g., two unsupervised uses). We agree that if these studies are conducted the sponsor should collect information regarding all devices perceived by the user to be broken or malfunctioning and data capturing reports that the injection was not successful. Such information can be captured using patient diaries or responses to simple questions included in the protocols or case report forms. Only these devices should be retrieved[2] for evaluation and identification of the root cause of the reported problem. Single use devices should be examined for any evidence of malfunction or failure to deliver. Reusable or multiple use devices can be evaluated by in vitro performance testing.

However, there should be no requirement to collect devices that are not perceived to be broken or malfunctioning. Re-testing of an arbitrary number of used, returned, released samples with no suspicion of failure, packaged in a potentially uncontrolled manner that may generate invalid

[1] As the study would not be designed to test the safety and effectiveness of the drug constituent part, Sponsors should be able to use the identical device constituent part with a placebo that mimics the delivery characteristics of the drug in such a study.

[2] CPC is in full agreement that products associated with complaints or failures should be returned for root cause investigation and most companies already have a defined procedure and a shipping container for the return of those products. These procedures can be burdensome since investigational sites are often located in many different countries with different shipping requirements for used "sharps" and they typically must be shipped as biohazards.

data if damaged in shipping, would yield little meaningful information beyond the product quality attributes already tested in released product lots from which the samples came. CPC believes that bench testing along with simulated use studies outside the clinical program is sufficient to demonstrate the reliability and usability of the delivery device. Specifically, before an injection device (e.g., autoinjector) is released for clinical trials, it undergoes design verification testing of specific performance and quality attributes with statistically justified sample sizes (often hundreds of samples). These verification tests often include drop tests and shipping conditioning tests defined in device and injector quality standards (e.g., ISO, ANSI, ISTA, etc.). The devices are typically assembled in a validated process with in-process controls (IPCs) and release tests that ensure device quality and performance, and are documented in Certificates of Analysis as clinical trial lots.

IV. FDA should reconsider its recommendation that HF studies be conducted early in the development of an RA drug product, as it is unlikely that manufacturers will begin developing a combination product prior to finishing key dose-ranging, safety and efficacy studies of the drug product.

Manufacturers should not be expected to develop combination products before establishing the safety and efficacy of the drug product. Generally, conducting HF studies early in development would be overly burdensome to industry sponsors without much benefit to patients. There are several reasons for this. First, sponsors would be required to conduct baseline (formative) HF studies prior to discharging key development risks related to the drug constituent part of the RA drug-device combination product. Manufacturers would have to make risky investment decisions to begin development of a combination product before they are sure the drug constituent part is safe and effective. Second, in addition to additional cost of developing the combination product for a drug that may not actually be effective, incorporating a device into the pivotal study of a novel drug adds another layer of complexity that may unnecessarily complicate the conduct of the study and the analysis of whether the drug itself is safe and effective. Third, because of these risky investments, the overall cost to develop RA drugs would increase. These factors would be a disincentive to the innovation of novel drugs that require a drug delivery device, such as RA drugs that must be administered subcutaneously.

However, there are certain circumstances where *formative* HF studies may need to be performed early in the development process, and limited HF studies may need to be conducted prior to any clinical studies using the combination product.[3] Where the device constituent part will be integral to the overall use of the combination product, simultaneous development of the drug and device constituent parts may be optimal and would likely require the manufacturer to use the device constituent part in Phase II and/or Phase III studies. In these situations, conducting HF studies prior to the Phase II or Phase III studies may be required if the drug-device combination product is intended to be used in self-administration.

[3] There also may be circumstances where the necessary human factors information could be obtained through methods other than simulated use studies.

But even in these cases, only formative HF studies (or other methods of obtaining the necessary human factors information) should be conducted[4] and these are generally only appropriate where a device constituent part has not been used previously. That is, when a device constituent part is novel or is being used in a different intended use population, different frequency of use, etc., then a formative study during development may be appropriate. But when a device constituent part has a safety and effectiveness history in the population intended to use the RA drug-device combination product, then a formative use study should not be necessary.

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Again, we thank FDA for acknowledging the need to address combination product issues in the Draft Guidance. However, we believe that the information provided in the draft guidance is more general in nature and should be addressed in a separate more generally applicable guidance document, and only that information that is RA product specific should be included in this Draft Guidance.

Kindest regards,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

[4] Summative studies should not be required as their purpose is to establish that the device can be used without patterns of preventable use errors. As such, they generally should not be conducted until the IFU is near final, which will not occur until after the pivotal study. Otherwise, if the sponsor makes changes to the IFU subsequent to conducting the summative HF study, the manufacturer may need to repeat the summative study.