SMG 4101

FDA STAFF MANUAL GUIDES, VOLUME IV – AGENCY PROGRAM DIRECTIVES

COMBINATION PRODUCTS

INTER-CENTER CONSULT REQUEST PROCESS

Effective Date: June 11, 2018
Change: November 13, 2023

1. PURPOSE

The purpose of this document is to describe the procedures for when and how to request, receive, process, and track the progress of Inter-Center Consult Requests (ICCRs) between the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH). Henceforth, this will be referred to as the ICCR process. This SMG outlines the standardized ICCR process across the medical product Centers to enable efficient and effective collaboration.[1]

2. SCOPE

The ICCR process covers inter-center consults that occur between CBER, CDER, and CDRH for combination products and non-combination products.[2] If staff have

[1] CBER, CDER, CDRH, and OCP also coordinate on regulations and guidance that pertain to combination products. See SMG 4103 Expectations and Procedures for Engagement among Medical Product Centers and Office of Combination Products on Regulations and Guidance Pertaining to Combination Products.

[2] Combination products are defined in 21 CFR 3.2(e). The term Part 3 combination product (hereafter "combination product") includes:

questions about this document, they should contact their Center Product Jurisdiction Officers (PJOs) or the Office of Combination Products (OCP).

In addition to describing the ICCR process, this document describes:

- Roles and responsibilities for the Lead Center, the Consulted Center(s), and OCP;
- The process for determining if an inter-center consult is needed;
- Critical steps in the ICCR process; and
- Standard critical elements to be included in a consult request.

3. BACKGROUND

Consultation with another Center may be needed for the review of a product. Such consultation between Centers, for example for premarket applications[3] or in postmarket, may occur when a unique aspect of a product's indication, formulation, design, or performance raises concerns that require review by another Center, or when the expertise to review a particular aspect of the product resides in another Center. In such instances, a consult is requested by one Center to another. This ensures a comprehensive review of the product.

In 2015, an external study (Attachment B) identified the need for a comprehensive strategy for managing combination product review and underscored the importance of cross-center collaboration. This study highlighted issues that had the potential to delay approval. The findings of the external study were confirmed by an internal

(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed
product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
(4) Any investigational drug, device, or biological product packaged separately that, according to its proposed labeling, is for use only with another individually specified investigational drug, device, or biological product, where both are required to achieve the intended use, indication, or effect.

[3] For purposes of this SMG, unless otherwise stated, the term premarket application includes investigational new drug application (IND), new drug application (NDA), abbreviated new drug application (ANDA), investigational device exemption (IDE), premarket approval application (PMA), premarket notification (510(k)), humanitarian device exemption (HDE), biologics license application (BLA), request for classification submitted under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act (De Novo request), presubmissions (e.g., pre-NDA, Q-submission) or supplements/amendments to any of these applications (as applicable).

study. A comprehensive assessment revealed several opportunities for improvement related to combination product review processes.

To address the issues identified in the studies and facilitate inter-center interactions, FDA developed and piloted a new ICCR process for premarket combination product review beginning in August 2016. The objectives of the pilot were to improve inter-center coordination for combination products and enhance the timeliness and consistency of inter-center reviews. Based on outcomes of the pilot and internal stakeholder feedback, the new process was implemented throughout CBER, CDER, CDRH, and relevant groups in FDA's Office of the Commissioner (OC), and the process was expanded to all inter-center consults. The process outlined in this SMG is based upon the results of the pilot and addresses the mandate in Section 3038 of the 21st Century Cures Act to ensure timely and effective review that involves more than one Agency Center.

4. ROLES AND RESPONSIBILITIES

A. **Lead Center**: The Center that has primary review responsibility for the product. This Center is responsible for identifying early in the review process whether the application or product issue necessitates an inter-center consult.[4]

B. **Lead Center Consult Requester**: The person in the Lead Center who fills out and submits an ICCR. The consult requester serves as the administrative point of contact for the consult request (e.g., location of review materials) and when additional information is needed from the external stakeholder (sponsor/applicant/manufacturer).

C. **Lead Center Submission Contact**: The person(s) in the Lead Center who serves as the point of contact for technical questions regarding the application or issue. The Lead Center Submission Contact and the Lead Center Consult Requester may or may not be the same.

D. **Consulted Center**: The Center that will provide the necessary expertise to the Lead Center. After the consult is completed, the Consulted Center is responsible for closing out the ICCR.

E. **Consulted Center Receiver**: The person(s) in the Consulted Center who is assigned to receive ICCRs (e.g., by monitoring a specific email inbox) and assist with triage and reviewer assignment within the Consulted Center.

[4] To aid in determining whether an Inter-Center consult is needed for certain combination products, agreements between the Centers exist that outline circumstances when a consult is or is not needed. When the Lead Center is unsure whether a combination product is covered by such an agreement, the Lead Center should contact its PJOs for a determination. In addition, when a combination product is not covered by any agreement and the Lead Center is considering not issuing a consult, the Lead Center should consult its PJOs, who should work with the relevant Center(s) to determine whether a consult is necessary.

F. **Assigned Consulted Center Reviewer**: The person in the Consulted Center who is assigned to conduct the review and provide a review memo or other deliverable in response to the consult request.

G. **Center Product Jurisdiction Officers (PJOs)**: The contact(s) within each Center for product classification, Center jurisdiction, and combination product information. The PJOs also serve as administrative support for Center stakeholders using the ICCR process.

H. **Office of Combination Products (OCP)**: The Agency office that administers the overall ICCR process and assists the Centers, when needed. For combination products, OCP oversees the statutory requirements for coordinating inter-center reviews by overseeing the timeliness of premarket reviews and the alignment of Centers' feedback to industry. OCP may serve in the same capacity for non-combination products, typically at the request of Centers.

5. PROCEDURES

The figure in Attachment A illustrates the general flow of the ICCR process, including the specific roles and responsibilities of the Lead Center, Consulted Center, and OCP. OCP and each Center's PJOs are resources for Center staff regarding the ICCR process. The Center PJOs should typically be contacted first for questions related to whether a product is a combination product, for assistance in identifying the appropriate Consulted Center Receiver, or for questions related to a Center's internal process for managing ICCRs. Center PJOs will engage OCP when needed in these discussions.

The ICCR process in brief is as follows:

a. **Identify the product as a combination product or a non-combination product (Lead Center)**

This should be done within the first few days of the receipt of the application or issue and, when applicable, documented within the Lead Center's records system.

b. **Identify need for expertise and initiate consult (Lead Center)**

The specific expertise needed for the consult, where that expertise resides, and the complexity of the request dictate the process for the request (see section d. below). Every effort should be made to identify the need for a consult as early in the review process as possible.[5] The Lead Center should provide the Consulted Center adequate time to complete the review while still ensuring that necessary due dates are met (e.g., any user-fee goal dates associated with the submission). OCP participation in discussions may be

[5] Staff should refer to internal process documents for specific timelines.

requested directly by the external stakeholder or by either the Lead or the Consulted Center(s).

c. **Draft/prepare consult request (Lead Center)**

At a minimum, the Lead Center Consult Requestor should include the following information in an ICCR to enable the Consulted Center to efficiently assess the scope of the request and identify appropriate reviewer(s):

i. Application and product information (application number and type (if applicable); product name(s); indications for use; and description of the product(s));

ii. Specific questions for which expertise is being requested and what is needed (i.e., deliverables being requested) from the Consulted Center;

iii. Location of review materials (e.g., links to electronic documents) and specific details on where the question/relevant product information can be found (sections, page numbers, etc.);[6]

iv. Requested due date for the Consulted Center's review or other deliverable, established to allow Lead Center to meet applicable user-fee commitments or other Center or Agency policies or requirements;

v. Any known interim milestones before consult completion (e.g., internal meetings, external stakeholder meetings, interactive review due dates, filing decision dates, draft memos, slides, minutes) for which feedback or participation from the Consulted Center may be needed; and

vi. Contacts (e.g., Lead Center Submission Contact) for the Consulted Center to follow up with if additional information is needed.

d. **Submit consult (Lead Center)**

i. For routine consults,[7] the consult request is sent to the relevant Consulted Center Receiver. OCP maintains a list of Consulted Center Receivers accessible to all staff. If the Lead Center Requester has questions about the Consulted Center Receiver, he/she can contact the Lead Center PJOs for assistance.

[6] When access to electronic systems and databases is needed to complete a consult review, the process to gain access to the Lead Center's electronic systems and databases should be expedited. Staff with questions about such access may contact their PJOs or OCP.

[7] A routine consult is one in which Lead Center staff knows which group(s) in the Consulted Center has/have the desired expertise. One application or issue may require multiple routine consults within the same Consulted Center (e.g., separate consult requests issued for facility inspection, clinical, and/or product design considerations).

ii. For non-routine consults,[8] ICCRs are initially sent to OCP. Prior to sending such a consult request to OCP, the Lead Center Requester should contact their Center PJOs for assistance. OCP schedules and coordinates a consult orientation meeting with the Lead Center and potential Consulted Center(s). During the consult orientation meeting, the Centers and OCP will discuss what expertise from the potential Consulted Center(s) is necessary for review of the product and/or issue.

After the consult orientation meeting, the Lead Center will submit any necessary consult requests to the identified Consulted Center(s) as discussed during the orientation meeting. Once all necessary ICCRs are submitted, the process and engagement between Centers follow that of a routine consult, outlined below.

e. **Assign reviewer (Consulted Center)**

Upon receipt of an ICCR, the Consulted Center Receiver assigns a reviewer in the ICCR electronic tracking system, which will automatically notify the Lead Center of the reviewer assignment. If an assigned reviewer cannot address all the questions in the consult request or if an ICCR has been sent to the wrong Consulted Center Receiver, the Consulted Center should expeditiously communicate the issue to the Lead Center so that the ICCR can be reassigned or redirected.[9]

Assigned reviewers from the Consulted Center are considered members of the Lead Center review team. The Lead Center will inform assigned reviewers from the Consulted Center of the other review team members. The Lead Center will invite assigned reviewers from the Consulted Center to internal and stakeholder meetings. Their supervisors may also be invited to these meetings.

f. **Consult review (Consulted Center)**

The scope of the Consulted Center's review should include the specific requests from the Lead Center and be limited to these requests. If a Consulted Center believes there are additional review considerations for which the Lead Center did not request a consult and for which the Consulted Center has expertise, the scope of the consult should be discussed with the Lead Center. If the Lead Center determines that additional expertise is

[8] A non-routine consult is any consult where another Center's input is needed, but the interaction is not straightforward. Non-routine consults typically occur when the scope of the consult is large/complex (e.g., multiple groups may need to interact), or when novel products or issues that present challenging questions regarding the scope or content of the consult or groups that may need to provide input are involved.
[9] Staff should refer to internal process documents for specific details and timelines.

necessary to inform the regulatory decision-making process, then additional consult requests may be issued.

The Lead Center is responsible for communication with the external stakeholder in accordance with the Lead Center's processes. This includes sending requests on behalf of the Consulted Center for additional information or clarification to the external stakeholder. The Lead Center should expeditiously notify the Consulted Center when the response is received. The Consulted Center's review of the information obtained does not require a new ICCR and should be incorporated into the final deliverable provided by the Consulted Center. New ICCRs are required for review of responses in a resubmission after an action has been taken (e.g., Complete Response, major deficiency).

User-fee and other goals are commitments that apply to the entire Agency. Therefore, the Consulted Center and its Assigned Reviewer(s) should make every effort to meet the consult due date identified by the Lead Center to ensure that goal dates are met. If the Consulted Center anticipates that a due dates will be missed, the Consulted Center must notify the Lead Center to discuss alternatives as soon as possible and, as necessary, update the ICCR with a new due date.

g. **Complete consult (Consulted Center)**

Centers may choose to interact with each other on draft or informal work products prior to finalizing the consult, and this can be done on an as-needed basis. Final deliverables (e.g., final written review, response to meeting questions) should go through appropriate signoff procedures within the Consulted Center before being provided to the Lead Center. Assigned Consulted Center Reviewers are responsible for ensuring their management has appropriate documentation to ensure timely signoff (e.g., application, previous consulting reviews) by the requested consult due date. Once the consult is complete, the Consulted Center sends the final deliverable to the Lead Center and closes out the ICCR in the ICCR electronic tracking system.

h. **Incorporate consult (Lead Center)**

If the Lead Center accepts the Consulted Center's consult recommendation, the Lead Center incorporates the recommendation in developing communications with the external stakeholder, determining application approvability, or taking other FDA action. If the Lead Center disagrees with the recommendations, it should reach out to the Consulted Center to discuss the disagreement prior to taking a regulatory action. If disagreements cannot be resolved, see i. below.

Copies of any communications with the external stakeholder (e.g., minutes, action letters) that are related to or result from the consult should be sent electronically to the Consulted Center in a timely manner.

i. **Informal and Formal Dispute Resolution (Lead and Consulted Centers)**

If the Consulted Center feels that rejection of information provided in a consult will affect the assessment of safety, efficacy, and/or quality of the product under review, it is encouraged to try to resolve these disagreements informally at the inter-center review team level and continue through the next level signatory if agreement cannot be reached. The outcome of any such discussions should be documented in the administrative record of the application. If the Lead Center and Consulted Center(s) cannot resolve the difference of opinion informally, the cross-center scientific or regulatory dispute resolution process may be initiated (see SMG 9010.2 Cross-Center Dispute Resolution at the FDA).

j. **Archive consult (Lead Center)**

The Lead Center is responsible for archiving the final deliverable from the Consulted Center (e.g., written consult memorandum) in the appropriate Lead Center administrative file. The Lead Center is also responsible for confirming that the combination product code in the Lead Center systems and databases appropriately reflects the type of combination product (see 5.a. above).

Communication between staff in the Lead and Consulted Centers should be frequent. Informal communication should ideally occur on a one-to-one basis between review staff, without the need for prior supervisory approval. For complex products and development programs, the Lead Center should schedule additional planning meetings as necessary to ensure an efficient review process. Such communications may involve discussion of updates to the product application, information requests to and from external stakeholders, attendance and discussions at milestone/review meetings, and interim review findings, among others.

6. PROCESS MONITORING AND IMPROVEMENT

OCP will maintain centralized resources on the Agency intranet for staff, including training materials on the ICCR process. OCP and the Centers will periodically review and update these resources as needed. The Centers will ensure that established timelines for ICCR activities are clear and predictable and will communicate target timelines for identifying the need for an inter-center consult, submitting a consult request, and assigning a reviewer for the consult.

Quantitative and qualitative data will be collected by OCP and the Centers to evaluate the need for process improvements. Data collected may include:

- Number of inter-center consults requested;

- Circumstances under which consults are needed for combination products;

- Timeliness of consult interactions, as compared to any established benchmarks (e.g., time from application receipt to consult request submission, time from consult request submission to reviewer assignment);

- Input on ICCR format and usability (e.g., through staff feedback, audits, monitoring users request for assistance with ICCR tasks); and

- Quality of the consult requests or reviews (e.g., through staff feedback, audits, collection of user complaints).

OCP will periodically review ICCR data and conduct additional assessments (audits, etc.) as needed to ensure the ICCR process supports timely, consistent, and effective review of combination products.

7. REFERENCES

U.S. Food and Drug Administration. Combination Product Review Inter-Center Consult Process Study. April 17, 2015. Available at: http://www.fda.gov/downloads/CombinationProducts/GuidanceRegulatoryInformation/UCM467128.pdf. Accessed October 31, 2016.

8. EFFECTIVE DATE

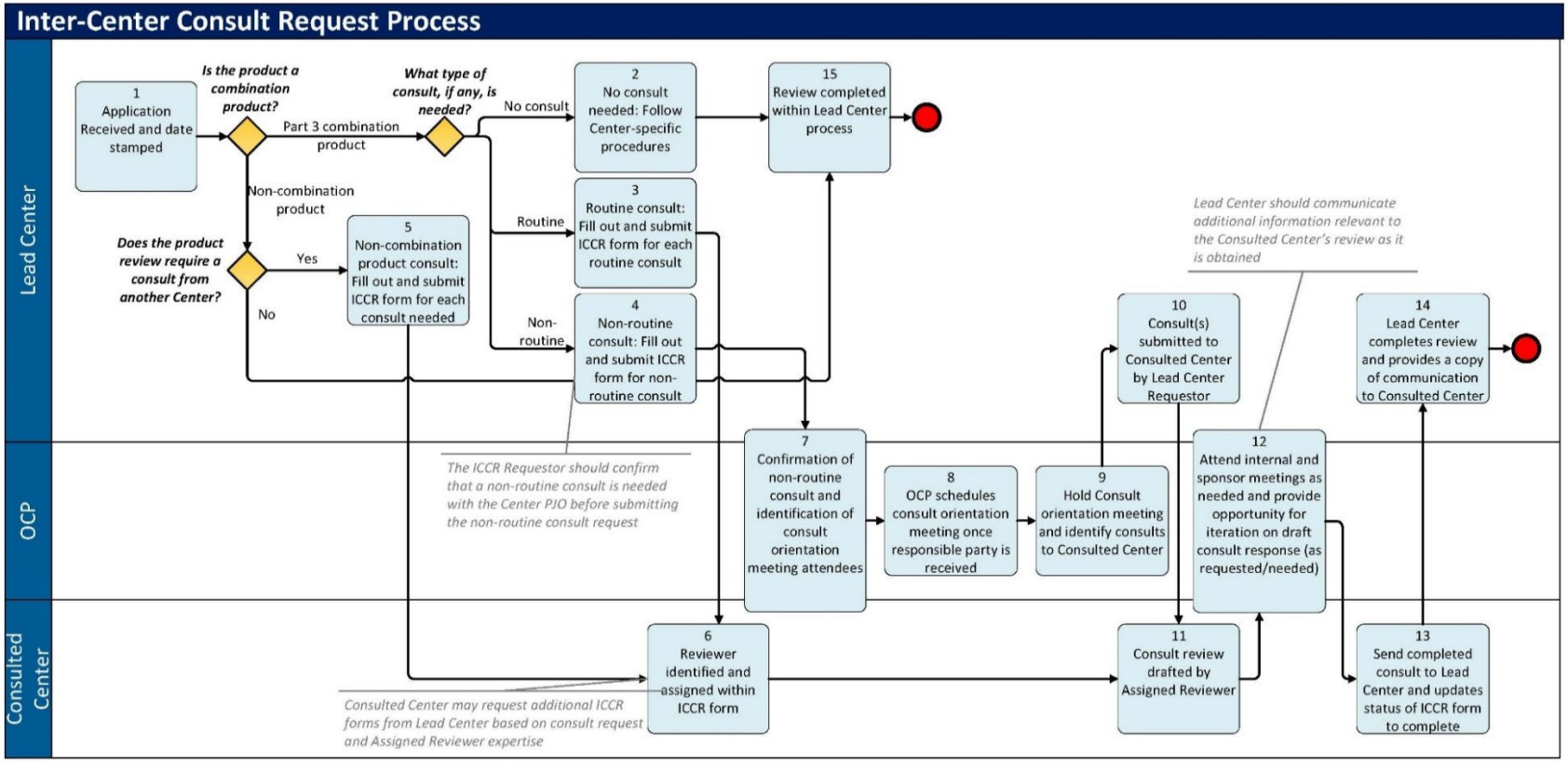
The effective date of this guide is June 11, 2018.

9. Document History – SMG 4101, "Inter-Center Consult Request Process"

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIALS
Initial	7/31/02	N/A	N/A	Steering Committee: J. Morrison, K.Cook, S.Lard, H. Rosecrans S. Unger Center Directors: K. Zoon J. Woodcock D. Feigal
Revision	2/14/03	Added interim procedures for	M. Kramer	D. Feigal J. Goodman

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIALS
		combination products tracking; Modified IRCR Form to denote type of product		J. Woodcock M. Kramer
Correction	7/1/03	Updated fax number of Office of Combination Products	M. Kramer	New approval not required; technical correction to OCP fax number only
Correction	6/18/04	Updated fax number of Office of Combination Products	M. Kramer	New approval not required; technical correction to OCP fax number only
Revision	6/11/18	Substantive revision of entire document to reflect revised inter-center consult process.	Office of Combination Products (OCP) combination@fda.gov	Jonette Foy, Associate Director for Policy, CDRH Diane Maloney, Associate Director for Policy, CBER Thinh Nguyen, Office Director, Office of Combination Products Douglas Throckmorton, Deputy Center Director for Regulatory Programs, CDER Rachel Sherman, Principal Deputy Commissioner
Change	11/13/2023	Attachment B	Office of Combination Products (OCP) combination@fda.gov	James Bertram, Director OCP

SMG 4101, Attachment A - Inter-Center Consult Request Process Map



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Improving Patient Care through Better Combination Product Regulation

Recommendations to FDA Centers from the Combination Products Coalition

May 23, 2014

Executive Summary: Combination product regulation is at a crossroads. To ensure it proceeds on the right path – one that improves the public health by promoting innovation – reforms are needed to:

(1) **Improve coordination** among FDA participants in combination product reviews (i.e., Divisions, Offices, and Centers);
(2) **Improve communication** with sponsors; and
(3) **Improve scientific and regulatory justifications** supporting Agency data requests to ensure optimal decision-making that facilitates patient access to new and better therapies.

Among the areas that would benefit from these reforms is the usability testing review process, where innovators have observed significant shifts in requirements over the last few years. The problems that innovators have had with usability testing requirements have their origin in different philosophies among Centers – specifically, CDRH generally favors simulated-condition "human factors" testing to evaluate product usability, whereas CDER increasingly favors "actual use" testing that (1) is more likely to delay patient access to therapies, and (2) often provides little or no benefit over the information gained through human factors testing. However, issues with communication, coordination, and justifications provided with requests, are transforming philosophical differences into impediments to innovation and creating patient access issues.

Appendix A presents a case for usability testing that emphasizes human factors testing, which is generally considered the best approach to assess combination product usability and its impact on safety and effectiveness. Appendix A also addresses those aspects of coordination, communication, and scientific justification that should be improved. To that end of improving the regulatory system, and thereby improving patient access to innovative new therapies, we recommend that FDA: (1) Adopt traditional, simulated-use human factors testing as the policy for combination product testing across Centers; (2) Develop and implement an Agency-wide policy that allows bridging of combination products that use different injectors (e.g., prefilled syringe and pen injector) – but the same liquid injectable drug, dose, and route & process of administration – based on nonclinical testing and human factors studies; (3) Require human factors validation testing only with participants from the indicated patient group (or an appropriate surrogate group) for the combination product; (4) Provide sponsors with comments from all reviewers in all Centers before human factors validation studies commence.

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Introduction

Over the last few years, manufacturers (innovators) have run into unexpected regulatory road blocks when pursuing combination product approvals. *Ad hoc* FDA data requirements and surprising requests during the latter part of Agency reviews are keeping medically significant product enhancements and better therapies out of physicians' and patients' hands. If this continues, innovation will decline to the detriment of the public health. But with some reasonable improvements, FDA can change direction and put combination product regulation on the right path.

The Combination Products Coalition (CPC) has made attempts in the past to support the FDA in making improvements to these regulations, but these efforts have not resulted in the improvements that are needed. These efforts are evidenced in the proactive submission of documents prepared by the CPC, such as the CPC – drafted guidance document regarding "FAQs on Pre-Clinical and Clinical Research on Combination Products" submitted in February 2009, the Human Factors Matrix submitted in December 2012, and the Labeling Matrix submitted in April 2013. Additionally, the Office of Combination Products and the CPC hold an annual meeting to review ongoing activities and priorities of both organizations. During these discussions, the CPC routinely offers to provide assistance to the FDA in driving these priorities. The CPC commits to support the FDA in implementing the recommendations contained herein, to the extent possible.

In the following pages, the Combination Products Coalition ("CPC") explores the problems innovators are now facing during the FDA review process. We start by summarizing key results of an innovator survey and interviews that were recently completed by the CPC and conclude with general suggestions for improving the regulatory process. We also include, as an Appendix to this paper, a detailed analysis of specific problems innovators face with usability testing, and suggest improvements FDA can make which will help assure the safety, efficacy, and availability of combination products. We call out usability testing in the Appendix because it represents perhaps the single largest trouble spot in combination product regulation today in terms of delaying access to important new products for patients.

We hope, as you read this paper, you will come to appreciate the importance of setting combination product regulation on the path towards increased growth, innovation, and safety, particularly with respect to usability testing. The CPC has been heavily involved with combination product regulatory issues for over a decade, and our members have deep roots in both device and drug regulation dating back decades more. Our consensus is that the problems innovators are facing today with usability testing exceed anything we have seen previously and that resolving these issues must be made an Agency priority. We hope to work with you in the coming months to set regulation on the right path, and allow patients to benefit from more innovations.

II. CPC Survey Results

During March-April 2014, the CPC conducted an online survey of combination product innovators. Survey respondents had cumulative experience with more than 80 separate combination product marketing applications.

Five results from the survey stood out – three related to regulatory review process problems, and two quantifying delays and costs that are associated with these problems (which translates to delaying or otherwise limiting patient access to therapies). These results are summarized in Table I, and illustrate the pervasiveness of the difficulties innovators face, and the significant consequences these difficulties have on research and development.

Table I: Key Survey Results

Regulatory Process Problems that Delay Patient Access to Combination Products	Quantitative Impact of Process Problems on Combination Product Development
• 100% of respondents stated that they had experienced problems with combination product regulation during Agency reviews. • 80% of respondents stated that significant problems were caused by "surprise" requests made late in the review cycle. • 50-85% of respondents stated that when a conflict arose with a Center around a combination product issue, the Center would communicate its position without offering scientific and regulatory support for its position.	• 70% of innovators reported delays as the result of problems during combination product reviews. These delays ranged from 1-3 months (15%) to 6-12 months (25%) to 12+ months (33%). • Survey participants said that the problems with combination products resulted in significant consumptions of human resources to resolve combination product problems. Sponsors noted that to solve problems, they needed to expend: o *"Effort=thousands of man-hours; Cost=hundreds of thousands USD"* o *"Too many hours to count"* o *"A team of 5 people of a label change, 3 months incl. review – net time: 9 man months plus scrapped material"* o *"A team of 15 people for redoing a usability study for color differentiation, 8 months incl. review – net time: 3-5 man years"* o *"Ballpark - $150K" plus "1500 FTE hours of employee time."* o *"~5-10% additional effort over that of a traditional NDA/BLA submission"*

IV. Interviews

To learn more about the origins of the problems unearthed in the survey, we conducted follow-up interviews with willing survey participants to discuss the kinds of issues they encountered. From these interviews and the survey we identified three interrelated root causes for the process problems:

- A lack of coordination and consistency between FDA groups, both across Centers and within Centers;
- A lack of timely communication with sponsors (e.g., groups within FDA getting involved in reviews late in the process, and completing reviews later than expected); and
- The absence of adequate scientific and regulatory justifications for decisions, which may reflect communication issues (i.e., FDA is not providing sufficient explanations) or substantive issues (i.e., FDA is not reaching scientifically supportable conclusions).

Many companies had similar stories about reviews that went awry, often well into the FDA review process. Some also expressed strong belief that there was significant value in Agency input, but that the value often was diminished as the result of coordination and communication problems (e.g., Agency units reaching contradictory conclusions on requirements, or communicating differences in opinion after extensive investment in development). In the following sections, we present some of examples of what we were hearing in *italics* and summarize the root causes associated with each to illustrate the problems and their origins.

Example 1: A Surprise during a Combination Product Review

A sponsor is navigating the approval process for a combination product, and conducts several human factors formative studies (early stage "stress testing" to evaluate subjects' use of the device and labeling to identify areas for improvement). The sponsor then:

- *Submits its formative study data and proposed labeling from FDA, and receives feedback from CDER division reviewers, Division of Medication Error Prevention and Analysis (DMEPA), and CDRH;*
- *Conducts additional formative studies based on that feedback and provides the results to FDA along with a revised instructions for use ("IFU") and a summative (final) study protocol to validate the use of the final device and labeling; and after receiving apparent agreement with the approach*
- *Conducts a summative (final) study in accordance with the protocol to validate its IFU, and submits what it believes are good results to FDA.*

After conducting its summative study, another group within CDER that had not been involved with the review to that point – the Division of Medical Policy Programs ("DMPP") – recommends significant revisions to the IFU. The specific reasons for the recommendations are not provided, and FDA does not provide substantive guidance on next steps the sponsor should take. Unfortunately, a sponsor who took great care to ensure the usability of its device, and worked diligently with FDA throughout to incorporate Agency input, was sent back to the drawing board based on late input from a different group, and was left with more questions than answers.

What went wrong?

- Lack of Coordination: The sponsor did its due diligence, conducted studies, worked collaboratively with FDA throughout. However, there was a lack of coordination between DMPP and other reviewers, which led to an unexpected change in Agency position very late in the review process. Simply including DMPP early in the process would have allowed its recommendations to be addressed in early stage formative studies, and may have avoided all of the problems.
- Lack of Communication: There were at least three groups within CDER, plus CDRH, involved in this review. It was the responsibility of these groups to adopt a single "FDA" policy and to communicate that to the innovator early enough so it could address the position by, e.g., revising its IFU before summative testing began.
- Lack of Justification: The sponsor conducted several studies to develop an IFU with input from multiple Divisions at multiple points, and then conducted an extensive summative validation study which showed good results. In light of this, a significant shift in position based on the DMPP review should have been accompanied by a very detailed rationale from FDA explaining the need for changes.

Example 2: Ineffective Meetings with FDA

A. A sponsor schedules a meeting to discuss a combination product review with CDRH and CDER. CDRH is supposed to provide CDER with an evaluation of a data package a few days prior to the meeting, CDER reported in the meeting that CDRH only recently provided their comments on the package to CDER. Having not had time to review CDRH's evaluation, CDER refuses to answer any questions relating the issues, making the meeting fruitless.

What Went Wrong?

- Lack of Coordination: The Agency should be prepared to speak to development issues on which it agreed to meet. Better coordination between CDER and CDRH could have prevented the problem.

B. In another instance, a sponsor schedules a meeting to discuss a summative human factors study protocol. The CDER project manager is not able to tell the sponsor which different groups at FDA are involved in the review, forcing the sponsor to (a) figure out who is participating in the review (which it does through individuals outside of FDA), and (b) request their attendance at the meeting. The sponsor proceeds as best it can, and learns shortly before the meeting that of the five (5) different groups at FDA evaluating the protocol, a crucial individual from one group was missed and not specifically invited to attend (when the sponsor discusses with other people within the Agency they confirm that person was essential, and do not understand why they would not be invited). The sponsor then needs to scramble to make the meeting meaningful by getting everyone in the room.

What Went Wrong?

- Lack of Coordination: The Agency should have been sufficiently coordinated to bring the right people to a meeting without putting the responsibility on the shoulders of the sponsor to identify those right people.
- Lack of Communication: The Agency should have shared who should attend the meeting with the sponsor.

Example 3: Unexplained Requests

A. *A sponsor consults CDRH regarding requirements for usability testing for a combination product and is told that standard human factors studies would be sufficient (e.g., recommendations from "CDRH Guidance: Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management"); studies are conducted and deemed acceptable by CDRH. The sponsor then receives a request for actual use testing from CDER. The sponsor explains why actual use testing is not necessary – past experiences with these kinds of devices and success of human factors testing, the inability to separate out user risk from other risks with actual use studies, etc. CDER responds that it disagrees with the sponsor's and CDRH's position, but does not address the merits of the sponsor's arguments.*

What Went Wrong?

- Lack of Justification: Human factors testing is a science that has developed over decades to assess the usability of products and identify potential failure modes to mitigate the risks they cause. In light of this, the substantive arguments made by the sponsor, and the fact that CDRH reached a different conclusion regarding the need for actual use testing, a detailed justification for CDER's disagreement should have been provided.

B. *A sponsor conducts formative studies with trained and untrained users; untrained users are included to "stress test" the use of the product, and develop the best possible labeling prior to conducting a summative study to validate the product and its labeling. The sponsor designs a summative study which includes trained users only, as training is one of the conditions prescribed by the proposed labeling. CDER insists that an untrained arm be included in the trial, although the value of including the arm at this stage of development is unclear. CDER offers no explanation for its request.*

What Went Wrong?

- Lack of Justification: Under the Food, Drug, and Cosmetic Act, FDA is required to judge products for approval under the conditions "prescribed, recommended, or suggested" in proposed product labeling. The sponsor in this case recognized the need for training, and included a training requirement as one such condition. Thus, although inclusion of untrained users in formative studies was valuable in developing data and designing training, their inclusion in a summative study was unnecessary.

V. Recommendations

As illustrated above, combination product innovators have had several problems navigating the path to product approval. Unfortunately, these problems delay access to innovative therapies that help patients and improve the public health. These are not problems with the products themselves.

What should FDA do to improve the situation? At a high level, the following steps would make a substantial improvement to the regulatory process for combination products by directly addressing the three root causes above. The CPC is available to assist, to the extent possible, in implementing these recommendations.

1. Improve Coordination within FDA. FDA should improve its internal coordination to ensure consistent decision-making. The Agency should develop cross-Center policies for issues impacting combination product regulation (like usability testing), so the different groups are coordinated as much as possible in advance.

   In addition, the Agency should ensure that groups involved in the review across all Centers work together from the start. There should be specific time points that all groups are required to provide input to a single FDA position on each issue (as opposed to several different Center, Office, or Division positions) reached shortly thereafter. To facilitate this process, we recommend having a single team leader who is responsible for collecting all feedback from all the groups within the Centers, and who is responsible for ensuring that the Agency develops a single coordinated response at each stage of review. To the extent that the groups do not see eye to eye, the team leader must have the authority to bring together the parties and develop a single FDA position. Given the role of the Office of Combination Products (OCP), CPC respectfully suggests that this role might naturally reside within OCP, provided that they are given the authority to ensure interCenter coordination. However, CPC acknowledges that it is the Agency's prerogative to decide the proper location and authority of this important team leader position.

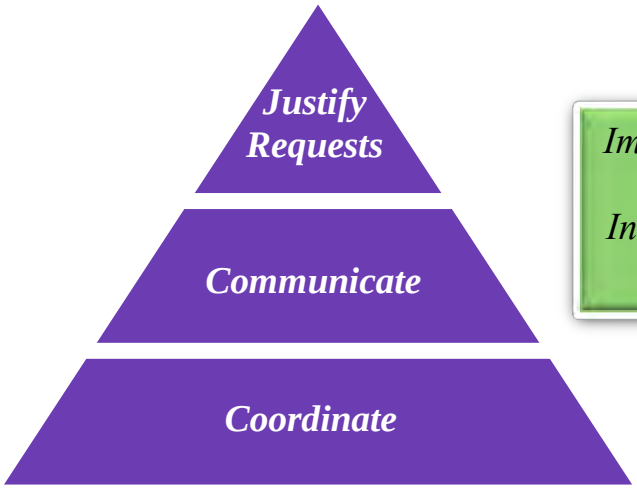
2. Improve Communication with Sponsors. Once the different groups within FDA are coordinated, they will need to communicate with sponsors. Communication includes guidance and regulations (general communications to all sponsors addressing standards and procedures related to product development and approval) and also communications with individual sponsors during product development and review. In all instances guidance must come from the three Centers (CDER, CDRH, and CBER) and OCP to ensure every Center recognizes and follows the guidance or provides reasonable justification for deviations from the guidance. Recommendations made to individual sponsors must reflect unified FDA positions developed through intra-FDA coordination.

   One guidance document the Agency must develop is a comprehensive procedural guidance which includes a list of "touch points" and timeframes which specifies points where FDA and sponsors plan to address key issues during combination product development and review. This may include, e.g., touchpoints and timelines related to feedback protocols for review (e.g., for a summative study), and pre-meeting information. This procedural

guidance should respect the regulatory timelines of each lead center review process as appropriate (i.e., PMA, NDA, BLA, 510(k), etc.).

The team leader should collect feedback for the sponsor and ensure that feedback is consistent and represents the FDA position, and is provided at designated touch points.

3. Improve Justifications for Decisions. Improvements in justifications will build on improvements in coordination and communication. Once the Agency is coordinating (to assure uniformity) and communicating (to ensure sponsors understand the Agency's thinking) much of the work should be done. What will remain is for FDA to keep an open mind when a sponsor makes a well-reasoned proposal.



Improvements Build on One Another to Create a System That Fosters Innovation & Brings New Therapies to Patients More Quickly

Improvements in coordination, communication, and justifications would benefit all aspects of the combination product review process and, thereby, bring better products to patients. However, one aspect of review where this is especially true, and where problems have been most significant, is the issue of usability testing. In Appendix A, we address this specific issue, and hope it will serve as an area of focus as the Agency moves to put combination product reviews on the right path.

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Appendix A --Usability Testing Issues in the FDA Review Process

Usability testing plays a pivotal role in the approval process of combination products, especially for those therapeutics that are combined with a drug delivery device (e.g., an autoinjector). Because usability of these products is determined almost exclusively by the function of the device constituent that delivers the therapeutic, historically the Agency followed the lead of CDRH and its applicable guidances in evaluating these issues.[1] The CDRH approach to usability testing focuses on human factors simulated-use studies—participants use the device constituent part in a simulated environment designed to mimic typical use scenarios under the observation of a human factors expert, who can identify and understand potential misuse. Using these environments, studies are conducted in phases using "formative testing" to evaluate opportunities to improve device features and labeling for product use, and "summative testing" to establish the safety and effectiveness of performance in the hands of the intended users according to the product's proposed conditions of use. This approach has developed over many years, and is supported by a significant body of scientific literature.[2]

More recently, however, groups within CDER have sometimes pressed innovators to use actual use studies—in which actual patients use the device on themselves to deliver the drug or biologic constituent part in a clinical setting. Actual use studies have several limitations[3] and under the CDRH regulatory approach are typically reserved for those situations where the device or use environment being evaluated is "particularly challenging or poorly understood."[4] This creates a regulatory inconsistency: if an innovator is dealing with a device-only product, it is subject to CDRH's human factors testing standards, but when the same product is combined with a specific drug, groups within CDER may impose an entirely different set of requirements (which are more burdensome without increased benefit), creating review inconsistencies that ultimately delay access to important therapies by unnecessarily lengthening the combination product approval process.

CDER also tends to position these requests and others related to usability testing as non-negotiable conditions for approval, but in many cases without reasoned justifications for its positions, leaving sponsors to wonder what is driving the Agency's concerns and how to address them. If sponsors are provided with FDA's detailed concerns, they would have opportunity to provide alternate suggested approaches to satisfy FDA's concerns which more closely align with

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[1] U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE: APPLYING HUMAN FACTORS AND USABILITY ENGINEERING TO OPTIMIZE MEDICAL DEVICE DESIGN (2011) [hereinafter FDA, DRAFT GUIDANCE: APPLYING HUMAN FACTORS]; U.S. FOOD & DRUG ADMIN., MEDICAL DEVICE USE-SAFETY: INCORPORATING HUMAN FACTORS ENGINEERING INTO RISK MANAGEMENT (2000) [hereinafter FDA, MEDICAL DEVICE USE-SAFETY] (final guidance).

[2] ANSI/AAMI HE75, 2009/(R) 2013 Human Factors Engineering—Design of Medical Devices.

[3] See discussion herein.

[4] FDA, Draft Guidance: Applying Human Factors, *supra* note 1, §§ 10, 10.2, at 23, 27.

the Least Burdensome Approach. Further, sponsors also struggle with a lack of communication and coordination amongst Centers, Offices, and Divisions of the Agency. It is not uncommon for an innovator to be coordinating with some groups at FDA only to later hear from a new group that wants to impose a different set of requirements (as detailed in the examples).

Through our survey and conversations with innovators, we have identified four particular areas within usability testing that are most affected by the following issues, which are considered below:

(1) CDER requests for usability testing to be incorporated in clinical trials;
(2) CDER requests for studies to "bridge" two combination products that use different injectors;
(3) Subject population selection for usability testing; and
(4) Requests for labeling revisions which come late in the FDA review cycle.

We consider each of these below.

A. Actual use Testing of Device Constituent Part During Clinical Trials

In pivotal safety and efficacy trials for combination products, CDER has begun requesting actual use data for combination products instead of allowing simulated-use human factors testing to supplement clinical data on corresponding drug or biologic constituent parts. Traditionally, human factors testing performed in accordance with CDRH guidance[5] and recognized consensus standards (IEC62366, AAM/ANSI-HE-75) has provided scientifically rigorous means for innovators to demonstrate that the intended users of a device constituent part can safely and effectively perform the relevant task as intended in the expected use environment.

Recently, some groups within CDER have requested that sponsors collect actual use data during pivotal clinical studies in addition to conducting traditional simulated-use human factors studies. However, no substantive explanation is provided for deviating from established human factors testing under simulated conditions. Human factors study is a science that has developed over decades and has been used to evaluate a variety of important items, including medical devices and combination products. Human factors testing is tailored to identify the most important problems with device or combination product use, and allow for development of optimal products and instructions that help patients get the best possible care. Actual use testing, on the other hand, may often fail to provide the kinds of observational data and insights that human factors testing can because it is not sufficiently tailored to detect and evaluate the causes of device problems. Also, the chance of detecting rare events would typically be low without a very large number of subjects. Thus, the lack of explanation as to why actual use testing is necessary makes it difficult for sponsors to respond to CDER concerns because of the many reasons that argue for using

[5] FDA, MEDICAL DEVICE USE-SAFETY, *supra* note 1; *see also* FDA, DRAFT GUIDANCE: APPLYING HUMAN FACTORS, *supra* note 1, § 10.

simulated-use testing instead of actual use testing. Other advantages of human factors, simulated use testing are listed below[6]:

- Simulated-use testing has a focused endpoint pertaining solely to the subject's interaction with the device and no other constituent part, increasing the probability of identifying usability issues. By contrast, clinical trials typically entail multivariate endpoints based on drug or biologic action. Device-related endpoints, which are readily determinable in simulated-use studies because an error *must* originate with use of the device constituent part, become unclear when combined with non-device endpoints because the observer cannot always discern a device failure from a drug or biologic failure. Additionally, a failure may be due to the interaction of the drug and the device making the detection of device problems quite confounded. Such confusion may result in false error reports, leading to inefficiency and delay.

- Human factors experts typically observe simulated-use studies, as opposed to formal clinical trials, which are observed by clinicians. While human factors experts are trained specifically to notice errors in device use, clinicians often cannot distinguish a device error from other errors. Also, post-trial interviews with participants in a controlled human factors environment can provide important information when conducted by a highly trained and experienced human factors expert.

- Simulated-use studies allow participants to make errors safely, allowing ample opportunity to observe close calls or potential patterns of misuse. In clinical trials, sponsors must provide participants the greatest protection possible by ensuring that they receive extensive training with a combination product to prevent any harm due to user error. However, simulated-use studies involve more basic training that more closely mimics post-market conditions, where a patient may receive initial training with a combination product, but the training may be inadequate or the patient may forget, and allows human factors experts to observe "naturally-occurring" user errors. The additional training participants receive in the clinical environment dramatically decreases the probability of identifying an error because an over-trained user is less likely to make a mistake.

- Investigators in drug clinical trials, often being medical specialists as opposed to device specialists, are not necessarily trained or experienced in the assessment of device-related problems and, particularly when the administration is un-witnessed, cannot differentiate a device problem from a drug problem, or the interaction between the two. Thus, the data in actual use trials are often dependent on patient reports of issues which are uninformed by knowledge of what a device can or cannot do. For example, a patient may report that the device malfunctioned when a dose was not delivered; however, the problem could be that a temperature sensitive drug product was not allowed to come to room temperature before an administration was attempted.

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[6] All of the factors in the following paragraphs were reviewed with human factors experts. The experts agreed that simulated-use studies have distinct advantages over actual use studies with respect to these factors and the ability to identify device-associated risks.

- A greater and more characteristically varied population may participate in simulated-use studies. Clinical studies are tightly regulated and recruitment is restricted to limited populations. Those restrictions do not apply to simulated-use studies, and consequently, sponsors may recruit more participants with a greater variety of characteristics (e.g., age, intelligence, general health, ability) that may affect device use.

- Simulated-use studies imitate real-life situations as well as clinical studies. FDA places much emphasis in its guidance on the ability of validation studies to represent real-life scenarios. At first glance, clinical studies appear superior because a participant will use the combination product in a clinical environment if necessary, but often, the participant will use the product unobserved and in her own home. However, according to human factors experts, simulated-use studies may be, and often are, conducted in the participant's home if those environmental factors will reveal more about methods of use. Although observation may affect a participant's use of the device constituent part, the effect may be reduced, or eliminated, by conducting the test in modern simulation labs, which allow unobtrusive observation.

- Simulated-use studies are significantly less expensive than clinical studies. With costs ranging from $47,000 per patient, on average, to as high as $85,000 per patient,[7] clinical trials, which involve highly specialized teams and regulatory requirements, are often expensive undertakings. By contrast, simulated-use testing or simple bench trials cost far less to set up and conduct because patient recruitment and testing parameters have fewer restrictions. Lower costs can translate to lower burdens and greater innovation, which benefits patients.

- Simulated-use studies can eliminate unnecessary risks from exposures to investigational drug therapies because they do not require that a patient receive drug.

In light of these benefits, the CPC asks FDA to publish guidance (or regulation) that adopts traditional, simulated-use human factors testing as the standard for usability testing across all Centers for all device constituents. In addition, consistent with Good Guidance Practices, FDA should only allow requests for actual use studies when reviewers (a) identify specific unassessed risks or facts relating to a particular product that make actual use testing necessary, and (b) receive supervisory approval for the request.[8]

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[7] D.J. Stewart & R. Kurzrock, *Fool's Gold, Lost Treasures, and the Randomized Clinical Trial*, 13 BIOMEDCENTRAL CANCER 193 (2013), *available at* http://www.biomedcentral.com/content/pdf/1471-2407-13-193.pdf.

[8] *See* Food, Drug and Cosmetic Act § 701(h)(1)(B) ("The Secretary shall ensure that employees of the Food and Drug Administration do not deviate from . . . guidances without appropriate justification and supervisory concurrence.").

B. Bridging Studies for Combination Products

Innovators may modify drug delivery systems between completion of Phase III pivotal trials and submission of an application for drug approval to help improve patient adherence, ease-of-use, or other attributes. Manufacturers may also develop modifications after product approvals to improve patient ease-of-use, convenience, etc. When making these modifications, the innovator must determine whether the changes impact product safety or effectiveness. Comments from some CDER reviewers suggest that an actual use, clinical bridging study where patients are required to use the device on themselves (e.g., inject themselves with medication)—as opposed to simulated-use studies where participants use the device in an artificial environment (e.g., inject saline into injection pads)—is necessary to demonstrate that the previously collected safety and efficacy data apply to the modified, to-be-marketed product. The practical problems with the approach can be significant, especially for drugs that may be used on a weekly, monthly, or as-needed schedule, where it could take a very long time to accumulate enough events for analysis. Moreover, for the reasons detailed below, the approach should generally be unnecessary.

Under the Food, Drug and Cosmetic Act ("FDCA"), FDA approves an injectable drug based on safety and effectiveness of: (1) the drug and (2) its delivery into the body. Once the safety and effectiveness of a given dose is established, the only questions to answer in a bridging study for delivery devices are: (1) whether the modified device will deliver an equivalent dose of drug using the same route of administration to produce bioequivalent results; and (2) whether a person can use the modified device as well as (or better than) the previously used device. Simple design evaluation and bench testing of the modified delivery device will validate accurate and consistent delivery of the set dose, answering the first question more effectively than clinical studies.

The second question requires usability testing to identify any risks of human error that may be a result of the modification to the delivery device. Simulated-use studies are particularly well-suited for bridging studies because the endpoint focuses solely on usability of the delivery device. Once the safety and effectiveness of the drug is established, whether a bridging study participant injects himself with the actual drug or injects an injection pad, the same relevant information will be collected with regard to injector use.

Therefore, FDA should develop an Agency-wide guidance or regulation allowing innovators to bridge products that use the same drug and dose, but a different injector (e.g., pre-filled syringe, pen injector, autoinjector) without repeating the drug clinical study, provided that:

(1) The product is a liquid injectable;
(2) The administration process (including route of delivery, approximate injection depth, needle gauge and length) and volume delivered remain the same; and
(3) The innovator can demonstrate product usability is not impacted by employing simulated-use testing with injection pads.

Actual use studies should not be required unless medical reviewers:

(1) Can provide a reasoned basis why simulated-use testing would be insufficient;
(2) Agree that the methodological issues inherent to an actual use study would allow the study to provide better information; and
(3) Receive supervisory approval to request actual use data.

C. Subject Populations for Usability Studies

Recently, some CDER reviewers have required that summative studies include: (1) untrained users for a combination product that requires training (and where the innovator seeks approval only for trained use); and (2) medical professionals to test combination products (e.g., pre-filled syringes) whose labels specify patient self-administration. Though the addition of these additional patient groups may seems innocuous, they unnecessarily increase regulatory burdens (which discourages innovation) and potentially raise "red herring" questions that shift the focus of the review away from the statutory standards of approval.

We do note that non-indicated users often play a role in formative testing as a product and its labeling is being developed. But once the summative testing phase is reached – the phase which validates the proposed use of the to-be-marketed product and labeling – the focus must be on the indicated population. Under the FDCA, innovators are required to demonstrate the safety and effectiveness of products when used under conditions "prescribed, recommended, or suggested" in labeling to receive FDA approval for those uses. Thus, in the summative phase of testing, expanding usability tests that validates the safety and effectiveness of a device constituent part to include users outside the scope of the labeled indications does not provide information bearing on approval and should not be required.

Therefore, FDA should adopt an Agency-wide guidance or regulation that limits requests for non-indicated study populations to formative studies (these populations should generally not be included in summative studies).[9] Any deviation from this request should require the FDA reviewer to: (1) provide a reasoned basis why testing with the indicated population would be insufficient; and (2) receive supervisory approval to request inclusion of a non-indicated population in the study.

D. Agency Labeling Recommendations

Some CDER reviewers have been providing input on patient instructions for use very close to PDUFA[10] action dates, and well past completion of human factors testing. These late recommendations sometimes require changes to the instructions for use, which, if adopted, may undermine reliance on prior human factors testing and associated use-related risk analyses. Moreover, CDRH sometimes objects to product labeling alterations based on reviewer input unless

[9] By "non-indicated" we mean users that would not be *representative* of the abilities of the indicated population. There may be instances where it is reasonable, or even necessary, to include individuals do not suffer from the indicated disease state in the human factors study. For example, if an indicated patient population is very small, an innovator may identify a "surrogate" test population that has characteristics similar to the indicated patient population with regard to ability to use the device and take required training (if any).

[10] Prescription Drug User Fee Act, Pub. L. No. 102-571, 106 Stat. 4491 (1992) (reauthorized by Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012)).

the innovator conducts new human factors testing with the new labeling – studies that will take months and delay approval.[11]

Expert FDA assessments of labeling have value, and are often part of the instruction development process prior to a human factors usability study. However, once a validation has proceeded to the summative phase, new FDA reviews and comments can cause significant delays, and should only be included in reviews under extraordinary circumstances. Therefore, reviewers from all involved Centers should coordinate their efforts and provide combined comments on proposed instructions for use ***before*** human factors studies commence. FDA should adopt a guidance or regulation that ensures reviewers override human factors validation results only if they can identify actual data or information suggesting that the wording of a relevant instruction is likely to cause harm to a user, and receive approval from their supervisor.

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FDA should adopt the suggestions above because they will improve patient access to innovative products. However, regulatory concerns the Agency must consider also weigh in favor of reform. First, unjustified requests for studies (which several requests described above appear to be) fail to meet Administrative Procedure Act ("APA") standards because they lack the kind of reasoned basis that is required for all Agency decision-making. Also, absent true need, requests for supplemental usability studies may be considered "arbitrary and capricious" under APA standards if human factors testing provides better safety and effectiveness data than actual use studies (which, as explained above, it would in most cases). This makes it all the more imperative that FDA reviewers consider all options, including those proposed by sponsors, and explain their reasoning when making decisions.

Second, innovation-delaying requests, such as requests for unnecessary actual use studies, are not consistent with the least burdensome principles. Under those principles, FDA must establish a regulatory regime that allows innovators to receive approval or clearance for their products without the burden of unnecessary testing.[12] In situations where approval is being delayed based on CDER requests related to a device constituent (e.g., actual use studies when human factors testing is sufficient), the Agency undermines these principles. However, if the Agency embraces these principles, it will allow patients to realize significant benefits from innovation more quickly.

Finally, because FDA is taking an *ad hoc* approach to regulation, it runs the risk of treating similarly situated parties differently, which violates the APA.[13] Establishing a uniform standard that clearly defines the roles and responsibilities of all Centers and that is based upon scientific

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[11] The CPC's Combination Product Survey found that almost 80% of respondents received late requests in the review process and over 50% received conflicting information regarding Instructions for Use.

[12] Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144 §§ 602, 901, 126 Stat. 993, 1051, 1082 (2012).

[13] 5 U.S.C. § 706(2)(A) (2012); *see also Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27–28 (D.D.C. 1997) (holding that FDA's failure to treat similarly situated innovators or products equally is arbitrary and capricious in violation of the Administrative Procedure Act).

reasoning will help ensure FDA regulates all similarly situated innovators and products equally and will prevent the Agency from making arbitrary and capricious requests during the review process.

Recommendations

In summary, a cross-Center set of policies should be created through regulation or guidance (including procedural guidance) to:

1. Adopt traditional, simulated-use human factors testing as the policy for combination product testing across Centers, and only allowing reviewers to request actual use studies only if they: (a) can point to specific unassessed risks or facts regarding a product that make actual use testing necessary; and (b) receive supervisory approval to make the request.

2. Develop and implement an Agency-wide policy that allows bridging of combination products that use different injectors (e.g., prefilled syringe and pen injector) – but the same liquid injectable drug, dose, and route & process of administration – based on nonclinical testing and human factors studies. Actual use studies would only be required if medical reviewers: (a) can provide a reasoned basis for why standard, simulated-use human factors testing to evaluate drug delivery differences with a design evaluation would be insufficient; (b) agree that the methodological issues inherent to an actual use study would allow the study to provide better information; and (c) receive supervisory approval to request the actual use data.

3. Require human factors validation testing only with participants from the indicated patient group (or an appropriate surrogate group) for the combination product unless a medical reviewer (a) can provide a reasoned basis for deviating from this policy based on specific facts, and (b) receives supervisor approval for deviating from the policy.

4. Provide sponsors with comments from all reviewers in all Centers before human factors validation studies commence. Decisions to override human factors validation results should only be made if an FDA reviewer (a) can point to published information that suggests, based on objective evidence (e.g., study data that contradicts a sponsor's human factors validation results), that the wording in the validated label would cause patient harm, and (b) receives supervisor approval.

These changes will create a better environment for innovation that improves therapeutic options for patients.