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VIA E-MAIL

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 2005N-0098
Comments on Concept Paper:
Number of Marketing Applications for a Combination Product

Dear Sir or Madam:

The Combination Products Coalition ("CPC") respectfully submits these comments on the concept paper entitled, "Number of Marketing Applications for a Combination Product" (the "Concept Paper), issued in September, 2005 by the Food and Drug Administration ("FDA"), Office of Combination Products ("OCP"). The CPC is a group of leading drug, biologics, and device manufacturers with substantial experience and interest in the combination products arena. Because of its diverse, cross-industry membership, the CPC brings an unusually broad and unique perspective to the regulation of combination products. From that perspective, we offer these comments.

We commend OCP and FDA for this effort to clarify the submissions process for combination products and, in particular, we find tremendous merit in the use of concept papers to explore approaches at an early stage of policy development. Furthermore, we agree with FDA that there is a need to clarify the ground rules for determining the number of marketing applications to be filed for a given combination product. Although this determination has been relatively straightforward for many of the combination products that have come before FDA, it also has presented very complex issues in some cases. Since these

issues can affect our ability to bring new products to patients, we feel FDA's efforts to clarify the ground rules are both timely and worthwhile.

CPC does, however, have a concern with the approach outlined in the Concept Paper. In a nutshell, FDA's proposed approach fundamentally limits sponsors' flexibility to choose the most suitable submissions strategy for the particular case. Because that flexibility can have an important impact on the pace of future product development and on the overall availability of combination products for patients, the CPC advocates an approach that instead first asks the manufacturer to identify and justify a submissions strategy for FDA review.

Section I below discusses the limitations of an approach that determines submission requirements based on generalized product characteristics, which do not capture all the essential circumstances of each specific new combination product. In that same section, we also describe CPC's alternative proposal. Notwithstanding those general concerns, section II provides specific comments on the Concept Paper's proposed algorithm and charts. Finally, section III responds to the Concept Paper's request for stakeholder views on implementation mechanisms (e.g., rulemaking vs. guidance) and on other issues that may need to be addressed by future policies.

I. General Comments

FDA's Concept Paper obviously was the product of careful analysis and thought, and CPC's members found it a very valuable starting point. The Concept Paper's text and charts lay out an excellent summary of FDA's current approach for assessing how many applications a sponsor should file for a given combination product. Having this clear statement of the current approach was useful as a tool for getting at the broader question: "How can regulation of combination products be optimized for the future?" CPC believes there are important reasons to take a different approach than the one outlined in the Concept Paper. We will start by explaining some criteria for evaluating approaches, then lay out an alternative and explain why we think it better meets those criteria.

A. Criteria for Evaluating an Approach to the Submissions Process

We suggest the following criteria for deciding the best, future approach the agency should take to defining the proper number of submissions for a combination product:

- Flexibility. The key criterion is flexibility, and unfortunately the decision rules in the Concept Paper algorithm limit sponsors' flexibility to make lawful choices regarding how many applications to file. For example, those rules would require a single application in some situations where

multiple applications would be lawful, and likewise would require multiple applications in some cases where a single application would be entirely lawful. As a result, there is only a narrow set of situations where the sponsor would be left with flexibility to choose. The quest for flexibility is in line with the device requirement that FDA seek the least burdensome approach to regulating the device.

- Is it lawful? The Food, Drug and Cosmetic Act (the "Act") and the Public Health Service Act ("PHSA") define the circumstances under which various submissions can be made, and again unfortunately the criteria in the concept paper do not tie back to those legal requirements. The Act and PHSA provide considerable flexibility to vary the number and types of submissions for a combination product. FDA should not, through its policy, take away the flexibility that the statutes and regulations were designed to provide. The approach outlined in the Concept Paper would have this effect because it implicitly links the allowed number of marketing applications to the perceived number of separately saleable products. Thus, according to the Concept Paper, integral combination products under 21 C.F.R. 3.2(e)(1)—i.e., combinations that are chemically, physically, or otherwise combined into a single entity—count as one saleable product and must be approved through a single application. Similarly, the Concept Paper would treat co-packaged kits under 21 C.F.R. 3.2(e)(2) as one saleable product if they contain constituents that cannot be sold separately, and they would be required to file a single application. *The law does not limit a sponsor's options in this way*.

- Is it possible? FDA already knows that the tremendous diversity of combination products does not lend itself easily to categorization of any type. Trying to go through and identify every circumstance that might determine when one submission approach is more appropriate than another, based on the actual technology and factual circumstances, is impossible.

- Does it treat *applicants* (as opposed to products) fairly and consistently? FDA's approach seems to flow from a presumption that it needs to treat consistently *products* that are technologically similar. On its surface, that might seem to be an appropriate goal, but in this instance it is not. The consistency that FDA should seek lies not in putting similar technologies into similar submission buckets, but rather in ensuring that the agency responds consistently to similar manufacturer requests. ***Fairness is judged in relation to people and institutions, not things.*** The whole philosophy of the Act, in the context of submissions, is that the agency should respond to manufacturer-initiated requests. FDA should not try to steer manufacturers in a certain direction, but rather should be prepared to respond in a consistent manner. Two manufacturers of an almost identical technology may well choose to proceed along different regulatory

paths, and so long as the law allows the manufacturers each to pursue their own path, FDA should permit it. In that case, FDA is responding consistently to the requests of manufacturers, as opposed to responding consistently on the basis of the technology involved.

B. CPC's Recommended Approach

So, what is our solution? CPC's proposal takes an entirely different approach. Rather than going through and trying to apply generalized rules for deciding when one submission versus two is appropriate, we approach the issue from the view that it is better to define the process through which that decision will be made and to identify the legal test to be applied in that process.

In a nutshell, our proposal is as follows:

1. Sponsors of combination products should have primary responsibility for deciding and justifying how many applications to file for a given combination product.
2. The sponsor may choose to address that issue prior to submitting any applications, but at the very least must do so when it submits its applications.
3. When the sponsor does address that issue, the sponsor should submit to FDA:
    a. A proposal, describing the number and type(s) of applications the sponsor plans to file, justifying its proposed approach in both the facts and regulatory requirements.
    b. If the proposal suggests multiple related submissions, a plan for how FDA can coordinate the review of those submissions.
4. FDA will review these proposals based on a single criterion: Are the proposed number and type(s) of applications permitted under the applicable statutes and regulations? A sponsor's decision about the number of applications to file will be respected by FDA, so long as the proposal is consistent with applicable law.
5. Administratively, if there are multiple related applications, FDA may choose to link to the applications in the agency's systems as suggested in the submitted plan so that coordinated agency review may result.

We recognize that this approach, at first glance, raises a number of downstream concerns that FDA mentioned in the Concept Paper. These include concerns about fairness and regulatory consistency as well as whether needed regulatory provisions will be available for use in regulation of the combination product and its constituent parts. Below, we explain the rationale for our proposed approach

and how the CPC proposal addresses these downstream concerns even better than does the approach outlined in the Concept Paper.

We should note that while the points below suggest the need for an approach that allows more than one submission in appropriate cases, our proposed approach may not in practice yield a much different outcome in terms of what submissions actually are filed, because one submission will remain preferable in most cases.

C. CPC's Proposed Approach Offers Advantages

CPC is proposing this alternative approach to achieve the flexibility provided in the statutes and regulations. That flexibility is crucially important to support the development of new combination products for patients and the objectives stated in FDA's recent Critical Path white paper.[1] Please consider the following three specific benefits of our approach:

- Impacts on Future Product Development. The full therapeutic promise of combination products can be achieved only in a regulatory environment where drugs, devices, and biologics are building blocks that can be combined, flexibly and dynamically, in new ways to form a wide variety of distinct combinations that serve different therapeutic purposes and different patient sub-populations.

  The Concept Paper links the number of marketing applications to the number of separately saleable products *as perceived by FDA at the time the combination product is being approved*. If one of the constituent parts of a combination has a clearly identified alternative use at the time the combination is being cleared or approved, then separate applications may be allowed[2] or even required.[3] However, the Concept Paper effectively treats this determination as static and backward-looking because the proposed algorithm fails to consider impacts this determination may have on future product development. The Concept Paper gives manufacturers little discretion to factor their future plans into today's determinations of the number of applications to file. The number of marketing applications is not merely a regulatory question that affects the particular combination product that is now before FDA; it also affects development of new products that may incorporate one or more of the same constituents.

  An example of this would occur if a sponsor were seeking approval of a drug/device combination product that had a drug primary mode of action (PMOA) and was going to be approved using an NDA. However, unknown to FDA, the sponsor has future plans to combine that same

[1] FDA, Innovation or Stagnation? Critical Path White Paper (2004).
[2] Lines 135 – 137 of the Concept Paper.
[3] Lines 94 – 95 of the Concept Paper

device with a different drug (i.e., other than the one included in the combination now being approved). Being able to obtain a separate approval for the device may make it easier, and less costly, to obtain approval for that second combination that includes the device and a different drug. The separate device labeling may need to be amended at the time the second combination is approved, but it may be possible to avoid re-opening the NDA for the first combination product.

Notice, too, that this example could be just as easily stated in reverse, in the sense that a small company, with few resources, that just wants to get a single product to market quickly, might want to file a single application.

The bottom line is that companies have their own reasons for the choices they make, and FDA will never know what all of those reasons are. So the law is deliberately set up for FDA to play a limited role—merely reacting to whether the approach laid out by the company violates the law.

- Access to Benefits and Incentives. The Concept Paper correctly recognizes that sponsors may need to submit multiple applications in order to receive some regulatory benefit that accrues to a particular type of application.[4] Unfortunately, the Concept Paper would give FDA fairly wide discretion to overrule sponsors' choices. In some cases, the benefits in question are statutory benefits, such as orphan drug status, that Congress intended to make available to the industry for a purpose (e.g., to encourage the development of such products). FDA should not be able to impede a sponsor's access to these benefits, unless the filing of multiple applications would be unlawful. Otherwise, FDA would be frustrating congressional intent. Again, the law is the only guide needed.

- Business strategy and corporate structure. The Concept Paper notes that, when multiple manufacturers co-develop a combination product, they may desire separate approvals of the constituent parts they respectively manufacture. CPC would like to add that there can be sound business reasons to seek multiple approvals, even when only one manufacturer is involved. In other cases, there can also be sound business reasons to limit the number of submissions to one.

  As an example of when two may be the most appropriate, a sponsor may have separate operating divisions that manufacture the constituent parts of a combination product and may need for its FDA approvals to match the product lines and manufacturing assets on the books of each of these divisions. For small businesses, having separate approvals that conform to their various products may be essential to get financing for further research and product-development activities involving those products.

[4] Line 36 – 40 of the Concept Paper.

Multiple applications may also foster a climate that encourages inter-company cooperation to develop new combination products. As the agency itself has observed, companies are often more comfortable having their own approvals even when they are collaborating with others.

These are not mere "business concerns" that are of isolated interest to the sponsor. They have a real impact on patients as well. The number of marketing applications affects the efficiency with which companies are able to finance, develop, and deliver combination products to consumers. This, in turn, affects the availability of combination products, the price patients pay, and the rate of at which new therapies reach the clinic.

D. CPC's Proposed Approach is Fairer and More Workable than the Concept Paper

While promoting a healthy climate for future product development is an important objective, CPC recognizes that it is not the sole policy objective. Fairness and ease of implementation also need to be considered in developing this policy. It was clear that FDA made a great effort, in developing the Concept Paper, to state a policy that would be fair, in the sense of treating like products alike. However, we believe that CPC's proposed approach would serve the objective of fairness even more effectively than does the Concept Paper approach because it focuses on fairness to people and institutions, rather than technologies. Also, as discussed below, we believe CPC's proposed approach would be more workable and easier to implement.

1. Fairness

Concerning the objective of fairness, the relevant standard of fair treatment in U.S. law is that the government must treat *similarly situated* individuals in a uniform manner. Notably, this does not require treating all persons exactly alike or subjecting all of them to identical outcomes and regulatory decisions. Rather, it requires uniform treatment for persons who are facing *the same conditions*. Fair treatment may, indeed, require disparate treatment for persons that are not similarly situated.

The approach described in the Concept Paper violates this notion of fair treatment by imposing identical substantive outcomes—in terms of the number of marketing applications that would be required for a given type of combination product—on all product sponsors, even when they are *not* similarly situated. As discussed in section I.C above, sponsors differ from one another in ways that the Concept Paper fails to take into account: For example, two sponsors are not in the same situation if one has a constituent part that is eligible for orphan-drug benefits and the other does not, or if one intends to collaborate with another company and the other does not. Two otherwise-similar requests are not similarly situated if one is based on a business plan that calls for combining parts made by

two manufacturers, and one does not. Two sponsors that make almost-identical combination products are not similarly situated if one of the sponsors intends to develop further a constituent part for use in additional combination products and the other has no further product development plans. The approach proposed in the Concept Paper would deny product sponsors fair treatment precisely because it treats all of them alike when in fact they are different in ways FDA may never know. In these examples, the agency's decision algorithm fails to consider a whole host of factors (*see* section I.C) that may cause sponsors to be "differently situated" for purposes of deciding how many applications to file.

2 Administrative Practicality

Concerning the ease of implementation, as already explained we have concerns about the approach outlined in the Concept Paper. FDA, in many cases, would be prescribing the number of applications that sponsors must file. A prescriptive approach, to be fair, requires due consideration of *all* the factors that can cause sponsors to be differently situated. It also requires an exhaustive and transparent algorithm that describes how FDA intends to weigh each of these factors in its ultimate decision about the number of marketing applications. It is not practical for FDA to identify and inquire into all these factors, nor could a comprehensive decisional algorithm feasibly be stated, nor would product sponsors be comfortable disclosing the sensitive details of their product development, business, and financing strategies. Yet failing to take these factors into account may result in decisions that impede development of new combination products.

For these reasons, CPC believes that a prescriptive approach, such as the one outlined in the Concept Paper, is inherently unworkable. To meet minimum standards of fairness, FDA's approach would require an unmanageable amount of input information and that a complex decisional algorithm be enunciated in advance. CPC believes the only workable alternative is to give sponsors discretion to propose the number of marketing applications that they intend to file, based on their knowledge of their particular business situations and product development plans. If sponsors desire to submit multiple applications when one would suffice, the presumption should be that they may do so, so long as this is consistent with applicable law. Because sponsors would have a say in this decision, they would have no grounds to complain about fairness: If two sponsors proceed down different paths, with one filing a single application while another files multiple applications, this difference would reflect their own respective preferences. This approach is consistent because it applies a uniform rule to all sponsors: All would be entitled to make their own lawful decisions about when to submit multiple applications, even in cases where FDA believes that one application would suffice.

E. Ensuring Regulatory Consistency Using CPC's Proposed Approach

In a closely related vein, in addition to ensuring that FDA is being consistent in its treatment of potential competitors, the agency needs to make sure that it is being consistent in its decisions with regard to a single company, or group of companies, over time. The agency should not, for example, issue conflicting decisions to the same company or companies making a combination product. FDA itself notes the importance of regulatory consistency.[5]

CPC agrees that it is crucially important to avoid contradictions in the labeling and other terms of approval for constituent parts that are being approved separately but as part of a combination product. However, we do not agree that limiting the number of applications filed is necessarily the right way to achieve that consistency. As already noted, sponsors may have important reasons for needing to file multiple applications.

In thinking about this problem, we came up at least two types of potential inconsistency. The first is accidental inconsistency where a lack of coordination means that two different FDA reviewing branches reach inconsistent decisions, for example with regard to labeling language. The second is inconsistency that somehow would result from the differing laws that guide different approval pathways.

CPC was not able to identify any examples where the law would compel FDA to reach inconsistent conclusions, simply because two different types of applications have been submitted. If FDA is aware of such examples, we request further information about them. Thus, we concluded that the principal concern here is that inconsistency might inadvertently arise when separate FDA Centers are processing multiple applications that relate to a given combination product and its constituents.

CPC believes inadvertent inconsistency can be avoided through communication and coordination of procedures, without having to limit the number of applications that can be filed. This is particularly true now that the Office of Combination Products is available to help sponsors arrange needed inter-Center coordination and cooperation. For example, it may be possible to "link" applications by noting clearly on the application documents that a given drug, device, or biologic application relates to a constituent part of a combination product, for which additional marketing applications are pending.

It also may be possible to make approval of "companion" applications conditional on one another. That is, the first application to be approved would be conditioned on the second approval being granted and having consistent terms. At the time a sponsor makes a proposal to file multiple applications, FDA and the sponsor would agree on a set of conditions and procedures for ensuring consistency.

[5] See Charts on pages 6 – 7 and Lines 71-72, 108-110, and 138-139 of the Concept Paper.

Optimal regulation of combination products requires thoughtful integration of the skills, authorities, and expertise of FDA's respective Centers. CPC believes that regulatory consistency can best be achieved through greater integration of the work of FDA's Centers, rather than by imposing rigid restrictions on the number of applications that can be filed.

F. Availability of Regulatory Authorities for a Combination Product

In addition to the objectives already discussed, it appears that the Concept Paper also intended to make certain that needed regulatory authorities will be available for postmarket regulation of a combination product. CPC, however, does not believe that the initial choice of how many applications to file has the effect of limiting the regulatory authorities that are available to regulate a combination product. We request clarification of this matter.

The following passages seem to us to treat the available regulatory authorities as depending on the number of applications that are filed: On Lines 83 – 86, the Concept Paper states that "there are some circumstances in which two marketing applications could be necessary for a combination product in order to ensure safety or effectiveness or consistent or appropriate postmarket regulation *because regulatory provisions may be necessary that are not available under the particular marketing application being submitted for the product."*[6] The charts on pages 6 and 7 treat the question, "Is a regulation/mechanism necessary that is not available under the lead application?" as determinative of whether two applications must be filed. These statements, if we read them correctly, seem to assume, for example, that the drug regulations cannot be brought to bear on a combination product that includes a drug unless a drug application is filed; the device regulations cannot be brought to bear unless a device submission has been filed; and the biologics regulations cannot be brought to bear without a biologics license application.

CPC does not agree with these assumptions. The Act, the PHSA, and FDA regulations define regulatory authorities, mechanisms, and regulatory benefits that accrue to defined categories of products (drugs, devices, and biologics). A product that fits within one of these categories does not lose its essential identity as a drug, device, or biologic when it becomes a constituent part of a combination product. Regardless of whether the combination product is an integral product described by 21 C.F.R. 3.2(e)(1), a kit described by 21 C.F.R. 3.2(e)(2), or a virtual combination product described by 21 C.F.R. 3.2(e)(3) or (4), its constituent parts retain their identities as drugs, devices, or biologics. As such, they remain subject to the respective authorities, mechanisms, and benefits that apply to drugs, devices, and biologics under the Act, the PHSA, and the FDA regulations, regardless of what the type of submission the sponsor used.

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[6] Lines 83-86 of the Concept Paper *(emphasis added)*

For example, if a product is a drug and is being approved as a stand-alone product, the Act requires the use of a drug submission, and the drug GMPs will apply to the product. However, it is not correct to say that the drug GMPs apply *because* a drug submission was used. Rather, they apply because the product is a drug, as defined by the Act. There is not a causal relationship between the use of a drug submission and the applicability of the drug GMPs. Rather, both flow out of the same fact: This product is a drug.

Now, when we go to the case where a drug is a constituent part of a combination product, the Act may allow additional possibilities for approving it. Nonetheless, it still is a drug. For example, if the combination product has a device PMOA, under section 503(G) of the Act FDA may approve the whole product, including the drug, in a device submission. Whatever submission is used, however, the constituent is still a drug and the drug GMPs can still be applied to it. If a device is approved as part of a drug submission, it is still a device and FDA may apply the MDR requirements to it. In all such cases, though, it is terribly important that FDA clarifies what requirements it deems apply.

FDA's other recent concept paper on "Postmarket Safety Reporting for Combination Products"[7] correctly recognizes that available regulatory authorities do not depend on the type and number of marketing applications that are initially filed. It would, for example, apply certain provisions of the device reporting requirements to a drug/device combination, even when the combination has been approved using an NDA. We believe the Concept Paper on number of marketing applications should adopt a similar assumption that drug, device, and biologics regulations are available to regulate a combination product and its constituent parts, regardless of the number of applications filed.

CPC recognizes that there is uncertainty in FDA's mind concerning which of the drug, device, and biologics regulations will apply to a particular combination product for various purposes. That does need to be clarified, but it in no way suggests that FDA should require sponsors to file multiple marketing applications. CPC believes a more comprehensive solution is needed in the form of FDA guidance that clarifies a set of "selection principles" (i.e., "choice of regulation" principles) that can be applied when deciding which of the drug, biologics, and device requirements apply to a combination product, in instances where these regulations state different or conflicting requirements.

II. Specific Comments

Without wanting to diminish the significance of our general concerns, below we are providing specific comments on a few matters that have not been

[7] FDA, Concept Paper for Comment Purposes Only: Postmarket Safety Reporting for Combination Products (September, 2005), *at:* http://www.fda.gov/oc/combination/adeventconcept.html

addressed in our General Comments. Comments are arranged in the order that issues appear in the text of the Concept Paper.

Comments on the section entitled, "When might one marketing application be appropriate?" on page 2 of the Concept Paper

- Integral combination products (21 C.F.R. 3.2(e)(1)). There is a potential contradiction between Lines 63 – 65 of the Concept Paper (which require a single approval for integral combination products) and Lines 94 - 95 (which require multiple approvals if a constituent has other uses beyond the combination product). If an integral product under 21 C.F.R. 3.2(e)(1) includes a constituent part that has other uses, it seemingly would be mandatory to file one application and mandatory to file multiple applications. The Chart on page 5 of the Concept Paper makes no allowance for filing multiple applications in this situation. CPC believes that multiple applications should be allowed in this, and many other, situations as already described.

- BLA for further manufacture. Footnote 1 on Page 2 and Lines 96 – 98 of the Concept Paper single out combinations that are regulated as a drug or device, but which contain a biologic product that may, at some point in its manufacture, need to be regulated under a BLA for further manufacture. CPC does not understand why appropriate regulation of these products could not be achieved using a single drug or device application, with appropriate coordination between the lead center and CBER as consulting center. We request further information on why FDA believes multiple applications may need to be mandatory.

- Additional examples of situations where one application is the only feasible alternative. FDA specifically requested additional examples to augment the list on Lines 62 – 72 of the Concept Paper. CPC is providing no additional examples because we do not believe that there is any situation where the Act, PHSA, and the FDA regulations require the filing of a single application.

Comments on the section entitled, "When might two marketing applications be necessary for a combination product?" starting on page 2 of the Concept Paper

- Additional examples of situations where multiple applications is the only permitted alternative. FDA specifically requested additional examples. CPC has no additional examples and would, in fact, remove from this list all except the example on Lines 100 – 104 (to effect labeling revisions for a constituent part that is already approved for uses that do not include the proposed combination product indication).

Comments on the section entitled, "When might FDA accept two applications when a single marketing application would be sufficient?" on pages 3 and 4 of the Concept Paper.

- Unfinished constituents vs. accessory parts. The proposed criteria for allowing sponsors to file multiple applications require that the constituents be "finished and separable"[8]; i.e., the number of applications cannot exceed the number of separately saleable products. While we fully agree that FDA cannot approve or clear unfinished drugs and devices, we believe an inadequate distinction has been drawn between unfinished constituents and those that are accessories. An unfinished constituent is not saleable because it needs further manufacturing in order to have any use. An accessory is finished in that it needs no further manufacturing; however, it serves an auxiliary purpose and would be unlikely to find willing buyers unless they can also buy the product it "accessorizes." CPC feels it should be clarified that FDA has the authority to approve finished accessory products, subject to appropriate conditions limiting them to their auxiliary uses.

- Multiple manufacturers. The introductory text, on Lines 125 – 129, notes that, when multiple manufacturers co-develop a combination product, they may desire separate approvals of the constituent parts they respectively manufacture. However, the decision criteria on Lines 135 – 139 do not indicate how this will be taken into account when deciding whether to allow multiple applications.

- Access to regulatory benefits. The introductory text, on Line 120 – 125, notes that manufacturers may wish to file multiple applications in order to avail themselves of incentives and benefits that are associated with specific types of marketing applications. However, the decision criteria on Lines 135 – 139 do not provide for this to be taken into account when deciding whether to allow multiple applications.

- Additional decision criteria. The Concept Paper specifically requested stakeholder input on its proposed decision criteria for allowing multiple applications when one would suffice. CPC believes that there is only one criterion that should be used to decide whether to allow multiple applications: Would multiple applications be consistent with law? Sponsors should have discretion to file multiple applications so long as this criterion is met.

Comments on Flowcharts on Pages 5 – 7 of the Concept Paper

- CPC proposes the alternative approach shown in Chart I attached hereto.

[8] Lines 135 – 136 of the Concept Paper

III. Implementation Mechanisms and Issues for Future Policy

The Concept Paper requested stakeholder views on implementation mechanisms. CPC's proposed approach is consistent with the Act, the PHSA, and current FDA regulations and can be implemented through guidance.

The Concept Paper also requested stakeholder views on additional issues related to this topic that need to be addressed in future FDA policy.

- Postmarket Modification of Combination Products. CPC refers FDA to our earlier white paper, "Combination Products: Proposed Policies to Enhance the FDA Regulatory Process,"[9] which highlights the need to clarify, via guidance, the regulatory pathway for changes to components of approved combination products. We continue to regard this as a critical problem, particularly with respect to combination products that include devices. In enacting the provisions of the Act that relate to medical devices, Congress recognized that medical devices differ fundamentally from drugs and biologics, in that devices undergo evolutionary changes throughout their lives. Thus, the available pathways for clearing and approving postmarket device modifications were designed to facilitate these evolutionary changes, so that consumers could receive the benefit of improved medical devices without undue delay. These same concerns exist when a device is a constituent part of a combination product. There needs to be a pathway for clearing and approving evolutionary changes to the device, in cases where the change does not affect other constituents of the combination product, in order to ensure that patients get the benefit of evolutionary device changes without delay.

- Applicable Regulatory Authorities. We refer FDA to CPC's "Response to Request for Comment on Primary Mode of Action,"[10] where we identified a need for clarification of which regulatory authorities apply to a combination product.[11] (see also, section I.F above).

- User Fees. We refer FDA to CPC's comments on the Draft Guidance on User Fees,[12] in which CPC explained why it is reasonable for FDA to provide access to waivers regardless of whether a decision to file multiple applications is made by FDA or by a manufacturer.[13] FDA's Final Guidance on User Fees, issued in April, 2005, appears to have been

[9] CPC, Combination Product: Proposed Policies to Enhance the FDA Regulatory Process (April, 2004).
[10] CPC, "Response to Request for Comment on Primary Mode of Action, Food and Drug Administration: Docket Number 2004N-0194" (August 18, 2004).
[11] Id. at page 6.
[12] CPC, "Comments on Draft Guidance for Industry and FDA Staff: Application User Fees for Combination Products: Docket Number 2004D-0410" (November 24, 2004).
[13] Id. at pages 3-4.

designed with the view that FDA would adopt a prescriptive approach for determining when multiple applications must be filed, and it considers whether FDA has required the filing of multiple applications in deciding whether a waiver will be granted.[14] CPC requests clarification of how waivers would be handled if FDA ultimately adopts a more flexible approach for determining the number of marketing applications to be filed.

IV. Conclusion

The CPC supports FDA's efforts to clarify the ground rules for determining the number of marketing applications to be filed for clearance, approval, or licensing of a combination product. We believe that current practices, as described in the Concept Paper, serve to restrict flexibility that Congress has provided to manufacturers in the Act and PHSA and which FDA has provided in its regulations. Because this flexibility has important ramifications for the development of new combination products to meet unmet medical needs, CPC urges FDA to consider the more flexible approach we have outlined in these comments. We appreciate the opportunity to share our thoughts with you at this early stage of policy development and we look forward to continued discussion of these important issues.

Respectfully submitted,

Bradley Merrill Thompson

BMT/slb

[14]FDA, Guidance for Industry and FDA Staff: Application User Fees for Combination Products (April, 2005), at Sections III.A, III.E, III.G

Chart I: CPC Proposal for Flexible Determination of Number of Applications