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Combination Products Selection Issue Working Group

Key Areas of Difference Among Regulatory Requirements for Drugs, Devices, and Biologics

Introductory Survey

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Introduction. Section 503(g) of the Federal Food, Drug, and Cosmetic Act (FDCA) requires FDA to assign a lead Center that will have primary jurisdiction for pre-market review and regulation of a combination product. This assignment must be based on primary mode of action (PMOA). In 2004, FDA sought comments on a proposed rule defining PMOA (Docket No. 2004N-0194).

CPC is concerned that FDA, having developed the PMOA concept, may tend to rely on it as a basis for most or all decisions surrounding the appropriate regulation of combination products. In fact, FDCA §503(g) requires the use of PMOA only for the limited purpose of designating the lead Center and would allow reliance on other criteria for other purposes.

PMOA may not always provide a good basis for selecting which of the requirements stated in the drug, biologics, and device regulations should apply to a particular combination product in specific circumstances. This problem, referred to herein as the "selection issue," is distinct from the problem of designating a lead Center. In a similar way, law distinguishes between jurisdiction and venue (which court may hear a case?) and choice of law (which body of law

should the court apply when hearing it?). Designating a lead Center does not settle the selection issue, any more than venue settles choice of law.

While PMOA may indeed be appropriate for some selection problems, it is inappropriate for others. For example, certain requirements reflected in the device regulations may have a statutory basis that makes them mandatory, regardless of whether the device is or is not part of a combination product with a drug PMOA. Using PMOA to select which requirements apply could cause these mandatory device requirements to be ignored and violate the statutory provisions that impose them.

The Selection Issue Working Group. CPC has established a Working Group to develop policy and proposals for draft guidance related to the selection issue. The purpose of this Introductory Survey is to identify areas where the drug, biologics, and device regulations state materially different requirements, to assist the Working Group in screening selection issues and setting priorities for addressing them. Table I on pages 3 – 5 summarizes important areas where drug, biologics, and device regulatory requirements differ. Subsequent pages provide fact sheets for each area listed in Table I. The fact sheets identify what the differences are and give examples of how these differences could create problems in the context of combination products.

The selection issue encompasses a large number of separate subproblems. One of the challenges facing the Working Group is to set priorities among them, identify common themes, and set an overall guidance-development agenda, which may need to include multiple draft guidances that focus on particular selection problems or types of combination product.

A key point that emerges from this Introductory Survey is that different selection principles may be appropriate for different aspects of regulatory selection. Various selection principles are possible, and the Working Group will need to assess which are best suited to particular problems. The following is a non-exhaustive list of alternative selection principles:

1. PMOA/lead Center: regulate the entire combination product based strictly on its PMOA and apply the regulations of the designated lead Center. E.g., if the PMOA is drug, then drug requirements would govern all aspects of regulation for the combination product.
2. Modified PMOA: use PMOA, but adapt its definition to reflect different or more subtle criteria and algorithms than were described in FDA's recent proposed rule. Various factors influence PMOA, and different ones may need to be emphasized for different regulatory selection issues.
3. Concurrent application of conflicting requirements: apply component-specific regulations simultaneously. E.g., simultaneously report adverse events under all regulations that apply to any component of the combination product. For a drug/device combination, both the drug and device reporting requirements would apply.
4. Most-affected component(s): select the regulatory requirement that governs the component that is most affected by, or which is causing, the particular problem that the regulations seek to address. E.g., if an adverse event can be traced to the device component of a combination product, then apply the device reporting requirements; if a manufacturing change affects the drug component of a combination product, then approve the change under drug approval requirements.
5. Application of the more stringent requirement: if requirements are in conflict, do whatever is most stringent in protecting of public health. E.g., if FDA would have grounds to halt clinical trials under the regulations applicable to any component of a combination product, then the most stringent action that could be taken will be taken.

Table I

Combination Products Selection Issue Working Group Key Areas of Difference Among Regulatory Requirements for Drugs, Devices, and Biologics

SUMMARY

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3	Selection of basic regulatory pathway for initial clearance, approval, or licensing of a combination product
4	Application of specific drug, biologic, and device clearance and approval requirements to combination products <ul style="list-style-type: none">a. Standards for approval, data requirements, and evidentiary standards for establishing safety, effectiveness, purity, potencyb. Restrictions on sale, distribution, and use of approved productsc. Post-market study and surveillance requirementsd. Denial, suspension, and withdrawal of approvale. Expedited approvals and humanitarian provisions
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 - c. Who must report
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 - e. Corrections and removals
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- 8 Modification of previously approved products**
- 9 Standards for determining equivalency of combination products, standards for determining equivalency of components of combination products, procedures for clearing and approving equivalent combination products, procedures for clearing and approving component substitutions**
- 10 Advertising and promotion**
- 11 Adulteration, misbranding, and prohibited acts**
- 12 Patent certification and market exclusivity**
- a. Patent certification for drugs
 - b. Patent-term extension and other sources of market exclusivity for drugs
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- a. Special penalties for prescription drug marketing violations and device violations
 - b. Notice to professionals and repair, replacement, and refund of devices
 - c. Device recall authority
 - d. Banning of devices
 - e. Administrative detention of devices
 - f. Revocation of approved device PMA in advance of administrative hearing
 - g. Special sanctions for ANDA-approved drugs
- 16** **Miscellaneous issues**
- a. Notice of discontinuation of life-supporting drugs
 - b. Distribution/chain-of-supply for drugs
 - c. Transferability of instruments approving the product for marketing

Selection Issue Fact Sheets

Selection Issue No. 1

Investigational requirements and clinical trials

Key sources of authority

- Drugs and biologics: Investigational New Drug Application: FDCA §505(i) (21 USC §355(i)); 21 CFR §§312.1-312.160
- Devices: Investigational Device Exemption: FDCA §520(g) (21 USC §360j(g)); 21 CFR §§812.1-812.150

Summary of key differences

- a. Flexibility in device requirements. For devices, §520(g) expresses a specific statutory purpose of encouraging discovery and development of useful devices and to maintain scientific freedom for investigators, and §520(g)(1)(C) expressly grants FDA statutory authority to vary IDE procedures and conditions in accordance with the extent and duration of testing, number of subjects, and the need to make changes in the device during the course of the investigation. E.g., device regulations distinguish significant and non-significant risk devices, and contain exemptions from IDE requirements for certain types of device testing (21 CFR §812.2(c))

For drugs, the content of an IND varies with the type of drug and scope of trials but there is less statutory authority for FDA to vary investigational requirements than there is for devices.

Key selection issue: What can be done to retain the flexibility that the FDCA envisions for devices, in cases where the device is part of a combination that has a drug or biologic PMOA and is being regulated under less-flexible IND regulations?

- b. Device changes during testing. FDCA §520(g)(6) envisions that devices may undergo developmental changes while testing is underway, and calls for the IDE regulations to allow modifications without additional approval (see 21 CFR §812.35(a)(3)(i), providing a notice procedure for changes).

Key selection issue: Section 520(g)(6) of the Act provides that FDA “shall” establish regulations that accommodate changes to a device without re-approval. Does this mean that IDE rather than IND procedures apply to developmental changes, even if the device is part of a combination product? How, exactly, would this work if the device is part of a combination with a drug PMOA that is being regulated under IND procedures?

- c. FDA power to halt research or terminate IDEs and INDs. For devices, the Secretary may, by order, disapprove an application or may withdraw an IDE after a hearing. (FDCA §520(g)(4),(5); 21 CFR §812.30(b),(c) list the grounds)). For drugs, Secretary may

issue a clinical hold at any time or terminate an IND if the drug represents an unreasonable risk to the safety of the human subjects. (§505(i)(3); 21 CFR §312.42 and §312.44 list the grounds.)

Key selection issue: Which grounds and procedures for termination apply to a given combination product? Will this be determined by PMOA or will a combination product be subject to termination for any ground that applies to any of its components?

- d. Specific differences in drug, device, and biologics requirements. IDE requirements were closely patterned after IND requirements and are similar in many respects (e.g., drugs and devices both require IRB review and informed consent; applications must be filed 30 days before trials are to commence, etc.). However, there are many specific differences between the drug and device investigational requirements (e.g., different reportability thresholds and timing for reporting adverse drug experiences (21 CFR §312.32) and for reporting unanticipated adverse device experiences (21 CFR §812.150(a)(1), (b)(1))). If the Working Group decides to focus effort on investigational requirements, the next steps would be:
1. Detailed comparison of regulations. Make a side-by-side comparison of specific differences in the regulations and guidances for drugs, devices, and biologics
 2. Requirement-by-requirement analysis of selection principles. Which principles should be used to choose among competing IND and IDE requirements, when they differ?
 - Do some of the differences reflect mandatory statutory requirements that must be followed, regardless of whether trials are primarily under an IND or IDE? E.g., certain reporting requirements for devices may be required by statute even when the combination has a drug PMOA and is otherwise under an IND.
 - Does it make sense for some of the requirements to apply simultaneously? E.g., in a drug/device combination, report drug safety problems according to the drug regulation, and device safety problems according to the device regulation—but what should be done if the cause of the adverse experience cannot be clearly attributed to either the drug or device?
 - When does it make sense to base the selection on something other than PMOA? E.g., handle developmental changes to devices via the IDE notice procedure, even if the combination is being regulated as a drug.

Decisions to make. The Working Group needs to decide how much emphasis investigational requirements should receive and identify specific analytical work products that are needed to develop policy in this area.

Selection Issue No. 2

Designation of Lead Center and the role of Consulting Centers

Context. FDCA §503(g) requires FDA to designate a Center to regulate a combination product, based on PMOA. For a product with a given PMOA (drug, biologic, or device), the Center that is charged with pre-market review of that type of product shall have primary jurisdiction. However, the Secretary may draw on other Centers to ensure adequate review of safety, effectiveness, or substantial equivalence of an article. This allows other Consulting Centers to be involved. Section §503(g) does not prescribe the criteria and algorithms to be used in deciding PMOA, nor does it require a particular allocation of responsibilities between the Lead and Consulting Centers. FDA's proposed rule defining PMOA has not yet been finalized, following public comments last year.

As CPC noted in its August, 2004 comments, FDA's proposed criteria and algorithm for determining PMOA fail to emphasize certain factors that may be important, when deciding which Center is best equipped to regulate a combination product at various points in its life cycle. For example, a drug/device combination that has a drug PMOA, in which the drug has long been in use but the delivery device is a new one, may present novel issues of safety and effectiveness mainly with respect to the device. CDRH, rather than CDER, may have the greatest expertise to address these novel device-safety issues during pre-market approval. Moreover, the Center best equipped to handle the initial product approval may not be the best one to address other regulatory issues that will become crucial later in product life. This would be the case, for example, if the product had a drug PMOA and presented problems of drug toxicity that needed to be resolved prior to approval, but thereafter presented complex manufacturing issues with respect to the device component, calling for close, ongoing regulatory oversight by CDRH. Different Centers may need to move to the forefront at different stages of a combination product's life.

Decisions to make. There are two possible approaches, which can be pursued alone or simultaneously:

1. Devote additional effort to refining the definition of PMOA, to improve the criteria and algorithms by which the Lead Center is selected.
2. Focus on clarifying the division of responsibility between Lead and Consulting Centers, for example, by developing criteria for deciding which Center should move to the forefront in various situations. The goal would be to ensure that the appropriate Center takes the lead at appropriate points in a combination product's regulatory life cycle, regardless of which one holds the title of "Lead" Center.

At the outset, the Selection Working Group needs to make a decision about how much of its attention to focus on the problem of selecting the Lead Center. A major theme in the Selection Issue work effort is that the problem of selecting applicable regulations should be distinct from the problem of choosing the Lead Center. By focusing on how to select the Lead Center, we risk drawing attention away from other pressing selection issues and perpetuating the tendency to "merge" venue (Lead Center selection) with choice of law (which regulatory requirements apply?). Lead Center selection certainly fits under the rubric of selection issues, and some attention to this problem is warranted; the question is "How much?"

Selection Issue No. 3

Selection of basic regulatory pathway for initial clearance, approval, or licensing of a combination product

Key sources of authority

- Drugs and biologics regulated as drugs: New Drug Application (NDA) under FDCA §505(b) (21 USC §355(b)) or Abbreviated New Drug Application (ANDA) under FDCA §505(j) (21 USC §355(j)) and related regulations.
- Biologics: Applications under §351 of the Public Health Service Act.
- Devices: Pre-market Approval (PMA) under FDCA §515 (21 USC §360e) or Clearance under FDCA §510(k) (21 USC §360) and related regulations.

Context. There are major differences in the regulations governing clearance and approval of drugs, biologics, and devices. How to choose appropriate pathways for initial clearance or approval of combination products has received previous attention, dating back to the old Inter-Center Agreements developed in the 1990s. By statute, the Lead Center must be designated based on the combination product's PMOA. However, there is no requirement use PMOA in deciding which regulations will apply (e.g., NDA vs. 510(k)/PMA vs. biologics application). In practice, the lead Center generally applies its own regulations or delegates portions of the approval to a consulting Center that applies its respective regulations. Thus, designation of the lead and consulting Centers often has the effect of determining the overall pathway for clearance or approval.

Decisions to make. The Selection Working Group needs to make decisions about its objectives and scope of work in this area:

- a. Likelihood that criteria other than PMOA will be considered. To what extent is the overall clearance/approval pathway likely to remain linked to PMOA and the designation of lead Center? How much room is there to refine the selection process to consider factors other than PMOA, when selecting among various clearance/approval pathways? Are there possible advantages in using other criteria? Could FDA's proposed definition of PMOA be modified slightly, to take better account of factors that matter when choosing the approval pathway—e.g., which component presents the most novel issues of safety, effectiveness, potency, and purity?
- b. Preserving sponsors' choices. In some cases, the sponsor of a combination product is able to make choices about the initial clearance/approval pathway. E.g., even if a drug/device combination has a drug PMOA and is required to go through the NDA pathway, the sponsor still could opt to seek a separate 510(k) clearance or PMA for the device component. The Working Group should consider:
 - What are the various alternatives for different types of combination product?
 - How will the sponsors' choices affect other selection issues? E.g., how does the choice between NDA-only vs. NDA-plus-510(k)/PMA affect the selection issues that

surround later product modifications, reporting obligations, exclusivity and trade-secret protection, etc.?

- What issues need to be addressed, in order to ensure that strategically valuable alternatives will be available in practice? E.g., are there unresolved fee issues or timing problems that limit sponsors' practical ability to pursue different strategies for initial clearance and approval?

Selection Issue No. 4

Application of specific drug, biologic, and device clearance and approval requirements to combination products

Context. Even after an overall clearance/approval pathway has been set (e.g., NDA for a drug/device combination that has a drug PMOA), this leaves many questions unresolved. For example:

- How should requirements that were designed for drugs apply to the device component of a combination that is being approved under an NDA?
- Are there component-specific requirements that are mandatory and continue to apply, even when the PMOA causes another regulatory pathway to be selected for the overall clearance/approval?
- What due-process protections does the sponsor have, when the various approval pathways specify different ones?

Decisions to make. The Working Group needs to analyze specific problems that may arise when applying NDA, 510(k)/PMA, or biologics application procedures to combination products and decide which of these issues should be given priority and addressed as part of the Summer, 2005 work plan. The following are a few examples of unresolved issues:

- a. Standards for approval, data requirements, and evidentiary standards for establishing safety, effectiveness, purity, and potency. These differ for drugs, biologics, and devices. There is a risk that similar combination products may be subjected to different data and evidentiary requirements by the various lead/consulting Centers that are involved.
 1. Data and evidence for approval. The FDCA imposes more rigorous data and evidentiary requirements for drug approvals than for device approvals. For drugs, §§505(d) and (e) require substantial evidence from adequate and well-controlled clinical trials. This usually entails two trials, although the Secretary can determine whether one adequate and well-controlled clinical investigation and confirmatory evidence is sufficient.

In approving devices, FDA has more flexibility. FDCA §513(a)(3) calls for "well-controlled investigations, including one or more clinical investigations where

appropriate...” However, the Secretary can determine that “other valid scientific evidence” that is not from clinical trials can be used to show effectiveness. The Secretary also may also apply post-market controls as a way to reduce the evidence of effectiveness that is required for pre-market approval of a device.

2. Special provisions for particular types of data.

FDCA §515(d)(1)(B)(iii) allows device PMA approvals to be based on “statistically valid and reliable data” from earlier versions of a device that has been modified during or after investigations if the modification is not a significant change. Data from other approved devices may also be used under certain circumstances.

For drugs, FDCA §505(c)(4) allows the use of drugs manufactured in pilot or small facilities to be used in demonstrating safety and effectiveness, unless the Secretary determines that drugs from a full-scale production facility need to be used.

Questions. If a device is being approved as part of a combination product under an NDA, will it be subject to drug-oriented data and evidentiary requirements that exceed what FDCA normally requires for devices? If a drug is being approved as part of a combination product under a PMA, will it be subject to device-oriented standards that are less than what the FDCA actually requires for drugs? What is the best way to make sure that appropriate data and evidentiary standards apply at appropriate stages of the process of approving a combination product?

How do special provisions in PMA and NDA data requirements apply to combination products (e.g., use of data from earlier versions of a device, tests on drugs from pilot facilities)?

- b. Restrictions on sale, distribution, and use of approved products. FDA has express statutory authority to place restrictions on the sale, distribution, and use of a device as a condition of approval (§§515(d)(1)(B)(ii), 520(e)). FDA can require prescription sale of a drug (§503(b)), but does not have broad authority to condition drug approval on other use restrictions (although FDA may be able to get sponsors to agree voluntarily to restrictions when that is the only way to get the drug approved.) FDA does have authority to impose use restrictions as a condition of drug approvals under the accelerated approval program (21 CFR §314.520).

Question: If a drug/device combination has a device PMOA and is being approved under a device PMA, does §515 give FDA authority to impose restrictions that relate to the *drug* component? Or must the restrictions relate to a safety problem with the *device* component, in order for FDA to impose restrictions under §515(d)(1)(B)(ii)?

- c. Post-market study and surveillance requirements. As a general matter, FDA has greater power to require post-market studies and surveillance for devices than it does for drugs. For drugs, FDA lacks specific authority to require post-market studies of safety and effectiveness, although it has occasionally required post-market studies under its general powers to enforce the FDCA and require record-keeping (§§505(k) and 701(a)). The accelerated approval program lets FDA require post-market studies of drug

effectiveness, to confirm the relation of surrogate end-points to clinical outcomes, but not of safety (21 CFR §§314.510,314.540).

FDCA §522 empowers FDA to order a device manufacturer to conduct post-market surveillance for Class II and III devices, if failure of the device would be reasonably likely to have serious adverse health consequences or if the device is intended for implantation in human body for more than a year or is a life-sustaining or life-supporting device intended for use outside a user facility. Up to thirty-six months of surveillance can be required under a protocol submitted by the manufacturer; mutual agreement is required for longer surveillance.

Questions: How do these provisions apply to combination products? When a drug/device combination is regulated as a device, does FDA have power to order post-market studies and surveillance for *drug*-related safety problems? If it is regulated as a drug, does FDA still have power under §522 to require surveillance of device-related safety problems?

- d. Denial, suspension, and withdrawal of approval. Standards and procedures vary, depending on the clearance/approval pathway that was initially selected, and this may affect the sponsor's due-process rights.

For devices, FDA is required, in some cases, to obtain advice on scientific matters from its standing advisory committees, before initiating proceedings to revoke a device PMA or during review of a denied PMA approval (§§515(e), (g)(2)). PMA regulations generally provide an opportunity for an informal hearing prior to revocation (§515(e)(1)). The drug regulations are somewhat more protective of the sponsor's rights: A full administrative hearing is required before approval is revoked (§§505(e)(5), 505(h)), although immediate revocation is possible if the Secretary makes a finding that there is immediate hazard to public health.

Question: If a device/drug combination has a device PMOA and has been approved under a PMA, is the sponsor still entitled to §505 due process during a revocation, or is the sponsor only entitled to §515 due process?

- e. Expedited approvals and humanitarian provisions. The device and drug regulations both contain provisions for expedited handling of applications, but apply different standards for determining whether an application is eligible. For combination products, there is a question of which standard applies:
- Accelerated approval for drugs or biologics (FDCA §506) covers products that are "intended for treatment of serious or life-threatening condition and demonstrate the potential to address unmet medical needs for such a condition."
 - For devices, §515(d)(4) allows FDA to provide review priority to devices representing breakthrough technologies, for which no approved alternative exists, if there are significant advantages over existing alternatives, or if availability of the device is in best interest of patients.

- The orphan drug program (FDCA §526) applies to drugs that serve fewer than 200,000 people, while the humanitarian device exemptions (FDCA §520(m)) apply to devices that serve fewer than 4,000 individuals.

Question: Which, if any, of these provisions apply to a combination product? Should the selection be based on PMOA or on other criteria (e.g., expedite approval if *either* the drug or device criteria are met)?

Selection Issue No. 5

Labeling requirements

Context. CPC already has efforts underway on labeling issues. In December, 2004, CPC provided a paper, "Combination Products Labeling: Issues and Principles" as input to the RAPS summit in January. CPC is currently developing a draft Guidance on cross-labeling.

Decisions to make. Are there specific labeling-related selection issues (e.g., determination of appropriate review time for labeling changes) that need to be addressed by the Selection Working Group?

Selection Issue No. 6

Current good manufacturing practices and quality system requirements

Context. Good manufacturing practices were the subject of an FDA Draft Guidance (Docket No. 2004D-0431), on which CPC provided comments in December, 2004.

Decisions to make. Should further work on cGMP/QSRs be included in the scope of work for the selection issue? Are there specific instances where it would be beneficial base the selection of cGMP/QSR requirements on factors other than PMOA and the criteria discussed in the Draft Guidance?

Selection Issue No. 7

Adverse-event reporting, post-market vigilance and surveillance

Context. This is another area where CPC plans broader efforts, beyond those of the Selection Working Group. However, there are a number of important selection issues that may merit attention from the Selection Working Group. In its April, 2004 paper, "Proposed Policies to Enhance the FDA Regulatory Process," CPC called for a two-phase approach to adverse incident reporting:

- FDA should develop short-term guidance to clarify how reporting requirements in the existing drug, device, and biologics regulations apply to combination products, both for investigational and post-approval combinations.
- Longer-term, FDA should move toward a single, unified framework for reporting adverse incidents to a single FDA office.

This first phase is largely a selection issue: For a given combination product that has generated a given adverse experience, which reporting requirements apply?

Sources of authority and key differences. This discussion focuses on post-market requirements (See Selection Issue No. 1 above for investigational reporting requirements). Sources of authority are:

- Drugs and biologics regulated as drugs: For drugs that have been approved under §§505(b) or (j), FDCA §505(k) requires the applicant to maintain post-market records, data relating to clinical experience, and other data necessary to enable FDA to determine whether there may be grounds for withdrawing approval under §505(e). Regulations at 21 CFR §§314.80-314.81 describe adverse event reports and other required reporting. Drugs approved under the accelerated approval program are also subject to §314.540 reporting requirements. Section 506B of the FDCA requires reports of post-market studies in cases where the sponsor has agreed to conduct such studies.
- Biologics: Certain biologics are subject to different or additional reporting requirements, as described in 21 CFR §§600.80 (post-market reporting of adverse experiences), 601.28, 601.70 (annual reports of post-market studies), 601.44 (post-market safety reporting for accelerated approvals), 606.160-606.170 (records and reports for blood and blood components), and elsewhere in the applicable regulations and guidances for specific products.
- Devices: As with drugs, the FDCA calls for FDA to develop regulations that describe the specific post-market reporting requirements for devices (FDCA §519). FDA has established regulations at 21 CFR §§803 (medical device reporting), 806 (reports of corrections and removals), 821 (medical device tracking requirements), 822 (post-market surveillance) and in related guidances.

Key selection issue. The key question is how much flexibility there is to make a selection among the competing post-market requirements: When the drug, device, and biologics reporting requirements are roughly parallel, it may be possible to choose among them so that

only one applies (drug or device or biologic). However, some requirements may be mandatory in nature, so that competing drug, device, and biologic reporting requirements *all* have to be followed.

This is particularly likely to be an issue for combinations that have a device component. Sections of the FDCA that deal with post-market reporting requirements for devices are somewhat more specific than the corresponding sections for drugs. Since many of the device reporting requirements have a specific statutory basis, this may limit flexibility to substitute a different (drug or biologic) requirement for devices that have been included in a combination product. A device, even if it is part of a combination that has a drug PMOA, may still be subject to statutory device reporting requirements. The following are examples of the specific statutory requirements for devices:

- a. Standard of reportability. FDCA §519(a)(1) requires device manufacturers to make reports upon becoming aware of information that reasonably suggests that a device may have caused or contributed to death or serious injury, has malfunctioned and would be likely to cause death or serious injury if malfunction recurs. Section 519(a)(2) defines “serious injury” as one that is life-threatening, causes permanent impairment of body function or permanent damage to body structure, or necessitates intervention to avoid permanent impairment or damage. This differs from the thresholds for reportability of adverse drug experiences, as defined at 21 CFR §314.80 of the drug regulations. Questions: Which reportability threshold should apply in particular situations? Should the choice vary, based on the type of combination product, the type of adverse event, or which component caused the event? Should problems with the device component be subject to the device reportability standard, and problems with the drug component be subject to the drug reportability standard? What happens if it is not known which component caused the adverse experience? Should one reportability threshold—based on the combination’s PMOA—apply to all adverse experiences, regardless of which component caused them?
- b. Avoidance of undue burdens in device reporting. FDCA §519(a)(4) prevents FDA from imposing device reporting requirements that would be unduly burdensome, taking into account the cost of compliance and the need to protect the public health. A device that is included in a combination product is still, presumably, entitled to this statutory protection. Question: Does this limit FDA’s ability to impose burdensome drug reporting requirements on devices that are included in combinations that have a drug PMOA?
- c. Who must report. FDCA §519(b)(1) imposes device reporting obligations on parties other than the manufacturer (e.g., user facilities). Question: If a drug or biologic is part of a combination that has a device PMOA, can FDA require user-facility reporting of *drug-related* safety problems, or does §519(b)(1) only provide authority to require this for *device-related* problems?
- d. Device tracking and traceability. FDCA §519(e) allows FDA to order device tracking for Class II or III devices, if failure of the device would be reasonably likely to have serious adverse health consequences, or if the device is intended for implantation for more than one year or is a life-sustaining or life-supporting device used outside a user facility. FDCA §520(j) does not allow FDA to require traceability beyond what is allowed by §519(e), unless additional requirements are necessary to protect the public health. Question: If a device is part of a combination that has a drug PMOA and is being regulated as a drug, can FDA still require device tracking? When the combination is not

being regulated as a device, does §519(e) still apply and, if not, where is the authority for tracking?

- e. Corrections and removals. FDCA §519(f) requires manufacturers to report corrections and removals of devices, if done to reduce a risk posed by the device. Questions: Are devices still subject to this, if they are included in a combination that has a drug PMOA? Are drugs and biologics covered by this, if they are included in a combination that has a device PMOA?
- f. Post-market surveillance. See discussion above Selection Issue No. 4, Item c (Application of approval requirements—post-market study and surveillance requirements).

Decisions to make. Which of the above issues should be addressed through guidance relating to the selection issue, and which should be deferred and addressed in a larger effort to resolve adverse-event reporting and other post-market surveillance and reporting issues?

Selection Issue No. 8

Modification of previously approved products

Context. A separate Modifications Working Group is developing a draft guidance related to the problem of clearing/approving changes to combination products.

Decisions to make. The Selection Working Group may wish to refer this issue entirely to the Modification Working Group. If so, what needs to be done to coordinate efforts to ensure overall consistency of approach?

Selection Issue No. 9
**Standards for determining equivalency of combination products;
standards for determining equivalency of components of combination
products; procedures for clearing or approving equivalent
combination products; procedures for clearing or approving
component substitutions.**

Key differences. The drug and device regulations both contain concepts for determining whether one product is equivalent to another.

- FDCA §513(i) defines “substantial equivalence” for devices. For a device that is being compared to a predicate device, it means that the device has the same intended use as the predicate and that the Secretary, by order, has found that it has (i) same technological characteristics, or (ii) different characteristics but is as safe and effective as a legally marketed device, and does not raise different questions of safety or efficacy. “Different technological characteristics” means a significant change in materials, design, energy source, or other features from those of predicate.

- For drugs, the key concept is bioequivalence. FDCA §505(j)(2)(A)(iv) defines it as the absence of a significant difference in the extent to which, and the rate at which, two products; active ingredients become available at the site of drug action when administered in the same molar does under similar conditions. The applicant must show evidence (in vivo or in vitro or both) of bioequivalence or information sufficient to allow FDA to waive the evidence requirement (21 CFR §§320.1(e), 320.21(b)(2))

Questions. What should be the standard for determining whether one combination product is equivalent to another? What clearance and approval options are available to combination products that are equivalent to an already-approved combination product? For example, if a combination product is approved under an NDA, can equivalent combination products be approved under an ANDA?

Can equivalent components be substituted for one another in a combination product? For example, can a substantially equivalent device be substituted for the device component of an existing combination product? What additional factors need to be considered, before determining that two devices are “substantially equivalent” for use in a combination product? What clearance or approval should be required, prior to making a component substitution?

Selection Issue No. 10

Advertising and promotion

Key differences. Drugs are subject to a number of special statutory provisions that affect marketing, advertising, and promotion. The FDCA addresses trading and selling of drug samples, who can distribute drug samples, and related record-keeping (FDCA §503(c), 21 USC §553(c)). Prescription drugs are misbranded unless advertisements and descriptive printed matter meet certain requirements regarding contents and typeface, including a brief summary of side effects, contraindications, and effectiveness. However, prior approval of drug advertisements is not required except in extraordinary circumstances (FDCA §502(n), 21 USC §352(n)). Special penalties apply to prescription drug marketing violations (FDCA §303(b), 21 USC §333(b)).

FDA has jurisdiction over advertising of restricted devices, but prior approval of advertising is not required except in extraordinary circumstances. Other devices are only subject to less stringent Federal Trade Commission rules (§502(r)).

Questions. How do these provisions apply to combination products? What criteria should be used to decide?

Selection Issue No. 11

Adulteration, Misbranding, and Prohibited Acts

Key differences. FDCA §501 (adulteration of drugs and devices), §502 (misbranded drugs and devices) and §301 (prohibited acts) treat drugs and devices alike in many respects.

The misbranding provisions relating to advertising of prescription drugs (discussed above under Selection Issue No. 10) are one of the more important differences. Other differences merely reflect the fact that drugs and devices have to comply with different substantive regulatory requirements. Drugs are subject to various specific requirements, concerning obligations to transmit informational material to physicians (§301(o)), counterfeit drugs (§301(t)), requirements for official compendium drugs (§502(g)), warnings for drugs liable to deterioration (§502(h)), and drugs subject to the Poison Prevention Packaging Act (§502(o)).

Selection issues. There do not appear to be major selection issues. The appropriate general rule appears to be that each component (drug, device, or biologic) of a combination product must separately comply with the conditions necessary to avoid adulteration, misbranding, or prohibited acts. E.g., if the drug in a combination product is liable to deterioration, the product as a whole needs to provide the necessary warnings to ensure that the drug is not misbranded.

Selection Issue No. 12

Patent Certification and Market Exclusivity

Key differences. Drugs are subject to a number of requirements aimed at protecting the rights of patent holders. They also are eligible for patent-term extensions and other provisions that can extend the period of market exclusivity.

- a. Patent certification for drugs. Drug applications (NDA and ANDA) must include the number and expiration date of any patent that claims the drug and with respect to which a claim of patent infringement could reasonably be asserted if an unlicensed person made, used, or sold the drug. (FDCA §505(b)(1)). Such patents are listed in Orange Book of “listed drugs” that have been previously approved. Paper NDA applications under §505(b)(2) and ANDA applications under §505(j), which rely on investigations conducted on other drugs, are required to make certifications related to patents for those other drugs: i.e., that patents were never filed on those other drugs, that their patents have expired, the date when their patents will expire in the future, or that their patents are invalid or will not be infringed by the new drug for which the application is being submitted. This triggers notice provisions and a period of time for the other patent owners to defend their rights.

Question: How do these provisions apply to combination products? Must patent certifications be provided for the drug component of a combination product, even if the combination has a device PMOA and is being approved under a device PMA?

- b. Patent-term extension and other sources of market exclusivity for drugs. Drugs are eligible for various provisions that can extend the period of market exclusivity:
1. Statutory patent-term restoration. U.S. patent law (35 USC §156) provides a patent-term extension to replace part of the time a drug sponsor loses while the drug undergoes regulatory review. This takes account of the testing period (from IND effective date to NDA submission) and the approval period. The patent term is extended to replace half of the testing period and all of the approval period.
 2. Statutory exclusivity for new chemical entities (FDCA §505(c)(3), 21 USC §355(c)(3); 21 CFR §314.108). After FDA approves a drug that contains a new chemical entity, no application under §505(j) (ANDA) or §505(b)(2) (paper NDA) that references the drug can be approved until five years from the date of approval of the drug.
 3. Additional exclusivity for new clinical studies. It is possible to get three years of additional exclusivity for a previously-approved active ingredient if the application (NDA or NDA supplement) contains reports of new clinical studies essential to approval of the application (FDCA §505(c)(3)(D)(iii), 21 USC §355(c)(3)(D)(iii))
 4. Orphan-drug exclusivity. FDCA §526(a)(2) (21 USC §360bb(a)(2) provides seven-year market exclusivity for the first applicant to obtain approval for a drug to treat a rare disease that affects fewer than 200,000 persons in the US or that

affects more than 200,000 when there is no reasonable expectation of cost recovery for the drug.

5. Pediatric testing exclusivity. FDCA §505A (21 USC §355a) provides six extra months of exclusivity if FDA requests, and a sponsor agrees to conduct, additional clinical studies related to pediatric populations.

Questions. Will §505 patent-certification and market-exclusivity provisions still apply to a drug if it is part of a combination product that has a device PMOA and is approved under a device PMA?

Are combination products that have a drug PMOA and are approved through NDAs eligible for patent-term restoration or marketing exclusivity? It is not a given that these provisions will apply, just because a product is approved as a drug. An old case found that the market-exclusivity and patent-certification provisions of §505 did not apply to antibiotic drugs that had been approved under the old FDCA §507 (which had provided a basis for waiving batch-by-batch biologic certification of these drugs) (*Glaxo v. Heckler*, 623 F. Supp. 69, 1985). How will the patent-certification and market-exclusivity provisions of §505 apply to combination products that are approved via NDAs?

Selection Issue No. 13

Confidentiality and trade secrets

Key differences. The drug, biologics, and device regulations all provide some protection of manufacturers' trade secrets, but there are subtle differences in what can be released by FDA, in what form, to whom.

- a. Public dissemination of safety and effectiveness data. For drugs, FDCA §505(l) calls for safety and effectiveness data submitted in new drug applications to be available to the public, upon request, unless various grounds exist for not releasing it. Section 506B provides that information submitted in reports on agreed post-market studies of drugs is public to extent necessary to identify the sponsor and establish the status of study.

For devices, §520(h) calls for FDA to issue regulations that require a detailed summary of safety and effectiveness data that were the basis for approving, denying, or withdrawing a PMA, or making decisions to ban devices.

Question. A more careful analysis of the regulations is needed. If differences are material, which standards should apply to combination products?

- b. Use of data submitted by other parties. For devices, there are limits on the ability of third parties to use data that were originally submitted to FDA by someone else to demonstrate safety and effectiveness of their own devices, and there are limits on FDA's use of data in reclassifying devices and amending performance standards (FDCA §§520(c) 520(h)(3)).

Question. For combination products, how do the data-use provisions of the device regulations interact with data-use/rights-of-reference for paper NDAs and ANDAs?

- c. FDA communication of drug data to Commerce Department and Patent Office. FDCA §702(d) allows FDA to provide information to the Commerce Department and Patent and Trademark Office (PTO) in connection with their processing of patent matters and drug patent applications.

Question. Can FDA provide information to the Commerce Department and PTO under §702(d) for drugs that are part of combination products that have been approved through device PMAs, rather than under separate NDAs? Can it provide information about device components of combination products that have been approved as drugs under NDA procedures? What are the pros and cons of handling this various ways?

Selection Issue No. 14

Import and export of combination products

Key differences

1. Exports. The FDCA's framework for exports (FDCA §§801,802) is basically the same for food, drugs, devices, and cosmetics. Products that are cleared/approved and legally marketed in the US can be exported. Products that are not approved for sale in the U.S. may still be exportable under a §801(e)(1) Certificate of Exportability or a §802 Certificate of Exportability. Section 801(e)(2) provides an additional avenue for exporting devices that could not be sold in the U.S. under an export permit from FDA. Section 801(f) addresses labeling of exported drugs.

Despite similarities in the overall statutory framework, the particular Certificates that must be obtained may differ somewhat for drugs, devices, and biologics and may be subject to different procedures and guidances issued by the various FDA Centers that are involved.

Moreover, the ability to export a product often depends on its regulatory approval status in the country to which it is being exported, or whether it has been approved in certain "listed" countries. This raises important issues for combination products, since other nations may regulate them quite differently than the U.S. does.

2. Imports. The general framework for imports (§§801,802) is similar for drugs and devices, although there are certain special provisions for drugs and biologics. §801(d) specially addresses the problem of reimportation of drugs. §801(e) contains special provisions for importation of certain biologics (blood, blood components, source plasma, source leukocytes, or components thereof) and tissues. §801(g) contains special provisions for warning notices that relate to importation of prescription drugs.

§804 calls for the Secretary to develop regulations for importation of covered products by pharmacists and wholesalers. “Covered products” means prescription drugs other than Schedule I, II, or III controlled substances and biologics under 42 USC §262.

Decisions to make. The Working Group needs to decide what priority to assign to import and export issues and what scope of work is warranted. Specific issues, such as how to decide which particular export certificates apply, may be worth addressing now. However, many of the issues surrounding export of combination products reflect the overall lack of harmony in how various countries regulate these products. These broader harmonization problems are probably beyond the scope of this Working Group’s efforts.

Selection Issue No. 15

Enforcement, penalties, and sanctions

Key differences. The FDCA contains a number of special provisions that allow FDA to move swiftly and decisively to address device violations. It also contains special sanctions for prescription drug marketing violations and for certain violations related to ANDA-approved drugs.

Key selection issue. It is crucial to clarify how these provisions will apply to combination products. For example, can FDA order repair, replacement, and refund of a device if it is separately approved as a device, but not if it is approved as part of a combination product under an approved NDA? The following is a summary of special provisions:

- a. Special penalties for prescription drug marketing violations and device violations. As a general matter, FDCA §303(a) provides relatively modest sanctions for prohibited acts (up to one year and \$1,000 on first violation; 3 years and \$10,000 on second violation). However, the following special provisions apply:
 - FDCA §303(b) provides special penalties for prescription drug marketing violations (10 years, \$250,000).
 - FDCA §303(f) provides significant civil penalties for device violations (\$15,000 per instance, up to an aggregate \$1 million).
- b. Notice to professionals and repair, replacement, refund of devices. FDCA §518(a) lets the Secretary issue orders to assure adequate notice to health professionals and user facilities if a device presents unreasonable risk of substantial harm to public health. Section 518(b) lets the Secretary order repair, replacement, or refund of a device if there is unreasonable risk of substantial harm, and there are reasonable grounds to believe the device was not properly designed or manufactured or does not meet the state of the art at the time it was designed (i.e., if the problem is not due to an installation, maintenance, or use problem), and notification would not be adequate to address the risk.

- c. Device recall authority. FDCA §518(e) allows FDA to order recall of devices if there is reasonable probability of serious, adverse health consequences or death.
 - d. Banning of devices. FDCA §516 allows devices to be banned if there is substantial deception or unreasonable and substantial risk of illness or injury.
 - e. Administrative detention of devices. FDCA §304(g) allows 20-day detention of devices that are adulterated or misbranded upon inspection, or 30 days if the Secretary provides justification. This is faster than the ordinary §304(a) *in rem* seizure process for food, drugs, and cosmetics that are adulterated or misbranded.
 - f. Revocation of approved device PMA in advance of administrative hearing. FDCA §515(e) allows an approved PMA to be revoked in advance of formal administrative hearing.
 - g. Special sanctions for ANDA-approved drugs. FDCA §§306-308 provide for debarment, temporary refusal to approve, suspension of distribution, and special civil penalties for ANDA-approved drugs.
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Selection Issue No. 16

Miscellaneous Issues

There are a number of miscellaneous provisions that create differences in the drug, biologics, and device regulations. The Working Group needs to develop proposed principles for deciding when and how these provisions apply to a combination product. Examples include:

- a. Notice of discontinuation of life-supporting drugs. FDCA §506C requires six months' notice prior to discontinuation of a solely manufactured life-supporting or life-sustaining drug. This is not a service obligation to continue providing the drug, but simply a notice requirement, which the Secretary can reduce to a shorter period under specified circumstances. Question: Should this only apply if the combination has a drug PMOA, or should it apply if the combination contains a drug and the combination as a whole is life-sustaining?
- b. Distribution/Chain of Supply for Drugs. FDCA §503(e) requires special record-keeping for wholesale distributors of prescription drugs and imposes other controls on the distribution chain. Question: Should this apply only if the combination has a drug PMOA or does it apply if any component is a prescription drug?
- c. Transferability of instruments approving the product for marketing. There may be variations in an owner's ability to transfer a biologics license, an NDA, a PMA, or a 510(k) clearance to other parties. Question: What is needed to ensure that interests in combination products can be sold, acquired, and transferred without hindrance and to ensure that conditions of transfer will be similar for similar types of combination products?