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Views from a contract manufacturer

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Important considerations:

- Standard for changing the FDA's product jurisdiction is public health standard;
- Existing safeguards, review processes assure public health and product safety;
- Absent serious safety issue that cannot be addressed under current regulatory oversight, consistency and predictability must be maintained;
- If public health is the basis for this reassignment, careful management of the transition is necessary.

Question 1 (part I):

What are the public health concerns related to these combination products as a whole and with respect to their individual components?

There are no health concerns that are outside the jurisdiction of any particular Center. For a product cleared or approved by FDA review, with interCenter consultation, manufactured in accordance with good tissue practices (GTPs) and under the Quality System regulations (QSRs), and subject to periodic inspections, safety issues have been addressed. The product jurisdiction process for all products recognizes that review is thorough regardless of Center lead.

Question 1 (part II):

What information should the agency require in the premarket submission to demonstrate the safety and efficacy of combination products that contain live cells used in combination with a device matrix for wound healing (e.g., wound repair, or skin regeneration, replacement or reconstruction)?

Regarding Agency lead Center, this question goes beyond the scope of a decision change a lead Center. Nevertheless, it is important for FDA to assure that regardless of lead Center, products with similar indications should be subject to similar clinical demonstrations and manufacturing controls.

Question 1 (part III):

What regulatory requirements are necessary to ensure that adequate manufacturing controls are in place for both the device and live cell components? What other issues are important (e.g., clinical trial design, informed consent, infectious disease concerns)?

QSRs and GTPs are adequate to assure safety and efficacy of these wound healing products.

Changing the requirements from device QSRs to other systems such as drug GMP will have enormous repercussions, redirecting resources that will delay product availability and product advances that have a real affect on safety and efficacy without adding value.

Question 2:

Given that primary mode of action determines jurisdiction for combination products, what information should the agency consider in identifying the level of contribution of each component to the therapeutic effect of the product?

> ***For example, skin replacement products are intended to act as wound coverings (historically considered a device action), and as mediators of tissue regeneration or repair by providing a living substrate to grow replacement tissue and through the production of soluble factors (historically considered to be biological product activities).***

What information should the agency consider in determining which action is primary?

Important considerations:

- Standard for changing the FDA's product jurisdiction is *public health* standard;

Current Requirements - Statutory

Sec. 360bbb-2. - Classification of products

The Secretary may not modify such statement except with the written consent of the person, or for public health reasons based on scientific evidence.

Current Requirements

(c) Inaction of Secretary

If the Secretary does not provide the statement within the 60-day period described in subsection (b) of this section, the recommendation made by the person under subsection (a) of this section shall be considered to be a final determination by the Secretary of such classification of the product, or the component of the Food and Drug Administration that will regulate the product, as applicable, and **may not be modified by the Secretary except with the written consent of the person, or for public health reasons based on scientific evidence.**

Current Requirements - Regulations

Sec. 3.9 Effect of letter of designation.

(a) The letter of designation constitutes an agency determination that is subject to change only as provided in paragraph (b) of this section.

(b) The PJO may change the designated agency component with the written consent of the sponsor, or without its consent **to protect the public health or for other compelling reasons**.

Current Requirements - Procedural

Sec. 3.9 Effect of letter of designation. Continued....

A sponsor shall be given 30 days written notice of any proposed nonconsensual change in designated agency component. The sponsor may request an additional 30 days to submit written objections, not to exceed 15 pages, to the proposed change, and shall be granted, upon request, a timely meeting with the product jurisdiction officer and appropriate center officials. Within 30 days of receipt of the sponsor's written objections, the product jurisdiction officer shall issue to the sponsor, with copies to appropriate center officials, a written determination setting forth a statement of reasons for the proposed change in designated agency component. A nonconsensual change in the designated agency component requires the concurrence of the Deputy Commissioner for Operations or the Deputy Commissioner for Policy.

Current Requirements - Procedural

Sec. 360bbb-1. - Dispute resolution

If, regarding an obligation concerning drugs or devices under this Act or § 351 of the PHS Act (42 USC 262), there is a scientific controversy between the Secretary and a person who is a sponsor, applicant, or manufacturer and no specific provision of the Act involved, including a regulation promulgated under such Act, provides a right of review of the matter in controversy, the Secretary shall, by regulation, establish a procedure under which such sponsor, applicant, or manufacturer may request a review of such controversy, including a review by an appropriate scientific advisory panel described in § 355(n) of this title or an advisory committee described in § 360(g)(2)(B) of this title. Any such review shall take place in a timely manner. The Secretary shall promulgate such regulations within 1 year after November 21, 1997

Public Health - Evidence

No specific public health/safety issues identified in the notice of this meeting.

Our own safety evaluation: *MedWatch*

One safety issue* (available on the web) regarding these products 1999-2002 that were managed adequately by CDRH under current authority (with labeling changes)

- One instance out of 203

Public Health

- New initiatives exist for devices in the event of new safety issues

Postmarket Surveillance

- http://www.fda.gov/OHRMS/DOCKETS/98fr/060602a.htm
- http://www.fda.gov/OHRMS/DOCKETS/98fr/060602a.pdf

FDA Steps Up Surveillance of Medical Devices To Prevent Unforeseen Problems, Better Protect Patients

http://www.fda.gov/bbs/topics/NEWS/2002/NEW00813.html

FR PrePublication Document - Postmarket Surveillance

http://www.fda.gov/OHRMS/DOCKETS/98fr/00n-1367_nfr0001.pdf

Consistency

- In this environment, we have the luxury of considering the benefits for *consistency*.

- Consistency might be achievable even if this is moved to CBER as a device, as long as the transition from CDRH is carefully executed.

- Consistency
- Historic experience
  - treating late comers differently
- Human heart valves
- Imaging agents
- Diapulse

Consistency

- Transitional issues:
  - Conserve FDA review resources
    - Consistency of reviewers
    - Review standards
- Retain inspection standards, and schedule
    - Manufacturing requirements (QSR)

Conserving Agency Resources:

- Application for Premarket Approval contains adequate information to protect public health.
- Changing to BLA or to cGMP, replicating expertise does not conserve resources
- Reducing delays from consults may conserve resources, but collaborations where no Center owns the review and deadlines, will not conserve resources

Question 1 - conclusion

- Current safety oversight is already exhaustive;
- There is no contention generally that safety review for devices is less adequate than that for biologics, no evidence that safety has been or will be sacrificed;
- There is no contention that any special safety issues exist regarding these products.

Question 3:

In instances where both components of a combination product containing live cells appear to make a significant contribution to the therapeutic effect of the product and it is not possible to determine which mode of action is primary, what other factors should the agency consider in the assignment of primary jurisdiction?

Is there a clear hierarchy among these additional factors that should be observed in order to ensure an adequate review?

Should these same factors be used to determine the appropriate type of premarket application?

Important considerations:

- Standard for changing the FDA's product jurisdiction is *public health* standard;

Important considerations:

It would be reasonable to consider where the expertise already exists to facilitate review, product availability; and to conserve agency resources.

It would be reasonable to consider the likely direction of the technology to prevent need for future duplication of expertise.

Existing requirements - conclusion

- Current review procedures are already exhaustive;
- There is no contention generally that review for devices is inadequate for these products, and
- No evidence that review issues have gone unaddressed for these products .

Other Complexities

- Delays are already occurring due to uncertainty; affects ability to prepare submissions, agreements with CDRH on clinical requirements;
- Agency consult delays, inconsistent review standards, also are occurring. These complexities, whether directly related to FDA or not, implicate product availability, a safety issue that FDA *is* challenged to address.

Other Complexities

The Federal Register Notice is not adequately specific in that it does not explain or suggest whether these products will go to CBER as a device or as a biological product.

Other Complexities

- Undermines the very purpose of product jurisdiction – certainty
- Undermines company decisions to proceed on products in the pipeline that must be made
- Undermines company decisions regarding GMP systems.

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