Aventis Pharmaceuticals

27 June 2001

Via fax and UPS

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

Re: Docket No. 01N-0191
Medical Devices; Global Harmonization Task Force; Study Group 1; Working Draft "Medical Devices Classification;" 66 Fed Reg, 27150-27151 (16 May 2001)

Dear Sir/Madam:

Aventis Pharmaceuticals is pleased to provide the following comments on the above-referenced working draft entitled "Medical Devices Classification." The document represents a harmonized proposal that may be used by governments developing or updating their premarket regulation schemes for medical devices.

Aventis Pharmaceuticals supports FDA's efforts in working toward global harmonization and in providing industry with guidance in achieving this goal. As manufacturers of human drugs and biologics, we are directly affected by this document and offer the following comments for your consideration:

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General Comments

The organization of four device classes matrixed across 16 rules creates difficulty in interpreting which devices are rule-exempt and which are not, for each device class. This becomes apparent when devices could fall into more than one class. The rules do not seem to have a provision for handling multi-class devices, other than to select the more stringent, which is not always the most appropriate solution.

Specific Comments

Aventis comments appear as boxed text below the working draft reference.

4.0 Definitions, p. 3-5

"Active medical device: Any medical device operation of which depends on a source of electrical energy or any other source of power..."

- Aventis suggests clarifying by adding *"external or extracorporeal"* such that the sentence reads: *"operation of which depends on an external or extracorporeal source of electrical energy or any other...."*
- Aventis also suggests adding a definition for "non-active medical device," so that it will not be merely defined by default.

"Invasive devices ... Implantable device"

Aventis suggests adding under the subcategory *"Implantable device"* a definition of resorbable implant devices (e.g., sutures, staples, bone pins, stents) and clarification that these also are implantable devices.

"Reusable surgical instrument: ... which can be used after appropriate procedures have been carried out."

Reusable surgical instruments (e.g., endoscopes) can exhibit high levels of microscopic tissue/blood contamination that are not removed by cleaning and sterilization procedures, as evidenced by post-cleaning SEM or TEM analysis of instrument surfaces. Furthermore, many reusable instruments simply cannot be sterilized. With the possible exception of the allusion to sterilization as *"appropriate procedures,"* this document does not address this critical topic, which directly impacts a patient's safety risk.

In addition, Aventis suggests adding definitions for the following:

- Conformity assessment
- Peripheral nervous system (and clarifying how peripheral nervous system devices would fall into this classification scheme)

6.2 Factors Influencing Device Classification, p. 6

"Each Regulatory Authority may assign names or numbers to the risk classes, based on local preference."

What, then, is the purpose of the harmonization effort?

6.4 Proposed Classification System for Medical Devices, Figure 2, p. 7-8

"Figure 2 shows a conceptual illustration of increasing levels of regulatory requirements as the device risk class increases. These regulatory controls may include, for example:-
•operation of a quality system (recommended for all devices);
•documentation of clinical evidence to support the manufacturer's claims;
•technical data;
•product testing using in-house or independent resources;
•the need for and frequency of independent external audit of the manufacturer's quality system; and
•independent external review of the manufacturer's technical data."

- What additional criteria will be used to classify devices into the four proposed categories?
- The document provides no insight as to the weighted importance of these six regulatory controls, nor which would be required for each of the various device classifications. Will classification depend on how each device meets or satisfies each regulatory control?
- *"Technical data"* is not defined. Technical device characteristics are critical in determining current U.S. classification (I, II, III). It is not clear in this GHTF document what role or weighted importance "technical data" have in the proposed four-level classification scheme. Are "technical data" assessed equally against the other five regulatory controls listed, or does it carry more importance in determining the conformity of a device?

7.0 The Determination of Device Class, p. 8

"4. Determine that the device is not subject to special national rules that apply within a particular jurisdiction. NOTE: Where special national rules are applied, resulting in a device class other than that suggested by the present rules, then a different conformity assessment procedure may be indicated. This may have an effect on the acceptability of such devices for free movement in the global context unless other or additional, conformity assessment procedures are carried out."

Aventis believes that harmonization of national jurisdictional rules must occur before mutually recognized conformity assessment can really work. Otherwise, a manufacturer will be faced with different conformity assessments for different global regions, resulting in disagreement on what data or criteria are acceptable to regional regulatory authorities. If regions classify devices differently and the manufacturer's device must comply with multi-class requirements, then conformity assessment will always defer to the most conservative testing requirements, based on higher risks and, therefore, higher costs. This paradigm provides no incentive for innovation.

8.0 Classification Rules – Rule 5, p. 10

The rule 4 comment *"Devices containing medicinal products are within the scope of Rule 13 and are in Class D"* should be repeated for rule 5.

8.0 Classification Rules – Rule 6, p. 11

Rule: "6. All surgically invasive devices intended for transient use are in Class B unless they are:
- intended specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class D,
- reusable surgical instruments, in which case they are in Class A,
- intended to supply energy in the form of ionizing radiation in which case they are in Class C,
- intended to have a biological effect or be wholly or mainly absorbed in which case they are in Class C,

- intended to administer medicines by means of delivery system, if this is done in a manner that is potentially hazardous taking account of the mode of application, in which they are in Class C."

There are many exemptions to Rule 6, making classification more arbitrary. While a note clarifies that *"the 'biological effect' referred to is an intended one rather than unintentional,"* no guidance is provided on how to address unintended biological effects. Aventis suggests defining "intended biological effect" and "unintended biological effect."

8.0 Classification Rules – Rule 7, p. 11

Rule: "7. All surgically invasive devices intended for short-term use are in Class B unless they are intended:
- either specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class D,
- or specifically for use in direct contact with the central nervous system, in which case they are in Class D,
- or to supply energy in the form or ionizing radiation in which case they are in Class C,
- or to have a biological effect or to be wholly or mainly absorbed in which case they are in Class D,
- or to undergo chemical change in the body, or to administer medicines, in which case they are in Class C."

Comments: "...NOTE: the term 'administration of medicines' implies storage and/or...."

- The quoted comment properly belongs in the comments for Rule 6, as the term *"administer medicines"* first appears in rule 6.
- Aventis suggests adding another exemption for Rule 7: *"- or are implantable,"* together with a comment referring the reader to Rule 8. Otherwise, the reader might be misled to classifying a short-term implantable device as Class B, while Rule 8 instructs otherwise.

8.0 Classification Rules – Rule 8, p. 11

Rule: "8. All active and non-active implantable devices, and long-term surgically invasive devices, are in Class C unless they are intended:,
- to be used in direct contact with the heart, the central circulatory system or the central nervous system, in which case they are in Class D,
- to be life supporting or life sustaining, in which case they are in Class D,
- to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class D,
- or to undergo chemical change in the body, except if the devices are placed in the teeth, or to administer medicines, in which case they are in Class D.

Comments: "Active implantable medical devices are in Class D."

- The quoted comment for this rule appears to contradict the rule itself.
- The document does not define "non-active," which makes interpretation of rule 8 difficult, particularly where bone cement and hydroxyapatite are given as examples. Many exogenous orthopedic implant materials (Class C) make use of autologous sources of bone and blood to augment device efficacy. According to Rule 14, however, by incorporating *"animal or human cells/tissues/derivatives thereof,"* such devices are Class D. Why would the use of autologous materials make these high-risk devices rather than high-moderate risk?

8.0 Classification Rules – Rule 13, p. 14

Rule: "13. All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, and which is liable to act on the human body with action ancillary to that of the devices, are in Class D."

Comments: "These devices cover combination devices that incorporate medicinal substances in a secondary role."

Rule 13 attempts to cover drug-device combination products, however, the comment to this rule states that the rule applies to devices in which the drug action on the body is ancillary to the device. Does this mean that a device in which the drug action is primary, and the device secondary, would fall outside the scope of medical device regulations?

8.0 Classification Rules – Rule 14, p. 14

Rule: "14. All devices manufactured from or incorporating animal or human cells/tissues/derivatives thereof, whether viable or non-viable, are Class D
- except where such devices are manufactured from or incorporate non-viable animal tissues or their derivatives that come in contact with intact skin only where they are in Class A."

- See comment on rule 8.
- What are the differences in jurisdictional requirements for biologic devices, and how will they affect global harmonization of device classification?

Figure 3, p. 15 to end

Given the broad scope of the category of medical devices, in terms of their degree of complexity and their myriad applications, the document's clarity and effectiveness would be well enhanced by providing specific examples to demonstrate the application of the proposed decision-tree schemes. Aventis suggests adding, beneath each final decision parallelogram in Figure 3, several specific examples of devices meeting the criteria that lead to the specific classification decision.

Thank you for your consideration.

Sincerely,

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N.A. Regulatory Center Head
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REMARKS: ☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please comment

Re: Docket No. 01N-0191

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To Whom It May Concern:

Aventis Pharmaceuticals is pleased to provide comments on the above mentioned Draft Guidance.

We will also be sending a copy by UPS.

Regards,

Patti Stasiulaitis

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