November 24, 1999

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AMERICAN MEDICAL SYSTEMS

Docket No. 99D-2873
Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD 20852

To Whom It May Concern:

American Medical Systems, Inc. respectfully submits the following comments in regard to the Draft Guidance entitled **Evidence Models for the Least Burdensome Means to Market.**

We propose that the Evidence Model Decision Schematic on page 11 be changed to the following (see attached schematic):

Q1. Are all risks addressed by valid scientific evidence?
Yes – then submit device-specific data
No – Can risks be addressed using bench testing, in-vitro test&g, or in-vivo testing?
If yes, run studies and return to Q1. If no, go to Q2.

In regard to obtaining valid scientific evidence, can safety & efficacy issues be addressed individually rather than in 1 large study or smaller controlled studies? To clarify, is it acceptable to address the risks individually from different sources of information, for example, from a literature review for one risk, and from a patient tracking system for another risk? In addition, if a particular company utilizes a Data Safety Monitoring Board (DSMB), will FDA give more credibility to the data than when not using a DSMB, even if a shorter clinical trial is used?

We propose that Question #2 on page 4 be rewritten such that a randomized controlled trial (RCT) **is not the default** pathway for obtaining valid scientific evidence. FDAMA mandates that FDA and industry enter into a dialog to determine together what will be the least burdensome pathway. If an RCT is considered by FDA to be the default least burdensome pathway, the burden is then placed on industry to prove that it is **not** the least burdensome, rather than working together without any preconceived notions.

We support the guidance document questions on pages 5 and 6 and believe they provide a meaningful tool for determining whether data outside of an RCT are valid. However, we have the following comments. Do all of the questions on pages 5 and 6 require

10700 Bren Road West
Minnetonka, MN 55343
Tel: 612.933.4666
Toll Free: 800.328.3881
Fax: 612.930.6592

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affirmative answers for FDA to accept the data? If we answer "no" to some of the questions, will FDA still accept the data? If we do answer "no" to some of the questions, is a rationale required to explain why the data still qualify as valid scientific evidence?

We disagree with the sentence on page 7 which reads **"A major advantage of the RCT design is the assurance that confounding factors, such as selection biases, will not be a problem because of the randomization. If there is no randomization then there is a greater need to check for potential confounding factors, hence potentially more burden validation."** We disagree with the premise that a randomized trial is free of bias. We assert that every study, randomized or not, needs to be checked for confounding factors and bias, and therefore this supposed advantage of an RCT will not necessarily make it the least burdensome pathway.

On page 8, the question is posed: **"Is randomization necessary (i.e., is it the least burdensome design) to prevent/reduce bias, allow for direct comparison with an established device?"** We suggest that the parenthetical contents be removed. The goal is to define the least burdensome pathway to demonstrate safety and efficacy, not the least burdensome pathway to reducing bias.

The Study Monitoring section on page 9 references ICEC and IDMC. We suggest these references be removed since they refer to drug and not device evaluation.

Also on page 9, in reference to the duration of patient follow-up, the bullet point reads: "How long must patients be followed after treatment in order **to establish durability of effect and safety?"** We propose that the sentence be re-worded to the following: "How long must patients be followed after treatment in order **to establish safety and effectiveness, consider such factors as durability, complications, reliability, etc."** We base this suggestion on the fact that durability is just one means of determining device effectiveness and may not be appropriate for all products.

American Medical Systems appreciates the opportunity to respond to and offer suggestions for modifying the draft guidance. We look forward to a new guidance reflecting FDA and industry dialog regarding the least burdensome means to market. If you have any questions or would like clarification regarding our comments, please contact Mark McIntyre at (612) 930-6120.

Thank you.

Sincerely,

Mark McIntyre
Director, Regulatory Affairs & Biostatistics
(612) 930-6120
mark.mcintyre@VisitAMS.corn

Appendix 1
Evidence Model Decision Schematic

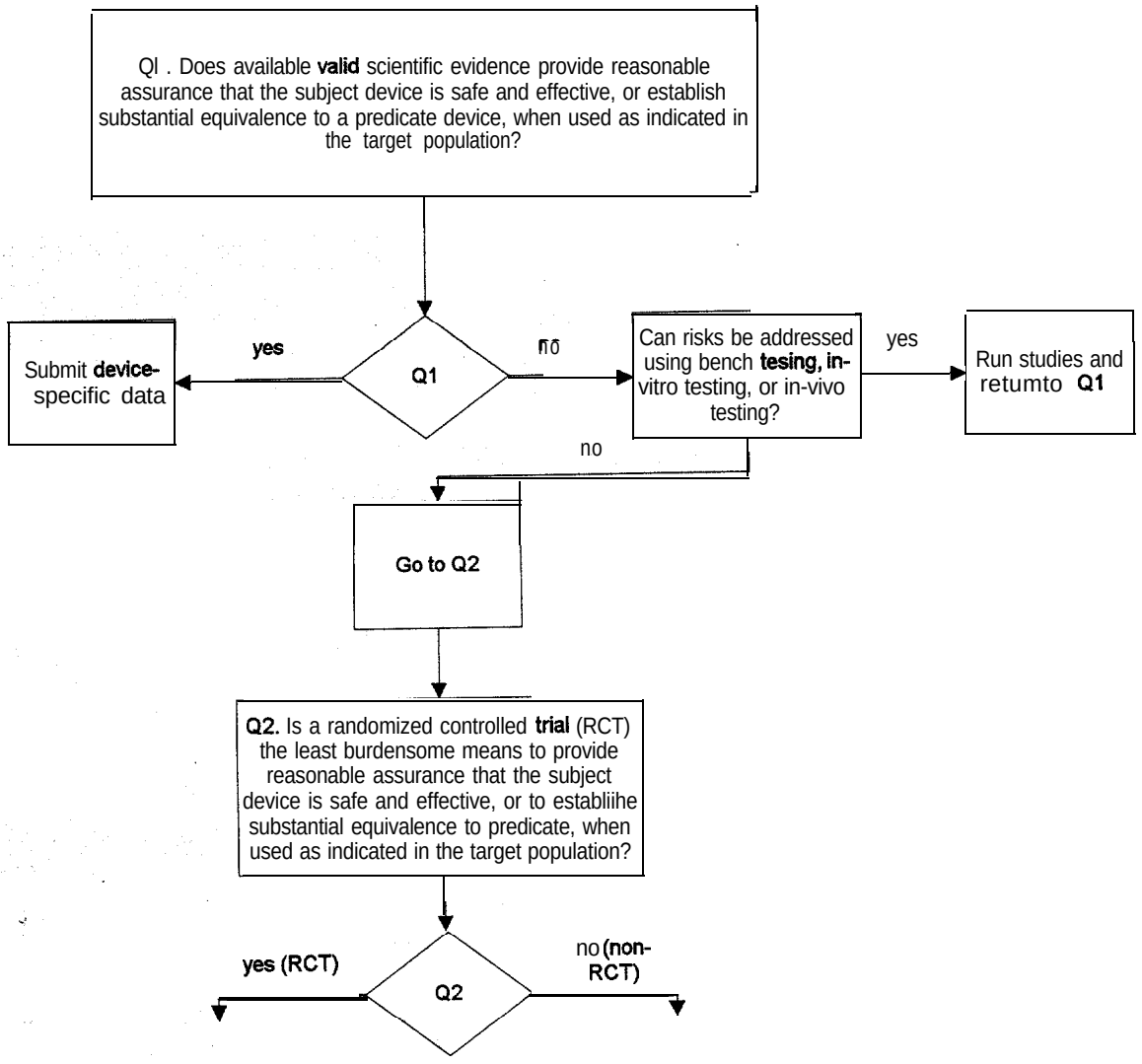

Chart continues as orginally described

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