

Dec. 2, 2004

Division of Dockets Management  
HFA-305  
Food and Drug Administration  
5630 Fisher's Lane, Rm. 1061  
Rockville, MD 20852

Re: Docket #2004D-0431

Dear Sir or Madam:

American Medical Systems (AMS), a manufacturer of medical devices and combination products, appreciates the opportunity to comment on the draft guidance document entitled "Guidance for Industry and FDA, Current Good Manufacturing Practice for Combination Products."

In general, AMS agrees with the idea of following the respective GMP system for each constituent part of a combination product. However, we do have some concerns about the potential application of the concept of complying with both GMP systems after joining the constituent parts together, as detailed below.

1. The terminology used in medical devices and drugs is not consistent and this may cause confusion. Specifically, 21 CFR 211.103 is titled "Calculation of Yield." It is our understanding that this generally is interpreted in a way as to account for the entire amount of drug originally placed into the manufacturing process. This definition is different than the term "yield" as generally interpreted in medical device manufacturing, which refers to the rate of production of good devices after all manufacturing steps have been completed. This could be confusing and should be clarified.
2. Further, once drug and device components are combined into a single entity, it may be difficult or impossible to calculate yield in the sense of 21 CFR 211.103, due to the nature of the devices and the destructive nature of much of the testing required when evaluating the levels of drugs on each device. For example, processing of a drug-coated device may involve placing devices into a liquid solution. Accounting for the exact quantity of drug solution absorbed into the devices as well as scrap or remaining solution becomes very difficult within normal drug tolerance limits of accountable yield.
3. Under 21 CFR 211.165, sampling and testing for conformity to the identity and strength of the drug agents is required for each batch, prior to release. In addition, this sampling is required to be based on statistical sampling methods. This

required seems tailored to the large batch sizes commonly seen in the production of drug products. For example, a mid-size lot of very large (1g) tablets might be approximately 300 kg, yielding 300,000 tablets. Statistical sampling represents only a small portion of the total saleable yield at a nominal cost.

However, medical devices are often produced in much smaller batches that may have only 8-15 units per batch. Sampling even a single medical device represents a much higher portion of saleable yield and could have a cost of thousands of dollars, and which could be prohibitively expensive. Thus, this sampling approach may not be appropriate for combination devices with an integrated drug component.

4. The requirement (under 21 CFR 211.65) that the strength of each active ingredient be verified for each production lot can become extremely complicated for a medical device with a drug coating. For instance, the very low levels of drugs typically used on these devices can be difficult to quantify with accuracy, particularly when only a small number of samples are available. This is both a limitation of current test methods and a result of the variability inherent in extracting the drugs from the device prior to quantification. Additionally, many drug coated medical devices are available in a wide variety of configurations and sizes. Each of these configurations would have to have a separate specification. The combination of a large number of sizes and specifications and large variability in test outcomes make it extremely difficult to establish a release test for the finished devices. Lastly, in many combination drug-device products, the drug component is used only as a preventative measure (i.e. drug coated stents), rather than to deliver a therapeutic level of drug (i.e. insulin pumps). In the former case, it is reasonable to relax the drug quantification specification for each case based on the products claims and benefit-risk ratio.

AMS appreciates the Agency's developing guidance in this area, and we thank you for the consideration of these comments.

Sincerely,



Ginger Sackett Glaser  
Regulatory Affairs Manager