4. Failure to maintain and/or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to posses and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by quality control [21 CFR 211.100]. For example:

a) The batch production record (BPR) 40-06, entitled "Additional Precautionary Sterile Filtration for Fraction V, IGIV and Placebo Bulks," states the procedure is only to be used in the case of potentially compromised bulk integrity and the filtration must be initiated within 12 hours of observation of the potential compromise. However, the BPR does not limit the number of filtrations. In addition, there is no data to support that the procedure was adequately validated.

Batch Production Record (BPR) 40-06, "Additional Precautionary Sterile Filtration for Fraction V, IGIV and Placebo Bulks," does not currently limit the number of times a product may be filtered. Rather, it instructs manufacturing personnel how to perform the refiltration process. To prevent possible contamination of bulk product when a potential breach of integrity is recognized, personnel must perform the refiltration within the time limit specified in the BPR. The BPR also delegates to Quality Assurance (QA) ultimate oversight for determining batch eligibility for refiltration.

Bayer has drafted a new standard operating procedure that specifies the number of times a product may be filtered and establishes a method to track refiltered lots. The validation data collected to date supports the conclusion that refiltration does not affect the safety, quality, purity, and efficacy of product, and additional data on refiltration continues to be collected and validated. The procedure has not been implemented, however, due to questions raised in the May 22, 2001 approval letter for an Alpha-1 Proteinase Inhibitor (Human) rework supplement (STN BL103174/1068). The issue of refiltration will be discussed in the September 13, 2001 meeting between CBER and Bayer. Once the new standard operating procedure is approved, BPR 40-06 will be revised to specify the number of times product may be filtered.

Bayer has revised its BPRs to track product that has been refiltered. Specifically, BPR 24-56, "Precautionary Sterile Filtration of Alpha-1 Bulk," and BPR 40-06 were revised to require that a Discrepancy Event Report (DER) be issued for any bulk refiltered more than once, and to require collection of microbial load and LAL samples prior to each refiltration. No product is filtered more times than is supported by the validation data. Further, no product that has been refiltered more than once is released, pending the September 13, 2001 meeting between CBER and Bayer.