

**Pharmaceutical
Division**

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September 20, 2002

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

**Re: Comments – FDA Guidance for Industry – Handling and Retention of BA and
BE Testing Samples (Docket No. 02D – 0350)**

The Bayer Corporation Pharmaceutical Division would like to take this opportunity to provide the attached comments on FDA Guidance for Industry – Handling and Retention of BA and BE Testing Samples.

If there are any questions regarding this submission please feel free to contact me at (203) 812-2681.

Sincerely,



Frederich K. Sundermann
Deputy Director – Regulatory Affairs

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OAD-0350

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Bayer would like to comment on the Draft Guidance for Industry “Handling and Retention of BA and BE Testing Samples”.

We are aware that some of the comments do not only address the draft guidance, but primarily the final rule on which the draft guidance is based, and that the FDA might not have flexibility in applying the rule to address all of our comments. Nevertheless, we would like to use our response as an opportunity to express our position.

As explained in section II. of the draft guidance the rule was issued in response to the generic drug scandal in the 1980s, mainly to deter possible bias and fraud in BA and BE testing by sponsors and/or (generic) drug manufacturers. Bayer’s position is that the rule need not be extended to apply to new drug manufacturers. The scope of the guideline should be limited to BA and BE testing for generic drug applications, and should exclude BA and BE testing for new drugs under NDAs and NDA supplements.

BA/BE studies during new drug development are conducted to show comparability of the medication used in the clinical trials at the different phases of development. These studies are not necessarily contracted to CROs, but frequently performed in facilities owned and managed by the drug manufacturer as sponsor. The rule, and consequently the draft guidance, do not seem to sufficiently accommodate such a situation, in particular for cases where the manufacturer maintains a quality assurance system that allows for reserve samples to be randomly sampled, and for keeping them in a location with controlled access. To exclude any potential bias, sampling and reserve sample storage are usually performed under the responsibility of the GMP quality control unit.

Bayer feels that manufacturers who maintain such a system during new drug development should be allowed to use their GMP quality control unit to sample and keep reserve samples for in-house BA/BE studies, and also for studies contracted to a CRO. This should include separating out the reserve samples of the test article and reference standard before sending the material to the in-house or the CRO’s testing facility. Using the sampling techniques per section III. of the draft guidance results in the same samples, independent of the location of sampling.

Use of a manufacturer’s retention sample storage area should be generally permitted for storage of BA/BE reserve samples, as long as the area is under the control of the GMP quality control unit, and as long as access is controlled.

We do not understand why an alternative use of the manufacturer’s independent GMP quality control unit for sampling and keeping of retention samples is not possible, though the GMP quality control unit is generally trusted to be independent and non-biased when performing similar tasks under GMP.

The text in section IV.D.:

“The in-house clinical research unit should operate as an independent unit for the purposes of sample retention. All matters (e.g., manufacturing, purchasing, packaging, transfer records) concerning the test article and reference standard should be clearly documented and available to FDA investigators during an inspection. Standard procedures concerning security and accountability of the test article and reference standard for each study should be established to eliminate the possibility of sample substitution. To preclude any potential appearance of possible substitution, it would be prudent for study sponsors and/or drug manufacturers to remove themselves from reserve sample selection and retention. It is recommended that the firm engage a third party for retention of reserve samples.”

should be changed to:

“The in-house clinical research unit, or the in-house GMP quality control unit, should operate as an independent unit for the purposes of sample retention. All matters (e.g., manufacturing, purchasing, packaging, transfer records) concerning the test article and reference standard should be clearly documented and available to FDA investigators during an inspection. Standard procedures concerning security and accountability of the test article and reference standard for each study should be established to eliminate the possibility of sample substitution. To preclude any potential appearance of possible substitution, it would be prudent for study sponsors and/or drug manufacturers to remove themselves from reserve sample selection and retention by engaging (a) an in-house clinical research unit, or (b) an in-house GMP quality control unit, or (c) an independent external third party, including a CRO, for retention of reserve samples.”

Either of those units should be considered non-biased. In addition, either unit should be allowed to separate out the reserve samples of the test article and reference standard before sending the drug product to the testing facility. Using the sampling techniques per section III. of the draft guidance should result in representative samples, independent of the location of sampling.

Use of a manufacturer’s retention sample storage area should be generally permitted for storage of BA/BE reserve samples, as long as the area is under the control of an in-house clinical research unit or an in-house GMP quality control unit, and as long as access is controlled.”

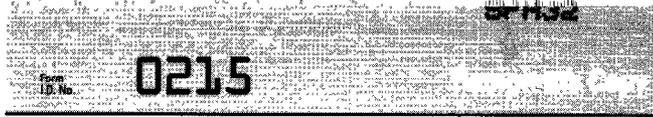
It is Bayer’s position that the draft guidance introduces standards for BA/BE studies that contradict standards used to regulate analogous processes under GMP. New standards to reduce the potential appearance of possible substitution are unnecessary, as long as study sponsors and/or drug manufacturers can remove themselves from the reserve sample selection and retention process by following the procedures that we propose above.

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