May 18, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-FDA-2014-D-1525]

Re: “Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved BLA”

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on the Food and Drug Administration’s withdrawal of a proposed rule and publication of a new proposed rule entitled “Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application” as part of the agency’s ongoing implementation of §503A and 503B of the Food, Drug and Cosmetic Act. As FDA considers the implementation of this draft guidance, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to share our perspectives and to work with FDA in the future on this very important issue.

IACP is an association representing more than 4,000 pharmacists, technicians, students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians, to create customized medication solutions for patients and animals whose healthcare needs cannot be met by manufactured medications.
ISSUE:  Beyond-Use-Date (BUD) Guidance is Overly Restrictive

Proposed Guidance Document Lines 327-335

327  a. If the biological product is mixed, diluted, or repackaged by a state-licensed
328  pharmacy or a Federal facility, it is given a BUD that
329  - is not longer than 4 hours, or is equal to the time within which the opened product
330  - is to be used as specified in the approved labelling, whichever is shorter; or
331  - is up to 24 hours if microbial challenge studies performed on the formulation of
332  the diluted, mixed, or repackaged biological product in the type of container in
333  which it will be packaged demonstrate that microbial growth will not progress to
334  an unacceptable level within the period of the BUD. (See Appendix 1 for a
335  description of microbial challenge study design.)

Comments

Although the agency cites in footnote 17 that the quoted four (4) hour BUD timeframe is
consistent with the labeling of “many” biological products, we note three areas of disconnect.
First, there are biological products which provide for a longer BUD once the original vial is
opened. Second, the agency provides for an extended BUD of 24 hours based upon the
completion of a microbial challenge study that demonstrates sterility. Third, while repackaging
of biologicals by non-outsourcing facilities must comply with techniques and standards within
USP <797>, the FDA has chosen to override the scientific methodology and incorporation-by-
reference general chapters that provide for the evaluation of BUDs through testing and
validation.

IACP strongly opposes this arbitrary assignment of BUDs.

It appears that the FDA has chosen to ignore reasonable possible BUDs that may be longer than
4 hours even when they are supported by approved package labeling (e.g., the “many” versus
“all”). At a minimum, this section should be revised to provide for a minimum BUD based upon
the package labeling rather than a “lowest floor” limitation of 4 hours.

Additionally, a microbial challenge test as outlined in Appendix 1 may support a BUD of greater
than 24-hours. This section should be revised to provide for a maximum BUD that is shown to
be valid through such a test that exceeds the “lower floor” limitation of 24 hours that the agency
has proposed. Other tests provided for within USP General Chapter <797> outline the means by
which a longer justified BUD may be achieved through testing. Most notably USP <71>,
referenced within <797>, specifically provides for means by which additional testing for
potency and sterility may support longer BUDs of sterile medications.
In other words, USP <797> upon which FDA is drawing in some areas of this guidance is ignored in others, especially in the setting of a longer BUD justified with scientific documentation and testing as outlined in USP General Chapter <71>. USP <797> addresses the compounding of medium or high risk sterile preparations that have inherently more risk than repackaging a medium risk preparation; yet, USP <797> allows BUDs to be extended under certain circumstances for those compounded preparations. That should also be the case for biologicals.

**ISSUE: Provision of FDA Approved Package Inserts by 503B Outsourcing Facilities**

*Proposed Guidance Document Lines 418-420*

418 c. Each mixed, diluted, or repackaged biological product is also accompanied by a copy of the prescribing information that accompanied the original FDA-licensed biological product that was mixed, diluted, or repackaged.

*Proposed Guidance Document Lines 520-521*

520 c. Each prescription set also is accompanied by instructions for use and the FDA approved package insert for each allergenic extract.

**Comments**

IACP notes that the agency in this guidance document as well as in the guidance document for repackaging by outsourcing facilities of non-biological drug products is requiring that these entities provide copies of the FDA approved package insert. Although §503B(a)(10)(c) provides for the Secretary to impose additional labeling requirements through regulation, we are not aware of any formal regulatory promulgation which would mandate the inclusion of package inserts by outsourcing facilities.

We are also concerned that since package inserts created by manufacturers in collaboration with the FDA contain trademarked references to the manufacturer’s brand names and other proprietary information; such a requirement may necessitate some sort of formal agreement between the manufacturer of the biologic and the outsourcing facility. What consideration has been given to an instance where a biologic manufacturer declines to provide permission to what could be construed to be a competitor in the marketplace for reproduction of the package insert and other approved labeling? What potential liability might the manufacturer incur when an outsourcing facilities repackaging of its biological, when accompanied by the manufacturer’s package insert with the product’s brand name included, may give rise to an inference by practitioners or consumers that the repackaged biological is “the manufacturers”?

IACP has seen no other guidance or information provided to outsourcing facilities on the use of package inserts and we believe that this requirement is premature and has unintended ramifications.
Recommendations

IACP recommends that lines 418-420 and lines 520-521 requiring copies of package inserts be removed from the final guidance document.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

David G. Miller, R.Ph.
Executive Vice President & CEO