The New FDA Draft Guidance for Biocompatibility: What You Need to Know

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In a draft guidance document, FDA has placed its summary of ideas regarding biocompatibility and possible changes that could eventually replace FDA G-95 Blue Book Memorandum #G95-1 on biocompatibility.

The draft document has been out since April and is widely available, though it has not been formally released. In fact, there is a lot of buzz about the document, but many people are having a difficult time interpreting what is different, what has changed, and what kind of impact it will have moving forward. The document is only a draft, but it does give insight on what FDA is thinking.

Nelson Labs [1] has broken down the document into three categories:

- Summary of Ideas—A summary of ideas FDA has expressed for a few years, but for the first time has written in the form of guidance.

- Justification Ideas—FDA spells out general ideas of how to justify your biocompatibility choices. FDA has never done that before.
- Possible Impacts—Shows possible impacts that we have never seen before regarding biocompatibility.

The following outlines some of the key items listed in the guidance document:

Summary of Ideas

- Full test reports need to be provided to FDA for submissions.
- Additional testing for target organ (neurotoxicity) is required for organ intended devices.
- Possible device failure options should be considered in the testing.
- For prolonged contact devices, extraction should be performed at 50°C unless sample chemical changes about 37°C.
- No manipulation of extracts (e.g., filtering or centrifuging).

Justification Ideas

- Can weigh benefit of the device to any potential risk associated (failure justification).
- Reviewers are encouraged to apply “scientific judgment” when reviewing alternative data from animal tests.
- Literature can be used to justify out of systemic toxicity tests, but the correct data has to be used for the corresponding endpoint.
- Biocompatibility testing and/or adequate chemical characterization in conjunction with supplementary biocompatibility testing may be acceptable to minimize animal testing.
- If the intended use, physical form, formulation, processing, component interaction, and storage conditions were the same as a predictive sample that no limited testing would be required.
- Functionality test can be designed to look for some of the endpoints of the biocompatibility testing to help reduce animal testing.

Possible Impacts

- With devices that have multiple types of exposure, you should consider testing from both categories for your device. For example, gas path contact devices such as anesthesia machine as some contact with the skin or lays across the skin, but other parts have the gas that goes into the body. Multiple exposures need to be tested for both exposures of the device. The tests used to be combined into one, but now, both will need to be performed.
- Devices that include components with different lengths of contact (e.g., implant and its delivery system), conduct extraction tests on the components separately. Extractions should be done separately for devices

that have components with different lengths of contact in the delivery system such as with an implant versus a delivery device. For example, with an IV port, the device placing the needle is a short contact, but the IV port may stay in contact for several days.

- Implants, devices in contact with cardiovascular, lymphatic, or cerebrospinal fluid, or labeled as “non-pyrogenic” need to perform the LAL tests along with rabbit pyrogen. (The comma after the implant suggests that all implants, regardless of contact, might require LAL testing.) Right now, not all implants need this test, but the comma suggests all implants regardless of length of contact. This could have a huge impact on items such as orthopedic implants. This will increase LAL testing substantially. (Confirmation is being sought from the FDA to ensure they meant to use the comma where it says, “…implants, as well as sterile devices and contact….”)
- Mouse Lymphoma test is preferred over chromosomal aberration since it detects the broadest set of genotoxic mechanisms associates with the cardiogenic activity. Currently, FDA requires an AIMS test with either the mouse lymphoma or the chromosome aberration test. The new document says the same thing, but that mouse infoma is preferred since it detects the broadest set of genotoxic mechanisms associated with Carson genic activity.
- The new version of the chart is identical as the G95 version except the optional tests used to have an associated comment, “additional tests which may be applicable,” which has been changed to, “these additional tests should be addressed in the submission, either by inclusion of the testing or a rational for its omission.

As mentioned above, the formal document has not yet been formally released. It does give clear understanding of FDA’s thinking regarding biocompatibility and the items medical device manufacturers should be considering as they move forward.

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[1] http://www.nelsonlabs.com/