Clinical Chemistry

US Food and Drug Administration Perspectives on Clinical Mass Spectrometry

Article:
Julia Lathrop et al.
US Food and Drug Administration Perspectives on Clinical Mass Spectrometry.
Clin Chem 2015;62:41-47.
http://www.clinchem.org/content/62/1/41.abstract

Guests: Dr. Julia Lathrop and Dr. Doug Jeffery are Scientific Reviewers in the Division of Immunology and Hematology in the office of In Vitro Diagnostics and Radiological Health in the Center for Diagnostics and Radiological Health at the U.S. FDA.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Applications of mass spectrometry have revolutionized analysis of the human proteome and dramatically improved clinical assay throughput and precision. The U.S. Food and Drug Administration has cleared and approved mass spec-based devices as diagnostic tests for screening newborns, for identifying microbes, and for measuring the concentration of therapeutic drugs.

However, there are no such FDA-approved devices for measuring proteins and peptides in clinical samples. The factors that contribute to this situation and the FDA's experience in regulating mass spec-based devices are reviewed in a paper in the January 2016 issue of *Clinical Chemistry,* a special issue devoted to mass spectrometry and the clinical laboratory.

Two of the authors of that paper join us in this podcast. Dr. Julia Tait Lathrop is a Senior Scientific Reviewer in the Division of Immunology and Hematology in the Office of In Vitro Diagnostics and Radiological Health in the Center for Diagnostics and Radiological Health at the FDA.

She is joined by Dr. Doug Jeffery, also a Scientific Reviewer in the Division of Immunology and Hematology in the Center for Diagnostics and Radiological Health at the FDA.

And we will start with Dr. Lathrop, just why did the FDA want you to write this paper?

Dr. Julia Tait Lathrop: So we are in the Center for Devices and Radiological Health (CDRH) at FDA, which regulates in vitro diagnostic tests, in addition to more conventional devices. And we have been involved in mass spec for

quite some time, the first GC-MS clearance was in 2002.

And one of the missions of the FDA is promoting public health, and doing so by reaching out to the various stakeholders and people who are involved in different disciplines, and letting them know how we work, how we look at devices, the regulatory standards that we apply, how we work with all that.

And so when we saw this clinical mass spec special issue, we thought this would be an ideal opportunity to pull all these disparate outreach efforts that we had had and some of the other information that can be found in multiple places, and put it in one place for the community to have a reference to know where to look and give the background.

Bob Barrett: Dr. Jeffery, talk about the regulatory pathway for liquid chromatography tandem-mass spectrometry devices. How are submissions to the FDA reviewed?

Dr. Doug Jeffery: So submissions to the FDA are reviewed the same way irrespective of the technology that's being used. So I think that's the first important point to make, is that, in our view in many ways an LC-MS device is no different from any other device that uses a different technology to measure proteins, for instance, an immunoassay or an immunohistochemistry assay.

There are several types of submissions that can be made. They fall into two general classes. The first is a submission, which we call presubmission, which I think we will talk about later on in the podcast, where a manufacturer is asking for feedback to specific questions, sort of an opportunity to get feedback about a device before making a premarket submission.

So the second type of submission I think is worth talking a little bit more in detail, and that's a premarket notification or premarket application, where a manufacturer has developed a device and performed all of the analytical performance testing and clinical performance testing that is required by the FDA to review. And the idea behind the premarket notification or premarket application is that the manufacturer is asking for the FDA to clear or approve a device so that it can be marketed in the United States.

So when these submissions come in as either a 510(k) or PMA, they contain the analytical

performance and clinical performance testing data that the manufacturer has performed.

The lead reviewer will assemble a team of experts, including experts in statistics, as well as medical experts who understand the disease area being addressed, and we will evaluate the data that has been submitted by the manufacturer, and provide feedback then to the manufacturer as to whether the data are appropriate or not for premarket clearance or approval.

Bob Barrett: So doctor, how does a device developer start communicating with FDA about a new submission? What information is out there to help device developers get started?

Dr. Doug Jeffery: There are two ways to interact and to communicate with the FDA. One is more of a sort of passive mode, where there is a lot of information out there on the FDA website. And then there is a more active, direct communication with the FDA.

So the information that's out there on the FDA website includes a lot of information about guidance documents and many of these are referenced in the paper that we have published in *Clinical Chemistry*, and these documents range from very general guidance about how to write a submission with the information that's required in the submission, to very specific information about specific devices and specific analytes.

So there are guidance documents, for instance, about CRP, as an example, and then the requirements for the device which is used to measure that protein. So I would recommend that device manufacturers go to the FDA website, particularly the CDRH website, and look at what the guidance documents are that are available.

The second way is a direct communication with the FDA, and this is through a process which is called the presubmission process. And this is a very good way for manufacturers to get specific information, specific feedback, about the device that they would like to submit for premarket approval or clearance.

And in this process the device manufacturer submits an actual submission--it's free, to submit it to the CDRH--and this includes information about the device, what it does, how it works, the technology behind it, as well as information about what it's

intended to be used for, what patients is it meant to be tested in, and what the outcome of the test is meant to tell the physician or the patient.

And then the device manufacturer can ask really any question about their devices: what does the FDA think about the intended use population, what does the FDA think about the proposed analytical performance testing, the proposed clinical performance testing? And FDA will provide feedback to these questions, essentially answers to these questions, which will help guide the device manufacturer to help develop the device.

And the idea behind the presubmission process is that by asking the FDA questions about study design and the type of device that's being developed, the manufacturer can tailor their studies, the experiments and the studies that they do around this device, to fit the feedback that the FDA has provided. And that way when the actual submission is made in the form of 510(k) or PMA, the FDA is already aware of the device and has provided feedback such that the data and the studies that are provided as part of that submission will be more in line with what the FDA is expecting.

And so the idea is that it expedites the review of the actual submission and hopefully makes the process more straightforward for both the FDA and the manufacturer.

Bob Barrett: Okay. And finally, Dr. Lathrop, what else is the FDA doing to communicate with the clinical LC-MS community?

Dr. Julia Tait Lathrop: So we encourage people to contact us. Our contact info, phone, emails are all publicly available and also included in the paper in *Clinical Chemistry*.

We are also hoping to have a public meeting in the spring where we can talk about some of the analytical validation requirements that are going to be needed for protein and peptide mass spec devices.

The FDA really hasn't seen any of these come in, and we want to make sure that we and the community are on the same page in terms of what the regulatory standard for review are going to be. So we are very actively interested in looking for feedback from the stakeholders, be it academics who are at early stage, be it manufacturers, instrument vendors,

from all the different parts of the community, to interact with us and give us feedback so we can develop regulatory standards for these devices.

We also encourage people just to come and talk to us. We can set up meetings where they can talk to the various people in FDA that would be involved, or informal communications, just touching base with us to see what we are thinking about various issues that they might have.

We are really actively pushing forward with this initiative to bring more of these protein and peptide, especially LC-MS devices, into the clinic and see how we from our side can help to accomplish that.

Bob Barrett: That was Dr. Julia Lathrop. She was joined by her colleague Dr. Doug Jeffery. They are both Scientific Reviewers in the Division of Immunology and Hematology in the office of In Vitro Diagnostics and Radiological Health in the Center for Diagnostics and Radiological Health at the U.S. Food and Drug Administration.

They have been our guests in this podcast from *Clinical Chemistry* on FDA perspectives on clinical mass spectrometry. Their paper appeared in the January 2016 issue of *Clinical Chemistry*; a special issue devoted to mass spectrometry and the clinical laboratory.

I am Bob Barrett. Thanks for listening!