

Welcome (FDA): Steven Galson MD

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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Highlights

- **FOREIGN REGULATORY AUTHORITIES PRESENT:** Special guests included “representatives from the drug regulatory authorities of the member countries of the European Union and six separate countries--Canada, Japan, Singapore, Australia, Switzerland and Mexico”.
- **ANXIOUS TO HEAR ALL POINTS OF VIEW:** “I want to emphasize that we are anxious to hear all points of views from the advisory committee and, of course, from agency staff. It goes without saying that all FDA staff are free to make any presentation without fear of any retaliation.”
- **COMMITTEE MEMBERS SCREENED FOR CONFLICT OF INTEREST:** “I want to remind the public that all members of this committee have been carefully screened for conflicts of interest and we have used the same standards in this process that we have used for other committees and similar meetings.”
- **CHANGING INFORMATION ENVIRONMENT:** “You will be assessing the risk/benefit balance of these products this week in the midst of a changing information environment.....”. “We are aware of at least a half dozen ongoing meta-analyses and huge population-based studies, in addition to several of the studies you will hear about this week for which data analysis continues as we speak.”
- **CAUTION IN INTERPRETING PRELIMINARY, NON-PEER-REVIEWED DATA:** “We must be very cautious about interpreting data for regulatory decision-making that has not been thoroughly vetted and peer reviewed, and even more cautious about interpreting data of preliminary studies that are not even complete.” “As scientists, we have all seen examples of ongoing studies whose findings have changed as analysis is in the final stages, or examples where inadvertent errors have led to misclassification in epidemiologic studies, or when data that comes in at the end of the data gathering stage influences results.”

Presentation Text

Thank you. I want to welcome everyone and thanks in particular to our Chair, Dr. Alastair Wood, committee members, special guests, members of the public and FDA staff who have really done a tremendous job in putting together a particularly and unusually complex meeting.

We have some special guests today that I want to point out. We have representatives from the drug regulatory authorities of the member countries of the European Union and six separate countries--Canada, Japan, Singapore, Australia, Switzerland and Mexico, and I really want to welcome them. Thank you for being with us. We also have several guests from congressional staff offices and we are very pleased that they are with us as well to learn about this important issue.

There is really an unprecedented level of international attention to one of our advisory committees today, and we are very proud that this is taking place and we think it represents a new level of collaboration and discussion around the world about an emerging public health issue.

Many millions of people all over the world are taking the products that we are discussing. Indeed, they depend on them for a range of conditions from the mild to the severe and life-threatening. We must keep the interests and health of these patients front and center in these deliberations.

I wouldn't be complete in this introduction if I didn't acknowledge the controversy surrounding these products, particularly over the last year. I want to emphasize that we are anxious to hear all points of views from the advisory committee and, of course, from agency staff. It goes without saying that all FDA staff are free to make any presentation without fear of any retaliation. I don't want anyone sitting around this table to be shy.

Also, we look forward to hearing a wide range of views from the more than 50 members of the public who are going to be making brief statements later in the meeting. I want to remind the public that all members of this committee have been carefully screened for conflicts of interest and we have used the same standards in this process that we have used for other committees and similar meetings.

A few comments about the challenging risk/benefit balance that the agency must achieve in making its regulatory decisions: Although you have all heard strong opinions in the media and medical literature about safety issues related to the drugs we are discussing, our job and, indeed, your job is to assess any safety concerns when balanced by the benefit of these products. We cannot lose sight of the reduced morbidity, pain and suffering achieved by the products that are under discussion and the real impact on people that changes in the regulatory status may entail.

You will be assessing the risk/benefit balance of these products this week in the midst of a changing information environment and this represents a particular challenge. We are aware of at least a half dozen ongoing meta-analyses and huge population-based studies, in addition to several of the studies you will hear about this week for which data analysis continues as we speak.

Although we have a full three days, the time really isn't long enough to hear details about every single ongoing, or incomplete, or un-reviewed study of which we are aware. Leaving them out of the agenda has absolutely nothing to do with wanting to keep information from you and everything to do with allowing you to focus so that you have time to get to our critical advisory questions.

We must be very cautious about interpreting data for regulatory decision-making that has not been thoroughly vetted and peer reviewed, and even more cautious about interpreting data of preliminary studies that are not even complete. You will be hearing about some data in these categories and I would remind you to exercise caution in their interpretation.

As scientists, we have all seen examples of ongoing studies whose findings have changed as analysis is in the final stages, or examples where inadvertent errors have led to misclassification in epidemiologic studies, or when data that comes in at the end of the data gathering stage influences results.

In today's 24-hour news environment, it is difficult to not react to these incomplete reports but we must go back

to the basics of relying on sound science and use the peer review system to strengthen findings before utilizing them to make regulatory decisions.

Lastly on the risk/benefit balance, as you members know but it is sometimes difficult for us to convey to the public, our job at FDA and your job in the advisory group is to balance risks and benefits on a population basis for the nation as a whole. This is very different from the risk/benefit assessment physicians do with individual patients where specific risks of the medications, family history, a patient's risk tolerance and other factors must be taken into consideration.

A drug may, based on the weight of evidence, have a positive benefit/risk balance the population leading to approval, yet, cause grievous harm in a specific subset of individuals. We say over and over again that all drugs have risks, but when a person you know suffers an adverse event the faulty assumption is sometimes made that we must have made a mistake in the approval.

I would also like to mention an unusual feature of many of the data from the trials you will be hearing over the next few days. The data on safety of these drugs is, as I have mentioned, unusually complex and represents the fact that clinical trial methodology to look at cardiovascular effects as adverse events has changed dramatically. When discussions began about cardiovascular safety of NSAIDs there was no standard methodology by which cardiovascular adverse events were confirmed or categorized. Analyses vary by trial. Confirmatory processes vary by trial.

Only after the VIGOR trial did the methods of establishing confirmatory processes and standardization become better established. <??>course, in population-based cohorts and case control studies case reporting and confirmation is both rudimentary and completely inconsistent between studies.

In addition, as you know already, unlike drugs designed to treat cardiovascular disease, these trials have not been designed to do a full cardiovascular assessment. So, major pieces of information that you might like to have are simply not available. So, in many ways we are forced to compare apples to oranges in these trials and studies, and when you are not doing that you are trying to draw conclusions based on insufficient information, making your task even harder.

In spite of all the ambiguity, work in progress, changing standards and questions, we ask you for the miraculous job of crystal clarity in your responses to our questions. We know this is tough on such challenging scientific and controversial issues, and we are enormously grateful to you because we know that you all are up to this challenge.

The agency will act within the next few weeks to act on the recommendations you communicate to us over the next few days.

I would like to quickly go to the agenda. Today through midday tomorrow you will hear from sponsor companies, FDA staff and NIH researchers about data on both approved and unapproved COX-2 selective and non-selective products. Tomorrow afternoon we have 54

members of the public registered to speak. On Friday you will hear about important methodological issues in interpretation of these studies, and then we will move on to the questions.

Again, thank you and on behalf of the FDA I wish you the very best of luck on this important endeavor. Thanks, Dr. Wood.