W:PEARS (discussion)

DR. SZARFMAN: My name is Ana Szarfman from FDA. Sorry that I missed many discussions, but I am thinking about even more mundane things that we may need to take into account. For example, congestive heart failure as a risk factor. We may need to allocate time and resources to study the hepatotoxic effect of drug-disease interactions.

DR. PEARS: Thank you very much. Thank you for your comments but I guess we didn't discuss it. I don't know if you were here in the session this morning. I apologize but we didn't discuss patients with congestive heart failure today as being a specific case, but I think we did come up yesterday as being a specific case where the feeling was there was lack of reserve in the liver should they get drug-induced liver injury, and I think that is recognized.

DR. SZARFMAN: Maybe we will arrive at the conclusion that we need to reduce the dosage in those patients.

DR. SENIOR: I think Ana is quite right here. The comment made yesterday by Jim Freston, who I think mentioned it, that congestive failure, particularly in very elderly people, may be a considerable risk factor that has to be considered when you give the drug, that may cause toxicity.

DR. AVIGAN: Right. I would actually also like to

say, Ana, that's an excellent point and beyond reserve questions, the liver -- the hepatocyte gradient across the globule from the very plural to the central globular zones, actually those cells differentiate and make sort of different combinations of metabolizing enzymes, and so when you change the -- with congestive heart failure, ischemia, et cetera --, that gradient of cells and the enzymatic potential of capacity across the gradient change, it may be actually be the basis for changing metabolism dose requirements that's not a reflection of the loss of reserve hepatocyte. That's a very important point.

And drug-drug interactions is another, and we at the FDA, when we see cases which are confounded by heart failure of the DILI, we sometimes are wondering whether there's a dynamic interaction between the two things.

The only thing I wanted to add to what John said was about the biomarkers, was a plea for a systemic collection of samples because I think that that's a very concrete conclusion that the industry could make, that they will systematically collect pharmacogenomic or metabonomic serum samples from all patients and studies prospectively before they know what they got but they will have both controls as well as active treatment groups.

DR. PEARS: All right. I took that as being explicit in the Guidance anyway. We kind of accepted it but thanks for

emphasizing it again.

DR. VIERLING: John Vierling. I think you've already emphasized the point that whether we know it or not, we're enrolling into trials larger-than-recognized numbers of patients with liver dysfunction, based on of the fact that the normal upper limit of ALT has been expanded on the basis of body weight and nonalcoholic fatty liver disease.

It would seem therefore that for any given trial, the risk of pre-existing liver disease in the target population for the use of a drug can be better defined by applying the demographic date from the CDC regarding the expected frequency of liver diseases within that particular population. For example, if you had a drug that might be disproportionately used in Asians, there would be a much greater representation of chronic hepatitis B than in the general U.S. population. Similarly, if a drug were to used primarily in late middle age, the aging cohort of the population with hepatitis C in the United States, would be disproportionately likely to be included in the drug trial.

One could try to identify patients with pre-existing liver diseases by using serologic testing for both hepatitis B and C, when target populations would have the demographic characteristics of the most infected subgroups, and to assess for the risk of non-alcoholic fatty liver disease by assessing the diagnostic criteria of metabolic syndrome or calculating a

HOMA score. Perhaps a high BMI alone would be enough to be concerned about non-alcoholic fatty liver disease. Individual who develop evidence of DILI, should be assessed to determine if they have characteristics of one of those populations so that more specific testing can be done to clarify the role of drugs, compared to an underlying liver disease, in the injury.

DR. PEARS: That's a very useful idea. Thank you very much.

DR. SENIOR: It looks like we are coming to the end. The hard-core audience is still here. I want to remind all the speakers, all of whom were asked to submit references with their presentations, if they mentioned references during their presentation or in this discussion, please send us those citations directly, so that we can get the pdf files and post them on the website so you can all see them.

Now I also want to say that Diane has prepared a list of all the registrants with their e-mail addresses, so that we can get in touch with each other if we have questions for each other.

So with that, I want to thank our three superb moderators with a lusty round of applause. (Applause.)

(Whereupon, at 4:00 p.m., the meeting concluded.)