Okay. Well, I was assigned the task of talking about this is all John's fault, I assume limits of labeling and warnings. So, I am not really going to be talking about most of the stuff we have been talking about. I am going to try to talk about what we do when we get certain information. And I am going to do it in several cases, just to lay out what we generally do. But, as I went through this, I realized that, although we know which drugs have been rejected because of liver toxicity, which drugs have been withdrawn because of liver toxicity, I am not sure what we have done with all the ones where there is a little suggestion of toxicity and we thought there was some problem, and I can't tell you whether we are enthusiastic about monitoring all the time or what we say, because I don't think we have taken a systematic look. But I looked at a few of them. So, I will tell you what I looked at.
This is in part how we apply risk/benefit considerations to evidence of liver injury. So, take the first and, if you like, clearest case. This is going to be mostly about what labeling would say regarding liver injury and monitoring, but that depends on what the drug is for, what the alternatives are, and the nature of the injury.

So, take Case 1. You have clear Hy’s Law cases, say at least two. We have done this sometimes when there was only one, I have to admit. Or, in the post-marketing period we found unequivocal severe hepatic injury. We may have missed it during the pre-marketing period or we didn't interpret it right, or whatever. And there is plenty of available therapy, either pharmacologically similar, which is sort of easy, or even mechanistically distinct, and just no documented advantage over alternatives. That doesn't mean a new method of working couldn't prove to have an advantage, but at least at the moment it hasn't.

I would say the regulatory conclusion, if we recognize a Hy's Law case, is invariably non-approval. That is what we did with ximelagatran and lumiracoxib and dilevalol. I always like to mention those because they were all approved in Europe and subsequently withdrawn for hepatotoxicity. So, without being smug, I am just taking note of that. (Laughter.)

Two very similar cases were the withdrawal of bromfenac and troglitazone, which conceivably could have been rejected in the first place on the basis of Hy's Law cases.
that were, in fact, present and abundant evidence of transaminitis. What we tried to do with bromfenac was to limit it to short-term use, because most of the cases of problems occurred after a while. In retrospect, that was an implausible thing to do for a nonsteroidal anti-inflammatory drug, which is plainly intended for long-term use.

And troglitazone, interestingly, was left on the market after its hepatotoxicity was unequivocally discovered, with a request for monitoring which plainly failed, because it was a unique anti-diabetic drug. There was nothing similar to it. So, we withdrew it only after we watched the two follow-on drugs, ROSI and pioglitazone, and satisfied ourselves that they were not hepatotoxic, which took about six to nine months. We had a working group that met every month or few weeks to see if they looked clean, and then, we yanked it.

Probably, if I had been signing off on those, I wouldn't have signed them because of the Hy's Law. But, anyway, we have it now, and it is quite clear that, if the drug has no advantage and has Hy's Law cases, it's gone. Sometimes that would be true even for drugs that had attractive characteristics. I recall ticrynafen, for which I was responsible party for approving it. We didn't know that it was hepatotoxic before we marketed it, and it was a very attractive drug, a uricosuric diuretic at a time when one-third of the gout in this country was due to use of diuretics. So, that was not trivial. Of course, that is because we overdosed the diuretics.

It is worth mentioning that in some cases like this where drugs were oh, I should say what our expectation is, that if you see a couple of cases in a database of 1,000 people, you are expecting, roughly, 1 in 10,000 or more. This is what Hy would have predicted, 1 in 10,000 deaths or nowadays transplants. Bad enough. Severe liver injury that is life-threatening.

But we have approved other drugs with problems. We approved clozapine with a 1.5 percent rate of agranulocytosis. And how many deaths that causes depends on what you think the survival rate was going to be. We used to think that agran led to about a 10-percent mortality. That hasn't been true with clozapine, but maybe 1 percent. That is in the same neighborhood as 1 in 10,000. But it was approved because they showed that it worked in people who had failed therapy with other drugs. And if you have a drug that treats psychotics who can't respond to any other drug, that is a big deal.

Similarly, a calcium channel blocker called bepridil, which is a clear QT prolonger. And there are torsade de pointes deaths reported every single year. It remained on the market because they did a study that showed that in non-responders to diltiazem randomized back to diltiazem and bepridil, bepridil was the more effective antianginal drug. So, if you can show some spectacular benefit, you might be able to overcome even Hy's Law cases. And in terrible diseases, oncologic diseases and things like that,
we tolerate all kinds of things.
Cases (cont)

2. Clear Hy's Law cases, but drug has worthwhile advantages over alternatives.

Drug could be approved or remain marketed with label urging monitoring (isoniazid) or required monitoring/REMS (bosentan) but the monitoring needs to be realistic. E.g., for a serious lifelong illness like pulmonary hypertension, monitoring is feasible/credible and we have seen few fatal outcomes with bosentan. Monitoring, however, did not alter outcomes at least not enough) with troglitazone, either because
- it wasn't done
- it doesn't work (deterioration too rapid)

Now let's say there clearly are Hy's Law cases, but the drug has worthwhile advantages that is sort of what I was talking about over alternatives. The drug could be approved or remain marketed with labeling urging monitoring. That is true for isoniazid. And we believe that monitoring reduces the risk of severe liver injury or required monitoring and REMS. And that is what we did with bosentan, which was the first drug available that was effective for pulmonary hypertension. But the monitoring needs to be realistic. For a serious lifelong illness like pulmonary hypertension, where people come to the doctor every couple of months and stuff like that, maybe monitoring is credible.

It also appears, for reasons that I don't think we know the full answer to, that monitoring seems to limit the likelihood of severe liver injury, because we have seen very few cases of fatal liver injury with bosentan or transplants. I don't know how many, but not many. On the other hand, the call for monitoring didn't seem to do a thing with troglitazone, either because it wasn't done or because it doesn't work. I think probably it is a little of each, but you can go downhill very fast.
So, when we would call for monitoring or ask for monitoring, and things like that, it is not terribly well-established. One of the things that I think would be worth considering is, when might monitoring work? Are the signals of hepatotoxicity different? Is it the steepness of the curve or whether it continues to occur after you withdraw the drug? I mean, I don't know. I have no answer to this. But you would like to know how to distinguish the troglitazone case from the bosentan case, in case you did want to make a drug available with monitoring.

So, the experience to date is not so easy to know. Troglitazone monitoring didn't work at all. Bromfenac monitoring, which they were supposed to do, didn't seem to work. Isoniazid, as I said, seems to work at least some, and bosentan seems to work very, very well. You seem to be able to monitor... your way around it.

So, if there was a way to anticipate this, it could be informative. As we were discussing earlier, if there is some genetic marker that predicts who is going to get into trouble, that would be fabulous, but whether that is even worth thinking about isn't so clear.
So, the third case. Aminotransferase elevations, but you really don't have any Hy's Law cases in, say, 1,000 or 1500 patients. And we know that there are drugs, heparin, aspirin, statins, and tacrine all cause AT elevation but rarely, if ever, cause bilirubin elevation or liver failure. Labeling has sometimes called for monitoring (statins did).

Labeling for these drugs has sometimes called for monitoring. As probably everybody knows, statins did until we decided it was silly because there were never any bad outcomes. And one of the things I realized in getting prepared for this is that I couldn't catalog what we have done with respect to monitoring and calling for liver enzyme monitoring on drugs. I don't think we have ever looked at it systematically. I think it would probably be worth doing to see whether it is really worth it and what we actually get out of it.
4. Severe liver injury, even fatal, but very rare, e.g., labetalol,
diclofenac, cause severe injury but diclofenac not as bad as
bromfenac, ibufenac, etc. and may be COX-2’ish, and
labetalol has both beta-blocking and vasodilating
properties (i.e., not a typical beta-blocker).

Such drugs remain with warnings and call for monitoring
(diclofenac, labetalol) but cause some fatal injuries, either
because monitoring doesn’t work or isn’t done.

Now there are also cases where there is severe liver injury, and even fatal, but it is
pretty rare. I say "very rare"; I'm not sure what "very" means. There is no question
there are fatal cases of liver injury with labetalol, diclofenac, things like that. But
diclofenac is, not in the United States but in the rest of the world, probably the most
popular NSAID, and it is not as bad as bromfenac, ibufenac, and something like that. It
is probably COX 2-selective, at least a little bit. So, maybe people like it because of the
bleeding.

Labetalol also has some advantages. It is actually a diastereoisomer, and it is really two
drugs, not one, which we didn't know at the time. It is a beta blocker and it is a
vasodilator. It has properties that other beta blockers mostly don't have. So, it is out
there, even though we get case reports all the time.

So, those drugs remain out there with warnings. They both called for monitoring, but
they give some fatal injuries. And that is either because monitoring doesn't work or it
isn't done, and we don't really know. As I said, I would be interested in looking into
those cases and trying to pin them down better than we have to date, which I think
would be worthwhile.
Conclusion

Serious hepatotoxicity is not dealt with by labeling or monitoring unless 1) Drug has important benefit (bosentan, isoniazid) or serious injury is very rare (diclofenac, labetalol), and usually for a drug with advantage (labetalol).

So, it is pretty clear that serious hepatotoxicity, that is, the kinds of drugs we don't approve in the first place, is not really dealt with by labeling or monitoring. We just don't think that the risk is worth it, and we don't approve them. But, if a drug has an important benefit, like bosentan or isoniazid, we do leave it out and we try to help people get around it by monitoring and stopping, and with the two where we have done that, pretty successfully, I would say.

Diclofenac and labetalol I think need a close look to see just how much toxicity we have and, if possible, to figure out why. Is it because nobody was monitoring or because you can't monitor anyway? The rates of liver injury there are much less than the 1 in 10,000 that we think Hy's Law would predict, but I don't know what they really are. And there are other drugs where this issue has come up. Haldol might have rare cases, and so on.

So, that's all I wanted to talk about. I am interested now and we will try to see if we can do something about looking into what our pattern has been with respect to monitoring and things like that. So, that's it.