Public Citizen Health Research Group Comments on Draft Guidance for Industry--Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (Docket number 2007D-0396).
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Section I Introduction: Public Citizen would like to commend the FDA for putting together an excellent set of guidelines for analyzing potential liver toxicity in patients enrolled in clinical trials. Most useful are the clear standards for tests to be run, the frequency with which these tests should be done, and the interpretation that will much permit an unambiguous diagnosis of drug-induced liver toxicity. If pre-approval clinical trials are adequately powered and these guidelines are followed, there will be no excuse for liver toxicity to emerge in the post-marketing period, thus endangering the lives of many patients.

However, this guidance document confirms FDA's continued reluctance to seriously and publicly engage in post-mortem analyses of the growing number of mistakes the agency has made concerning failed decision-making about either the approval of known hepatotoxic drugs or the dangerously delayed removal of ones showing hepatotoxicity shortly after approval. In our comments on Sections II, III, and IV as well as the drugs chosen for Appendix A (Illustrative Examples of DILI), we will discuss these serious problems further.

Section II Hepatotoxicity: The FDA makes the case that hepatotoxicity cannot be detected in animal models; however, it is not clear that this has been tested adequately. If it is true that DILI is a rare event in humans (1 in 5,000 to 10,000), it could also be true that it is a rare event in animals and thus difficult to detect. Since it is only feasible to test small numbers of animals, it is important to be sure that doses are high (a true maximum tolerated dose), that tests are of adequate length, that the necessary lab values are measured, and that liver pathology is examined carefully and reported for each animal, not as an average. Since bilirubin elevation is considered such an important indicator, this (and ATs) should be measured and reported individually, not only as means. It would be useful to go back to a drug known to cause DILI and see if this could have been detected in an animal model using the most stringent methodology; it would also be useful in this model to see if there were other warning signs of liver toxicity. Both rats and dogs should be tested to see which is the most sensitive indicator, and if DILI occurs in one and not the other, that should be taken as a positive outcome and not a "species specific effect".

It would seem plausible that the combination of pre-clinical (animal) hepatotoxicity along with subsequent premarketing clinical hepatotoxicity might combine to provide an even stronger signal.

Section III Signals of DILI and Hy's Law: It appears that it might be worthwhile to go back and look at the data from all RCTs where DILI subsequently occurred, now that one knows what to look for. FDA should have data in its files that could shed light on this.

There is mention of the number of patients but not the duration of the trial needed to get the power necessary to detect DILI. The duration as well as the numbers needed should be included in the discussion.

Section IV Clinical Evaluation of DILI: There is no discussion of the importance of the ongoing information about efficacy, especially efficacy relative to other drugs in the same therapeutic class. Such issues as the decision to stop drug administration or to rechallenge with the drug for a particular patient should be related to the existence of comparably effective alternative drugs. Thus, except in the uncommon case in which the experimental drug is potentially a clinical breakthrough drug (not the case for Bromfenac, Rezulin, Trovan and most other hepatotoxic drugs [that had black box warnings added or have subsequently been withdrawn), the decision to

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stop drug administration in patients with strong evidence of potential hepatotoxicity should clearly be yes and the decision to rechallenge with the drug should clearly be no. Equally important, any unresolved questions about hepatotoxicity should be answered before approval, not after, by requiring more clinical studies.

As discussed in further detail below, in a recently published review of cases in which pre-approval hepatotoxicity signals were not adequately heeded, the authors comment, with respect to trovafloxacin and tolcapone, that "Considering the seriousness of the ADR reports about hepatotoxicity and the observations from clinical studies, the manufacturer should have been requested, prior to marketing of the drug, to conduct further clinical trials to clarify the extent of the risk of ADRs."[1]

Appendix A: Illustrative Examples of DILI

Before commenting on the incomplete critiques of the three drugs mentioned in this section (Duract, Rezulin and Exanta), a fourth example, Trovan (trovafloxacin) needs to be discussed. Although the drug was banned in the EU in 1999, it was allowed to continue in the U.S. (for hospitalized and nursing home patients) until 2003. As of December 31, 2004, a total of 58 cases of liver failure, including 29 deaths with nine people requiring liver transplants had been reported to the FDA. Trovafloxacin, never thought by the FDA to have any unique therapeutic advantage over any other approved antibiotics, including other fluoroquinolones, should never have been approved in the light of what was known from preclinical and pre-approval studies. According to the above-mentioned study[1], "One clinical study (indication not claimed [actually chronic prostatitis]) with a prolonged treatment period of 28 days showed an 'unacceptable' rise, defined by the pharmaceutical company, in liver function disturbances (protocol no. 6A). One case of hepatocellular damage was in study no. 1B."

Our own analysis of FDA pre-approval documents for trovafloxacin showed further evidence of concern about hepatotoxicity that should have stopped its approval. It also illustrates the importance of using pre-clinical data along with pre-approval clinical trials in assessing hepatotoxicity (see below):

FDA Pharmacology Review of Trovafloxacin (December 18, 1997)

The FDA knew about liver toxicity with trovafloxacin before approval based upon animal studies contained in the FDA's pharmacology review of this drug, dated December 18, 1997:

- In a six month rat toxicity study, the FDA pharmacologist reviewing the animal studies noted the following: "A dose-related increase in the incidence of minimal to mild 'fatty change' was seen in the livers of male rats from all trovafloxacin groups."[2] This means that there was no safe dose established for this drug in this species.
- In a six month dog toxicity study, hepatocellular vacuolar degeneration and necrosis (direct damage to liver cells) was seen in two of eight dogs at higher doses. Elevated liver enzymes (an indication of liver damage) were seen in both animals.[3]

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[1] Aagaard L, Soendergaard B, Stenver DI, Hansen EH. Knowledge creation about ADRs - turning the perspective from the rear mirror to the projector? Br J Clin Pharmacol. 2007 Oct 24 [Epub ahead of print]

[2] Trovafloxacin/alatrofloxacin. *Pharmacology Review* December 18, 1997, p. 42.

[3] Ibid, p. 43.

- In a second six month dog toxicity study, the drug was stopped in three of sixteen dogs because their liver enzymes increased three-fold and biopsies revealed liver changes (necrotizing hepatocellular inflammation). The FDA pharmacologist wrote: "Data from this study indicated that elevation in liver enzymes, especially ALT, accurately predicted the presence of necrotizing inflammation of perivenular hepatocyctes. The necrotic changes were no longer evident approximately 2 months after discontinuation of the drug."[4]

Human Premarketing Studies of Trovafloxacin: NDA Medical Review--December 1997

Liver adverse events in the pharmacology studies: The Medical Officer (MO), in addition to the reviewing Pharmacologist for this drug, had been concerned over findings in the two six month dog toxicity studies: increased liver function tests (LFTs) at two months and histologic findings at six months coupled with a small safety factor between human and canine exposure.

Liver adverse events in the clinical trials: In one clinical trial involving 140 patients with prostatitis, lasting 28 days, five patients were discontinued by the investigator for treatment-related increases in liver function transaminases [TAS--a liver test] (values redacted from the FDA document). Ten additional patients had elevations of LFTs ≥3x normal (data redacted). "Despite the fact that the investigators did not consider the LFT abnormalities in the 10 patients as attributable to trovafloxacin, the MO determined that the pattern of the abnormalities was consistent with that of the previously listed 5 patients. . .both in terms of the timing of the events as well as the duration. . . .Therefore, the MO determined that the true incidence of LFT abnormalities (≥3x normal), attributable to the study drug was 14/140 (10%). "[5]

"A trend was observed for liver enzyme elevations after 3 to 4 weeks of trovafloxacin therapy, suggesting that subjects receiving prolonged treatment (≥21 days) may need to have periodic assessment of hepatic function."[6]

Comments on Drugs Reviewed in the Guideline Appendix

Duract (bromfenac): The Guideline Appendix mentions that "during longer term clinical trials in arthritis, ALT elevations >3xULN were seen in 2.8 percent of patients on bromfenac, compared to none in placebo group. Among 1,195 exposed patients, there were two cases in which there was elevated TBL [total bilirubin] as well as AT elevation in the clinical trial data submitted for review in the NDA. Concerns about possible liver toxicity led to the approval of bromfenac in July 1997 for short-term use only."

But there is no mention that the FDA medical officer reviewing bromfenac sodium, the 20th nonsteroidal anti-inflammatory drug (NSAID) approved in the United States, unsuccessfully advocated a black box warning label as a condition of approval because, "The review of the 'liver' laboratory data from the submission shows that bromfenac sodium causes hepatocellular damage to a greater degree than other NSAIDs"(R. M. Widmark, unpublished data; FDA medical officer review memo, bromfenac sodium, December 22, 1995). After at least 4 deaths and 8 liver transplants, bromfenac sodium was removed from the market.

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4 Ibid, p. 44.

5 FDA Medical Officer's Review, December 1997, p. 227.

6 Ibid, p. 228.

Rezulin: (troglitazone), the 11th drug for diabetes in the United States, was approved in early 1997 even though 1.9% of patients in the pre-marketing trials, 54% of whom had taken the drug for at least 6 months, had liver function test results greater than 3 times the upper limit of normal, and 0.4% and 0.2% had 10-fold and 20-fold elevations, respectively, the latter group including, as admitted by the FDA, two patients with jaundice. Using the criteria in this guidance, why was it not a mistake to approve the drug? Well before it was removed from the market, troglitazone had already been associated with a minimum of 43 cases of liver failure, including 28 deaths. Omitted from the discussion of Rezulin is that, based largely on cases of liver failure in the U.S. the drug was removed from the market in the U.K. by the end of 1997.

Exanta (ximelagatran): Whereas the good news for the public for this drug was that it was never approved, since, in addition to its hepatotoxicity, there was evidence from controlled trials of an excess of coronary artery disease events as well as major bleeding that strengthened FDAs decision not to approve the drug.