

Spotting DILI for FDA submissions

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ABSTRACT

According to the FDA (Food and Drug Administration), severe drug-induced liver injury (DILI) is the most frequent single cause for safety-related drug marketing withdrawals for the past 50 years. Even after approval for marketing, numerous drugs have been limited in use when hepatotoxicity (chemical-driven liver damage) was discovered.

Identifying DILI is a challenging task for two reasons:

1. There are no findings that are specific to DILI and make a diagnosis certain. The liver injuries caused by DILI are similar to almost all other liver diseases like viral hepatitis or biliary tract disorders. It is therefore necessary to also seek alternative causes of the liver injury.
2. Even significantly hepatotoxic drugs rarely show a single case of severe DILI when studying several thousand subjects. The low incidence rate makes it hard for the reviewer to assess the potential of DILI for a new drug.

An approach is needed that can distinguish drugs likely to cause severe DILI from those that do not, as early as possible in new drug development.

The purpose of this paper is to summarize the FDA's current thinking on the subject of DILI and to introduce a SAS tool that is now used by FDA reviewers for their assessment of the potential for DILI in new drug applications.

DRUG-INDUCED LIVER INJURY (DILI)

The characteristic of a drug to cause damage to liver cells is called hepatotoxicity. Liver damage induced by a hepatotoxic drug is referred to as drug-induced liver injury (DILI). The severity of DILI can vary depending on the hepatotoxicity of the drug, the duration of the exposure and each individual's constitution. Severe DILI is a DILI resulting in a liver transplantation or the death of the patient. The goal of the FDA is to assess the potential for drugs to cause severe DILI and identify the drugs that are likely to do so.

Hepatotoxicity is a reason for not approving or limiting the use of various drugs in the United States (US). Some drugs have not been approved in the US, as marketing in European countries showed hepatotoxicity (e.g.: ibufenac, perhexiline, alpidem). Some drugs' usage has been limited after marketing approval when hepatotoxicity was discovered (e.g.: ticrynafen, benoxaprofen, bromfenac). And finally, some drugs have not been approved in the US because premarketing evaluation of the drugs' potential to cause severe DILI showed a high likelihood to cause severe DILI (e.g.: divalalol, tasosartan, ximelagatran). Looking at the past 50 years in drug safety, DILI was the most frequent single cause for drug marketing withdrawals.

When assessing a drug's potential for severe DILI two problems emerge:

1. Drugs and liver diseases cause injuries to the liver in many different ways. Injuries caused by drugs resemble almost all known liver diseases. Even after performing a liver biopsy, there are no characteristic findings that rule out a liver disease and make the diagnosis of DILI certain. It is therefore necessary to gather additional information on alternative causes of the liver injury. This information is: (previously existing) liver diseases (e.g.: acute viral hepatitis A, B or C and biliary tract disorders), the use of hepatotoxic concomitant therapy, laboratory data and the time course of the injury.
2. Severe DILI is rarely found in a clinical database even for significantly hepatotoxic drugs. Most drugs withdrawn from the market for hepatotoxicity showed one or less cases of severe DILI per 10000 patients. So even for a significantly hepatotoxic drug and a clinical database of several thousand patients it is likely

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not to observe a single case of severe DILI. That is why it is essential to look for a predictor of a drug's potential for severe DILI, instead of relying on the observed cases alone.

Severe DILI, in most cases, is a consequence of hepatocellular injury. An indicator for this kind of liver injury is a rise in serum aminotransferases (AT), reflecting the release of alanine or aspartate aminotransferase (ALT or AST) from injured liver cells. Even so, elevations of serum AT are not a strong predictor of a drug's potential to cause severe DILI. Serum AT elevations are seen for drugs that cause severe DILI as well as drugs that do not cause severe DILI even if drug administration is continued (e.g.: aspirine, tacrine, heparin). Severe DILI is a consequence of hepatocellular injury strong enough to impair the liver's ability to clear bilirubin or synthesize prothrombin. Drugs that cause this kind of liver injury need to be identified as early as possible in the drug development process.

The following example shows how severe DILI was discovered in a clinical database and the drug Exanta was abandoned as a result:

Exanta (ximelagatran)

Exanta (ximelagatran), an oral anticoagulant (antithrombin), was not marketed in the United States because of hepatotoxicity and other concerns discovered during clinical trials. Issues related to potential liver toxicity of ximelagatran were presented and discussed at an FDA advisory committee meeting in September 2004 (He 2004). During short-term clinical trials of the drug for prevention of thromboembolic complications after joint replacement surgical procedures, there was no increased rate of transaminase elevations in the ximelagatran group compared to the enoxaparin-warfarin group, and no serious hepatotoxicity was seen. But in longer term trials (more than 35 days) in patients with chronic atrial fibrillation to prevent embolic or thrombotic strokes, an increase in ALT >3xULN occurred in 7.6 percent of 6,948 patients compared to 1.1 percent of patients receiving warfarin treatment; and 1.5 percent of ximelagatran-treated patients had ALT >10xULN.

Increases in AT typically occurred 1 to 6 months after the initiation of ximelagatran administration with peak levels within 2 to 3 months postrandomization. Among the 531 ximelagatran patients with ALT >3xULN, 39 percent completed the trial on treatment, while 61 percent discontinued the drug. Almost all patients with ALT >3xULN returned to <2xULN whether the drug was stopped or not, although the return to normal was faster if ximelagatran was stopped. Of 18 patients who resumed drug after ALT returned to normal, only 2 had elevations recur. Concomitant elevations of ALT >3xULN and bilirubin >2xULN were observed in 37 of about 7,000 patients with ximelagatran and 5 of 6,230 patients with comparator. At least 13 of 37 patients in the ximelagatran group had no alternative explanation for the concomitant ALT and bilirubin elevation. Nine of the 37 patients died, but in most cases the deaths were not clearly hepatotoxicity-related. Only one autopsy was done and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis, but liver failure from ximelagatran might have contributed to some of the other deaths (He 2004; Lewis 2006; Kaplowitz 2006; Senior 2006; Temple 2006).

Because severe hepatotoxicity was observed in an orthopedic surgery trial in an extended treatment of 35 days, Exanta was withdrawn in February 2006 from the 22 countries in which it had been approved, and further development in the United States was abandoned.

Source: [1] page 24-25

SPOTTING DILI FOR FDA SUBMISSIONS

As severe DILI is only rarely observed in a clinical database even for significantly hepatotoxic drugs, a strong predictor is needed to identify drugs with a high potential to cause severe DILI.

Hepatocellular injury (indicated by an elevation of ATs) is a necessary precondition for a drug to cause severe DILI. However, an elevation in AT activities to 3, 5 and more than 5 times the upper limit of normal (ULN) can be observed for drugs that cause severe DILI and those that do not. Hepatocellular injury is therefore a necessary but not sufficient precondition for severe DILI. A higher rate of AT elevations in the test-drug group compared to the non-hepatotoxic control group is for this reason a sensitive, but not specific, signal for a drug's potential to cause severe DILI. In general, ALT is considered to be a more liver-specific AT than AST and may be favored in the evaluation of laboratory

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data.

The most specific predictor for a drug's potential to cause severe DILI is hepatocellular injury followed or accompanied by altered liver function. This was discovered by Hyman ("Hy") Zimmerman, an FDA scientist and expert for hepatology. Zimmerman found out that hepatocellular injury sufficient to impair bilirubin excretion is a strong predictor for a drug's potential to cause severe DILI. The reason for this observation is clear: The liver has a huge excess capacity for the excretion of bilirubin. Strong enough hepatocellular injuries cause an elevation of total bilirubin (TBL) to more than 2x ULN. This is a strong enough injury from that some patients may not recover. This observation by Hyman Zimmerman, which is today referred to as Hy's Law, was used to identify drugs with a high potential to cause severe DILI over the years.

A patient in a clinical database is classified as a Hy's Law case if the following three components are met:

- I. The drug causes hepatocellular injury, indicated by a higher incidence of AT elevations to 3 (or more) times the ULN in the test drug group compared to the (non-hepatotoxic) control group
- II. Serious liver injury, indicated by an elevation of TBL to more than 2x ULN for patients with AT elevations (without initial findings of cholestasis indicated by elevated alkaline phosphatase (ALP))
- III. No alternative reason for the elevation of AT and TBL can be found (e.g. a disease or a concomitant drug)

A single case of Hy's Law in a submission database is a worrisome sign and a strong predictor for the drug's potential to cause severe DILI. Finding two or more cases of Hy's Law is a highly predictive signal for severe DILI and there is no known occurrence of multiple false positive cases of Hy's Law.

Two or more cases of Hy's Law in a submission database have always led to the outcome of severe DILI when the drug was administered to a larger treatment population.

Finding no Hy's Law case in a database does not rule out the possibility of a potential for severe DILI. If a higher incidence of AT elevations can be observed in the test drug group compared to the non-hepatotoxic control group, factors like the size of the treatment population and the length of the treatment administration need to be considered. It was confirmed in a number of larger trials that a solid estimate for the rate of severe DILI is at least one tenth of the number of Hy's Law cases in the database. Accordingly, finding ten cases of Hy's Law, the database should contain at least one case of liver failure leading to a liver transplant or the death of the patient as well.

As a predictor for a drug's potential to cause severe DILI Hy's Law is one of the major indicators. The FDA uses three major indicators:

- I. An excess of AT elevations to >3xULN compared to a control group
- II. Marked elevations of AT to 5x-, 10x-, or 20xULN in modest numbers of subjects in the test drug group and not seen (or seen much less frequently) in the control group
- III. One or more cases of Hy's Law in the test drug group

Points I and III have already been discussed before. Marked elevations to 5x-, 10x- or 20x ULN indicate high sensitivity for predicting severe DILI. However, some non-hepatotoxic drugs cause these marked elevations as well, so the specificity of this indicator is not very good.

The following example illustrates how Hy's Law was used in the approval of bromfenac to indicate hepatotoxicity and to estimate the rate of severe DILI for a larger treatment group:

Duract (bromfenac)

Bromfenac was a nonsteroidal anti-inflammatory drug (NSAID) studied for both short-term analgesia and long-term arthritis treatment. There was little evidence of hepatotoxicity in the short-term analgesic trials, but 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 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 and not for osteoarthritis or rheumatoid arthritis. As an NSAID, however, it was prescribed long-term off-label in arthritic patients, and severe hepatotoxicity emerged. Within 6 months of approval, reports of severe hepatic failure, including two cases requiring liver transplant, were received. All severe cases involved the use of bromfenac for more than 10 days, the maximum duration of treatment recommended in the labeling.

In response, the FDA and the manufacturer strengthened the warnings in the package insert with a boxed warning, and issued a Dear Health Care Professional Letter. Despite these efforts, the manufacturer and the FDA continued to receive reports of severe injuries, including reports of death or need for liver transplantation (Moses and Schroeder et al. 1999; Hunter and Johnston et al. 1999; Rabkin and Smith et al. 1999; Fontana and McCashland et al. 1999). Given the availability of other effective NSAIDs, bromfenac was withdrawn from the market in June 1998. The two Hy's Law cases in the long-term-exposed population of about 1,000 subjects during drug development predicted an occurrence of severe hepatotoxicity during chronic use at a rate of about 1/5,000 to 10,000 people. Following approval, rates of acute liver failure for bromfenac were estimated to be in the range of 1/10,000 (Goldkind and Laine 2006).

Source: [1] page 23

EVALUATION OF DRUG-INDUCED SERIOUS HEPATOTOXICITY (EDISH)

Assessing the potential for severe DILI in new drug applications (NDA) is a burdensome work. Data on thousands of patients has to be searched to identify the rare but serious cases which may be an indicator for severe DILI. A software tool was needed to handle this task easily and efficiently.

The requirements for this tool are as follows:

- I. Summarize the patients' laboratory data
- II. Identify the cases of interest
- III. Drill-down to find a detailed presentation of a specific patient's overall data over time.

This tool, named eDISH (evaluation of Drug-Induced Serious Hepatotoxicity), is now in use by FDA reviewers for NDAs.

eDISH was created using SAS/Intrnet, a broadband web-application for SAS and consists of a little fewer than 50 SAS programs.

EDISH DATA STRUCTURE

Only a minimum of necessary outcome variables representing original values is used as input data for eDISH. Derivations are done by eDISH to give the FDA full confidence of the derivation algorithms. These original input variables can be divided into two categories: Firstly, the liver test results which change over time (e.g. ALT, AST, TBL) and secondly, variables which will most likely not change over time (SEX, HEIGHT). For the former an input dataset with multiple records per patient is created, for the latter an input dataset with one record per patient is created. An additional input dataset is created containing one record per patient with patient narrative information, explaining the liver test results.

For NDAs the data requirements are described using CDISC terms. The data requirements for eDISH are described by the FDA (see [2], page 4). eDISH visualizes the data as follows:

SUMMARY PLOT

The eDISH summary plot was created to firstly, summarizing the patients' laboratory data and secondly, to identify the cases of interest. This is achieved by plotting each patient's peak TBL against the peak ALT value. The following example shows a concept plot of the eDISH summary plot with actual trial data:

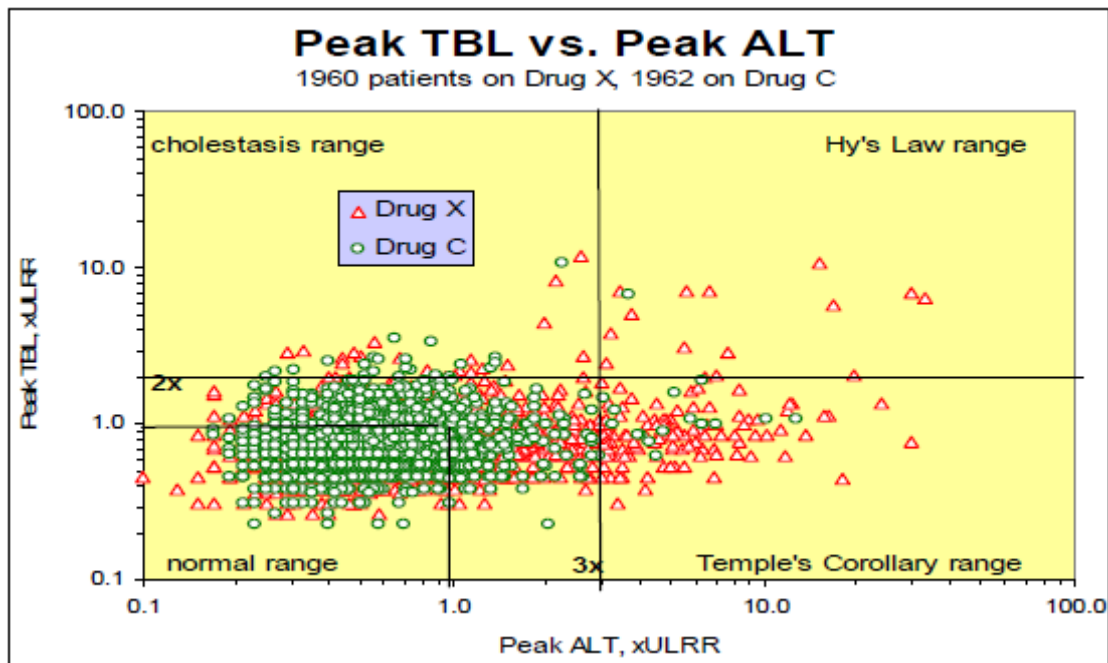


Figure 1: eDISH summary plot, source: [2], page 3

Figure 1 shows an eDISH summary plot. Each symbol represents one patient. The red triangles show patients on drug X (test drug), while the green circles show patients on drug c (control group). For each patient the peak TBL times the ULN (refers to the upper limit of the reference range (ULRR)) is plotted against the peak ALT times the ULN. For both axes a log10 scale was chosen. Two reference lines, one horizontal at 2x ULN for TBL x ULN and one vertical at 3x ULN for ALT x ULN, are drawn to divide the plane into four areas. The upper right quadrant is referred to as "Hy's Law range" as patients in this quadrant qualify for the laboratory components of Hy's Law. All patients in this quadrant are potential Hy's Law cases and are therefore subject to further investigation.

Looking at the eDISH summary plot makes an assessment of drug X's potential to cause severe DILI simple: it illustrates that we have 14 to 1 potential cases of Hy's Law in the test drug group compared to the control group. A large number of ALT elevations to more than 3x ULN for the test drug compared to very few in the control group is a second strong indicator for drug X's hepatotoxicity.

EDISH TIME COURSE OF LIVER TESTS PLOT

Clicking on one of the symbols, representing a patient in the eDISH summary plot, opens the eDISH time course of liver tests plot for that particular patient. The following example shows an eDISH time course of liver tests plot for a patient who died because of acute liver failure:

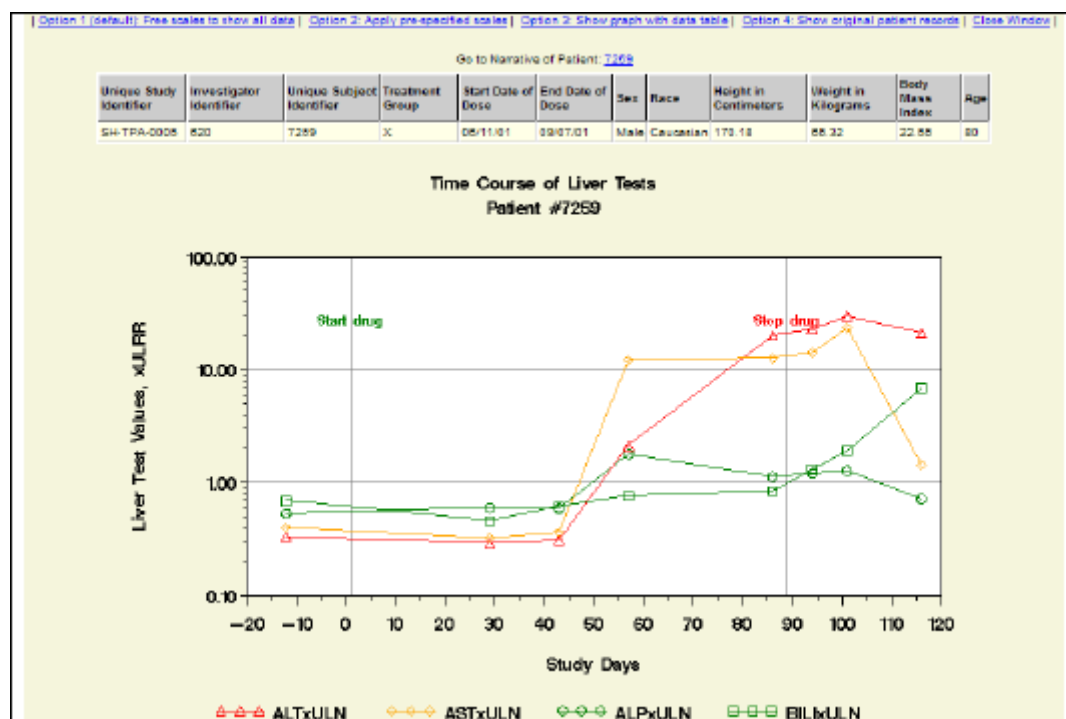


Figure 2: eDISH time course of liver tests plot, source: [2], page 14

The upper part of figure 2 shows patient information that is not likely to change over the course of the trial, like treatment group, age and sex. The lower part of figure 2 shows the actual eDISH time course of liver tests plot. Liver test values for ALT, AST, ALP and TBL times the ULN are plotted against study days. Log10 scale is used for the y-axis. Two vertical reference lines show the start and stop date of drug X.

AST is the first liver test to elevate to more than 10x ULN, followed by ALT, increasing to 20x ULN. Both ATs only start to normalize after drug X was stopped. This activity in ATs indicates hepatocellular injury for this patient. TBL x ULN elevates to nearly 10x ULN, indicating a strong enough hepatocellular injury to impair bilirubin excretion. ALP x ULN does not elevate significantly and therefore does not indicate cholestasis, an alternative explanation of the elevation of ATs. For a final assessment whether this acute liver failure was induced by drug X, additional information like the patient narrative has to be evaluated.

CONCLUSION

Evaluating a drug's potential for hepatotoxicity is a challenging task and therefore results in a number of additional requirements for sponsors. In addition to a detailed analysis of the incidence of abnormalities in AT, bilirubin, and ALP levels as described in [1] the following tasks can/should be performed to support the identification of DILIs:

- ✓ Provide a listing with all possible Hy's Law cases identified by treatment group (e.g., subjects with any elevated AT of >3x ULN, ALP <2x ULN, and associated with an increase in TBL $\geq$ 2x ULN)
- ✓ Provide a patient narrative for all possible Hy's Law cases
- ✓ If eDISH should be used for DILI evaluation, please provide the three input datasets as specified (see [2], page 4)
- ✓ Any potential Hy's Law case should be handled as a serious unexpected adverse event. The FDA should be informed immediately and all available patient information should be provided (see [1], bottom of page 13).

These requirements, of course, only provide a rough idea of the FDA's wishes to receive/see concerning DILI. Information should be provided as agreed upon with the FDA.

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