Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2009
Drug Safety

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I. INTRODUCTION

This guidance is intended to assist the pharmaceutical industry and other investigators who are conducting new drug development in assessing the potential for a drug[2] to cause ***severe*** liver injury (i.e., irreversible liver failure that is fatal or requires liver transplantation). In particular, the guidance addresses how laboratory measurements that signal the potential for such drug-induced liver injury (DILI) can be obtained and evaluated during drug development. This evaluation is important because most drugs that cause severe DILI do so infrequently; typical drug development databases with up to a few thousand subjects exposed to a new drug will not show any cases. Databases may, however, show evidence or signals of a drug's *potential* for severe DILI if the clinical and laboratory data are properly evaluated for evidence of lesser injury that may not be severe, but may predict the ability to cause more severe injuries. This guidance describes an approach that can be used to distinguish signals of DILI that identify drugs likely to cause severe liver injury from signals that do not suggest such a potential. This guidance does not address issues of preclinical evaluation for signals of DILI, nor the detection and assessment of DILI after drug approval and marketing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Gastroenterology Products in the Office of New Drugs, the Office of Medical Policy, and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] This guidance uses the term *drug* or *product* to refer to all products, except whole blood and blood components, regulated by CDER and CBER, including vaccines, and uses the term *approval* to refer to both drug approval and biologic licensure.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND: DILI

DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Hepatotoxicity discovered after approval for marketing also has limited the use of many drugs, including isoniazid, labetalol, trovafloxacin, tolcapone, and felbamate (Temple 2001). Several drugs have not been approved in the United States because European marketing experience revealed their hepatotoxicity (e.g., ibufenac, perhexiline, alpidem). Finally, some drugs were not approved in the United States because premarketing experience provided evidence of the potential for severe DILI (e.g., dilevalol, tasosartan, ximelagatran). Although most significant hepatotoxins have caused predominantly hepatocellular injury, indicated by leakage of aminotransferase (AT) enzymes from injured liver cells without prominent evidence of hepatobiliary obstruction or intrahepatic cholestasis, the pattern of injury can vary. Many drugs cause cholestasis, but in general this condition is reversible after administration of the offending drug has stopped. Cholestatic injuries are less likely to lead to death or transplant, although there have been exceptions.

Drugs cause liver injuries by many different mechanisms. These injuries resemble almost all known liver diseases and there are no pathognomonic findings, even upon liver biopsy, that make diagnosis of DILI certain. Therefore, when possible DILI is suspected, it is essential to gather additional clinical and laboratory information necessary for differential diagnosis of the cause. It is important to observe the time course of the injury, and to seek alternative causes of the liver injury, such as acute viral hepatitis A, B, or C; concomitant use of a hepatotoxic drug or exposure to hepatotoxins; autoimmune or alcoholic hepatitis; biliary tract disorders; and circulatory problems of hypotension or right heart congestive failure that may cause ischemic or hypoxic hepatopathy. It is also prudent to assess the subject for previously existing liver disease, such as chronic hepatitis C or nonalcoholic steatohepatitis (NASH), that may or may not have been recognized before exposure to the experimental drug. It should be recognized that DILI may occur also in persons with preexisting liver disease as a superimposed problem.

Only the most overt hepatotoxins can be expected to show cases of severe DILI in the 1,000 to 3,000 subjects typically studied and described in a new drug application (NDA). Overtly hepatotoxic agents (e.g., carbon tetrachloride, chloroform, methylene chloride) are toxic to anyone receiving a large enough dose, and drugs that cause such predictable and dose-related injury generally are discovered and rejected in preclinical testing. More difficult to detect is toxicity that is not predictable or clearly dose-related that occurs at doses well tolerated by most people, but seems to depend on individual susceptibilities that have not as yet been characterized. Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of $\leq$1 per 10,000, so that a single case of such an event rarely would be found even if several thousand subjects were studied. Severe DILI cases rarely have been seen in drug development programs of significantly hepatotoxic drugs.

What are often seen during drug development are mild elevations of serum aminotransferases, usually without any symptoms. The problem is that these types of signals can be generated by drugs that are capable of causing severe DILI as well as by drugs that have a low potential for causing severe injury (e.g., aspirin, tacrine, heparin, hydroxyl-methylglutaryl coenzyme A-reductase inhibitors (*statins*)). Therefore, an approach is needed that can distinguish drugs likely to cause severe DILI from drugs unlikely to do so.

In general, the type of liver injury that leads to severe DILI is a predominantly hepatocellular injury. Hepatocellular injury is indicated by rises in AT activities in serum reflecting release of alanine or aspartate aminotransferase (ALT or AST) from injured liver cells. The ability to cause some hepatocellular injury, however, is not a reliable predictor of a drug's potential for severe DILI. Many drugs that cause transient rises in serum AT activity do not cause progressive or severe DILI, even if drug administration is continued. It is only those drugs that can cause hepatocellular injury extensive enough to reduce the liver's functional ability to clear bilirubin from the plasma or to synthesize prothrombin and other coagulation factors that cause severe DILI. It is important to identify those drugs as early as possible.

The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals, generally have not shown dose-related toxicity, and, as noted, generally have caused low rates of severe injury in humans (1 in 5,000 to 10,000 or less). One of the few exceptions to these findings is acetaminophen, whose toxicity can be shown in animal models and whose toxicity is clearly dose-related. These reactions thus appear to reflect host factors and individual susceptibility. Consequently, they have been termed *idiosyncratic*, meaning dependent upon the individual person's particular constitution. Whether they are the result of genetic and/or acquired differences has not yet been established, and to date no genetic, metabolic, or other characteristic has been found to reliably predict severe DILI in an individual.

Some severe DILI examples have presented differently from the more commonly seen hepatocellular idiosyncratic type. Perhexiline, an anti-anginal drug marketed in Europe, produced toxicity within months of starting the drug that had the histological appearance of alcoholic cirrhosis (Pessayre and Biachara et al. 1979). Fialuridine caused modest acute liver injury, but most strikingly led to severe metabolic acidosis and multiorgan failure as mitochondrial oxidative capacity was obliterated over a period of months (Kleiner and Gaffey et al. 1997; Semino-Mora and Leon-Monzon et al. 1997). Valproic acid causes hyperammonemic encephalopathy even without notable rises in serum AT activities. Benoxaprofen (Oraflex) induced intrahepatic cholestasis that over many months led to significant, sometimes fatal, liver injury, especially in elderly patients (Taggart and Alderdice 1982).

Past experience indicates that appropriate testing and analysis in premarketing trials can detect drugs that can cause severe hepatocellular injury.

III. SIGNALS OF DILI AND HY'S LAW

Hepatocellular injury (usually detected by serum AT elevations) can be caused by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, tacrine, statins, and heparin) as well as by drugs

that do cause such injury. Evidence of hepatocellular injury is thus a necessary, but not sufficient, signal of the potential to cause severe DILI (note, however, that the drugs causing hepatic injury through mitochondrial toxicity may not cause early hepatotoxicity). The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI, because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of patients. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver *function* accompanying or promptly following evidence of hepatocellular injury (see below).

As noted, a typical NDA or biologics license application (BLA) database usually will not show any cases of severe DILI, even for a drug that can cause such injury, because the rate of severe injury is usually relatively low (1/10,000 or less). Many drugs, however, including both significant hepatotoxins and drugs that do not cause severe liver injury, cause laboratory evidence of mild, transient hepatic injury, with leakage of liver enzymes and the appearance in serum of elevations in AT activities to levels of 3, 5, and sometimes greater than 5 times the upper limits of normal (ULN). Generally, ALT is considered a somewhat more liver-specific aminotransferase enzyme than AST, although it also occurs in many tissues (Green and Flamm 2002). The finding of a higher rate of such elevations in drug-treated subjects than in a control group is a sensitive signal of a potential to cause severe DILI, but it is not a specific signal.

A more specific signal of such potential is a higher rate of more marked peak AT elevations (10x-, 15xULN), with cases of increases to >1,000 U/L causing increased concern. The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, however, is the occurrence of a small number of cases of hepatocellular injury (aminotransferase elevation) accompanied by increased serum total bilirubin (TBL), not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K-dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Zimmerman's observation that drug-induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). The reason for this now seems clear. Because the liver has a large excess of bilirubin-excreting capacity, injury to hepatocytes sufficient to cause jaundice or even mild hyperbilirubinemia (i.e., a bilirubin >2xULN) represents an extent of liver injury so great that recovery may not be possible in some patients. Zimmerman's observation that hepatocellular injury sufficient to impair bilirubin excretion was ominous has been used at the Food and Drug Administration (FDA) over the years to identify drugs likely to be capable of causing severe liver injury. The observation of the critical importance of altered liver function has been referred to informally as *Hy's Law* (Temple 2001; Reuben 2004).

Hy's Law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. It is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated. In all cases to date, the small number of Hy's Law cases has arisen on a background of an increased incidence of more modest signs of hepatocellular injury (e.g., greater incidence of 3xULN elevations in AT than seen in a control group).

Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population. Clinical trials of the beta blocker dilevalol (enantiomer of labetalol, a diastereoisomeric mixture) showed two such cases in about 1,000 exposures. The drug was not approved in the United States, and examination of a postmarketing study in Portugal revealed fatal liver injury. Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. This led to a request for a much larger premarketing database and the drug was abandoned.

Severe DILI can be estimated to occur at a rate of at least one-tenth the rate of the so-called Hy's Law cases (Temple 2001). This observation was recently confirmed in large studies of DILI in Spain (Andrade and Lucena et al. 2005) and in Sweden (Björnsson and Olsson 2005) in which approximately 10 percent of subjects with hyperbilirubinemia or jaundice died or needed liver transplants.

Recent examples of some drugs causing idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran) further illustrate the predictive value of Hy's Law, where findings during clinical trials were noted and severe DILI occurred after marketing. These examples are described in detail in Appendix A.

Hy's Law cases represent one end of a spectrum of laboratory abnormalities that indicate liver injury. Each of these cases has different sensitivity and specificity as a predictor for the potential for severe liver injury. Although it is not possible to provide precise specificity and sensitivity

estimates for the various signals, guidance can be provided on use of these major indicators of a potential for severe DILI, as follows:

- **An excess of AT elevations to >3xULN compared to a control group**

  AT elevations to >3xULN are relatively common and may be seen in all groups, but an excess of these elevations compared to a control group is nearly always seen for drugs that ultimately prove severely hepatotoxic at relatively high rates (1/10,000). Therefore, the sensitivity of a significantly increased incidence compared to control (e.g., of >3xULN AT elevations) as an indicator of a potential for liver injury is high. But many drugs show this signal without conferring a risk of severe injury (e.g., tacrine, statins, aspirin, heparin), indicating low specificity for an excess of AT elevations alone. There are no good data to predict how great this excess incidence of AT elevations should be compared to controls to suggest an increased risk of DILI. Such an excess may not be apparent for drugs with a potential to cause idiosyncratic DILI that are used for short treatment courses, such as many antibiotics.

- **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**

  Many, but not all, severely hepatotoxic drugs show such elevations, indicating high sensitivity for predicting severe DILI; again, however, some drugs, such as tacrine and others that are not severely hepatotoxic, also can cause AT elevations to this degree, so that specificity of this finding is suboptimal.

- **One or more cases of newly elevated total serum bilirubin to >2xULN in a setting of pure hepatocellular injury (no evidence of obstruction, such as elevated ALP typical of gall bladder or bile duct disease, or malignancy, or impaired glucuronidation capacity caused by genetic (Gilbert syndrome) or pharmacologic (treatment with atazanavir or other drugs) factors), with no other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs), accompanied by an overall increased incidence of AT elevations >3xULN in the test drug group compared to placebo**[3]

  The sensitivity of this observation appears high for any given incidence rate of severe DILI if enough people are exposed to the drug. For example, if the true incidence of severe injury is 1/10,000, and the rate of Hy's Law cases is 1/1,000, about 3,000 exposed subjects (*Rule of 3*) would be needed to have a 95 percent probability of observing at least one Hy's Law case in the treated population (Rosner 1995).[4] The specificity of this

[3] This constellation of findings is the hallmark of a Hy's Law case. The predictive value of these three findings for a drug's potential to cause DILI may be different if these findings are identified in patients with preexisting liver disease, fatty liver disease such as NASH, chronic hepatitis C or B, or bilirubin metabolism abnormalities (Gilbert syndrome), or in patients on drugs that treat liver disease or that inhibit bilirubin glucuronidation, such as indinavir or atazanavir (Zhang and Chando et al. 2005).

[4] The Rule of 3 is derived from simple binomial calculation. There will be at least a 95 percent chance of seeing one or more cases of DILI in 3n trial subjects if its true incidence is 1 in **n** subjects, and the group is well observed.

finding appears very high if two or more cases are seen (e.g., dilevalol, bromfenac, troglitazone, ximelagatran). We are not aware of the occurrence of false positive Hy's Law findings for a drug that was subsequently found not to cause severe DILI in a larger treatment population. Therefore, the finding of two Hy's Law cases, and probably even one, is a strong predictor of a significant risk of severe liver injury. Failure to find a case, however, does not imply that a drug with AT elevations is free of a risk of severe DILI. The degree of assurance depends on the population exposed for a long enough time, the discontinuation rules used in the protocols, and the true incidence rate of severe DILI.

IV. CLINICAL EVALUATION OF DILI

A. General Considerations

For most drugs in development that reach phase 3 testing, the chances of encountering severe DILI are low. An increased incidence of mild hepatotoxicity (AT elevations) in early trials usually results in heightened screening to detect and evaluate liver injury during phase 3 testing. It is critical, however, to determine whether mild hepatotoxicity reflects a potential for severe DILI or reflects a capacity for only limited injury. To make this distinction, it is important to detect any cases of more severe injury and to examine such cases closely, observing the course and outcome of the injury, and seeking additional information that might identify other causes. The following general recommendations for evaluating and monitoring potential drug-induced hepatotoxicity may not be suitable for all situations and should be modified for special populations, such as people with preexisting liver disease or malignancies, and in light of accumulating data. In addition, clinical trials of cellular and gene therapies and of vaccines pose specific challenges related to trial size and design, biodistribution and persistence of vectors, the function and anatomic location of cellular products, and other factors. Applicants are encouraged to discuss these issues with the relevant review division.

1. Patients with Liver Abnormalities or Disease

Patients are sometimes excluded from clinical trials because of baseline liver test abnormalities or a history of liver disease, but there is no well-established reason to do this, except perhaps to avoid confusion between the previous disease and an effect of the test drug. Patients with acute viral, autoimmune, alcoholic, or other types of hepatitis are unstable and generally not appropriate subjects for clinical trials other than trials of treatments for their acute illness. Patients with stable underlying liver disease can be included cautiously in late-stage clinical trials, but probably not if bilirubin excretory or protein synthetic functions are impaired, unless there is a strong need that they be treated. This implies that diagnostic screening for liver test abnormalities should be conducted before enrolling subjects into trials. Patients with stable liver disease generally should be included in at least some phase 3 trials if they are likely to be treated with the drug if it is marketed. Preexisting liver disease has not been thought to make patients more susceptible to DILI (Zimmerman 1978, 1999), but it may be that a diminished *liver reserve* or the ability to recover could make the consequences of injury worse. This appears to be the case with highly active antiretroviral therapy in patients with chronic viral hepatitis. If the drug

is intended to be prescribed or marketed to such patients after approval, they should be enrolled in controlled trials.

2. Detection of DILI

Depending on the mechanism underlying DILI, different drugs can be associated with different treatment time/hazard profiles. In many cases, there is a delay of at least a few weeks between initiation of treatment and onset of liver injury. However, for some drugs, rapid onset of injury may occur, sometimes in the presence of a systemic hypersensitivity reaction that can be associated with multi-organ involvement, fever, eosinophilia, and/or rash. In general, early trials of a drug in trial subjects with presumably normal liver function should involve obtaining liver enzyme (ALT, AST, ALP) and bilirubin tests every 2 to 4 weeks, at least for a few months. For drugs being studied with short treatment courses, both baseline and post-treatment liver enzyme testing should be performed, since there may be a gap between the end of treatment and the onset of liver injury. In circumstances when there is a high likelihood that such a drug will be chronically used in an off-label fashion, long-term treatment trials to measure risk for DILI may be warranted.

It is uncertain whether early and nonspecific symptoms (e.g., anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting) precede or follow the first laboratory signs of hepatic injury (rising ALT, AST, or ALP), and the pattern of clinical and laboratory changes may vary with different drugs and recipients. In most cases, however, the first evidence of a problem is the discovery of elevated AT or ALP during routine serial measurements. In longer trials, if there is no sign of liver injury after a reasonable length of exposure (e.g., 3 months), the monitoring interval can be increased to once every 2 to 3 months. Later trials also can use less frequent liver chemistry monitoring if there is no indication of hepatotoxicity in earlier trials.

As previously noted, if symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. Reliance on early symptoms, rather than serum enzyme monitoring, has become the standard for monitoring isoniazid therapy for prophylaxis of tuberculosis and seems to prevent severe liver injury if acted upon promptly by discontinuation of isoniazid (Nolan and Goldberg et al. 1999). Attention to symptoms does not supplant routine periodic assessment of AT, TBL, and ALP in trials of investigational drugs.

3. Confirmation

In general, an increase of serum AT to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious. Of greater concern, delay in retesting may allow progression to severe worsening if the initial abnormality was the herald of a severe reaction to

follow. The need for prompt repeat testing is especially great if AT is much greater than 3xULN and/or TBL is greater than 2xULN. For outpatient trials, or trials in which subjects are far away from the trial site, it may be difficult for the subjects to return to the trial site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AT >3xULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening (see below). If close monitoring is not possible, the drug should be discontinued.

4. Close Observation

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of aminotransferase levels greater than 3xULN seems reasonable, as lesser elevations are common and nonspecific. If additional testing, beyond that specified in the trial protocol, is carried out, it is important that the subject's information be added to the case report forms and database.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

5. Decision to Stop Drug Administration

It has been observed that *dechallenge* (stopping drug administration) does not always result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen

overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity). Promptly stopping the offending drug usually is the only potentially effective therapy.

A difficult question is when should the investigational drug be stopped? Because transient fluctuations of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of trial drug upon finding a greater than 3xULN elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continued exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine, which cause liver injury but do not cause severe DILI. On the other hand, continuing drug appears unacceptably dangerous if there is marked serum aminotransferase elevation or evidence of *functional* impairment, as indicated by rising bilirubin or INR, which represent substantial liver injury. Although there is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision will be affected by information on related drugs, the accumulating clinical experience, the clinical status of the patient, and many other factors, the following can be considered a basic guide. Discontinuation of treatment should be considered if:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It should be noted that although these guidelines have not been evaluated systematically in a prospective fashion, they represent an approach that is similar to current practice.

6. Evaluating Data for Alternative Causes

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

- **Acute viral hepatitis.** The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

- **Alcoholic and autoimmune hepatitis.** Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).

- **Hepatobiliary disorders.** Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

- **NASH.** NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.

- **Cardiovascular causes.** Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (*ischemic hepatitis*) with rapid and sometimes spectacular increases of serum AT (e.g., AT >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.

- **Concomitant treatments.** It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

7. Follow-Up to Resolution

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

8. Rechallenge

Whether or not to rechallenge a subject who showed mild DILI is a difficult decision. Reexposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with reexposure. Rechallenge may not be considered *negative* unless the subject is exposed to and tolerates the same dose and treatment duration that preceded the original reaction. A *negative rechallenge* does not necessarily allow a conclusion that the drug did not cause the injury. Most people can adapt to xenobiotic substances, including new drugs, and develop tolerance for them. This has been observed even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury while taking isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance has developed, the use of rechallenge to verify drug causation would give a false negative result.

Generally, rechallenge of subjects with significant AT elevations (>5xULN) should not be attempted. If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe injury. The subject should be made aware of the potential risk, and consent to the rechallenge, and the institutional review board consulted.

B. Research Opportunities

It is not known why only a few people show severe DILI in response to a hepatotoxic drug while others show nothing or seem to adapt. The current thinking is that both genetic and acquired factors may be important in determining the susceptibility to injury. Close observation provides a major opportunity to gather and store serial samples of blood and urine, to investigate characteristics of subjects who show evidence of mild or severe DILI, and to see how they differ from each other and from people who do not show any effects despite being similar in age, sex, and drug exposure. These serial samples can be studied by genomic, proteomic, and metabolomic methods to determine how subjects differ, and to seek biomarkers that identify the susceptible persons.

As part of the Critical Path Initiative,[5] the FDA is working with industry, academia, and other experts to broaden its understanding of the biochemical and genetic bases of DILI. It is hoped that predictive bioassays and biomarkers can be identified through analysis of systematically collected biospecimens that will help determine which patients are most likely to suffer liver injury from specific compounds. If tests that identify people susceptible to severe DILI can be developed, a drug that is hepatotoxic to them could remain available to other people who are not susceptible to severe DILI.

In addition, identification of common genotypic characteristics among patients experiencing DILI in response to one or more class-related hepatotoxic drugs might permit the development of

[5] See http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm.

in vitro or ex vivo tests or genetically altered animal strains that can be used to better predict serious hepatotoxic potential, or the lack thereof, of new drugs belonging to the same or closely related classes.

C. Case Report Forms

Because DILI has resulted in the marketing withdrawal or cessation of development of many drugs, every clinical trial should include case report form pages specifically designed to capture information pertinent to the evaluation of treatment-emergent liver abnormalities. In addition to collecting information on laboratory abnormalities, clinical symptoms, and the potential cause of any hepatic illness, case report forms and narratives should include the following information for cases in which liver injury is found (including control subjects with such injury):

- Time and date from start of drug administration to start of illness.
- Time and date of cessation of drug, or interruption of drug administration.
- Complete description of the injury, including systemic symptoms, other organ involvement, rash, fever, and eosinophilia.
- Outcomes such as death, liver transplant, hospitalization, recovery, and treatment for DILI.
- Free text describing the course of illness, including pertinent physical examination findings, such as hepatomegaly, splenomegaly, right-upper quadrant tenderness, the time course of abnormalities of aminotransferases, ALP, TBL with dates of testing, normal ranges, and results for tests done in addition to those specified in the original protocol, and tests done during any unscheduled visits. These additional laboratory test results, including reference ranges, should also become part of the overall database. Supportive tabular and/or graphical display of serial laboratory data is often desirable in addition to narrative information. Pre-study AT values should be sought, which may suggest chronic liver disease and/or an acute process that may have preceded exposure to the investigational drug.
- Risk factors, especially history of alcohol use; risk factors for NASH such as diabetes, obesity, and hypertriglyceridemia, which may prompt ultrasound examination of the liver to detect steatosis.
- All concomitant drugs (dose, start and stop dates, whether they are known to be hepatotoxic, information on rechallenge or dechallenge with drugs with the same or similar structure).
- Evaluation of nondrug causes: recent hepatitis A, B, and C serology; evidence for biliary obstruction; imaging study results; acute alcoholic hepatitis (recent drinking and AST >2xALT are supportive); recent history of severe hypotension or congestive heart failure; other underlying viral disease.
- All supplemental information, including consultation reports, narrative information, and special studies.

Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to the FDA promptly (i.e., even before all other possible causes of liver injury have been excluded). It should be promptly reported to the FDA before fully working up the patient to rule out other etiologies. Reporting should include all available

information, especially that needed for evaluating the severity and likelihood that the drug caused the reaction, and should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

D. Interpretation of Signals of DILI or Acute Liver Failure

1. Frequency and Magnitude of Liver AT Abnormalities

The presence of even a single case of severe liver injury resulting from treatment in the premarketing clinical trials database is a signal of a high level of hepatotoxic risk. More commonly, however, there will be no identifiable cases of severe liver injury, but rather varying degrees of serum AT abnormalities that need to be interpreted. As previously noted, slight abnormalities of this kind (to <3xULN) are common in untreated and placebo-treated subjects and are not informative about the potential for the development of severe DILI. Subjects with such abnormalities should be watched.

Therefore, it has become standard practice to look at greater deviations, such as AT values ≥3x-, 5x-, or 10xULN. Because these abnormalities are often associated with other causes, such as NASH or hepatitis C, they can occur in placebo-treated groups, and it is important to compare their incidence in drug-exposed subject groups to that observed in control groups (i.e., placebo or treatment with products that do not cause elevation of aminotransferases). A significantly increased incidence of AT abnormalities >3xULN is a signal of a potential for severe DILI, but, even though it has high sensitivity, it is not specific. Abnormalities of greater magnitude (e.g., ≥10xULN) are rarely seen spontaneously in placebo arms of clinical trials in most settings. Therefore, greater magnitude AT elevations can be examined in the entire clinical trials database, not just in the controlled trials. Serum AT activity is a relatively volatile measurement, often rising and falling within days. It cannot be concluded from one measurement that a peak value has been seen, so detection of an abnormal rise calls for serial measures to determine which way the abnormality is moving, whether increasing or decreasing.

A number of factors may confound interpretation of AT abnormalities seen in NDA or BLA databases. Although the more extreme AT elevations may be better predictors of toxicity than smaller elevations, close monitoring can affect the magnitude of abnormalities seen if it leads to earlier cessation of drug treatment. In addition, the contribution of drug treatment to an exacerbation of preexisting liver disease or the effects of concomitant hepatotoxic drugs may be difficult to determine. Finally, normalization of abnormalities on continued treatment is not proof that the abnormality was not drug-caused, as it can result from liver adaptation to the drug.

2. Combined Elevations of Aminotransferases and Bilirubin

When AT abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation >2xULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe DILI. Experience has indicated that the occurrence of even

one or two well-documented cases of this combination is ominous, indicating a likelihood that the drug will cause severe liver injury.

The absence of Hy's Law cases in an NDA or BLA database may allow an estimate of an upper limit of the rate for severe DILI, using the Rule of 3 derived from simple binomial calculation. There will be at least a 95 percent chance of seeing one or more cases of DILI in 3n trial subjects if its true incidence is 1 in **n** subjects, and the group is well observed. Thus, if no cases of AT and bilirubin elevations are seen in 3,000 well-observed subjects, it can be concluded with 95 percent confidence that the true rate of such occurrences is not more than 1 per 1,000. This calculation would then suggest a rate of expected severe liver injury ≤1 per 10,000 exposed patients, assuming that the rate of severe injury among patients with concomitant AT and TBL elevations is about 10 percent (Andrade and Lucena et al. 2005; Björnsson and Olsson 2005).

E. Analysis of Signals of DILI

Based on the FDA's experience, the following analyses related to liver injury potential should be carried out and included in an NDA or BLA, or included in an investigational new drug application when DILI is suspected and being evaluated.

1. Assessment of Drug Metabolism

The metabolism of a drug can markedly affect the safety profile of the drug. A drug may be metabolized to a hepatotoxic metabolite (e.g., acetaminophen, halothane, isoniazid). Most hepatotoxic drugs have been oxidatively metabolized by the CYP450 system.

2. Assessment of Liver-Related Adverse Events in Controlled Trials

Applicants should provide an analysis of the incidence of abnormalities in AT, bilirubin, and ALP levels seen in subjects in controlled trials with at least one dose of drug exposure. Generally, the analysis should be for pooled data, although trial-to-trial differences may be of interest. Incidence can be given as the number of events per number of subjects exposed, or can incorporate treatment exposure, as the number of events per subject-years of exposure, preferably both. Changes in mean values for groups are not informative. For many drugs, it appears that a minimum duration of exposure is needed before DILI occurs. Therefore, it is useful to describe liver-related adverse events for subjects who have had the minimum duration of exposure (e.g., subjects with at least 1-month exposure). For some drugs, patterns of early injury after initiation of treatment may occur, and for these patients testing intervals should be modified appropriately. Incidences for pooled data should include, but are not limited to:

- 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated TBL to >2xULN.
- Any elevations of ALP >1.5xULN.
- Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN).
- Elevation of AT in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue.

- Possibly liver-related deaths and liver-related treatment discontinuations. These cases should be described and time-to-event analyses should be performed. Follow-up status also should be provided. There should be a description of any histologic and rechallenge data.

All incidences should be calculated separately for drug-, placebo-, and active-controlled groups. Normal ranges for all tests should be provided. Time-to-event analyses for events occurring with increased incidence should be provided (e.g., elevated AT, bilirubin). The contribution of sex, age, risk factors, and drug dose or regimen to the abnormalities seen should be explored.

3. Assessment of Liver-Related Adverse Events in the Entire Clinical Trials Database

Applicants should provide an analysis of the incidence of abnormalities in AT, bilirubin, and ALP levels for the entire clinical trials database, including subjects with exposure of at least one dose of trial drug in phase 1 or phase 2 trials, or in uncontrolled, open label, extension trials. We recommend the same evaluation as for the controlled trials database discussed in section IV.D.2. Time-to-event analyses of events occurring at increased incidence, and rates of death and trial withdrawal in subjects with abnormalities, should be provided. The contribution of sex, age, drug dose or regimen, use of concomitant drugs, and underlying disease to the abnormalities seen should be explored.

4. Assessment of Hy's Law Cases in the Clinical Trials Database

NDA and BLA submissions should include a listing of possible Hy's Law cases identified by treatment group (e.g., subjects with any elevated AT of >3xULN, ALP <2xULN, and associated with an increase in bilirubin ≥2xULN). A narrative summary for each Hy's Law case should be provided. Narrative summaries should not only provide, in text format, the data that are already presented in the case report tabulation, but also should provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing for a better understanding of what the subject experienced. For a narrative summary to be useful, it should contain the following information:

- Subject's age, sex, weight, and height
- Discussion of signs and symptoms related to hepatotoxicity: type and timing to exposure
- Relationship of exposure duration and dose to the development of the liver injury
- Pertinent medical history
- Concomitant drugs with dates and doses
- Pertinent physical exam findings
- Test results (e.g., laboratory data, biopsy data and reports, with dates and normal ranges)
- Time course of serum enzyme and bilirubin elevations (consider tabular and/or graphical display of serial laboratory data)
- A summary of all available clinical information including, if known:
  - Prior or current history of ethanol use
  - Presence of risk factors for NASH (e.g., obesity, diabetes, marked hypertriglyceridemia)

  - Evidence for pre- or co-existing viral hepatitis, or other forms of liver disease, pre-study AT values, if available
  - Symptoms and clinical course including follow-up to resolution
  - Special studies (i.e., ultrasound, radiologic examinations, liver biopsy results)
  - Presence or absence of possible confounders, including concomitant illness, use of concomitant drugs that are known hepatotoxins, such as acetaminophen
- Discussion of hepatotoxicity as supported by available clinical data and overall assessment of the treating physician, consultants, and applicants as to the likelihood of DILI
- Treatment provided
- Dechallenge and rechallenge results, if done
- Outcomes and follow-up information
- Copies of hospital discharge summaries, pathology and autopsy reports

The availability of liver biopsy, explant, or autopsy slides for pathology review by review staff or external expert consultants has been helpful in the FDA's assessment of Hy's Law cases. Reports of external consultant opinions solicited by the applicant should be provided to the FDA.

Applicants also should provide complete narrative summaries that include the components previously listed for all subjects who died of hepatic illness, or who discontinued trial drugs for hepatotoxicity, including subjects with abnormalities consistent with protocol-specific stopping rules.

In some cases, a drug under consideration in the United States will have been marketed in other countries. In these cases it is important for the applicant to provide a synopsis of the global safety experience and level of usage and to describe in detail all cases of hepatotoxicity observed or suspected.

5. Overall Assessment of a Drug's Potential to Cause DILI

The overall assessment should characterize a drug's potential for DILI and should consider at least the following questions:

- Was liver monitoring sufficiently frequent and thorough to characterize DILI risk?
- Were there any cases of probable severe DILI?
- Were there signals of a potential for DILI (e.g., AT elevations, Hy's Law cases) and how were these signals assessed?
- What doses and durations of exposure were associated with hepatotoxicity signals?
- What approximate incidence of mild, moderate, and severe DILI can be expected postmarketing?
- Is the trial information sufficient to inform an overall risk-benefit assessment?
- Was there sufficient drug exposure (i.e., number of trial subjects and duration of treatment of each trial subject) and adequate liver test monitoring to reliably set an upper boundary for risk of severe DILI after marketing?

- What rate of severe injury (assuming Hy's Law cases occur at about 10 times the rate of severe injury) has been suggested or has been ruled out (e.g., no Hy's Law cases in 3,000 subjects implies a rate of such cases of <1/1,000 and thus a rate of severe DILI of <1/10,000)? This consideration should reflect the presence or absence of other signals, such as marked elevations of AT.
- Will some form of monitoring, by symptoms or serum testing, be needed? Usually, this would be considered only if there was evidence of severe liver injury or the potential for it. If so, effectiveness of monitoring, whether by symptoms or laboratory tests, and at what intervals should be discussed, and whether the results justify a monitoring recommendation in product labeling at the time of marketing approval.

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APPENDIX A: ILLUSTRATIVE EXAMPLES OF DILI

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).

Rezulin (troglitazone)

Troglitazone was approved by the FDA in January 1997 for the treatment of Type 2 diabetes mellitus. In reviews of the clinical trials of troglitazone conducted before approval there were no cases of liver failure among 2,510 subjects exposed to the drug in the NDA database, but 1.9 percent of troglitazone-treated subjects had ALT >3xULN compared to 0.3 percent of placebo-treated subjects, 1.7 percent had ALT >5xULN, and 0.2 percent (5 subjects) had ALT >30xULN (2 subjects in the last group also experienced jaundice). The median duration of troglitazone therapy before peak ALT elevation was 121 days. In the Diabetes Prevention Trial at the National Institutes of Health (NIH) performed after approval, 4.3 percent of 585 troglitazone-treated subjects had ALT ≥3xULN, 1.5 percent had ALT >8xULN, and 2 subjects had ALT >30xULN, compared to 3.6 percent of subjects with ALT ≥3xULN in the placebo group (Knowler and Hamman et al. 2005). One of the subjects in the Diabetes Prevention Trial with ALT >30xULN developed liver failure and died, despite receiving a liver transplant. The

second subject recovered. These data suggest that the rate of severe liver injury would be about 1 in 3,000 to 10,000.

After marketing, there were numerous reports of acute liver failure associated with troglitazone use (Gitlin and Julie et al. 1998; Vella and deGroen et al. 1998; Herrine and Choudary 1999), and four letters were sent to practicing physicians between 1997 and 1999, urging monthly monitoring and careful use. These letters did not significantly affect the monitoring done by physicians, and AT monitoring recommended in the Dear Health Care Professional Letters and in the package insert was not regularly performed (Graham and Drinkard et al. 2001). Moreover, an analysis of 94 cases of liver failure reported spontaneously to the FDA showed that the progression from normal hepatic test results to irreversible liver injury occurred in less than a month (the recommended monitoring interval) in 19 patients. The onset of injury began after 3 days to more than 2 years of troglitazone use (Graham and Green et al. 2003; Graham and Drinkard et al. 2003). Time from jaundice to hepatic encephalopathy, liver transplantation, or death usually was rapid, averaging 24 days. Troglitazone was withdrawn from the U.S. market in March 2000, when other drugs in the same class with similar efficacy but little or no evidence of hepatotoxicity became available (i.e., rosiglitazone, pioglitazone).

Apart from constituting another example of the predictive value of evidence of hepatocellular injury accompanied by even two cases of elevated bilirubin, there were other lessons learned from the troglitazone experience: 1) monitoring recommendations may not be well followed by physicians, even after warning letters are sent to all practicing physicians; and 2) some cases of severe hepatotoxicity occur rapidly, within less than a reasonable and practical recommended interval for monitoring, indicating that monitoring would provide at best only partial protection, even if recommendations were followed.

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.

Again, short-term tolerance of ximelagatran, with resolution of even substantial elevations of ALT in most cases, did not predict long-term safety. The relatively high rate of Hy's Law cases, about 0.2 percent or 1/500 (13 cases among 7,000 exposed patients), predicted the occurrence of severe hepatotoxicity, at a rate of about 1/5,000 (10 percent of the rate of Hy's Law cases). In fact, at least one death occurred among the 7,000 exposed patients from subsequent liver toxicity, further supporting such an estimate.