

# Drug safety, medication safety, patient safety:

## An overview of recent FDA guidances and initiatives

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### Key words

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### Abstract

Drug development and pharmacotherapy are components of integrated pharmaceutical medicine. The term 'drug safety' can be used when evaluating adverse events during clinical trials, and when evaluating adverse drug reactions to a correctly prescribed, dispensed and administered drug. The term 'medication safety' refers to the evaluation of medication errors that occur at the prescribing, dispensing and/or administration level; endeavours to educate clinicians and patients about the correct use of a particular drug; and the design and implementation of safety systems and educational programmes to minimise these errors. Drug safety and medication safety are subsets of patient safety.

Recent guidance documents and initiatives at the US FDA indicate the agency's awareness of the paramount importance of safety considerations throughout drug development and pharmacotherapy, its commitment to expand and enhance its governance role in lifecycle drug development, and its commitment to play an influential role in the safe use of medicines.

### Introduction

There is considerable current interest in patient safety among multiple stakeholders in the United States, including Congress,<sup>1</sup> individual congressional committees,<sup>2,3</sup> the FDA,<sup>4-6</sup> the Supreme Court,<sup>7</sup> the Institute of Medicine (IOM),<sup>8-12</sup> pharmaceutical and biopharmaceutical companies, patient advocacy groups, the media,<sup>13</sup> and, not least, prescribing physicians and their patients. This article focuses on some

recent FDA guidances and initiatives, listed in Table 1. The associated activities will complementarily enhance patient safety throughout drug development and pharmacotherapy, two components of integrated pharmaceutical medicine.

### Operationalising drug safety

No drug is immune from the possibility of causing adverse reactions in certain individuals who are genetically and/or environmentally

**Table 1: Guidances and initiatives discussed**

Date	Title (see references section for related websites)
<b>Guidances</b>	
March 2005	Premarketing Risk Assessment <sup>17</sup>
March 2005	Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment <sup>18</sup>
March 2005	Development and Use of Risk Minimisation Action Plans <sup>19</sup>
October 2007 (Draft)	Drug-induced Liver Injury: Premarketing Clinical Evaluation <sup>20</sup>
December 2008	E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: Questions and Answers <sup>22</sup>
December 2008	Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes <sup>25</sup>
<b>Initiatives</b>	
March 2008 (Draft)	Prescription Drug User Fee Act (PDUFA) IV Drug Safety Five-year Plan <sup>5</sup>
May 2008	The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety <sup>6</sup>
October 2008	Safety First/Safe Use Initiative <sup>27</sup>

susceptible. The concept of drug safety therefore needs to be operationally defined. One relatively simple but nonetheless meaningful conceptualisation of safety is as the inverse of harm: the less a drug's toxicity, the greater its safety.<sup>14</sup> A definition in terms of benefit–risk assessment was provided by the FDA's Sentinel initiative:<sup>6</sup>

'Although marketed medical products are required by federal law to be safe for their intended use, **safety does not mean zero risk**. A safe product is one that has acceptable risks, given the magnitude of benefit expected in a specific population and within the context of alternatives available.'

Benefit–risk assessment occurs at two levels in integrated pharmaceutical medicine. At the regulatory (public health) level, an investigational drug must have a favourable benefit–risk balance to receive marketing approval. Second, at the level of the individual patient, the prescribing physician and the patient must decide that a particular course of pharmacotherapy has a favourable benefit–risk balance.<sup>15,16</sup> In both cases benefit–risk assessment can be represented as follows:<sup>15</sup>

Benefit–risk estimate =  $\frac{\text{Estimate (probability and degree) of benefit}}{\text{Estimate (probability and degree) of harm}}$

While the qualitative aspect of a favourable benefit–risk balance is readily apparent, our quantitative abilities in this arena are not well developed, and the Sentinel initiative regards benefit–risk analysis to be 'one of the important facets of the science of safety that urgently requires additional development.'<sup>6</sup>

## Guidance documents addressing drug safety issues

**I. Risk assessment, characterisation, minimisation and management.** In 2005, three FDA guidances discussing risk assessment, pharmacovigilance and risk minimisation plans were released.<sup>17-19</sup> Each document focused on one aspect of risk management, an iterative process consisting of several actions that should be conducted continuously throughout a drug's lifecycle. In this manner, the results of ongoing risk assessment inform a sponsor's decisions regarding risk minimisation. This four part process is outlined in Table 2.

The first guidance in this trio discussed the generation, acquisition, and analysis of premarketing safety data. The larger and more

comprehensive the preapproval safety data base, the more likely it is that safety signals will be seen. However, the FDA points out that 'even large clinical development programmes cannot reasonably be expected to identify all risks associated with a product,' and therefore 'some risks will become apparent only after approval, when the product is used in tens of thousands or even millions of patients in the general population.'<sup>17</sup> The second guidance therefore addressed the collection of postmarketing safety data, noting that these data and the related risk assessment 'are critical components for evaluating and characterising a product's risk profile and for making informed decisions on risk minimisation.'<sup>18</sup>

A risk minimisation action plan (RiskMAP) is defined as 'a strategic safety programme designed to meet specific goals and objectives in minimising known risks of a product while preserving its benefits.'<sup>19</sup> RiskMAPs should target the achievement of particular goals related to known safety risks. These goals should be stated in such a way as to achieve maximum risk reduction, and should be translated into specific, pragmatic and measurable objectives that result in processes or behaviours leading to the achievement of the RiskMAP's goals.

**2. Drug-induced liver injury.** A recent guidance discussed the preapproval clinical evaluation of drug-induced liver injury (DILI).<sup>20</sup> As this guidance noted, hepatotoxicity has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years. While it focuses on preapproval evaluation, the guidance also provides a useful reminder of the need for postmarketing evaluations. The IOM has noted that 'the approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug – preapproval clinical trials do not obviate continuing formal evaluations after approval.'<sup>12</sup> Relatively rare adverse drug reactions are probabilistically unlikely to be seen in preapproval trials. Therefore, 'only the most overt hepatotoxins' can be expected to show cases of severe DILI in the 2,000 to 3,000 subjects typically studied and described in a new drug application (NDA).<sup>20</sup> Postmarketing surveillance is therefore critical for their detection.

As the guidance noted, a fundamental issue in preapproval hepatotoxicity research is this:

'Cases of severe DILI have rarely been seen in drug development programmes of significantly hepatotoxic drugs. What are regularly seen during drug development are mild liver injuries, often laboratory signals without any symptoms. The problem is that both drugs capable of severe DILI and drugs that have a low potential for causing severe injury... can generate these types of signals. Therefore, an approach is needed that can distinguish drugs likely to cause severe DILI from drugs unlikely to do so.'

Such an approach requires consideration of liver function as well as liver injury. The most specific predictor to date of a drug's potential for severe hepatotoxicity is the occurrence of two events in clinical trials: an increased rate of aminotransferase enzyme elevation in the treatment group compared with the control group; and evidence of reduced overall liver function in one or more subjects, as manifested by

**Table 2: Components of the process of risk minimisation**

- Assessing a product's benefit–risk balance
- Developing and implementing tools to minimise the product's risks while preserving its benefits
- Evaluating the effectiveness of these tools and reassessing the benefit–risk balance
- Making any necessary adjustments to the risk minimisation tools to further improve the benefit–risk balance.

increased serum total bilirubin, in conjunction with aminotransferase enzyme elevation, not explained by any other cause.<sup>20</sup>

**3. Cardiac drug safety.** Assessment of an investigational drug's proarrhythmic liability is a central component of contemporary cardiac drug safety. While it is neither a perfect nor the only potential indicator of such liability, the clinical evaluation of drug-induced QT interval prolongation is specifically addressed in ICH Guideline E14,<sup>21</sup> and the 'thorough QT/QTc study' has assumed considerable significance. Accordingly, the FDA formed its Interdisciplinary Review Team (IRT) in June 2006. The IRT is responsible for reviewing thorough QT/QTc study protocols and reports submitted by sponsors via any of the FDA's Center for Drug Evaluation and Research's (CDER) therapeutic review divisions, all of whom send these documents to the IRT and then receive back their comments. While this strategy provides a degree of consistency across the divisions, the IRT's comments are nonbinding, with final decisions in each case resting with the respective therapeutic division.

Since ICH E14 does not provide precise and unequivocal formulaic instructions on the conduct of a thorough QT/QTc study, the FDA recently published a 'Question and Answer' document<sup>22</sup> (see 'Insight on the interdisciplinary review team for QT studies in the FDA' on page 22) with the intent of helping sponsors become familiar with their interpretation of the guidance. (Such documents have already been published by Health Canada and the European Medicines Agency.<sup>23,24</sup>)

The employment of 'thresholds of regulatory concern' is also seen in the recent FDA guidance concerning the preapproval evaluation of cardiovascular risk in new antidiabetic therapies.<sup>25</sup> Cardiovascular risks mentioned include cardiovascular mortality, myocardial infarction, hospitalisation for acute coronary syndrome, and urgent revascularisation procedures. Here, thresholds of regulatory concern are considered in terms of risk ratio point estimates and confidence intervals calculated for the incidence of cardiovascular events occurring with the investigational drug compared with the control treatment.

### Initiatives addressing drug safety issues

**1. The FDA's drug safety five-year plan.** In March 2008, the FDA released its five-year drug safety plan<sup>5</sup> to communicate its strategy for meeting commitments for enhancing and modernising the drug safety system as written in the Food and Drug Administration Amendments Act (FDAAA).<sup>1</sup> The FDAAA, signed on 27 September 2007, is the third five-year renewal of the Prescription Drug User Fee Act (PDUFA) passed in 1992. Under PDUFA, sponsors pay a fee to the FDA every time an NDA or biologics license application (BLA) is submitted. Of particular note here is that PDUFA I and PDUFA II prohibited the use of fees for any postmarketing drug safety activities, and that PDUFA III allowed only a small percentage (around five per cent) of funds to be used in this manner: the focus was on getting new (effective) drugs to market. A major change in focus occurred in the FDAAA. Drug safety is a key component of this act, as reflected in Title IX, 'Enhanced authorities regarding postmarket safety of drugs'. This section provides the FDA with sweeping new safety authorities

**Table 3: The FDA's intended use of additional financial resources and new authorities for drug safety activities**

Increase staff levels of:

- Safety evaluators responsible for reviewing adverse events reported for, and evaluating the safety of, marketed drugs
- Epidemiologists responsible for reviewing protocols and study reports and conducting non-experimental pharmacoepidemiological studies
- Risk management experts, including risk management analysts, programme evaluators, and behavioural and social science experts. These personnel will be responsible for reviewing proposed and implemented risk management action plans (RiskMAPs) and risk evaluation and mitigation strategies (REMS), and reviewing and developing risk management communication tools
- Regulatory project managers responsible for providing regulatory input relevant to the management, tracking, and facilitation of projects related to drug safety, and the improvement of communication
- Medication experts devoted to medication error analysis and prevention.

With this increased staffing, the FDA will:

- Implement REMS
- Where appropriate, require postmarketing study/trial requirements
- Where appropriate, require safety labelling changes
- Enhance postmarketing risk identification by:
  - Linking, in a secure fashion, existing electronic databases run by private health plans, insurance plans, government agencies and industry
  - Querying electronic health records, claims databases, and other such repositories to pick up early warnings of adverse events
  - Studying de-identified data on millions of people in something much closer to real time.

and significantly increased funding with which to pursue safety activities. Table 3 provides a summary of the FDA's planned activities.

**2. Employment of risk evaluation and mitigation strategies.** Subtitle A of Title IX is entitled 'Postmarket studies and surveillance', and section 901 introduced risk evaluation and mitigation strategies (REMS). Prior to an investigational drug's marketing approval, the FDA can now require a sponsor to provide a REMS that addresses how safety will be optimised (how risk will be mitigated) once the drug is marketed. That is, a REMS will be required if the agency considers this necessary to ensure that, once marketed, a drug's benefits will outweigh its risks. Additionally, if the FDA becomes aware of 'new safety information' concerning a drug that is already marketed – where new safety information is defined as information tied to a serious risk associated with the drug – the agency can require a REMS to be submitted at this stage in the drug's lifecycle.

**Table 4: REMS components**

- A timetable for the sponsor's submission of assessments
- A medication guide
- A package insert
- A communication plan to healthcare providers. This plan may include sending letters to healthcare providers, disseminating information about the elements of the REMS to encourage healthcare providers to implement components that apply specifically to them, explaining safety protocols, eg, medical monitoring by periodic laboratory tests, and disseminating information through professional societies about any serious risks of the drug and any protocol to assure safe use
- Elements to assure safe use (see Table 5).

**Table 5: Elements to assure safe use**

- Healthcare providers who prescribe the drug have particular training or experience, or are specially certified
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain healthcare settings, such as hospitals
- The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
- Each patient using the drug is subject to certain monitoring
- Each patient using the drug is enrolled in a registry.

**Table 6: Objectives of the Safety First/Safe Use initiative****Specific objectives of the Safety First initiative:**

- Create and maintain a collaborative, multidisciplinary, team-based approach to the review of drug safety
- Use world-class project management skills throughout lifecycle drug development, including postmarketing safety issues
- Align policies and processes to ensure the most appropriate and best qualified experts lead, or have an equal voice in, regulatory decisions
- Build the scientific, administrative and technological capacity to carry out the provisions of FDAAA/PDUFA IV
- Ensure significant postmarketing safety issues are the CDER's highest priority.

**Preliminary objectives of the Safe Use initiative:**

- Develop a cutting-edge pharmacovigilance system for evaluating drug performance using electronic health data
- Collaborate with stakeholders in the healthcare system to devise effective, efficient steps to ensure drugs are used as appropriately as possible, in ways that minimise medical errors and manage risks aggressively.

Like RiskMAPs, REMS are not general 'how to use the drug' documents. Rather, a REMS addresses a specific potential risk indicated by a safety signal.<sup>26</sup> A REMS should therefore include a goal statement concerning the risk to be mitigated. Various possible additional components are listed in Table 4, and details of the 'elements to assure safe use' (ETASU) are provided in Table 5. The single required component of those listed in Table 4 is a timetable for submission of assessments of the REMS. At a minimum, assessments must be submitted by 18 months, by three years, and in the seventh year after the REMS is approved.

**3. The Sentinel initiative.** In May 2008 the FDA released the Sentinel initiative, a central goal of which is the creation of the Sentinel System, 'a national, integrated, electronic system for monitoring medical product safety.'<sup>6</sup> This system represents the application of information technologies to the way health-related information is collected, managed, and shared. This document notes that a lifecycle approach 'should be used for all medical products so that safety signals generated at any point in the process can be evaluated along with relevant benefit–risk data to inform treatment choices and regulatory decision-making.' The Sentinel initiative also discusses the emerging science of safety, which combines a growing understanding of disease and its origins with new methods of safety signal detection.

**4. The Safety First/Safe Use initiative.** The Safety First/Safe Use initiative was outlined in the CDER 2007 update.<sup>27</sup> This initiative 'builds on authorities and opportunities provided by the FDAAA,' effectively supporting the FDA's ability 'to manage safety throughout the entire lifecycle of pharmaceutical products.'<sup>27</sup> The Safety First initiative refers to steps that modernise and strengthen the CDER's internal policies and processes to manage significant drug safety issues, and the specific objectives are presented in Table 6.

As these changes are put in place, the Safe Use initiative will begin to focus on medication safety. Pharmacotherapy is a high risk field: tens of thousands of patients in the US die each year from adverse drug reactions resulting from medication errors, errors whereby patients are prescribed, dispensed, and/or administered an unintended drug or drug regimen.<sup>8</sup> Since 'human error cannot be eradicated',<sup>28</sup> key requirements for optimally safe pharmacotherapy include the development and implementation of safety systems that will identify and correct errors in the multi-step process before a patient actually takes the drug, encouraging a nonpunitive culture where 'admitting' mistakes is welcomed as a proactive step toward improving these safety systems and preventing similar errors in the future, and providing appropriate education during clinical training and practice.<sup>11,29-32</sup> Since the FDA does not control the healthcare system, it intends to improve the safe and appropriate use of marketed drugs by employing influence instead. The preliminary objectives of the Safe Use initiative are also presented in Table 6.

**Conclusion**

This article has provided an overview of recent FDA guidances and initiatives related to drug safety and medication safety, and hence

to patient safety. These initiatives span a broad range of activities within lifecycle drug development and the practice of pharmaceutical medicine. Like any other large and complex organisation, the FDA is not immune from criticism, and neither is it the only regulatory agency working hard to improve patient safety. Nonetheless, the FDA's current activities and commitments will have a considerable impact on the safe and effective use of pharmaceutical drugs in the US, and hence on the health and wellbeing of its people.

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