



# Clinical Research Risks and the Importance of Life-Cycle Safety Assessments

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**D**rug development is a high-risk business. Pharmaceutical companies spend billions of dollars each year testing compounds at various stages in development, only to shelve the vast majority. Reasons for product failure range from lack of efficacy to insufficient funds for development to serious safety issues. Approval is based, in part, on benefit-risk ratio, allowing drugs with significant safety concerns to gain approval only if the benefit and need are great enough.

Determining the benefit-risk profile is an ongoing life-cycle process beginning in the discovery and preclinical phases, continuing through clinical development, and into the postmarketing phase and beyond. In recent years there has been a trend toward increasing enforcement of regulatory compliance and with it, a focus on risk

assessment and management. Regulations are designed to provide a review and assessment of safety data, but legal compliance does not “guarantee” the safety of a drug.

On March 13, 2006, six male clinical trial participants experienced life-threatening severe adverse reactions after taking TeGenero’s investigational new drug TGN1412 at the trial site at Northwick Park Hospital in London, England. All subjects had a severe inflammatory response with multi-organ system involvement and were taken immediately to the Critical Care Unit. The media reported that United Kingdom’s Medicines and Healthcare products Regulatory Agency (MHRA) did not identify any concerns during the preclinical testing and these adverse events were not foreseeable. It was reported that a volunteer complained of being rushed to

sign the informed consent. The result was catastrophic for the company. On July 4, 2006, TeGenero filed for bankruptcy protection. The following day, Northwick Park Hospital reported on its website that all six subjects had recovered and been discharged home. The TGN1412 development appeared to have been legally compliant, but not safe.

A closer look at specific areas during clinical development provides some insight into why legal compliance may or may not identify or address a serious safety risk.

## Preclinical Clues

Establishing a drug’s safety profile begins with the discovery of a new chemical entity. Physical chemical properties of a compound provide alerts to solubility, stability, and compatibility with other drugs in solution.

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Stability issues, if not properly investigated can lead to lack of efficacy or other unwanted effects. For drugs used in critical or emergent care settings, this can lead to a serious safety risk for the patient, a well-recognized fact for outdated sublingual nitroglycerin tablets used for treating angina.<sup>1</sup>

Preclinical studies should anticipate clinical uses. Chymopapain (Chymodiactin<sup>®</sup>) was introduced in the early 1980s to dissolve herniated lumbar discs through the proteolytic action of the enzyme derived from papaya.<sup>2</sup> While it was anticipated that there would be subjects who would have allergies to papaya, another clinical use was not anticipated and not studied. When introduced into the marketplace, physicians were trained to use a radiopaque contrast media (Renografin<sup>®</sup>) to fluoroscopically guide the needle used to introduce the Chymodiactin<sup>®</sup> into the nucleus pulposus of the intervertebral disc. Besides dozens of patients who suffered anaphylaxis, neurological tragedies occurred as well, ranging from transverse myelitis to seizures. Examination of radiographic films taken during procedures demonstrated that the dye used to visualize the field migrated through anomalous vessels or through distinct needle ruptures into the spinal canal. Further examination of the Renografin<sup>®</sup> information demonstrated neurotoxicity when used intrathecally.

After dozens of neurologic tragedies, studies in primates combining the dye with the enzyme resulted in a 75% complication rate in the primates. Had these studies been undertaken preclinically, the product would probably not have gone into clinical studies, and certainly scores of patients would not have died, or had life-threatening and paralyzing reactions.

A clear understanding of pharmacodynamics is also essential. Most drugs have more than one mechanism of action, although a specific one may be the focus of the clinical development plan. Phenytoin, commonly administered intravenously in an emergency department, can lead to asystole if injected too quickly due to its properties as an antiarrhythmic.<sup>3</sup> Thoughtful consideration to investigating a drug's range of effects can help to identify and mitigate these risks.

Pharmacokinetic profiles have assumed an increasingly more important role as pharmacogenomics continues to emerge as a science. Cytochrome P450 (CYP) drug interactions, now an important part of development, can have fatal implications. Terfenadine (Seldane<sup>®</sup>) was approved prior to Food and Drug Administration (FDA) routinely requesting this type of data during development. Once in general use, the combination of terfenadine with ketoconazole or erythromycin led to increased serum terfenadine levels that resulted in prolonged QT intervals and fatal torsades de pointes due to ketoconazole's and erythromycin's ability to inhibit terfenadine's metabolism.<sup>4</sup>

As pharmacogenomics enhances our understanding of CYP enzymes and ability to identify individuals with variations of enzyme activity (e.g., poor vs. ultra-rapid metabolism), it is possible to anticipate pharmacokinetic-based adverse reactions through drug interaction studies and determination of genotype.<sup>5</sup> Genetic testing, while available, is not widely used. As a result, warfarin interactions remain a major cause of adverse reactions due to CYP 2C9 variants.<sup>6,7</sup> A few commercial companies offer such testing, such as Genelex (<http://www.healthanddna.com/professional/index.html>). FDA

and industry working groups have spent a great effort on identifying ways to use this new science in drug development, with an eye to improved medication selection and safety.<sup>8</sup>

Interpreting preclinical data and extrapolating it for human use remains a challenge. Results may be "species-specific" and not easily generalizable. Often doses selected for the first human trials are based on best estimates from the preclinical efficacy, pharmacokinetic, safety, and toxicology data. An integrated approach between the preclinical scientists and the clinical research team is critical to early anticipation, identification, and surveillance of significant and serious adverse reactions.

### Clinical Pitfalls

Clinical development plans seek to provide the best studies to demonstrate efficacy and safety for a new drug, as well as meet regulatory requirements needed for approval. Protocol design plays an important role in capturing anticipated and unanticipated adverse events. A Phase I protocol design based on safety concerns identified in preclinical trials will proactively gather data to evaluate these issues. Preclinical safety issues may be difficult to address in Phase I protocols, however. An investigational anticancer agent causing asymptomatic irreversible pulmonary fibrosis in a single primate species found only at necropsy may be difficult to detect in single or multiple dose Phase I human studies. Incorporating specific safety objectives and directed data collection into protocol designs as well as sufficient safety surveillance measures in the clinical development plan become paramount.

Safety surveillance, including trend analysis and signal detection, should



be ongoing activities throughout the clinical development period. Each clinical study is individually reviewed and analyzed, but often the clinical data is not examined in aggregate until certain milestones are reached (e.g., end of Phase II, new drug application (NDA) submission, and preparation of the Integrated Summary of Safety). Small, seemingly transient, elevations in serum creatinine following administration of a new anti-diabetic drug may appear innocuous during Phase I and II. When viewed collectively, however, this may signal a serious safety issue for diabetic patients with marginal or compromised renal function. If approved, patients may experience renal failure resulting in transplant or death in the postmarketing phase and approval may be withdrawn. Not only is this a considerable risk to patients, it also results in liability and decreased corporate credibility.

## Role of Clinical PI

A clinical trial's principal investigator (PI) has oversight and responsibility for conduct of the study and providing a safeguard for patients, as described in 21 CFR §312.60, General Responsibilities of Investigators, and subsequent sections in 21 CFR §312 Subpart D.<sup>9</sup> The PI determines eligibility for enrollment and reviews adverse reactions for each subject, intervening as needed to adjust drug dosing, terminate participation, suggest protocol revisions, or take other actions. As with pharmaceutical companies, the FDA may inspect the PI's office routinely or for cause. PIs are coming under increasing regulatory scrutiny over the past decade (1997-2006), when FDA-issued warning letters peaked at 32 in 2004.<sup>10</sup> Regulators review delegation of authority, investigator

supervision, site where research was conducted, how data were collected, as well as other aspects of the study.

Inspectors will also compare data already received by the agency with the investigator's study records. Common deficiencies include inadequate and inaccurate records, inadequate drug accountability, protocol violations, informed consent noncompliance and poor adverse event reporting. Following an inspection, FDA may decide no action is indicated or may request a voluntary or official response and issue a warning letter. Recent warning letters issued by FDA to Drs. Robert Hostoffer of South Euclid, OH,<sup>11</sup> and Clark Bishop of Provo, UT,<sup>12</sup> on June 6 and 7, 2005, respectively, are examples of clinical investigators cited for deficiencies related to protocol violations, informed consent issues, and improper or lack of reporting serious adverse events. Any of these deficiencies can place patients at risk, but inaccurate records or unreported adverse events can have a long-term impact if these deficiencies go undetected and subsequent data review and analysis are used for approval and subsequent product labeling.

## Role of the IRB

The Institutional Review Board (IRB) is also intended to provide patient protection and ensure proper conduct of clinical trials as described in 21 CFR § 50, Protection of Human Subjects<sup>13</sup> and 21 CFR § 56, Institutional Review Boards.<sup>14</sup> IRBs approve and monitor aspects of study conducted in conjunction with PIs, including protocols, informed consent documents, and ongoing review of serious adverse events reported by patients. IRBs have the authority and responsibility to stop a clinical trial

when necessary for safety concerns. As with clinical investigators and pharmaceutical companies, IRBs have come under greater regulatory scrutiny in the past decade, with a peak of 11 FDA warning letters to IRBs in 1999 followed by a decreasing trend.<sup>15</sup> Common deficiencies include IRB review of research, recordkeeping, functions and operations.

Patient protection through informed consent is critical. A recent warning letter issued by FDA to the Institutional Review Board of the Baltimore City Health Department on December 15, 2005, provides an example of IRBs cited for deficiencies related to following IRB procedures, informed consent issues, and "failing to conduct continuing review of research at intervals appropriate to the degree of risk."<sup>16</sup> Any of these deficiencies place patients at risk, but improper study conduct or inadequate review of adverse events can have both a short and long term impact on patient safety.

Patients are placed at greatest risk when both the PI and IRB fail to fulfill their obligations in clinical trials. The March 31, 2003, warning letter from the FDA to Dr. Alkis Togias of the Johns Hopkins Asthma & Allergy Center describes the worst possible outcome--the death of a healthy, normal volunteer.<sup>17</sup> In this widely publicized case, the PI failed to submit an investigation new drug (IND) application to the agency, did not notify or obtain approval from the IRB for changes in protocol or research activity, and did not include several essential elements in the informed consent (e.g., risk of lung toxicity and death). The PI was experienced in clinical research, Form FDA 1572 was signed and submitted for 11 IND applications previously. The docu-



ment also suggests the IRB was not providing adequate oversight, as seen with the deficiencies in the informed consent form.

## Role of Risk Management

Safety risks during clinical trials can be reduced through regulatory compliance, but not eliminated. Current approaches involve identifying and managing risk throughout the life cycle. In addition to long-standing safety reporting regulations, regulatory agencies globally have created guidelines to address this and expect ongoing risk assessments. In March 2005, FDA issued three Guidances for Industry regarding risk management: Premarketing Risk Assessment;<sup>18</sup> Development and Use of Risk Minimization Action Plans (RiskMAPs);<sup>19</sup> and Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.<sup>20</sup> The latter is similar to the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline E2E Pharmacovigilance Planning released in November 2004.<sup>21</sup>

Each of these documents addresses aspects of safety data collection, risk analysis, risk mitigation and ongoing safety evaluation for the pre- and postmarketing phases. Pharmacoepidemiology has a more important role in data analysis and work is ongoing to develop new methods for signal detection and risk assessment.

Risk management plans can be initiated by the pharmaceutical company or required as a postmarketing commitment by FDA, particularly for products with accelerated approval. Thiazolidinediones rosiglitazone (Avandia®) and pioglitazone (Actos®) were in late clinical development when serious and fatal liver complications became evident with another drug

in this class, troglitazone, ultimately requiring its withdrawal. A postmarketing commitment for a pioglitazone safety study<sup>22</sup> was initiated and enabled establishment of a more detailed safety profile based on the pioglitazone marketed experience. This subsequently provided better prescribing information and opportunity for diabetic patients to use pioglitazone safely. Without this ongoing risk assessment, a clearer safety profile may not have been available and the product may have been withdrawn early for presumed safety concerns.

## Conclusion

Safety risk minimization remains an ongoing challenge for pharmaceuticals. A life-cycle approach is most effective when started with discovery and preclinical data, with continual assessments throughout the clinical development and postmarketing phases. Newer pharmacoepidemiologic and statistical methods for signal detection will help in the identification of risk. Thoughtful and comprehensive risk assessment and mitigation through RiskMAPs and other variations of risk management plans should be effective in enhancing patient safety and reducing risk. ▲

<sup>1</sup> D.P. Page & N.A. Carson et al., *Stability Study of Nitroglycerin Sublingual Tablets*, 64 JOURNAL OF PHARMACEUTICAL SCIENCES 140-7 (1975).

<sup>2</sup> J.T. O'Donnell, *Chymopapain: A New Therapeutic Agent*, 7 INFUSION pp.(1983).

<sup>3</sup> S. Zonerach & O. Zonerach et al., *Sudden Death Following Intravenous Sodium Diphenylhydantoin*, 91 AMERICAN HEART JOURNAL 375-7 (1976).

<sup>4</sup> B.P. Monahan & C.L. Ferguson et al., *Torsades de Pointes Occurring in Association with Terfenadine use*, 264 JAMA 2788-90 (1990).

<sup>5</sup> G.R. Wilkinson, *Drug Metabolism and Variability Among Patients in Drug Response*, 352 NEW ENG. J. OF MED. 2211-21 (2005).

<sup>6</sup> M.K. Higashi & D.L. Veenstra et al., *Association Between CYP 2C9 Genetic Variants and Anticoagulation-related Outcomes During Warfarin Therapy*, 287 JAMA 1690-98 (2002).

<sup>7</sup> M.J. Rieder & A.P. Reiner et al., *Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose*, 352 NEW ENG. J. OF MED. 2285-93 (2005).

<sup>8</sup> Lawrence J. Lesko & Ronald A. Salerno et al., *Pharmacogenetics and Pharmacogenomics in Drug Development and Regulatory Decision Making: Report of the First FDA-PWG-PhRMA-DruSafe Workshop*, in THE PROCESS OF NEW DRUG DISCOVERY AND DEVELOPMENT Chapter 11 (C.G. Smith & J.T. O'Donnell, 2nd Edition, Taylor and Francis, Boca Raton, (2006)).

<sup>9</sup> Investigational New Drug Application, Subpart D Responsibilities of Sponsors and Investigators, 21 C.F.R. § 312.50 – 312.70 (2005).

<sup>10</sup> J. Andrew Lemons, Attorney at Law, Baker Donelson Bearman Caldwell & Berkowitz, Trends in FDA Warning Letters to Clinical Investigators, Drug Information Association Annual Meeting oral presentation, (June 22, 2006), Phil. PA (Source: FDA, Office of Compliance and CDER Division of Scientific Investigations, based on review of publicly available data from 1 June 1977 to 15 May 2006).

<sup>11</sup> Warning letter from Mary A. Malarkey, FDA Center for Biologics Evaluation and Research, to Dr. Robert W. Hostoffer, Allergy and Immunology Associates, (June 6, 2005) available at [http://www.fda.gov/foi/warning\\_letters/g5355d.pdf](http://www.fda.gov/foi/warning_letters/g5355d.pdf) (last visited July 12, 2006).

<sup>12</sup> Warning letter from Drs. Leslie Ball and Joanne L. Rhoads, FDA Center for Drug Evaluation and Research, to Dr. Clark Bishop, Utah Valley Institute of Cystic Fibrosis, (June 7, 2005) available at [http://www.fda.gov/foi/warning\\_letters/g5365d.pdf](http://www.fda.gov/foi/warning_letters/g5365d.pdf) (last visited July 12, 2006).

<sup>13</sup> Protection of Human Subjects, 21 C.F.R. § 50 (2005).

<sup>14</sup> Institutional Review Boards, 21 C.F.R. § 56 (2005).

<sup>15</sup> J. David Vulcano, Chief Research Officer, Psychiatric Solutions Inc., Trends in FDA Warning Letters to IRBs, Drug Information Association Annual Meeting oral presentation, (June 22, 2006), Phil., PA (Source: Publicly available FDA Warning Letters to IRBs 1997-2005).

<sup>16</sup> Warning letter from Mary A. Malarkey, FDA Center for Biologics Evaluation and Research, to Dr. Nkossi Dambita, Institutional Review Board Chairman, Baltimore City Health Department, (Dec. 15, 2005) available at [http://www.fda.gov/foi/warning\\_letters/g5667d.pdf](http://www.fda.gov/foi/warning_letters/g5667d.pdf) (last visited July 12, 2006).

<sup>17</sup> Warning letter from Drs. Antoine El-Hage and Joanne L. Rhoads, FDA Center for Drug Evaluation and Research, to Dr. Alkis Togias, Johns Hopkins Asthma & Allergy Center, (Mar.31, 2003) available at [http://www.fda.gov/foi/warning\\_letters/g3936d.pdf](http://www.fda.gov/foi/warning_letters/g3936d.pdf) (last visited July 12, 2006).

<sup>18</sup> FDA, CDER, & CBER, Guidance for Industry: Premarketing Risk Assessment, available at <http://www.fda.gov/cder/guidance/6357fnl.pdf> (issued Mar. 2005).

<sup>19</sup> FDA CDER & CBER, Guidance for Industry: Development and Use of Risk Minimization Action Plans, available at <http://www.fda.gov/cder/guidance/6358fnl.pdf> (issued Mar. 2005).

<sup>20</sup> FDA, CDER, & CBER, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, available at <http://www.fda.gov/cder/guidance/6359OCC.pdf> (issued Mar. 2005).

<sup>21</sup> International Conference on Harmonisation (ICH): ICH Harmonised Tripartite Guideline E2E, Pharmacovigilance Planning, available at <http://www.ich.org/LOB/media/MEDIA1195.pdf> (issued Nov. 2004).

<sup>22</sup> Takeda Actos® Postmarketing Study Commitment available at <http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm> (last visited July 12, 2006).