



A Symbol of Excellence

Drug Safety

Providing strategies and
solutions to help sponsors
maximize drug safety



The challenge of safety

Every day, around the globe, pharmaceutical researchers are working to develop safe, effective medicines to relieve suffering and promote health. Although there have been many significant accomplishments in the pharmaceutical industry, over the last 20 years, there have also been serious setbacks. Numerous, highly publicized instances of drug safety recalls have had lasting repercussions within the industry and have led to an increased focus on issues related to drug safety and surveillance.

A global and growing problem

All drugs have inherent risks associated with them. In the U.S. alone, it is estimated that over 100,000 people die each year from adverse drug reactions (ADRs) or medication mistakes (nearly double the rate of deaths reported just a decade ago). In Europe, an Impact Assessment carried out for the EU Commission estimated that ADRs kill over 197,000 per year in European hospitals.

Most side effects surface during the clinical trial phase and are addressed either by changing the drug's formulation, adjusting the dosage, or identifying groups of patients who should not use the drug. However, many side effects, including some that are serious or even life-threatening, only come to light after the drug has reached the general population and it may be many months, or even years, before their dangers are revealed or fully understood.

Safety today: Regulators are taking a closer look

As more patients around the world take more medications and the incidence of adverse events keeps rising, regulatory bodies are increasingly scrutinizing the safety profiles of both new and established drugs. They are now requiring pharmaceutical companies to conduct more research and provide more data related to the safety of their products.

“The new safety regulations have an appreciable impact on the industry as a whole”

According to 77% of respondents surveyed in a recent research study *

The FDA Amendments Act of 2007 was created primarily to fund additional safety review resources within the FDA. Safety agencies in Europe are also engaged in strengthening safety regulations. The EU Clinical Trials Directive made the failure to report adverse events from clinical trials a criminal offence, while the Medicines and Healthcare Products Regulatory Agency has also begun to aggressively press for changes in EU and British law relating to drug safety assessment and monitoring.

Safety is also clearly identified as one of the four pillars of the European Innovative Medicines Initiative that aims to improve the predictivity of safety evaluation by addressing problems and bottlenecks specifically related to safety evaluation and risk-benefit analysis.

Safety management: The importance of a global strategy

Safety management requires a strategic plan that anticipates and addresses multiple scenarios, risks and contingencies. As the drug and device market becomes ever more multi-national, these strategic plans need a global focus. However, tracking products, compiling adverse event data and meeting the regulatory requirements of many different countries can be a daunting challenge.

* According to the findings of a research study "Safety First: The Impact on New Regulations on Clinical Development," May 09, conducted by IMS/ICON plc. This study was based on a survey of 140 industry safety specialists including Heads of Medical, Drug Safety, Pharmacovigilance, and Regulatory within large and mid-sized pharmaceutical companies and biotech firms.



At ICON, we have the expertise that spans the entire lifecycle of drug development. Our team of global safety experts is ideally positioned to design and implement comprehensive drug risk management programs and Phase IV safety surveillance programs.





Getting a head start on safety in early development

The most successful development programs incorporate safety considerations right at the outset of the process. At ICON, we assist sponsors in creating and executing comprehensive development plans that include processes and methodologies for identifying and addressing important safety issues. Our Development Solutions division acts as an early “translational medicine” research resource for sponsors who are developing new drugs and providing sponsors with critical insights on how a new compound is likely to behave under a variety of scenarios.

Early Formulation

ICON can examine and analyze the chemical structure of the active substance ingredient(s) and the initial formulation of a new product. Our analyses include time and cost-saving screening procedures for the purpose of acquiring predictive information with both safety and efficacy implications.

Our services include:

- Advice on quantification methodologies to provide key information about the active and inactive ingredients of the compound
- Advice on light, temperature and humidity sensitivity testing requirements
- Guidance to refine and further develop the formation and initial dosage forms for the product

The goal in all these procedures is to ensure that any new therapeutic compound will be as safe and stable as possible.

During this early formulation process, we can also help clients to plan and execute non-clinical pharmacology and toxicology testing, a critical regulatory requirement on the drug development pathway.

Pharmacology and Toxicology Testing

ICON’s toxicology professionals have the expertise to review the information about your compound and provide advice on whether your development program should include sequential single and repeat-dose (subchronic and chronic) studies in a variety of rodent and non-rodent species to examine the effects of the drug at different dose levels and durations. The focus of these studies is to define target-organ toxicity following systemic exposure and to provide data on the no observable effect level (NOEL) and the no observable adverse effect level (NOAEL) - information critical to the selection of an initial safe dose in man. ICON can also provide guidance on what other in vitro and in vivo safety studies should be conducted including genotoxicity, reproductive, immunotoxicity, drug-drug interaction, local toxicity, and phototoxicity studies. ICON can also support nonclinical CV safety testing (ICH7SB) and the in-vitro assessment of CYP450 pathways of metabolism.

First-Time-in-Man

Once the pre-clinical package satisfies regulatory drug characterization and safety requirements, ICON can support the conduct of Phase I studies, within healthy human volunteers or patients who have a target disease. For these studies, ICON utilizes our specialized Phase I units in Texas, Nebraska, and Manchester, UK. We have extensive experience in a range of studies including first-time-in-man, dose escalation, PK/PD, multiple dose drug interaction, Phase I patient and special population studies. ICON’s bioanalytical labs in Whitesboro, NY and Manchester, UK can assay both small and large molecule drug products and interface with our PK-PD modeling group to provide Population PK analysis during the later development phases.

Tracking safety across later development phases

As potential new drugs move further through the development process, proactive monitoring, evaluation, and handling of safety issues are essential for safeguarding patient safety.

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“ the number of Phase IV trials are expected to increase in the next five years.”

According to 80% of interviewees surveyed in a recent research study.*

Our full spectrum of services include:

- Total Product Safety Center
 - Post-marketing Surveillance (Adverse Event Collection / handling)
 - Drug Information Services
 - Product Complaint Management
- Fully validated, E2B compliant global safety database
- Qualified Person for Pharmacovigilance (QPPV) in Europe
- Signal detection activities / data mining
- Global interaction with Competent Authorities
- Aggregate periodic reporting (PSURs / Annual Safety Reports)
- Registry / Post-marketing authorization study design and implementation
- Specialized Safety Consulting

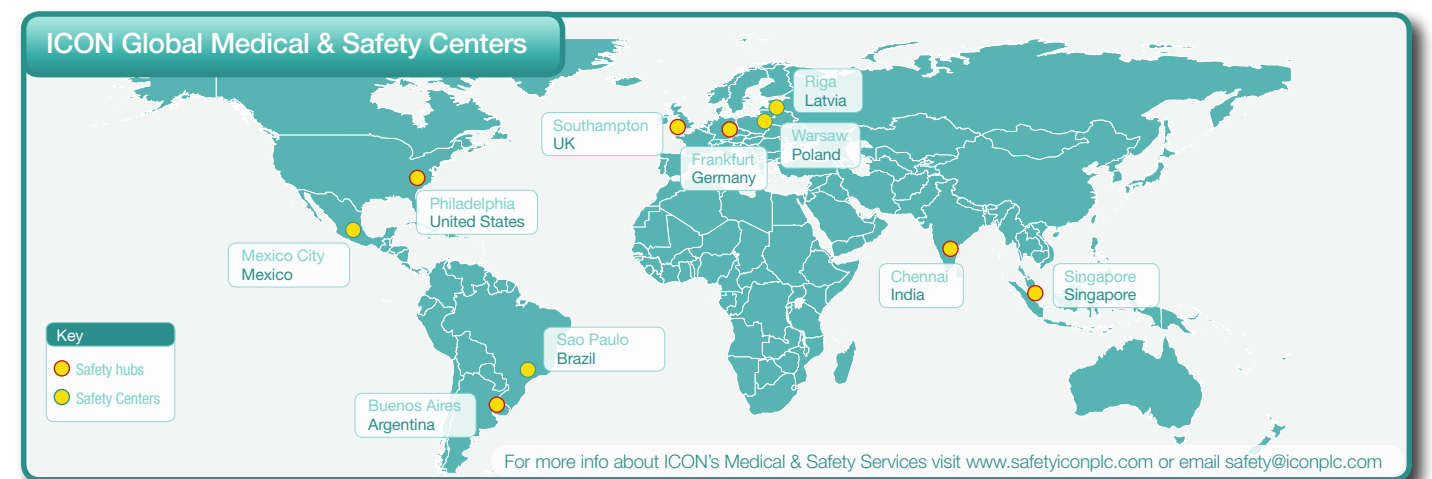
ICON’s experienced medical and regulatory staff comprised of healthcare professionals, including physicians, nurses, and other allied health professionals can provide a roadmap to navigate through regulatory “grey areas” and ensure risk minimization activities are implemented effectively and swiftly.

Drug Safety and Pharmacovigilance services are centralized at six global safety hubs located in the United States, United Kingdom, Germany, India, Argentina, Singapore and supported by 4 additional Medical and Safety Centers in Mexico, Brazil, Latvia and Poland. This global reach places us in a strategic position to offer expert drug safety and pharmacovigilance services with a high degree of oversight, consistency, and reliability.

Registries, Observational Studies and Epidemiology - An evolving requirement

ICON has extensive experience designing and coordinating prospective and retrospective safety studies for our clients. These studies, which include patient registries and observational studies, have been designed to meet a wide range of objectives, from fulfilling a post-marketing regulatory commitment to assessing the comparative safety associated with the treatments for a specific disease. Programs have ranged from a single center to over 2,000 centers with patient populations ranging from 20 to over two million across all major therapeutic areas.

The range of our specialties, combined with our technical expertise, allows ICON to support the scientific research needs of our clients through multiple publications and presentations of research findings. Additionally, ICON has a scientific core team of epidemiologists experienced in cohort analyses, conducting retrospective healthcare-related database analyses, and safety registries. These individuals average 10 years of government, academic, industry, clinical, and consulting experience in epidemiology.





Data Safety Monitoring Boards

Data Safety Monitoring Boards (DSMBs) and Clinical Event Committees (CEC) are becoming a more prominent element of clinical research trials. They are comprised of physicians with expertise in the relevant therapeutic area or clinical specialty that review all relevant study data to provide an independent determination of trial endpoints or events.

DSMBs, also known as Data Monitoring Committees (DMCs) or Independent Data Monitoring Committees (IDMCs) have responsibility for regularly reviewing all interim safety data collected during the clinical trial process. Following these reviews, DSMBs advise sponsors, investigators and institutions on issues related to subject safety as well as the continuing validity and scientific merit of the clinical trial under scrutiny.

ICON has experienced professionals who can assist sponsors in establishing and managing a DSMB in compliance with relevant regulatory guidelines. Since 2002, we have incorporated DSMBs into more than 100 studies across all major therapeutic areas. ICON's unique cross-functional team approach allows all members of the study team, including the DSMB, to interact easily, for maximal customer service and benefit.

Imaging, event adjudication and DSMB support

ICON's Medical Imaging division provides core laboratory imaging services and customized medical informatics solutions. Their market leading experience and expertise has resulted in unique technology solutions for assessment of efficacy and safety in drug development. The technology used by ICON Medical Imaging (IMI) for image and non-image based assessment is based on proprietary technology called MIRA™ (Medical Image Review and Analysis System).

This technology can be coupled with ICON's clinical expertise in Clinical Endpoint Committee (CEC) and DSMB to create a unique integrated service for sponsors.

MIRA™ enables clinical data and related images to be posted online and viewed by CEC or DSMB members. For CEC, data is "cleaned" prior to posting and quality controlled for completeness by adjudication monitors in our Medical Safety & Services group. Entries are made in an eCRF integrated in the system. DSMB multipart tables and listings can be displayed, filtered and searched remotely, which facilitates safety review.

Imaging as a Biomarker for cardiac safety

ICON Medical Imaging also provides expertise in the design, toxicity thresholds, site training, centralized collection, masking, technologist quantitation, reader training and cardiologist over-read of all major cardiac imaging modalities. Each imaging modality can be used to assess for a possible toxic effect of a drug on cardiac or vascular function. Our academic links, wide experience in prior studies and regulatory background in cardiac imaging is unique amongst commercial core imaging laboratories.

Our Services include:

- Chief Medical Officer is a practicing Cardiologist, certified in multiple modalities
- Imaging specialists are registered cardiac technologists
- Quantitative measurement of left ventricular function by echocardiography, MUGA (Multiple Gated Acquisition Scan), coronary angiography, cardiac MRI (Magnetic Resonance Imaging), SPECT, CT angiography
- Measurement of myocardial perfusion by SPECT, MRI
- MIRA system allows on-line review of echocardiography images for rapid reporting

Our academic links, wide experience in prior studies and regulatory background in cardiac imaging is unique in the commercial core imaging sector.



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Central Laboratory testing - Ensuring clinically relevant safeguards

Laboratory test results often provide the first indication that a potential safety issue may exist, either in an individual study subject or in the study population as a whole. As a global central laboratory, dedicated exclusively to clinical trials, ICON Central Laboratories works closely with sponsors from the time a clinical protocol is in development until study closeout to ensure clinically relevant safeguards for subject safety.

Due to the ever-changing scope and complexity of available laboratory testing, we recommend pre-study collaboration to determine appropriate marker selection and to help ensure that the required specificity is available to monitor study subjects and make certain that clinical endpoints are met.

Rapid test result turnaround is critical and our scientific affairs and global logistics staff help expedite this process. Front-end study planning and consultation services help sponsors evaluate required assays against sample transit times from geographically diverse sites. This ensures timely availability of subjects' test results for appropriate medical management.

We work closely with sponsors and sites to provide robust tools to detect and respond to clinical issues that may arise, using capabilities such as study-specific alert ranges, delta flags and toxicity grading, to offer maximum protection to study subjects. And we continue to look for new ways to support safety reporting activities. For example, we utilized an on-demand language interpretation service via telephone for use when site services staff must communicate panic values and urgent alerts to sites with limited English-speaking ability.

To drive efficiencies ICOLabs™, a secure, web-based remote data access tool gives medical and safety monitors the ability to review laboratory results against specified criteria or across result histories for one subject, the entire study population or a user-defined sub-population. This tool improves the quality of the pharmacovigilance process and increases the efficiency of personnel responsible for monitoring subject safety.

ICON sets the standard

The safety of marketed drugs as well as those in development has never been such a priority. Today, safety management requires a strategic plan that anticipates and addresses multiple scenarios, risks and contingencies. Clinical research organizations must demonstrate that they can ensure that safety programs are conducted according to the highest scientific standards. ICON understands the safety lifecycle – from product inception through commercialization. Our team of global safety experts is ideally positioned to design and implement comprehensive drug risk management programs and Phase IV safety surveillance programs.



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