Reducing Regulatory Risk for the Development of **Drugs, Biologics,** and **Devices**

Organizations that consistently develop and launch new products efficiently in an environment of increasing regulatory scrutiny, successfully manage regulatory risk.

A thorough review of all FDA activity in the area of clinical development provides insights into regulatory risks. This information can be used to:

- Evaluate and review clinical investigators and CROs.
- Develop effective strategies for managing clinical initiatives.
- Establish improved monitoring programs.
- Ensure proper investigational review board (IRB) involvement and review.
- Effectively report key clinical information to regulatory authorities.

Commonalities exist in regulatory activity for drugs, biologics, and devices regarding causes of regulatory citations. These commonalities further highlight areas of ongoing risk for clinical research/development and provide a means of proactively addressing clinical process gaps. Additionally, regulatory trends highlight areas of concern for clinical investigators and CROs. This provides sponsors with greater insights into the regulatory risk of organizations whose services are outsourced as part of clinical initiatives.

For the previous 18 months the highest level of regulatory activity involved clinical investigators, followed by IRBs, and then sponsors. Review of the chart below indicates a clear regulatory priority for clinical investigators.

DRUG DEVELOPMENT OVERVIEW

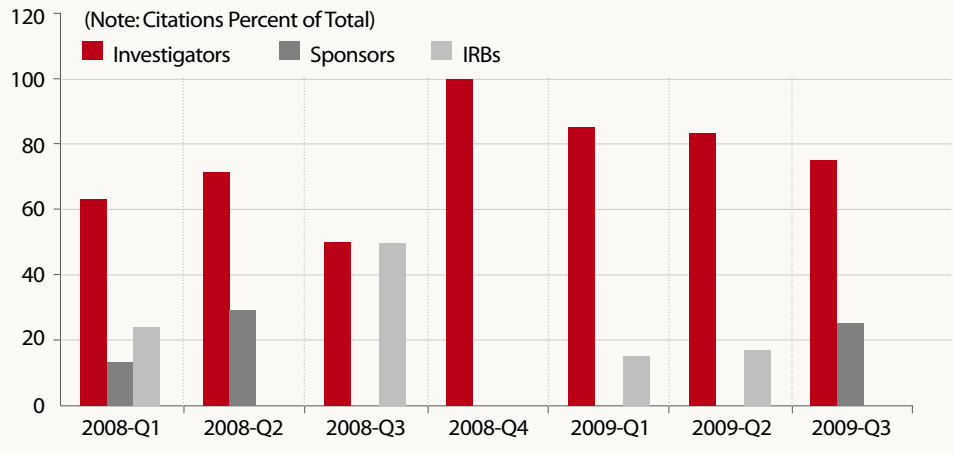
A review of clinical regulatory action for drug development shows the greatest number of citations in the areas of adherence to an established clinical investigation plan and the acquisition of informed consent.

For the investigation plan, the largest number of citations occurred due to failure of investigators to conduct studies in accordance with an established investigation plan. Also contributing to the citations were investigator failures to establish an approved investigation plan before initiating a clinical study. Informed consent citations were focused on the lack of proper informed consent, as well as problems with the review and approval of informed consent forms.

While overall trial responsibility resides with sponsors, it is critical to the success of clinical initiatives to ensure that proper documentation is developed and maintained by the investigators. This documentation includes investigation plans, case histories, trial records, adverse event reports, and communications with IRBs. Additionally, investigators must ensure the quality of informed consent forms and that all trial subjects have completed, signed informed consent agreements on file.

When clinical regulatory citations are considered in the context of all drug-related citations, a high degree of regulatory involvement in clinical activities is observed. Increasing scrutiny is given to the drug development process and, specifically, to the clinical research process. All aspects of clinical research from

Regulatory Priority for Clinical Investigators



Regulatory Detail for Drug Investigators and Sponsors

Investigators received elevated levels of regulatory citations for:

- Failure to maintain adequate records of the disposition of drug including dates, quantity, and subject use for test product.
- Failure to maintain adequate and accurate case histories that record all observations and other data relevant to the investigation on each individual.
- Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

Sponsor regulatory citations were found in the following areas:

- Failure to ensure proper monitoring of the clinical investigation.
- Failure to ensure investigator compliance with the investigation plan and applicable FDA regulations.
- Failure to ensure that only investigators who were qualified by training and experience were selected as appropriate experts to investigate a drug.

A review of individual citations confirms a consistent theme of planning, documentation, and communication across all parties involved in a clinical investigation. Of greatest risk is the investigation plan and informed consent; however, accurate records and case histories along with communication/involvement of the IRB present additional areas of risk. Although to a lesser degree, investigator statements, investigator monitoring, and records retention serve to further support the larger trends.

Developing proactive capabilities for managing the clinical research process through monitoring of regulatory trends can provide a competitive advantage for all development stages.

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ACSYS Inc. (Applied Compliance Systems) focuses on providing quality and compliance tools, technology solutions, and training to the pharmaceutical, medical device, and biotechnology industries. ACSYS applies current best practices to the assessment, analysis, design, and global execution of quality and compliance business systems.

sponsor to investigator and IRB are monitored at a level that is consistent with the drug production process.

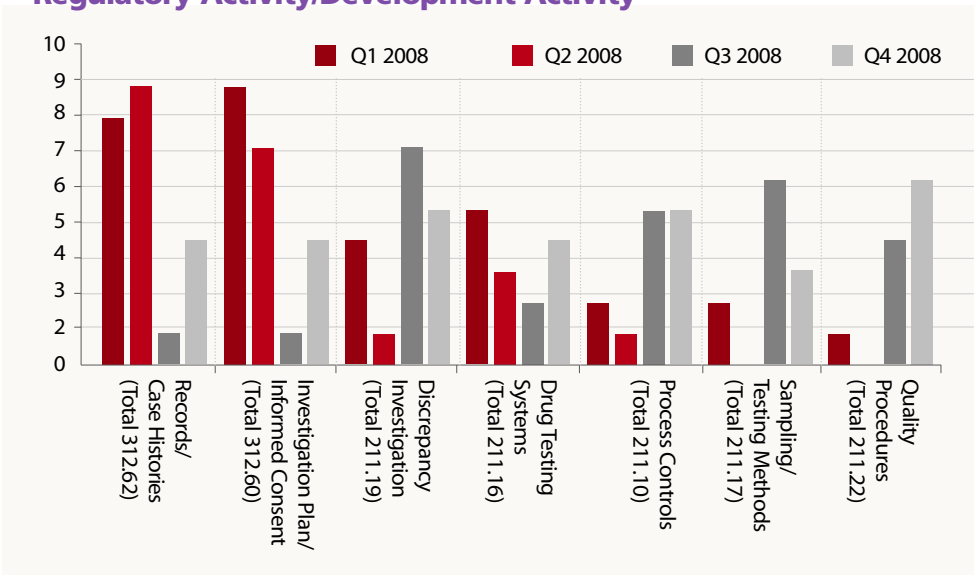
Clinical risk, from a regulatory perspective, is similar to risk seen for pharmaceutical manufacturing when looking at the regulatory activity for each area. This can be seen in the chart below.

Regulatory action in the clinical development area is similar in magnitude to the activity found in the post-clinical drug functions. Specifically, clinical activity is addressed by regulatory agents as frequently as the production processing, laboratory testing, in-process test methods, and overall quality procedures governing drug development and manufacture. This shift in regulatory action from a more production process focus to a more balanced approach, increasing the clinical regulatory action, highlights the importance of clinical process compliance.

The implications for sponsor organizations are that they must ensure investigators are carefully selected using formal established criteria. Sponsors must also provide detailed clinical monitoring to verify investigator compliance and adherence to the established investigation plan. Additionally, sponsors must ensure informed consent agreements meet all study guidelines and requirements and are properly documented and maintained.

Upon initiation of clinical studies, it is equally important the investigators maintain complete and accurate records. This includes all information regarding reporting of unanticipated adverse events as well as study progress reports. Case histories need to be established according to defined compliance guidelines and clinical study requirements to ensure all relevant clinical data are captured and maintained. When changes are made to an existing study or when adverse events occur, they must be reviewed and approved by the IRB before the implementation of changes. FDA reporting must be done on a timely basis in compliance with regulatory guidelines.

Regulatory Activity/Development Activity



BIOLOGICS DEVELOPMENT OVERVIEW

A review of clinical regulatory action for biologics shows the greatest number of citations in the areas of study responsibilities, study protocol, and reporting. For the study responsibilities, the largest number of citations occurred with regard to failure of study directors, quality assurance units, and testing facilities to fulfill their responsibilities.

Quality assurance units failed to inspect each nonclinical laboratory at intervals sufficient to assure a high degree of integrity for the study. Quality assurance units also were not established by testing facilities to monitor studies.

Study directors were noted to have failed to assure:

- Experimental data were accurately recorded and verified.
- Unanticipated responses of test systems were accurately recorded and verified.
- Reasons for changes in data entries were documented.

Study protocol citations involved:

- Failure to follow the study protocol when conducting nonclinical laboratory studies.
- Failure to assure each study has an approved written protocol with clear objectives and methods identified.

Report citations were focused on:

- Failure to complete reports of nonclinical laboratory study results.
- Failure to include a description of all circumstances that may have affected the quality or integrity of data in the final report.

THE IRB FACTOR

A review of the combined categories of drugs and biologics supports the increasing trend of regulatory actions and subsequently, increased regulatory risk, associated with clinical investigators. The next greatest area of risk resides with IRBs. As mentioned previously, the communication between investigators and IRBs as well as the reporting accuracy and documentation of interactions is of significant reg-

ulatory scrutiny. Sponsors must provide additional monitoring and oversight of trials to ensure the investigators and IRBs work in a coordinated manner and in accordance with all regulatory guidelines and study requirements. From a regulatory perspective this may be accomplished by:

- Careful selection of investigators and review of procedures, records, and communications used by perspective investigators.
- Ensuring investigators have and follow a documented investigation plan and have procedures in place to manage any changes in investigation plans.
- Managing subject documentation and particularly informed consent agreements.
- Increased monitoring of investigators in the areas of documentation and communication with IRBs.
- Ensuring the accuracy of case histories to reflect all information regarding subjects.
- Improved sponsor monitoring programs to review all risk areas and investigator, IRB responsibilities.

Sponsors that effectively address high-risk areas will minimize the possibility of costly delays in clinical studies because of compliance issues, poor data, documentation of results, and deviations from investigational plans. This will facilitate a timely and effective clinical study providing the organization with critical information to determine the future of a potential new product.

DEVICE DEVELOPMENT OVERVIEW

Regulatory actions for clinical trials/research in device manufacturers address many similar areas of concern as with drug/biologics manufacturers but with focus in slightly different areas. Analysis of the chart below indicates the following areas of risk from highest to lowest:

- IRB responsibilities/actions and documentation of IRB activities.
- Reporting of serious events and study protocol changes to IRBs and FDA as required.
- Procedures detailing IRB review of all research conducted by investigators.
- Development, documentation, and adherence to an approved clinical protocol.
- Monitoring of clinical trials by sponsors.
- IRB review of clinical research.

For medical devices, the primary areas of risk reside with the IRB. Sponsor responsibilities should include ensuring IRBs have accurate, approved procedures for conducting research review and all responsible individuals have been trained to established procedures. Monitoring of IRBs should address IRB documentation as well as the manner in which research reviews are conducted. Reporting of unanticipated adverse device effects (UADEs) is an area of heightened regulatory scrutiny and risk. Reporting of UADEs is an element to be considered when establishing an IRB as well as proper documentation of UADEs.

Regulatory risk for investigators is centered significantly on the clinical protocol compliance as well as the manner in which changes to the clinical protocol are made. Citations in this area occurred as a result of not obtaining IRB or FDA approval for changes to an approved protocol. Proper documentation, approval, and adherence to clinical protocols help mitigate regulatory risk. Again, an effective monitoring plan that addresses areas of greater risk will ensure that timely delays are avoided because of regulatory mistakes and poor compliance planning.

Data show the amount of regulatory activity is concentrated on investigators followed by IRBs and sponsors.

As is the case with drugs, clinical investigators are the area of highest regulatory risk. Organizational focus on the investigator selection criteria, monitoring, and subsequent reporting of trial events will mitigate risk presented by investigators. Training of investigators by sponsors should be thorough and accurate to assure investigator understanding of all required policies and procedures associated with a study. Data collection and reporting, which typically are well-defined in procedures and guidelines, must be accurate and timely, reviewed, and approved to assure the integrity of the data.

Additional regulatory actions resulted in citations for the following items:

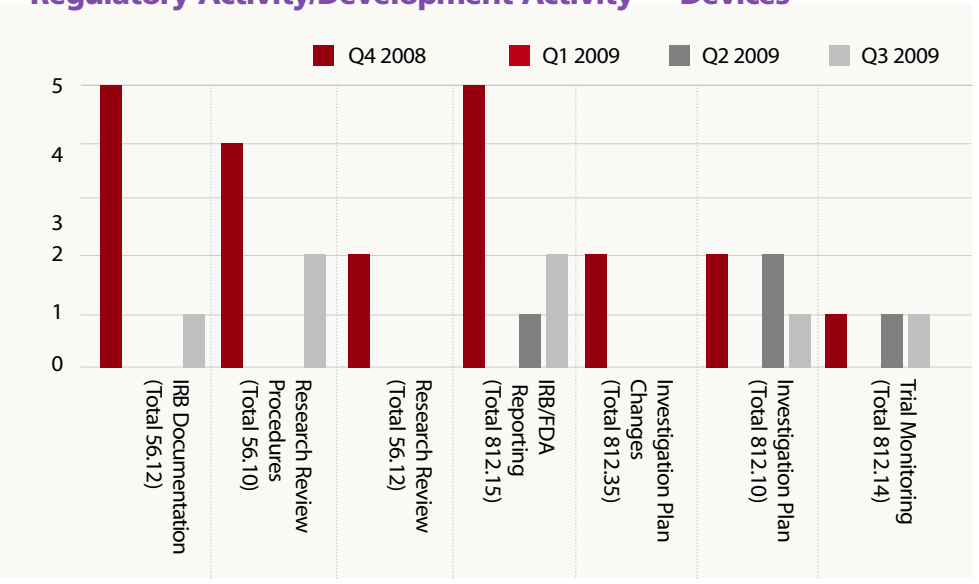
- Failure to maintain accurate records for the receipt, use, and disposition of a device.
- Failure to obtain from investigators a curriculum vitae and sufficient financial disclosure.
- Failure to ensure no IRB member participates in a project review where there is a conflicting interest.
- Failure to ensue proper monitoring of an investigation.

Device manufacturers with well-defined, detailed clinical trial procedures should effectively manage all clinical trial initiatives and mitigate regulatory risk. Sponsors must effectively communicate all requirements and approve all clinical protocols as well as ensure investigators and IRBs are working in coordination and in accordance with sponsor's requirements. While these are time-consuming tasks, they are necessary to avoid potential project delays, costly rework, and correcting information needed for product decisions and possible regulatory submissions.

CLINICAL SUMMARY

The analysis of regulatory trends for drugs,

Regulatory Activity/Development Activity — Devices



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biologics, and devices strongly indicates the greatest risk is with the investigators. This trend has shifted from previous sponsor focus to the actual testing/investigating organizations. Closely linked to the investigators is the IRBs that play a critical role in the clinical investigation and also present an elevated regulatory risk. The full integration of IRB involvement with investigators as well as documentation of all interactions, including review of ongoing research, is a key element for sponsors to ensure documentation is properly performed. Sponsor monitoring, focused on investigator and IRB procedures, is a good starting point to determine the capabilities of each organization. Where good procedures exist, it is imperative that the procedures are followed and clinical activities adhere to all applicable regulatory guidelines.

Although regulatory action is least with sponsors, the responsibility is greatest to ensure clinical trials are developed, initiated, documented, and performed according to sponsor and regulatory requirements. Sponsor organizations must have an active, well-documented training and monitoring program for investigators. Monitoring should be increased as needed according to perceived regulatory risk as well as business risk. Trials that occur across regional or country boundaries have additional requirements that may vary and require greater sponsor involvement. Sponsors that aggressively manage investigator and IRB activity, communications, and the integrity of data collected regarding subjects and trial events greatly increase the chances of success. Regulatory risk is also subsequently reduced and clinical trials are completed in a timely manner supportive of product decisions for market introduction. ✦

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