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Research Article

Internal Safety Advisory Groups (ISAG): A Win-Win for Effective Decision-Making in Biopharmaceutical Companies

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ABSTRACT

Consultation of external experts (EE) has been a standard used by biopharmaceutical project teams (PT) to help evaluate signals of drug toxicity. This process is challenging and cannot address all the complexities associated with patient safety throughout the lifecycle of a drug. AbbVie is a biopharmaceutical company that launched organ-specific Internal Safety Advisory Groups (ISAG) in 2017 to address these unmet needs. **Objective:** To describe AbbVie's ISAG experience from 2017 to the present, including the consultation process, breadth of consultations and methods of self-assessment. **Methods:** Detailed records for 7 ISAGs (hepatic, renal, ocular, cardiovascular, skin/immunology, neuropsychiatric and health literacy) were reviewed. ISAG recommendations were compared to feedback from EE and regulatory agencies as a means of comparison to industry standards. **Results:** The ISAGs received 41 consultations within three main categories: (a) clinical case review, (b) clinical trial management and (c) external-facing documents. The hepatic ISAG was consulted with the greatest frequency (n=24). Phase 1 (34%) and post-market (34%) were the phases with the most frequent consultations. Recommendations mirrored feedback from industry standards in 12 of 13 consults. **Discussion:** ISAGs provide AbbVie with broad, cross-functional expertise that is objective and readily available. Standard approaches to collection, analysis and presentation of data help guide PT and the company as a whole. ISAGs provide guidance to mitigate safety risks and communicate these risks to regulatory authorities, healthcare providers and patients. This ISAG model can be adopted within other biopharmaceutical companies and serve as a template for current or future safety advisory activities.

Keywords: Pharmacovigilance; Drug Development; Drug Safety; Internal Advisory; Pharmaceutical Industry; Safety Governance

Abbreviations: External Experts (EE); Internal Safety Advisory Groups (ISAG); Project Teams (PT)

INTRODUCTION

Safety governance within a biopharmaceutical company ensures an integrated approach to drug safety from the development through post-marketing product stages. [1-4] Optimization of drug safety requires a dedicated, multidisciplinary team of specialists who proactively monitor safety throughout the lifecycle of a drug. Signals of drug-induced toxicity are best detected early and evaluated expeditiously, and all aspects of risk mitigation need to be considered and implemented in a timely, comprehensive and cross-functional manner with appropriate safety governance oversight in the best interest of patients. [5]

Historically, for critical or complex safety-related issues, external experts (EE) with a balance of relevant research and clinical expertise have advised companies, individually or in advisory group settings. [6, 7] The incorporation of EE is challenging at multiple levels: contract negotiations may be lengthy, availability may be limited, familiarity with the company's developmental drug may be limited, and the EE experience is specialty focused rather than multidisciplinary by nature. Therefore, the EE consultation process is not optimal for meeting the company's immediate needs. Additionally, safety-related protocol modifications and review of documents for clear safety messaging may benefit from expert review, but EE are not often consulted for such activities.

Biopharmaceutical companies develop drugs spanning a wide range of therapeutic areas, the most common toxicities leading to discontinuation of drug development or withdrawal of a drug from the market are attributed to a relatively small number of organ systems (Table 1).

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Within AbbVie, a global, research-driven biopharmaceutical company, a decision was made to leverage the internal expertise and experiences across the company to form several cross-disciplinary Internal Safety Advisory Groups (ISAGs). These ISAGs advise project teams (PT) on organ-specific safety and develop consistent approaches to assess key areas of safety interest common to drug development programs, including standardization of statistical outputs and protocols company-wide. The ISAGs are advisory by design, so the ultimate decision-making responsibility lies with the PT who seek ISAG consultation and who are the decision- making entities within the safety governance framework. Beyond consulting for PT, a critical activity of the ISAGs is to recommend standard approaches to the collection, analysis and presentation of safety data related to the ISAG domains.

While many companies, including AbbVie, have some "expert" groups, that evaluate liver (e.g. a Drug Induced Liver Injury [DILI] Group) or cardiovascular safety (e.g. a QT Group), little is known or published about a broader set of ISAGs. Notably, their consultation processes, their relationship with a company's safety governance, their added value to biopharmaceutical companies, and most importantly, the potential of these ISAGs to advance the science of patient safety.

This manuscript aims to describe AbbVie's experience related to the ISAGs, including the value that they provide to the company with respect to determining a safety signal, standardizing safety data collection, analysis, and presentation across the company, and providing guidance regarding timely, scientifically accurate and effective communications with health authorities, investigators, healthcare providers and patients. The ISAG processes, metrics and lessons learned are shared.

OBJECTIVES

The primary aim of the ISAG is to convene subject matter experts across AbbVie to serve as a readily available resource for PTs whose primary responsibility is for product safety monitoring. The objectives of the ISAGs include: (a) objectively and expeditiously reviewing relevant safety data for any product/program, and providing recommendations regarding management of specific safety issues during the complete lifecycle of the product, (b) providing guidance regarding timely, scientifically accurate and effective communications with health authorities, investigators, healthcare providers and patients, (c) developing consistent approaches to assess key areas of safety interest including standardization of statistical outputs and protocols, and (d) supporting knowledge management, best practices and expertise on topics relevant to the ISAGs and sharing information within the ISAGs and across the company.

METHODS

AbbVie established 7 ISAGs, 6 are organ-specific ISAG: hepatic, renal, ocular, cardiovascular, skin/immunology, and neuropsychiatric; 1 is health literacy, focused on patient and healthcare provider communication. The hepatic ISAG was the first ISAG to be established.

ISAG membership and participation for all roles is voluntary. All ISAGs are overseen by a senior pharmacovigilance (PV) physician who is a member of the safety governance leadership team. Each ISAG is led by two co-chairs, serving as primary contacts. In addition, each ISAG is comprised of a project manager, specialist physicians (i.e. physicians trained in the relevant specialty), and experienced colleagues within the organization, including PV scientists, statisticians, epidemiologists, pharmacokineticists, pre-clinical scientists and toxicologists, and regulatory affairs specialists. (Figure 1). The ISAG project manager facilitates all ISAG-related activities, including consults, and ISAG-sponsored knowledge sharing initiatives. The senior PV physician is responsible for (a) ensuring that each ISAG includes appropriate experts, (b) ensuring data collection and analytic methods are standardized across

Table 1: Body System Categories Most Commonly Leading to Discontinuation of Drug Development / Withdrawal from Market [1].

Target Organ or Tissue	% of All Advanced Molecules
Cardiovascular	27.30%
Liver	14.80%
Teratogenicity	8.00%
Hematologic	6.80%
Central and Peripheral Nervous System	6.80%
Retina	6.80%
Mutagenicity/Clastogenicity	4.50%
Reproductivity Toxicity	4.50%
Gastrointestinal/Pancreatic	3.40%
Muscle	3.40%
Carcinogenicity	3.40%

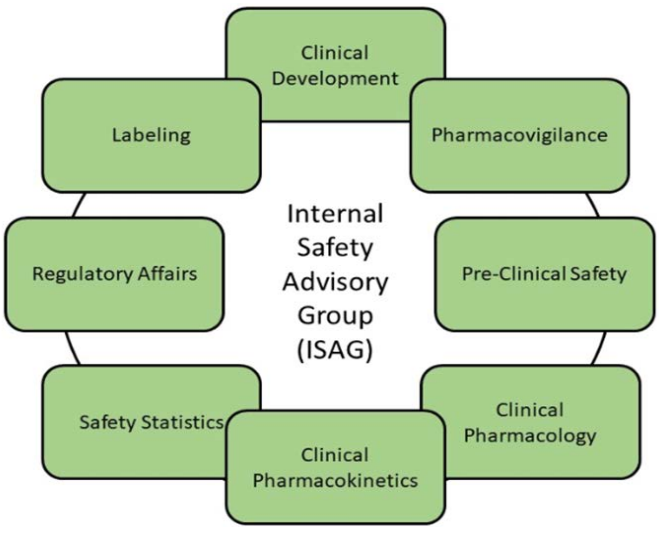

Figure 1: Membership of AbbVie's Internal Safety Advisory Groups (ISAG).

the company, (c) knowledge sharing activities are appropriately conducted and, in general, support the objectives of the ISAGs.

PROVIDING CONSULTATIONS

Requesting a Consult

Any AbbVie PT may approach an ISAG for any safety question needing further subject- matter expert guidance. The consultation may occur at any point in the lifecycle of the product, ranging from pre-clinical to post-marketing. For example, it may arise from an event in an animal study, from a healthy volunteer in a Phase 1 study or from a clinical trial subject anywhere in the world. The question may pertain to designing a safety monitoring plan or crafting language for a regulatory document. Examples of other ISAG consultations are listed in (Table 3).

When a question(s) arises, an ISAG consultation request may be made proactively or via mandate from the safety governance leadership team. The ISAG consultation request includes specific clinical questions to focus the ISAG review and to facilitate inclusion of ISAG members with appropriate expertise to support the request.

Preparing a Pre-read Data Package for Consult

To appropriately prepare for discussion with the requesting PT, the ISAG members request background data on the drug in question.

Background data and supporting information, relevant to the questions being asked of the ISAG, are provided proactively for review as pre-read materials prior to the scheduled consultation as shown in (Table 2). Preclinical, pharmacokinetic, and pharmacodynamic data serve as important background information in order to fully contextualize safety data. For example, the presence or absence of certain organ or system-specific toxicities observed in animal species may inform the likelihood of human toxicity. Pharmacodynamic profiles are equally important; absorption, distribution, metabolism and excretion of a drug can help predict the probability of a safety signal. The ISAG also reviews all available data, as applicable to the nature of the consult, from clinical trials (including QT interval prolongation and drug-drug interaction studies) and post-marketing experience.

Useful program-level data include the number and breadth of clinical trials, the types of subjects evaluated, and relevant summaries of the clinical trials data. While seeking consultation on a specific case or on the design of a study, aggregate summaries of the clinical trial data for a product provide important safety context for the product.

For example, an ISAG may be asked to evaluate and comment on two study subjects meeting biochemical criteria of Hy's Law for hepatocellular injury with jaundice. Evaluating such cases in isolation would be myopic, and potentially misleading. They must be evaluated in context of the entire development experience. As an illustration: are these two cases out of 20 or out of 2,000? And of the remaining, "non-Hy's Law" cases, is the liver profile pristine or are there dozens (or hundreds) of cases of laboratory data that trend towards, but fail to meet biochemical Hy's law criteria? Part of Hy's law stipulates that a true case of hepatocellular injury with jaundice will emerge from a clinical program with cases that trend towards hepatocellular injury, but not likely from a program with no cases of hepatocellular injury. Here, the consulting team works with ISAG statisticians to determine the best way to summarize these data. Graphical presentations including Kaplan-Meier curves, evaluation of drug induced serious hepatotoxicity (eDISH) plots and shift plots are also reviewed.

Subject-level data are critical for proper case adjudication from an ISAG. These data include study drug dosing or administration, patient demographics, past medical and surgical history, concomitant medications, adverse event details, baseline laboratory values and relevant laboratory trends, and diagnostic images with reports. Presentation of these data to facilitate review and assessment of the key data is important. Subject-level data can come from Phase 1-3 clinical trials or from post-marketing reports if a drug is already approved for use. Given the nature of post-marketing reporting, available data may be limited.

As the ISAG consult team is reviewing the requisite data, a consultation is scheduled.

ISAG Meeting for the Consult

Timing of the consultation depends on the urgency of the request from the PT and consults generally occur within one week from

Table 2: Examples of Pre-Read Materials Shared with ISAG Members Prior to Consultation.

Examples of Pre-read Materials
Organ or system-specific toxicities of study drug or drug class
Investigator Brochure
Clinical trial protocols
Absorption, distribution, metabolism and excretion (ADME) data or modeling
Aggregate data summaries
Individual cases including medical history, clinical data, narratives etc.

Table 3: Examples of ISAG Consultations

Categories of Consultation	Number of Consults a	Examples
Clinical Case Review	20	• Causality assessment for clinical and post-marketed cases (single or multiple)
Clinical Trial Management	16	• Management of guidelines for hepatic toxicity
		• Standardization of data collection b
		• Eligibility criteria
External Facing Documents	8	• Review of Adverse Events of Special Interest Query Letters
		• Risk Management Plan
		• Investigator's Brochure
		• Informed Consent updates
		• New Drug Application submission documents

a Some consults provided recommendations for more than one category.
b Consults involved standardization of statistical outputs and protocols company-wide.

the date of request. If an ISAG member is also part of the PT, the member does not participate in the closed session, to maintain objectivity of the ISAG.

At the consultation, the PT provides a high-level overview of the pre-read package, highlighting key data pertinent to the consultation and the team's assessment, and the specific questions to the ISAG. ISAG members may ask clarifying questions of the team during the presentation or may request additional data be provided after the consult. At the conclusion of the PT presentation, the ISAG convenes a closed-door session to share their opinions and work toward a consensus understanding of the information. Once a consensus among the ISAG team members is reached, a co-chair drafts the response, comments are solicited from the ISAG, and final ISAG recommendations are sent to the PT for consideration. The format is typically via e- mail or an attachment to an e-mail. When consensus is not reached, voting is part of ISAG processes.

ISAG recommendations are not binding for the PTs; the team discusses ISAG recommendations and documents their own decisions. It is required for teams to document a clear rationale when they choose to deviate from ISAG recommendations, and they may be required to present this information to the central safety governance oversight board. When the ISAG recommends that the PT consult external experts, the ISAG provides guidance to PTs regarding that external consultation, and ISAG members serve as subject matter experts to enable focused discussions with the external experts.

Maintaining ISAG Metrics

Records are maintained so the ISAG can review the number of consults and the timeframe in which ISAG decisions were conveyed. The extent to which teams agreed with the ISAG recommendations is also tracked. External experts' recommendations are not sought in parallel with every consultation. However, in situations when feedback is also obtained from external sources, including EE, a regulatory agency or an institutional review board (IRB), comparisons are made with the ISAG recommendations and serve as an important metric for learning and understanding industry best practices.

RESULTS

AbbVie established 7 ISAGs over a 2-year timeframe, initiating them gradually, while solidifying processes through lessons learned. The 7 ISAGs were consulted 41 times (Figure 2) over a 3-year period and provided recommendations related to the following general categories: (a) clinical case review, (b) clinical trial management and (c) external-facing documents (Table 3).

Recommendations were provided within an average of 2 days from the time of consultation (range: same day – 1 week post-consultation). In some instances, additional information was requested by the ISAG prior to sending a recommendation to the PT.

Of the 41 consults

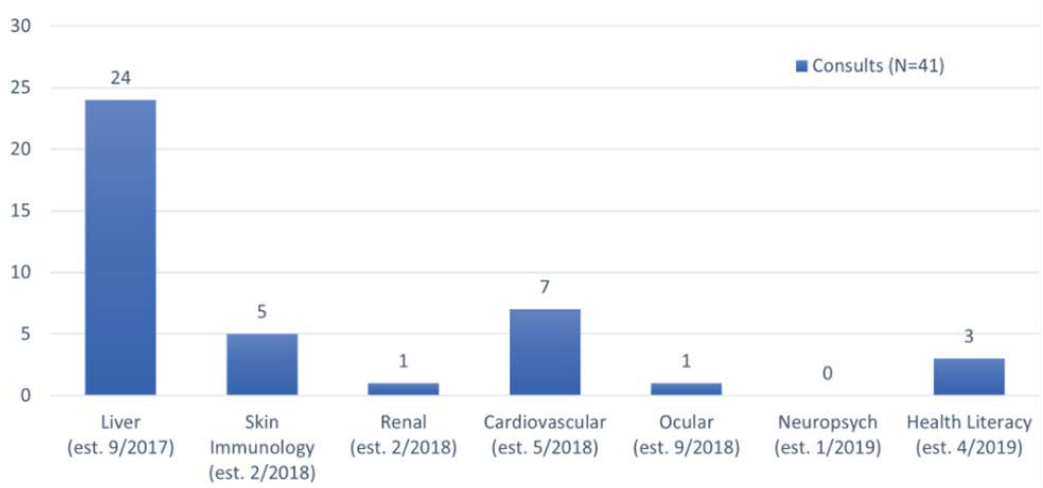

Figure 2: Distribution of Consults by Type of ISAG, as of 31 July, 2020.

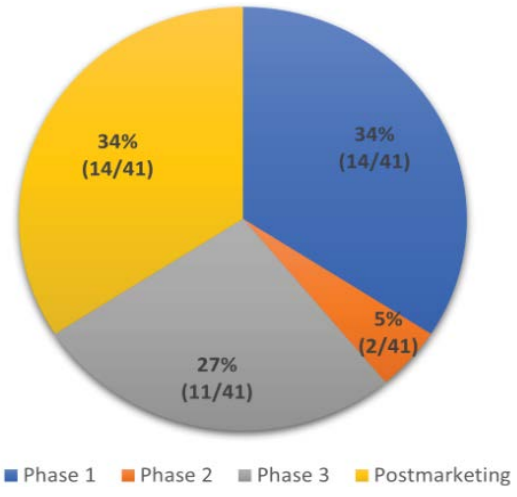

Figure 3: Distribution of Consults by Phase of Drug Development.

- 3 coincided with a consultation with external experts. All 3 were hepatic ISAG related and were requested for evaluation of a safety signal. In all 3 of these instances, the recommendations of the ISAG and the external experts were consistent.
- 7 coincided with feedback from a regulatory authority. Regulatory feedback aligned with the ISAG recommendations in 6 instances. In the 1 instance where opinions were not congruent, a regulatory authority did not agree with the ISAG opinion that a new safety (issue) did not belong in a post-marketed product label.
- 3 coincided with feedback from an IRB. All 3 showed consistency between the ISAG recommendation and the decision of the IRB.

Standardizing Safety Data Collection, Analysis, and Presentation

In addition to consultations with product teams, the ISAGs also provided recommendations for rigorous and standardized processes for safety data collection and analysis to promote a consistent approach to assess key areas of safety interest common to drug development programs across the company. Key clinical questions for each area of toxicity were considered and then based on these questions, the key data and summaries to best answer the questions were determined by the respective ISAG. Regulatory requirements and guidance documents, best industry practices, input from key opinion leaders, and recent experiences were all drawn upon for making these determinations.

For example, the hepatic ISAG developed recommendations for assessing drug-induced liver injury. The safety statisticians and statistical programmers worked together to develop standard programs to efficiently produce the recommended tables and figure3 (including eDish plot, shift plot, cumulative incidence plot, patient profiles). This allowed for a standardized approach to evaluate and present data across PT. The hepatic ISAG also made recommendations on the collection of direct and indirect bilirubin in lieu of the earlier practice of collecting total bilirubin in clinical trials, and on how to interpret alkaline phosphatase values when assessing a case for Hy's law.

Enhancing ISAG Expertise and Knowledge Sharing

The ISAG members assume the responsibility for enhancing and staying current on cutting edge research in their areas of expertise. This is critical for the success of the ISAG. Individual experts on the ISAG participate in congresses and industry/regulatory collaborations where ongoing research is discussed, and ideas are shared and developed. At these venues, the company ISAG experts are in regular contact with academic experts and regulators and gain valuable insight into current standards and practices. Furthermore, the company ISAG experts attend lectures in the spirit of continuing medical education. In this manner the ISAGs remains at the forefront of science and continually expands their knowledge so they can provide expert advice to AbbVie teams.

The ISAG members also strive to enhance knowledge within the company. Towards this end, each ISAG convenes on a quarterly basis to present and share recent developments in the field. Throughout the year, ISAG members from all functions are given the opportunity to present relevant scientific updates from their functions and other learning points to the team, including journal articles. Furthermore, in order to enhance knowledge sharing within ISAGs and across the entire company, the ISAGs convene an annual symposium, inviting EE and regulatory experts.

DISCUSSION

The ISAGs function as critical, objective consulting bodies to provide timely and consistent recommendations to any function within the company with an organ-specific, toxicity-related question. Thus, the ISAGs serve as a vehicle for leveraging the expertise and experience within a company to enhance pharmacovigilance of all products.

In the 3 years following the launch of the AbbVie ISAGs, 41 consultations were requested and completed. The majority were directed at the hepatic ISAG, which was also the first ISAG to be launched. This may be expected, as the liver is responsible for the metabolism of many drugs. [8-10] Other than the cardiovascular system (which had the second-highest number of consults), the liver is the second most common organ system responsible for terminating drug development programs or withdrawal from the market.

The ISAG consultations were distributed across the spectrum of drug development phases and included on-market products. Consultations helped characterize product safety, minimized patient exposure after a safety signal was confirmed and helped design risk mitigation strategies. Furthermore, dossiers for submission to regulatory agencies for marketing authorization contained clearer characterization of risks.

One of the metrics includes comparing ISAG recommendations to external expert recommendations that are sought in parallel by the PT. It is interesting to note that very few ISAG consultations coincided with an external expert consultation. Perhaps the immediate availability of internal consultation lowers the threshold for expert inquiry and augments the wealth and breadth of perspective received by PTs. Though the explanation for this observation is not known, without the feedback of ISAGs, vital safety decisions would be made with less expert-driven information.

Overall, AbbVie's ISAGs are effectively leveraging the expertise and experiences within the company and sharing and applying the ongoing knowledge attained from external conferences and collaborations. Over the course of the first 3 years of existence, the ISAGs evolved as more experience was gained. In order to give timely feedback on emerging safety signals, the ISAGs had to be agile and meet and respond quickly. This is sometimes challenging, given that members are participating in these groups in addition to their primary responsibilities. Another key to the visibility and success of the ISAGs was the establishment a coherent outreach program between the ISAGs and the PTs that may need consultation. Short Power Point presentations at PT meetings, emails, posters and even the annual ISAG symposium are all methods the ISAGs used to increase awareness within AbbVie about the existence of the ISAGs.

As more ISAG consultations were conducted, the ISAGs noticed considerable variability in the pre-consult and consult information provided by development teams. Consequently, the ISAGs identified this as an opportunity to develop recommendations for a consistent approach to summarizing and assessing these key areas of safety interest across projects. These recommendations may also lead to changes in protocol development throughout a company, so that the necessary (e.g. laboratory) data for analysis are captured.

Objectivity is essential for the success of the ISAG, when patients bear the ultimate impact of safety-related decision making. It is

imperative that the ISAGs are unbiased in adjudicating clinical cases and crafting recommendations. This is accomplished in several ways. Already mentioned was the practice of withholding opinion during the PTs presentation. There are other practices that serve a similar purpose. PTs are encouraged to present their cases and questions to the ISAG objectively, so as not to bias the ISAG recommendations. If an individual is both a member of a consulting PT as well as the ISAG, he or she will be on hand to present the data but be recused from closed-door ISAG activities. Lastly, bias is avoided by requiring a multi-disciplinary team of experts within an ISAG to agree upon a singular response, subject to post hoc scrutiny by company executives and international safety agencies.

The establishment of the ISAGs is a win-win for the biopharmaceutical company and other stakeholders. Experiences can be shared, and best practices defined, both within a company and among companies. There are several industry-led consortia working together to advance the science of drug-induced liver injury. Representatives from more than a dozen companies convene biannually to collaborate. At these meetings, AbbVie shared the concept of the ISAG and interest in the concept has grown.

Another stakeholder that stands to benefit is the regulatory health authorities, who will receive expert-driven documents with more consistent safety data analyses and presentations based on current industry best practices; consequently, this promotes more efficient and timely communication with biopharmaceutical companies.

The process is iterative; feedback received from a health authority can inform and guide the ISAG on future data presentation. Lastly, and importantly, it is the patients that stand to benefit from the ISAG. By signaling and characterizing toxicities as early as possible, making the drug development process more efficient and drug labels more clear, patient safety also benefits greatly. The ISAG concept can be utilized within any biopharmaceutical company safety governance framework, and AbbVie's ISAG processes might serve as a useful template for current or future safety advisory activities.

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