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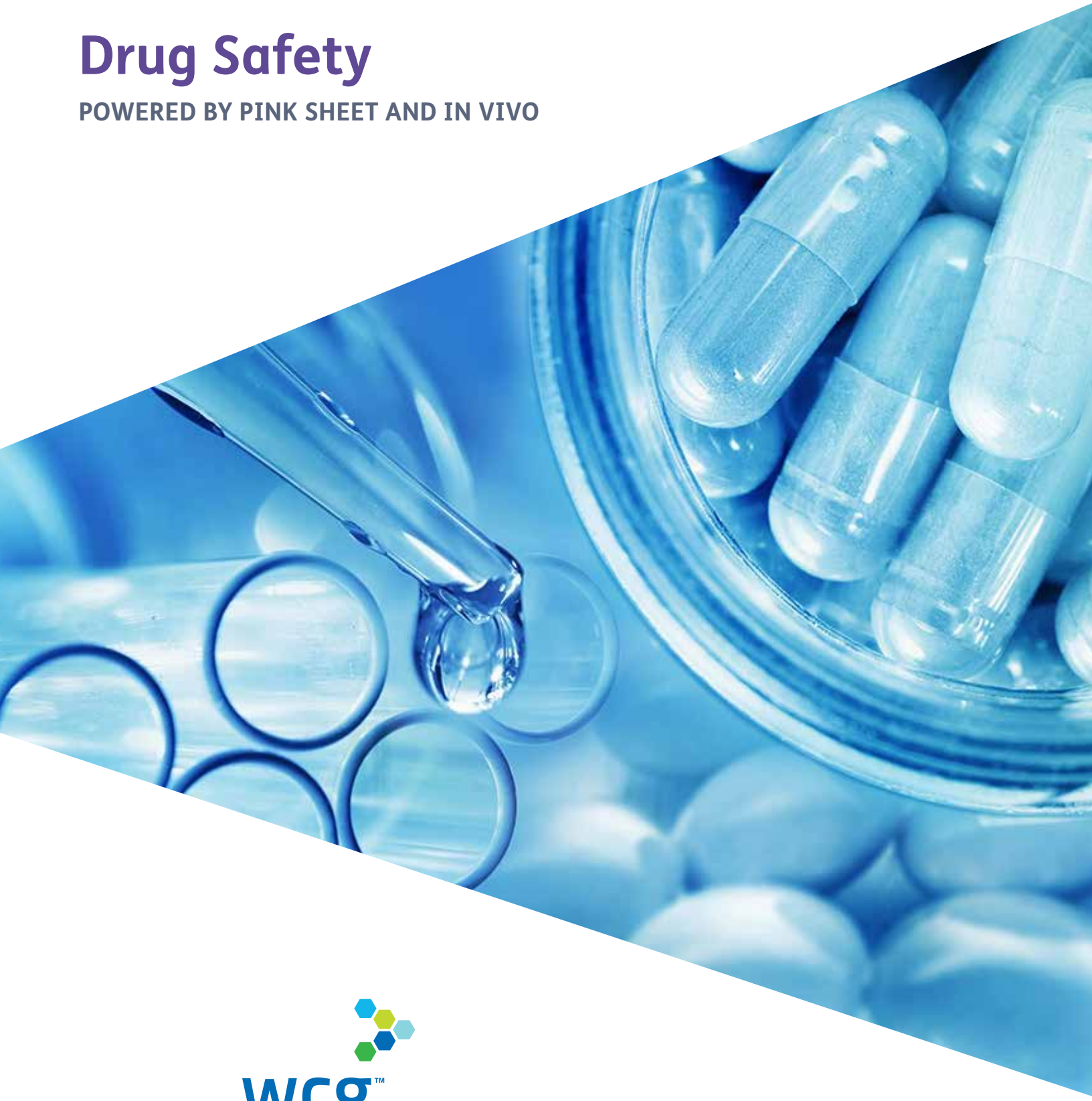

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Clinical trials are a costly affair and there is much at stake for the drug makers that conduct them.

It is not surprizing then that pharmaceutical companies are mostly reluctant to experiment with new risk-adapted methodologies that are designed to make trials more efficient. Their fear of receiving an inspection finding results in them controlling the quality of every aspect of their trial.

Industry is being urged by the regulators to get past its worries and embrace the spirit of the revised international guidance on good clinical practice (ICH E6 R2). The guideline outlines a common-sense approach to risk-adaption to help sponsors focus on the two areas that really matter: patient safety and data integrity.

Patient safety and data integrity are taken seriously by GCP inspectorates and are often at the center of most findings. However, there is a tendency for some companies to use inspection findings as a reason to blame or reward individual staff members. Inspectors want this culture to stop. Companies should use inspection findings as an opportunity to improve their processes instead.

Regulators and industry are also collaborating on how patient safety can be further strengthened by taking advantage of new technologies such as those relating to Big Data.

In the US, for example, the Food and Drug Administration and four companies recently tested the feasibility of a new digital framework to report important safety events occurring in clinical trials subject to investigational new drug regulations.

The project aimed to uncover missing or inconclusive safety data and included AI-based methods to conduct safety signals detection and systematically identify gaps in meeting regulatory requirements. The FDA has since decided to institutionalize the digitization of the adverse event reporting process, which it believes will be a major productivity booster.

Finally, in the interest of transparency, it is important to convey the results of the clinical trials for authorized drugs to the scientific community and patients so that they can understand the reasons for the approval. The move also supports innovation and can help avoid duplicative studies. However, companies today are struggling to cope with global differences between regulatory policies for publishing clinical data for authorized drugs. They can end up creating multiple versions of their clinical study reports to support transparency initiatives in various jurisdictions.

All these and other regulatory issues that companies are facing are explored in more detail in this e-book.

Vibha Sharma
Senior Reporter, Pink Sheet, Pharma Intelligence

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Managing The Unmanageable: Meeting The Challenge of Appropriate Safety Report Distribution

▶ Kristy Fusco, MLD

A major concern in the clinical research industry is the over-reporting of expedited safety reports to investigative sites; letters notifying of new, urgent safety issues are distributed during clinical trials, even though the safety event does not meet criteria for being reported in such a manner. The volume of safety reports being sent to investigative sites is frustrating for investigators, sometimes causing them to disregard letters which may result in clinically-significant safety signals being missed in the noise of non-significant event reports, and the workload volume may even lead sites to consider ending their participation in the clinical trial. How can we ensure that investigative sites only receive the reports they truly need to review? This question must be answered in order to bring efficiency back to the review process and to ensure that investigators are spending their time where it matters most, with the study participants.

Within the realm of clinical trials, participant safety is, and always should be, at the forefront of everyone's focus. With incredible advances in medicine and technology, a large number of new investigational drugs continue to cycle through the clinical trial process, bringing with them hope to cure disease or to provide preferred alternatives to the existing options. To monitor participant safety in an ongoing trial, sponsors rely on their investigative sites to record and submit data on any adverse events study participants have experienced. The sponsor is responsible for reviewing and determining which adverse events meet the criteria to be considered as serious and unexpected, thereby representing new potential risks for trial participants. These must be disseminated to investigative sites in the form of a safety report. The purpose of these reports is to notify investigators, Institutional Review Boards/Research Ethics Committees, and regulatory agencies of any new, safety concerns that are suspected to be caused by the study drug and unexpectedly arise from its use so that necessary action can be taken to protect trial participants. However, in their effort to ensure that all events which meet the criteria are promptly distributed and that under-reporting does not occur, far too often sponsors instead over-report, by sending out notifications of events that actually do not represent new, serious, or clinically-significant risks.

Impact of Over-Reporting

The over-reporting of safety events has had a negative impact on both sites and sponsors. Investigators are

Comparison of Safety Letter Distribution Methods

Electronic Solution	Overnight	Email	Fax
Automated acknowledgement tracking & reporting capabilities	Poor tracking of receipt by investigator	Cannot confirm receipt	Hard to confirm intended recipient received the fax
Dependable distribution algorithms	Package may make it to PIs facility, but not the individual themselves	Mistakes are made when spelling recipients email address or choosing from pick list	Potential for incorrect fax number to be entered or safety doc gets accidentally picked up by unintended recipient
Real-time distribution worldwide	Delay in investigator receipt due to shipping and slow internal courier services at the medical facility	Emails get caught in spam filters delaying receipt	Delayed fax distribution in large facilities
Secure sign-on	Once delivered, safety document can be viewed by anyone if not secured	No authentication required to access safety document	Safety document can be accessed by anyone who has access to fax machine
Audit trail reporting	No audit trail	No audit trail	No audit trail
Instantaneous Gap Pack at time of site activation	Delayed receipt of gap pack due to manual labor of packaging and shipping	Manually compiling safety documents could lead to missed documents	Room for error when faxing large numbers of documents

overwhelmed and frustrated with the volume of reports they are required to review. Sites feel they are spending too much time figuring out how to handle the administrative burden of a voluminous number of safety reports so that they do not fall out of compliance, when they should really be concerned with assessing safety issues and communicating new risks to their trial participants. Continuing frustration amongst investigators also stems from the content of the reports; many of the safety reports are uninformative, are difficult to translate into meaningful clinical actions, and contain information that has already been identified in the investigator brochure.

This reaction from sites has had a negative impact on sponsors. Sponsors receive complaints from sites making it difficult to maintain positive working relationships. In some cases, sponsors have found that sites do not want to conduct additional clinical trials with them. It is a challenge for any sponsor to find high performing sites, and to lose a high performer due to over-reporting of safety information is not something sponsors want to see happen.

Why Do We Have Over-Reporting?

Initial FDA Guidance Interpretation

Historically, the over-distribution of safety reports often stemmed from sponsors' interpretation of safety reporting rules and guidelines. Sponsors misinterpreted the phrase "reasonable possibility" in the Food and Drug Administration's (FDA) guidance on safety reporting . The rule stated that sponsors were required to notify participating investigators of any adverse experience associated with the use of the drug that was both serious and unexpected if "there

was a reasonable possibility that the experience may have been caused by the drug." Sponsors, sometimes relying on the causality assessment of the investigator reporting the event, often interpreted "reasonable possibility" very conservatively; if a causal relationship could not be definitely ruled out, there was a possibility of a causal relationship. Therefore, sponsors processed many events that had little evidence to support a causal relationship between the event and study drug as expedited safety events.

Lack of Harmonization Amongst Countries

Another reason for the over-distribution of safety reports is that there is a lack of harmonization in the rules around safety reporting amongst countries and their governing bodies. As sponsors conduct multi-national clinical trials, it is important that each trial is conducted in accordance with participant countries' rules and regulations. For example, the conduct of a global trial that includes sites in the United States, Europe, and Japan would need to adhere to rules and regulations in accordance with the FDA, the European Medicines Agency (EMA), and the Japanese Pharmaceutical and Medical Devices Agency (PMDA). It is common that expectations concerning safety reporting vary across regulatory authorities; mostly in terms of the information that must be reported to investigators and in what time frame it must be reported.

For example, many countries require the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigators regardless of whether the adverse reaction originated within that country or outside of that country. However, there are several countries such as Iceland, Norway, and Switzerland that only require SUSARs to be reported if they occurred within the country. Some unique rules also exist; for example, Malaysia requires both unexpected and expected serious adverse reactions to be reported to investigators.

Resolving the Problem of Over-Reporting

Clarification of FDA Expectations

In 2010, the FDA addressed the issue of over-reporting and issued a Final Rule for safety reporting under an Investigational New Drug (IND) application; guidance for the operationalization of the new rule was then issued in 2012. This provided sponsors with clarified definitions and a much more clear indication of which events qualify for expedited reporting to investigative sites. Under the new guidance, sponsors "must report any suspected adverse reaction that is both serious and unexpected" and "the sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest causal relationship between the drug and the adverse event," with several examples provided to clarify what FDA considered to be a reasonable possibility of a relationship. The FDA's goal was to stop sponsors from distributing safety reports for events that did not have a causal relationship or were anticipated and already outlined in the investigator brochure, so that new safety signals could be more easily recognized.

Adhering to Country-Specific Regulations

The International Conference of Harmonization (ICH) has been involved in initiatives to harmonize reporting rules across countries and their associated regulatory bodies, however more work needs to be done before harmonization becomes a reality. Before this reality is met, understanding and adhering to the varying country rules is no easy task for sponsors.

As sponsors have moved towards automated technical solutions for the dissemination of safety reports, they are finding it difficult to accommodate the varying rules and regulations as many technologies that allow report distribution do not consider these complexities. Not wanting to

risk regulatory non-compliance by failing to report an event to any given country agency, sponsors are still leaning towards the trend of over-distributing reports.

Moving Toward Real Solutions

An emerging trend is that sponsors are now pursuing advanced technical solutions to aid them in handling and adhering to the varying regulations. As many available technologies have not considered such complexities in rules, sponsors have voiced the need for an improved solution that allows for the tailoring of distribution rules by country. Key items must be considered when addressing the varying rules and regulations in a technical solution (see sidebar).

Allowing rules to be set with such precision enables sponsors to ensure that they are compliant in all countries and across multiple governing bodies while at the same time preventing sites and regulatory agencies from receiving safety documents they do not want or need.

Key Considerations for AddressingVarious Rules and Regulations in a Technical Solution

- Ability to distinguish if a country is only required to receive adverse reactions if the event took place in that country.
- Ability to distinguish whether a country should receive adverse reactions based on causality assessment. For example, there are a few countries including the United States, Israel, and United Arab Emirates that only require the distribution of adverse reactions that have sponsor drug causality; if it was only the investigator that determined drug causality, distribution is not required.
- Ability to distinguish which countries require which specific document types. For example, some countries do not require 15 day SUSARs, but instead require a 6 month line listing.
- Flexibility to update country rules as regulatory rules and regulations continue to evolve.
- Ability to automatically utilize cover letters in a country's native language.
- Ability for sponsor and clinical research organization staff to access only the site and country information relevant to them.

Conclusion

As sponsors strive to distribute only events that qualify for reporting to investigative sites, and as technological advances continue to improve the control sponsors have on adhering to varying regulatory guidelines, the industry will continue to see a decline in the number of unnecessary safety reports being disseminated. The industry can expect these improvements to have a positive impact on both sites and sponsors. Sites will be allowed to focus their attention on safety reports that truly affect the safety profile of the drug, while sponsors will find they have an improved relationship with their sites; both key items in ensuring that participant safety remains at the forefront of the clinical trial process.

About the Author

Kristy Fusco, MLD, is a Product Manager for Safety Letter Distribution with WCG.

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Companies Urged To Get Past Fear Of Using Risk-Adaptation In GCP

By Vibha Sharma

Pharmaceutical companies are reluctant to take a risk-adapted approach to their clinical trials in the EU for fear of receiving a negative inspection finding. Good clinical practice (GCP) inspectors are urging them to consider their implementation.

The inspectors want companies to use their common sense and focus on areas that really matter, and document the reasons for their decisions. They also want the trend for some companies to reward or blame individuals following an inspection to end.

During a frank discussion between GCP inspectors and clinical trial investigators at a recent forum in London, both sides explored industry's reluctance to adopt the risk-adapted approaches that are set out in the International Council for Harmonisation GCP guideline (ICH E6 R2).

ICH E6 R2 places much emphasis on following a risk-adapted approach to make trial processes more efficient. But clinical trials, especially those in the commercial sector, are still being run in a way so as to "cover all bases," delegates at the forum said, noting that pharmaceutical companies are very risk averse and their approach to conducting clinical trials is such that it goes against the very tenets of undertaking proper risk-adaptation.

The forum was organized by the European Forum for Good Clinical Practice (EFGCP) and took place on June 18.

There is still a fear among people working in commercial as well as academic organizations "that if they implement a risk-adapted approach, then the inspectors may come in and question why they didn't do X, Y or Z instead," said Paula Walker, GCP inspector at UK's Medicines and Healthcare products Regulatory Agency.

Delegates at the forum generally agreed that inspection findings in relation to patient safety and data integrity are "very serious" and should not be taken lightly. However, other issues – such as checking for transcription errors, counting pills and ensuring signatures on every amended version of a document – may result in a quality control finding, but would not lead to a study being rejected.

The risk-adapted approach outlined in the revised ICH E6 requires sponsors, and investigators acting on their behalf, to identify all possible risks to a trial and to initiate "common sense" measures to mitigate these risks, delegates at the forum were reminded.

"But it takes courage" to follow this approach, "especially in the commercial environment, where people get judged on the outcome of an inspection and are worried about its impact on their careers or their organizations," said Ingrid Klingmann, EFGCP chairperson.

"Common sense is meaningful, but we should also educate people on how to apply their courage," said Klingmann, who is also managing director of Belgium-based consultancy firm Pharmaplex.

There is a culture in some companies to reward or blame individuals following an inspection, the forum delegates heard. Walker believes that this needs to end. "We have actually done inspections, where we have been asked after [giving] an inspection finding whether the person [responsible] should be sacked? And our answer to this always is 'absolutely no'," she said.

Some companies hand out bonuses or threaten to sack people after an inspection. This "is not the kind of organizational culture that we are looking for," Walker said, adding that in her experience, organizations that draw the most inspection findings are the ones that have a blame culture. "People feel that they are not able to say 'Ok, this has happened – let's put a process in place to correct it.' The problem is hidden and then it spirals and results in bigger issues."

An "inspection is not like the police coming in," Delforge added. "It is just an experience, which may be good or bad. It's very seldom that we have to go in for prosecution against the [sponsor or the] investigator." He acknowledged that it may be difficult for sponsors or investigators to foresee all the risks in relation to a clinical trial, or there may be instances of inspectors disagreeing with the sponsor's or the investigator's risk assessment or the mitigation measures proposed. But companies should look at this as an opportunity to improve their processes, he said.

Delegates at the forum heard that the clinical trial community should "learn to live with the imperfections" that are likely to be present when following a risk-adapted approach. Moreover, Walker said that "there are always going to be some issues," no matter how well a trial is planned and conducted, but serious risks can be planned for and mitigated.

During an inspection, we judge the system, and not the person - Dominique Delforge, GCP inspector at Belgium's Federal Agency for Medicines and Health Products

It takes courage to follow the risk-adapted approach, especially in the commercial environment, where people get judged on the outcome of an inspection - Ingrid Klingmann, chairperson of the European Forum for Good Clinical Practice.

The MHRA GCP inspector noted that risk assessments are not new and that the risk-proportionate approach is something that has been talked about in the UK since 2012. "But when we are out and about on inspections, we still find common [old school] perceptions" that continue to prevail, she said. For example, sponsors/investigators believe that full source data verification is needed for every data point for every trial, every single adverse drug reaction

"During an inspection, we judge the system, and not the person," said Dominique Delforge, GCP inspector at Belgium's Federal Agency for Medicines and Health Products.

must be recorded and reported to the sponsor, and that risk adaptation may lead to negative inspection outcomes.

The MHRA is "extremely supportive of the risk proportionate approach" and sponsors and investigators are encouraged to carry out the risk assessment process as early as possible so that mitigation measures can be incorporated into the protocol, Walker said. For investigators especially, she said that earlier risk assessments can help them understand what is expected of them and ascertain whether the trial would fit in with the routine clinical practice of the hospital in which the trial is taking place.

Walker explained that a well-designed trial – i.e., where the design of the protocol fits in with the way that investigators

are working in different therapeutic areas – can help prevent data-related errors. If the investigators are not involved in designing the protocol or in the risk assessment process, "then you are going to face a lot of errors" because if the protocol significantly differs from how things are done in terms of standard clinical care, "then it may be almost impossible to achieve the aims of the protocol right from the start," she said. "The way the protocol is designed is really key to try and prevent errors from occurring right from the beginning."

Not A Numbers Game

There are several ways of conducting a risk assessment. Walker said the industry has started to move away from the scoring system under which sponsors or investigators look at the possibility of a risk being present and the impact of that risk if it did materialize and then gave it a score. But nobody actually knows what that score means in terms of how the trial must be conducted, and the oversight and mitigation measures that are needed to match a score, she said.

There is still wide variability in terms of how risk assessments are conducted. Walker said the MHRA would want the exercise to include: risks posed by the investigational medicinal product; risks to the reliability of trial results; risks from trial clinical procedures (e.g., an advanced therapy product being administered using a novel device); risks to patient rights; and risks to compliance.

Last year, the MHRA Inspectorate wrote a blog on risk adaption in clinical trials of investigational medicinal products. The Inspectorate is planning to write a second blog on this topic on how investigators conduct risk assessment, what things they consider, and what the inspectors "see when we look at their risk assessment," Walker said.

The risk-assessment process, she said, was "not a numbers game or a tick-box exercise." Its focus should be on ensuring the reliability of results and "what really matters in relation to the clinical trial protocol." Whatever risk-based approach is adopted, Walker said it was important for investigators to be able to demonstrate that they can execute the protocol and have full oversight of the trial.

The verb "document" is mentioned over 200 times in the 66-page ICH E6 guideline. This emphasizes the importance of recording all decisions taken in light of the risk-adapted approach. If, for example, the investigator decides not to monitor the temperature of an investigational product because this is not standard clinical practice, "then document that decision so that when an inspector comes in and asks why you haven't monitored the temperature of the product, you can say 'well, this is my risk assessment of the product and this is why I haven't done it'," she said.

Walker said documentation should be in place to demonstrate oversight in relation to, among other things:

- **Training**: All training should be documented. It is not always necessary to have a specific certificate to prove that GCP training has taken place. During inspections, Walker said investigators are often asked how they change their team and make sure that the current investigators, and those on rotation from one department to another, keep up with the protocol. "Their usual reply is that they sit down with the team and go through the protocol to make sure that everyone is aware of what happens... But when we ask them to show how this is done, there is no documentation." All training should be recorded, and it does not have be complex. "it can literally be a case of just writing down what the training was, when it was done and who was there," she said.

- **Review of safety data**: In the majority of trials, the person completing the forms for serious adverse events is not the investigator, but the research nurse or the clinical trial coordinator, who submits the form to the sponsor. During an inspection, investigators should be able to demonstrate that they had had an input on reviewing these events regarding causality and expectedness. Often "this piece in the puzzle is missing," said Walker. In addition, investigators sometimes receive safety data from sponsors about issues detected at other trial sites, and they should be able show that they are aware of these. "It doesn't have to be a complicated process, it can just be a case of signing off the safety information as it is being sent in," she said.

- **Investigator site file**: Although there is enough guidance available on this topic, Walker said one aspect that is commonly missed on this front is the recording of meeting minutes/emailed notes about key decisions affecting patient safety. The meeting minutes do not have to be lengthy; they can be a list or bullet points of key decisions, which will be easier for inspectors to scan and see who was involved in those decisions.

- **Clinical result review**: Walker said this is another area where inspectors commonly find issues. If, for example, lab results are key for determining the inclusion/exclusion of a patient in a trial, then those results – whether on paper or in the form of electronic health records – should be signed off before the patient is randomized and dosed. Quite often, inspectors find that the lab results are signed off a couple of months later. The investigators should be able to demonstrate that they had reviewed the safety and eligibility of the patients before enrolling them in the trial.

- **Key Decisions:** Important decisions affecting patient safety should be documented. If, for example, a patient needs to be withdrawn from the study based on test results "then document that decision so that we can see the medical input to that," Walker said.

- **Reviewing vendor's performance**: Although this responsibility is usually retained by the sponsor, this task may be delegated to investigators running academically-led trials.

- **Departmental oversight:** Discussion on what is considered enough in terms of investigator oversight of all departments is quite subjective. "However, if a department is involved in a really key aspect of the trial, then the investigator should ensure that its staff does things exactly as the protocol needs them to," Walker said. She cited the example of a recent inspection involving a trial with an advanced therapy medicinal product (ATMP) that had an extremely short shelf-life – around eight minutes from the point of being manufactured to being administered to the patient – which meant that a very tight process was needed to get the product from the lab to the theatre where it was going to be administered. "In these kind areas, the investigator should ensure that the concerned department knows exactly what and how they need to do things through protocol training," Walker said, adding, however that "oversight certainly doesn't mean looking over the shoulders of everybody involved in every aspect of the trial," she said.

- **Escalation and resolution of issues**: There should be a defined process to deal with instances of non-compliance with the protocol. If the staff in a department "is continuously missing the window in terms of protocol requirements" – for example, by failing to take to take the necessary samples or conduct the tests needed – "then there should be a written process for escalating and resolving that," said Walker.

From the editors of Scrip Regulatory Affairs.

Un-blinding, Pharmacovigilance Issues Among Top GCP Findings, Says UK Inspector

By Vibha Sharma

Non-compliance with the clinical trial protocol, un-blinding issues and a lack of understanding of pharmacovigilance aspects are some of the issues that the UK Medicines and Healthcare Products Regulatory Agency commonly sees in relation to trials being conducted in the EU.

At a recent open forum in London aimed at EU good clinical practice inspectors and clinical trial investigators, MHRA GCP inspector Paula Walker discussed some of the issues that she usually comes across during clinical trial inspections. The event was organized by the European Forum for Good Clinical Practice (EFGCP) on June 18 and had the revised international GCP standard (ICH E6 (R2)) as its main theme.

At the event, Walker also discussed the challenges that the onset of new technologies is posing for investigators when it comes to maintaining oversight of a trial and for inspectors in terms of verifying compliance.

Common findings by inspectors at investigator sites relate to:

- **Protocol compliance issues**: This includes things like visits not being done within the specified time window, specific safety events not being captured or reported as per the protocol. Such issues could be mitigated through appropriate application of training, said Walker.

- **Un-blinding issues**: This is a common finding at investigator sites. Walker cited an example that "always sticks in my head" regarding a double-blinded crossover trial, where neither the patients nor the investigator knew whether the trial participants were randomized to the placebo or the active drug. "The active [product] was a green tablet with some letters on it, while the placebo was a white capsule. The patients started on one tablet and crossed-over on to the other, so obviously they could see the difference in the tablets," she said. Although the inspectors at site were assured that "there was a spectrum of double blinding"

in place, they felt that patients could easily work out the switch by comparing symptoms on both tablets, and by comparing notes when they talk to each other.

- **Lack of understanding of pharmacovigilance**: Problems relating to reference safety information (RSI) are often seen during investigator site inspections. *(Also see "UK MHRA Takes Companies To Task Over Trial Safety Information Reporting" - Pink Sheet, 4 Nov, 2016.)* "If we ask an investigator - when they are responsible for doing the expectedness assessment of a serious adverse reaction - as to how they know whether an event was expected or not, they still often talk about the patient population or the patient's medical history rather than referring back to the RSI," Walker said. Inspectors still see confusion regarding as to exactly what the RSI is for the product being tested, she said. The MHRA has already written two blogs on RSI, and another one will be published soon in light of revised guidance from the EU Clinical Trials Facilitation Group. *(Also see "Revised EU Guide Addresses Ambiguities In Reporting of Safety Info From Trials" - Pink Sheet, 20 Dec, 2017.)*

Other common GCP investigator site inspection findings relate to: investigators failing to review or document key clinical tests; sign-off of data corrections at the end of the trial; and an inability for inspectors to reconstruct a medical review of serious adverse events through the documentation.

New Challenges

The advent of electronic systems in clinical trials is also bringing new challenges for investigators and inspectors in terms of demonstrating oversight and checking compliance. The use of these systems includes electronic trial master files, electronic case report forms, electronic patient diaries, electronic health records and electronic source data. *(Also see "EMA Clarifies Sponsor's Role In Validating Electronic Systems Used In Clinical Trials" - Pink Sheet, 24 May, 2018.)*

In response to queries on when exactly an investigator should have access to these electronic systems, Walker said considering that investigators are responsible for data and should have control of that data, "they should have a login right from the start of the trial" even if they do not plan to enter all that data into the electronic systems themselves.

The investigator should be able to go into the system to access data and see all the data points from the start of the trial. If, for example, an Interactive Response Technology system is being used for an emergency unblinding, "if you don't have your login from the start of the trial... as an investigator how do you do that?" she asked.

When checking for an investigator's oversight of these electronic systems, Walker said that in most cases, inspectors would ask for an audit trail to see who did what and when. Using an excel spreadsheet as a tracker is not always ideal, she said, as data can be added at any time and it is not always clear whether the entries were made retrospectively.

In addition to the common use of electronic patient diaries – usually developed by the sponsor and given to investigator sites to be handed over to the patients to record their daily symptoms - the emergence of "bring your own devices" is also posing new challenges. These involve the use of apps that patients can download on their smartphones to collect patient-recorded data. "So rather than having to train a patient to use a trial-specific system, they bring their phones along... But it raises a lot of questions in terms of investigator control and ownership of data," Walker explained.

Considerations on this front that need to be addressed include: What is considered source data, who is responsible for it, how do you know who is actually entering data into that app, is it password controlled, can you see if the patient is meeting protocol requirements in terms of data entry, have changes been made to the submitted data, and how is data archived? These questions pose concern for inspectors as well as investigators, she said.

From the editors of Scrip Regulatory Affairs.

US FDA's Khozin On Defining Big Data, Safety Signaling, And The Patient Experience in Cancer

▶ William Looney

This interview accompanies a larger discussion of INFORMED and the perspectives of Sean Khozin, acting associate director of the FDA Oncology Center and founding director of INFORMED. FDA describes INFORMED as an "incubator for collaborative oncology regulatory science research focused on supporting innovations that enhance FDA's mission of promotion and protection of the public health ... Special emphasis is placed on systems thinking in oncology regulatory science research to facilitate development and adoption of new solutions for improving efficiency, reliability, and productivity in a broad range of workflows related to oncology drug development and regulatory decision making."

In Vivo: What does the FDA mean when it references the term "big data"? Like so many issues today involving advanced technologies, the concept is fuzzy but the implications – particularly on patients – are profound. That's especially true given the focus of your work on INFORMED is cancer research.

FDA's **Sean Khozin**: The reason why big data is so important today is the potential it has in better capturing the actual experience of the patient in medicine. It is not just about the "big" factor – we don't evaluate its promise solely as a volume-based exercise, although this tends to appear first in the conversation. A common definition of big data is built around four dimensions: (1) volume (data size); (2) variety (data type); (3) veracity (data noise and uncertainty); and (4) velocity (data flow and processing). At the FDA, most approval decisions are still based on data of limited variety, mainly from traditional randomized clinical trials, and are highly structured within data sets that are relatively small in size and are processed intermittently as part of a regulatory submission.

The challenge for the FDA – and indeed all users of big data – is to develop the human organizational and technical capacity to turn the 'big' into the 'smart,' through applied analytics to personalize therapies around the distinctive disease characteristics of each patient. What this means in practice is to put much more emphasis on that second dimension, data variety. This includes tracking the patient journey through the health system to accurately and consistently record the outcomes of treatment. But it also must incorporate data generated by the patients themselves, on an ongoing basis, in the form of diverse, web-based apps and wearable devices. The FDA is aware that this approach works: in one trial published in the Journal of the American Medical Association (JAMA) last year, metastatic solid tumor cancer patients who were given a web-based platform to record their side-effects from chemotherapy for real-time evaluation by cancer care teams experienced a five-month improvement in overall survival versus those who did not record. It was a simple experiment but it showed nonetheless that involving the patient with data relevant to their own condition can produce a positive health effect.

INFORMED is embedded in the FDA's Oncology Center of Excellence. Why the focus on cancer and what impact will your work have on the pace of treatment for a disease that will strike nearly 2 million Americans this year alone?

Cancer is an extremely complex and varied condition, to the point where oncology drug development has largely become an exercise in evaluating huge volumes of data drawn from disparate sources. Our increased understanding about the genetic origins of individual cancers has led to the DNA sequencing of solid tumors, creating a data pool so vast it outpaces our technological capacity to analyze it. Big data in oncology also incorporates not just individuals' genetic information but data drawn from the microbiome, as well as in that larger environment outside the body – the exposome of external and life-style exposures occurring from the prenatal period onward through life. These drive in turn the similarly endless variations in treatment response, where data is critical to providing insights on the potential of an increasingly diverse set of therapies, many of which work differently in focusing on an immune system response or are administered in combination with both new and older drugs.

The important point is that this trend runs counter to the traditional reductionist approach to drug treatment, relying on a single drug to attack an undifferentiated set of tumor sites

and characteristics. This approach is not scalable to what we know about the biology of cancer today. For example, the most common mutation in non-small cell lung cancer, the epidermal growth factor receptor (EGFR), is present in only about 15% of the patient population, which means that fishing for the therapy that's right for the individual patient requires a much bigger net – and a more nuanced approach. It demands a holistic therapeutic strategy focused on the complex signatures identifiable through systems biology and the entire multiomic milieu of gene and protein-based analytics. Only the biggest data sets can help researchers do that, which makes cancer the place where an incubator like INFORMED has the potential to contribute to the science and benefit patients.

Collaboration is a key rationale for INFORMED. How would you assess the biopharma industry's response to your work to date – is it ahead of you or slower than it should be in helping advance your objectives on digital transformation?

Although we strive to cast our net widely, INFORMED welcomes the support we have earned from many big pharma players. One of INFORMED's first projects was a pilot we conducted with four companies – Astra Zeneca [AstraZeneca PLC], Genentech [Genentech Inc.], Merck & Co. [Merck & Co. Inc.] and Novartis [Novartis AG] – where we tested the feasibility of a new digital framework for reporting of important safety events occurring in clinical trials subject to investigatory new drug (IND) regulations. Instead of submissions that were disaggregated on receipt and sorted in paper and PDF files, INFORMED put together a team that included technical experts from the FDA Office of Surveillance and Epidemiology to develop a new digital framework in which the reports were processed electronically as machine-readable data sets, amenable to standardized visualization and analytical tools, including AI-based methods to conduct safety signals detection and systematically identify gaps in meeting regulatory requirements. The overall aim was to uncover missing or inconclusive safety signals. Reports from the four companies were successfully registered in the new system, validating the new digital format.

The format is now being institutionalized here in the US as the FDA Premarket Digital Safety Program announced by Commissioner Gottlieb last month, beginning with oncology NDA submissions. The FDA Office of Oncology has concluded that digitization of the adverse event reporting process will also be a major productivity booster, saving the equivalent of 500 man-hours of work time every month once the program is fully implemented. Overall, we see the four companies' contributions to making our idea work in practice as a highlight of what can be achieved through collaboration, using the big data tools allowed by the technology revolution.

What's important about this is that FDA reviewers used to have to read cumbersome paper and PDF files to identify safety signals; there was no signal detection based on an accessible, organized data-set approach, in the premarket setting. And it's really a global issue. We may decide in the near future to take our framework as a new foundation for the global harmonization of premarket safety event reporting.

Biopharma companies sometimes cite mixed signals from the FDA as a reason for not moving more aggressively to innovate in the use of data and evidence to advance pipeline performance. Is this perception still valid or has the situation truly changed?

It's no surprise that industry will worry about what the world's largest regulatory agency thinks. And siloed, insular thinking is a recurrent challenge to any large organization, including the FDA. I spend a good deal of time explaining to industry colleagues that the FDA today has a strong technology- and data-driven outlook toward innovation. We are in no means a barrier to the creative application of digital technology to generate more and better evidence to drive drug development. In fact, the agency is on the leading edge of change in this area, which in large part is due to efforts from the commissioner's office to promote technology innovations and greater evidence diversity throughout the agency. Ironically, that top-level commitment is not always present in the private sector. It is particularly hard in large biopharma companies to sustain that seamless flow of ideas where the clinical development teams join forces with the commercial leads in exploiting novel evidence generation tools like RWE; each group has a history of approaching the product development cycle from a different perspective. I see technology, data science and digital as a bridge across the divide, but it takes initiative and a willingness for taking calculated risks outside organizational norms. Some organizations have been slower than others in confronting the disruptions this may entail, but I am confident both government and industry are moving in the right direction.

Global Differences In Clinical Data Release Policies Cause Headaches For Sponsors

▶ Neena Brizmohun

Global differences between regulatory policies for publishing clinical data for authorized drugs can not only put a strain on companies, but they could lead to a situation where only one of these releases of data will emerge as a "first choice" for researchers.

The different requirements that the EU and the US have introduced and that Canada is planning, for example, could result in a company having to create a number of different versions of their clinical study reports (CSRs), according to Stephen Bamford, head of data transparency at Janssen Research & Development.

In addition, the differences globally between the regulatory agencies that publish the data submitted "could potentially lead to a situation where one of these releases of submission data will emerge as a 'first choice' for academics and researchers as it will have higher, more useful, data utility than other releases," Bamford said.

Janssen has been an advocate for clinical trial data sharing to advance science and medicine and enhance public health. In 2014, it was the first company to partner with the Yale School of Medicine's Open Data Access (YODA) Project, a pioneering independent data-sharing model.

Bamford discussed the issues relating to differences between regulatory policies globally at the DIA Europe 2018 conference in Basel last month. Specifically, he compared the European Medicines Agency's flagship policy that was launched in 2016 with a policy that the US Food and Drug Administration recently started trialing and the one that Health Canada is planning (see table below).

Five Different CSRs

He noted, for example, that all three countries take a slightly different position on how personal data in the CSRs should be anonymized to prevent patients and professionals who participated in the trials from being identified. The EMA permits the use of redaction and other

anonymization techniques such as randomization and generalization, though it favors anonymization techniques other than redaction and prefers that sponsors use them. The FDA uses redaction only, and Health Canada currently suggests that anonymization techniques other than redaction be used. As well as the approaches that are allowed, there are differences in what can be classified as personal data between the regulatory agencies.

For Janssen, the differences between these and other requirements "leaves us in a bit of a quandary," Bamford said. "We are in the position of potentially having to create five versions of the CSR."

The first version of the CSR would be used to support the regulatory submission for the drug's approval. Three slightly different versions would then need to be created for release under the EU, US and Canadian data publication policies respectively. Finally, Janssen currently chooses to create a fifth version for the YODA Project, which, according to Bamford, has higher data utility than the publicly available CSRs.

The Janssen executive questioned whether the global differences would "help anyone."

The aim of the policies is to preserve data utility as much as possible while ensuring adequate anonymization. But each anonymization technique has its own strengths and weaknesses. Redaction, for instance, is a simple method

for protecting an individual's privacy but is more likely to decrease the clinical utility of the data compared with other techniques.

Bamford wondered whether the global differences would result in researchers having "a preferred source" for their data.

EMA Collaborates To Promote Harmonization

During the same DIA session, the EMA's clinical data publication manager, Joao Ferreira, said that the agency had been collaborating with its international counterparts in an effort to share best practices and harmonize their clinical data publication requirements.

The FDA's Clinical Data Summary Pilot was launched in January this year. In March, the FDA said that the pilot would post the CSRs from up to nine approved new drug applications of participating sponsors. The first pilot participant was Janssen Biotech for the approval of *Erleada* (apalutamide), the first FDA-approved treatment for non-metastatic, castration-resistant prostate cancer, as well the first to use the clinical trial result, or endpoint, of metastasis-free survival.

At the end of the pilot the agency plans to seek comment from the public through a *Federal Register* notice to hear how the information was accessed and used.

Health Canada published proposed regulations for its Public Release of Clinical Information initiative last December, and released a related draft guidance that is currently under consultation (the deadline for submitting comments to the consultation is June 25). It appears that companies might be able to use the same data and information they have already submitted under the EMA's policy. Appendix H of the guideline says that a company can "certify that the following information and data listed and provided in this submission is complete, accurate and correctly represents the redacted and anonymized information and material provided to the European Medicines Agency under policy 070 and the Canadian submission to which it refers."

Clinical data publication policies are transparency initiatives that aim to help the scientific community and the public understand why a regulator has approved a drug, avoid the duplication of clinical trials, and foster innovation and the development of new medicines.

From the editors of Scrip Regulatory Affairs

Clinical data publication policies in the EU, the US and Canada

	EMA (Policy 0070)	FDA (Clinical Data Summary Pilot)	Health Canada (Public Release of Clinical Information)*
Who does the work?	Sponsor	Agency	Sponsor
Who takes legal responsibility?	Sponsor	Agency	Health department has a role
Technical requirements	Redaction accepted/ other anonymization techniques encouraged	Redaction only	Current documents suggest anonymization techniques other than redaction
Individual patient-level details	Part 2 of Policy 0070 (still to come)	Not in scope, no plan to release IPD	Yes, to be developed
Is there a penalty for sponsors?	Yes	No	Unclear

*Based on draft legislation
Source: Stephen Bamford, Janssen Research & Development.

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