



QUASAR #147

INFORMING AND ADVANCING OUR MEMBERS

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**THE NEED OF THE
HOUR TO STRATEGISE
AND PREPARE QA
FOR THE FUTURE**

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WELCOME



Hello Members,

Welcome to the latest edition of Quasar. I just wanted to share with you a few pieces of information from the RQA Board regarding new updates and initiatives for this coming year.

We had our first Board and Management Committee meetings of 2019 in January and have been working on revamping the RQA vision, mission and strategy. We hope to share these with you very soon.

I am excited to formally welcome Matt Jones, Tim Stiles and Sameera Thanathparambil as co-opted board members for 2019. Matt, Tim and Sam bring great experience, enthusiasm and fresh ideas to the Board meetings, so it's going to be an action-packed year for us all.

It is already going to be a very busy year and I would be thrilled to welcome any RQA members who want to get involved in new initiatives and projects coming through the pipeline. Please make sure you check out the Volunteer Programme on the RQA website for more details.

Regards

Kath



#146 WINNER

Congratulations to
Sharon Havenhand and
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VOLUNTEER PROGRAMME

There are a number of ways in which volunteers can support RQA activity:

- **Time-based** – usually for committee membership
- **Task-based** – generally for single-task projects
- **Virtual** – typically to promote RQA.

This approach allows volunteers to choose to support the RQA in a manner that suits them without over-committing their time. The opportunities are endless.

The time-based committee activities require a commitment of around 6-10 days per year which, when combined with project work, can entail a considerable obligation that only a small handful of RQA members are able to make.

For further information on how to sign up and what opportunities are available, please visit:

www.therqa.com/resources/volunteer



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THE RQA MANAGEMENT COMMITTEE

The RQA Management Committee was formed in June 2015 as part of the major remodelling of the Association's Board and management structure. The Committee comprises of the chairs of each of the RQA Committees – AVPC, DIGIT, GCP, GLP, GMP, GPvP and Medical Devices, with input and support from the Volunteer Programme Lead.

Prior to June 2015, the RQA Committee Chairs had been Board members and Company Directors; a role that required them to attend all Committee meetings and all Board meetings. That arrangement, while providing direct contact between Board and Committees, mainly dealt with operational issues which forced the Board to set up other Committees to deal with Board-related matters such as Finance, Strategy and so on.

The Management Committee meets face-to-face twice yearly – in January to formulate the strategy for the coming year and in August to review the progress of the strategic objectives. Those meetings are held with the RQA Board to facilitate the development and delivery of a strategy which will fulfil RQA's Mission:

1. To develop and promote quality standards in scientific research.
2. To facilitate knowledge sharing and transfer through discussion, training, seminars, forums, conferences, publications, partnership and co-operation.
3. To liaise with regulatory agencies in the development and interpretation of regulations and guidance.

Interim teleconferences are held to bring all the Committee Chairs up-to-speed with any changes and significant updates. The Management Committee meetings foster effective communication between committees and promote collaboration, which often leads to projects and assignments, such as data integrity, which are cross-committee initiatives.

All new product development activity is captured and monitored in the RQA product pipeline. A simple Gantt chart is used to map each new product and the progress of its development. The Management Committee reviews the chart quarterly to ensure that new products remain on-schedule for delivery. New products are essential to the Association and its members, they add value to RQA membership and allow the Association to grow; the new and increasing value keeps the organisation ahead of its competitors.

The Volunteer Programme has provided an additional pool of resources for the RQA Committees. Whether it's a one-off task or a continuing role, the Committees often look to the Volunteer Programme for any additional resource.

Without the input and support from RQA Committees and the Management Committee, the Association wouldn't operate effectively. The Management Committee is a vital link between the Board, the committees and the members.



Balaji Venkatnarayanan

THE NEED OF THE HOUR TO STRATEGISE AND PREPARE QA FOR THE FUTURE

This article discusses rapid technological innovations in clinical research and how QA should formulate new strategies and auditing areas to ensure the software applications developed are fit for purpose and comply with regulatory and other applicable requirements.



Emerging technologies such as artificial intelligence (AI), machine learning (ML) and data science (DS) allow healthcare and pharmaceutical industries to collect, store, process and analyse large volumes of healthcare data. Data driven analysis provides hidden insights, that can enhance efficiency and cost reduction.

Companies have already started establishing AI and DS functions within organisations, or started collaborating with vendors that are offering technology-based analytical insights to Real-World Data to speed up drug development. These advancements are in the early stages, therefore QA should start learning and understand these concepts to develop audit plans and tools to ensure that social, ethical values and the regulatory requirements are followed.

For ease of reference to readers, frequently used terminologies in this article are briefly described below:

Artificial intelligence: an advanced computer programming language emulating the human mode of reasoning. Source: United States Bureau of Census, Glossary of Selected Abbreviations and Acronyms.

Big data: extremely large data sets (structured/non-structured). Data sets that would be analysed computationally to reveal patterns, trends and associations.

Data sciences: an interdisciplinary field that uses scientific methods, processes, algorithms and systems to extract knowledge and insights from data in various forms, both structured and unstructured.

Data analytics: the process of examining data sets to draw conclusions about the information they contain, increasingly with the aid of specialised systems and software.

Machine learning: a method of data analysis that automates analytical model building.

It is a branch of artificial intelligence based on the idea that systems can learn from data, identify patterns and make decisions with minimal human intervention.

The following key areas need attention during audits:

ETHICAL ASPECTS OF AI APPLICATIONS

As per ICH GCP and World Medical Association guidelines, core ethical values such as the rights and safety of participating subjects will be considered for clinical trials. Whereas in AI-powered clinical trials, besides the above ethical expectations and based on the purpose of AIs application, the review should include, algorithm's efficiency to make error free predictions, ethical ability and unbiased and accountable decision-making, fairness and trust. For example, identifying the vulnerable and non-vulnerable populations without discrimination or malicious intent, to support the privacy, confidentiality and to compare the unbiased risk benefit ratio of a drug.

TRANSPARENCY AND TRACEABILITY OF DECISION- MAKING

The algorithms of a decision affect the safety of the subjects in clinical trials and the trial data submitted to regulatory agencies which are subject to inspection. Therefore, auditors should:

- Verify the transparency of data used for training the algorithms
- Have traceability of rationale for making decisions
- Have proficiency to supervise overall decision making
- Make periodic comparative analysis of results derived from AI and human experts
- Identify comparative efficiency as part of qualifications.

SECURITY AND PRIVACY OF AI

AI and ML are trained through the training data sets derived from large structured and unstructured data. Handling large volumes of data increases the high risk of security and privacy breaches. Therefore risk assessment methodologies and auditing techniques should develop strategies to verify the security, privacy, confidentiality aspects and legal control of healthcare data. Robust risk assessments should be implemented as part of 'quality by design'. The auditors should evaluate system robustness for security and privacy.

Big data security contains four stages – data collection, data transformation, data modelling and knowledge creations. The audit scope is dependent upon on the stage. For example, the collection phase: is dependant on access rights, source of the data, privacy and confidentiality.

In the transformation phase: data is filtered, enriched and altered to improve quality of the data prior to analysis. The evaluation criteria should verify the methods and processes employed to isolate and secure the data to avoid contamination with non-transformed data.

During the data modelling phase: the scope should include the data protection methods from mining-based attacks.

In the knowledge creation phase: the data should be stored in a protected format to maintain confidentiality. Therefore, the confidentiality and knowledge management process need to be included in the audit scope.

REGULATORY EXPECTATION FOR CLINICAL TRIAL AI APPLICATIONS

Specific regulatory expectations within clinical research are not available for data sciences and AI applications. The auditors should refer to ICH guidelines, other applicable requirements and may also need to refer guidelines related to data sciences and AI application development. Here are a few relevant guidelines issued:

- Guidelines on Artificial Intelligence and Data Protection issued by the Directorate General of Human Rights and Rule of Law dated 25th January 2019 issued by the Council of Europe
- Consultative Committee of The Convention for The Protection of Individuals with Regard to Automatic Processing of Personal Data (Convention 108) dated 25th January 2019
- Report on Artificial Intelligence and Data Protection: Challenges and Possible Remedies
- The Toronto Declaration: Protecting the Right to Equality and Non-discrimination in Machine Learning Systems published on 16th May 2018.

The auditors should have time to review the public domain for related guidelines released by the regulators.

AUDITING THE ALGORITHMS

Audits should include algorithm review to assure the outputs are meeting the predefined expectations, for example, Article 22 of EU GDPR requires that organisations manually review significant decisions.

A holistic approach should be adopted to include auditing the applications to verify the requirements against validations of real-world scenarios. The audit scope should cover the AI's decision-making, process to algorithm bias reduction, ethical and trustworthiness, transparency, right consenting, data repurposing, privacy and confidentiality and process of learning.

The audit team for algorithm review should include subject matter experts (SMEs) such as statisticians, programmers and data scientists to evaluate the robustness of the scenarios. For example, statisticians may raise questions related to the use of statistical methods and modelling, and data scientists may raise questions related to applicable tools used by algorithms for predictions. The audit should in principle ask questions such as: does the algorithm ensure transparency and ethical aspects?

QUALITY ASSURANCE OF HEALTHCARE BIG DATA

Machine learning relies on working with large data-sets, by examining and comparing the data to find common patterns and explore nuances. Therefore the quality of the data set used will determine algorithm effectiveness. To provide greater assurance, QA needs involvement in the risk plans, mitigation strategies, preparing the quality plans, setting the error thresholds, discussion with stakeholders and validation of appropriate documentation.

To plan methodologies for QA to audit the data science functions, it is essential to find the challenges in implementing the data quality in a big data perspective, as unlike clinical trial data, big data contains unstructured data from various sources. Understanding the factors affecting the quality of healthcare big data is important. The quality of big data is dependent upon factors such as sources of data (for example, the EMR, patient reported outcome, wearable data, imaging data, etc.), data volume, timely receipt of data from various sources, originating geography of data (for example, clinical data standards from each country with their own standards), robustness of electronic systems used to collect, store and analyse the electronic data and security of the system to protect data integrity.

In addition to ALCOA (Attributable, Legible, Contemporaneous, Original and Accurate) principles, considering healthcare big data includes large unstructured data, the characteristics should be: availability (who has access, if the data is timely available, who has authorisation to read or edit the data), usability (in which circumstances the data is collected) and credibility of the data and relevancy (fit for purpose of the data).

AUDITING VENDORS DEVELOPING AI APPLICATIONS

Considering some of the pharmaceutical companies and CROs use vendors for implementing data driven AI-powered clinical trials, the audit requires an appropriate strategy and planning.

AI application service providers require additional evaluation of corporate culture and commitments in implementing ethical values and transparency, to that of routine software vendor audit agenda. The audit scope should cover in detail a review of the systems, SOPs and processes to ensure the implementation of privacy requirements, methods employed to maintain the test data, security and integrity used for machine learning algorithms. Subject matter experts may need to accompany auditors to evaluate the specific area of review.

CONCLUSION

User cases demonstrate that AI application in clinical research is increasing the efficiency of trial performance. The applications being developed are in the initial stage. It's the right time for QA within organisations to strategise and plan to assure that the applications developed comply with regulatory requirements and maintain the ethical values and other applicable laws in the respective jurisdictions. Auditing these areas would require QA to develop plans to collaborate with the internal and external customers, who can act as SMEs. In addition, the auditors should learn the basics of DSs statistical approach, AI and ML.

QA auditors need to gain knowledge about the relevant guidelines issued relating to AI and ML.

To support auditors, QA management should develop SOPs for auditing the AI applications. The SOPs, in addition to covering the purpose, scope and procedures, should also include auditing tools and a checklist. Development of those checklists would require extensive collaboration between auditors and the SMEs.

With operations embracing AI, I think QA should develop new procedures and ensure auditors are appropriately trained, in order to verify compliance.

Disclaimer: The views expressed are the authors' own opinion. This does not express the view of the authors' affiliation organisation.

FURTHER READING

Guidelines on Artificial Intelligence and data protection issued by Directorate General of Human Rights and Rule of Law dated 25th January 2019 issued by Counsel of Europe

Medicine and Healthcare Products Regulatory Agency (MHRA) GxP data integrity data definitions and guidance for industry (July 2016)

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Wickramage, Narada. (2016). Quality assurance for data science: Making data science more scientific through engaging scientific method. 307-309.

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Guszcza J, et al, Why We Need to Audit Algorithms, HBR 28th November 2018, web

Simon London, Michael Chui and Chris Wigley, The McKinsey Podcast The ethics of artificial intelligence.

PROFILES

Balaji is a QA Management Professional with 14 years of experience in Bio Pharmaceutical Product Development and Medical Device Quality Assurance within large bio pharmaceutical service organisations and pharmaceutical companies. He has extensively travelled to over 25 countries leading audits and coordinating inspection activities in Asia Pacific, Europe and in the US. These involved quality audits, regulatory inspection hosting and providing consulting support for the investigator site, clinical monitoring, pharmacovigilance, biometrics and statistics, computer system validation and vendor management from a QA perspective. Balaji is a holder of Master's in Microbiology and a Certification from Harvard Business School in Disruptive Innovation.

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A NEW APPROACH FOR TEMPERATURE MONITORING IN A CHANGING CLINICAL SUPPLY CHAIN ENVIRONMENT

This article discusses the implications of shipping temperature-sensitive clinical supplies in a changing clinical supply chain, including shipments Direct to Patient's (DTP) homes and the need for temperature monitoring thereof.



+ Vaccine Monitoring

Dashboard

Monitoring

Report Table

Data logging

Profile

System

Setting

Logout

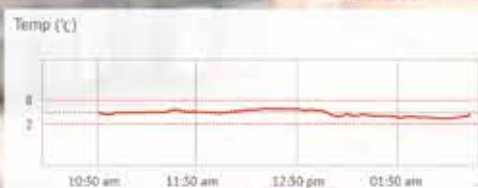
Status
ONLINE

Temp
4.52
realtime °C

Doors
Close
realtime

Power Realtime
927
realtime W

ALARM mode



The clinical supply chain of investigational medicinal products (IMPs) is complex. The time from designing and packaging a kit through to it reaching the patient can take several months and as well as the sponsor, involves many stakeholders, such as the contract manufacturing organisations (CMO), distribution centres including logistics service providers (LSPs) and clinical sites. The clinical supply chain frequently includes different countries, several transportation legs and many days and months with products sitting on a shelf in different storage locations. Thus, management of the temperature exposure of a sensitive IMP is critical. Temperature deviations can put a patient's health at risk, as well as their participation in the study due to non-availability of kits. Following a temperature excursion, kits would be quarantined until the viability is determined, which could result in their destruction if they were deemed unfit for use. An IMP supply chain where the temperature control is robust is therefore a vital asset.

'In recent years the 'patient's voice' with respect to clinical trials is increasingly being heard; they are requesting more convenience, more 'virtual communication' (fewer site visits, more electronic communication) and less travelling.'

NEW TRENDS ARE CHANGING THE CLINICAL SUPPLY CHAIN

Increasingly, we are seeing clinical trials that involve individualised/personalised medicines, such as gene therapies. These trials require a totally different clinical supply chain by the nature of the products and therapy areas. Speed to the patient is crucial. Additionally, in an increasingly competitive world and with spiralling development costs, there is more time pressure shortening the time for patient recruitment. Clinicians and sponsors need to consider: how can we get patients on board faster? However, it is not just about getting the patients into the studies, there is also a need to improve patient retention, how can clinicians keep patients in the study – in particular for lengthy studies? Moreover, how can we increase convenience for the patients?

In recent years the 'patient's voice' with respect to clinical trials is increasingly being heard; they are requesting more convenience, more 'virtual communication' (fewer site visits, more electronic communication) and less travelling. With patient recruitment and increasingly retention being a concern, many sponsor companies actively involve patient groups in various clinical trial design aspects. Additionally, in support of convenience, global patient surveys have indicated that patients would value the delivery of IMPs to their home. Therefore, we see an increasing need and benefit for delivering IMPs DTP.

This increasing trend of DTP intensifies the challenge of managing the complete clinical supply chain:

- The LSP or courier may not always be aware that they are carrying pharmaceuticals, so how can we be sure that the IMP has not been exposed to temperatures outside of its range and thus confirm the viability of the product? How can the status be documented?
- The patient should be aware of the storage conditions of the product via information provided by the sponsor and site teams. However, how can we expect the patients to review the temperature when it is delivered directly to them?
- Once delivered, how can patients monitor temperature efficiently while storing the IMP at home, if required? When they finally use the IMP – how can they decide at the point of administration, if it is still safe to use, if it is a temperature-sensitive product?

WHY MONITOR TEMPERATURES?

Biological and chemical medicinal products are in many cases, by definition, temperature sensitive. There are 40+ Good Distribution Practice (GDP) regulatory directives around the world, most recently the European Commission's Guidelines GDP (2013/C 343/01), state requirements for maintaining product integrity throughout the lifecycle of an IMP, using electronic temperature recording devices. Although using a summation of the total time out of range is not part of these regulations, there are other industry groups, namely the Parenteral Drug Association (PDA), that have outlined in their Technical Report 53 how using a 'stability budget' can provide visibility into maintaining proper temperatures in end-to-end clinical supply chains.

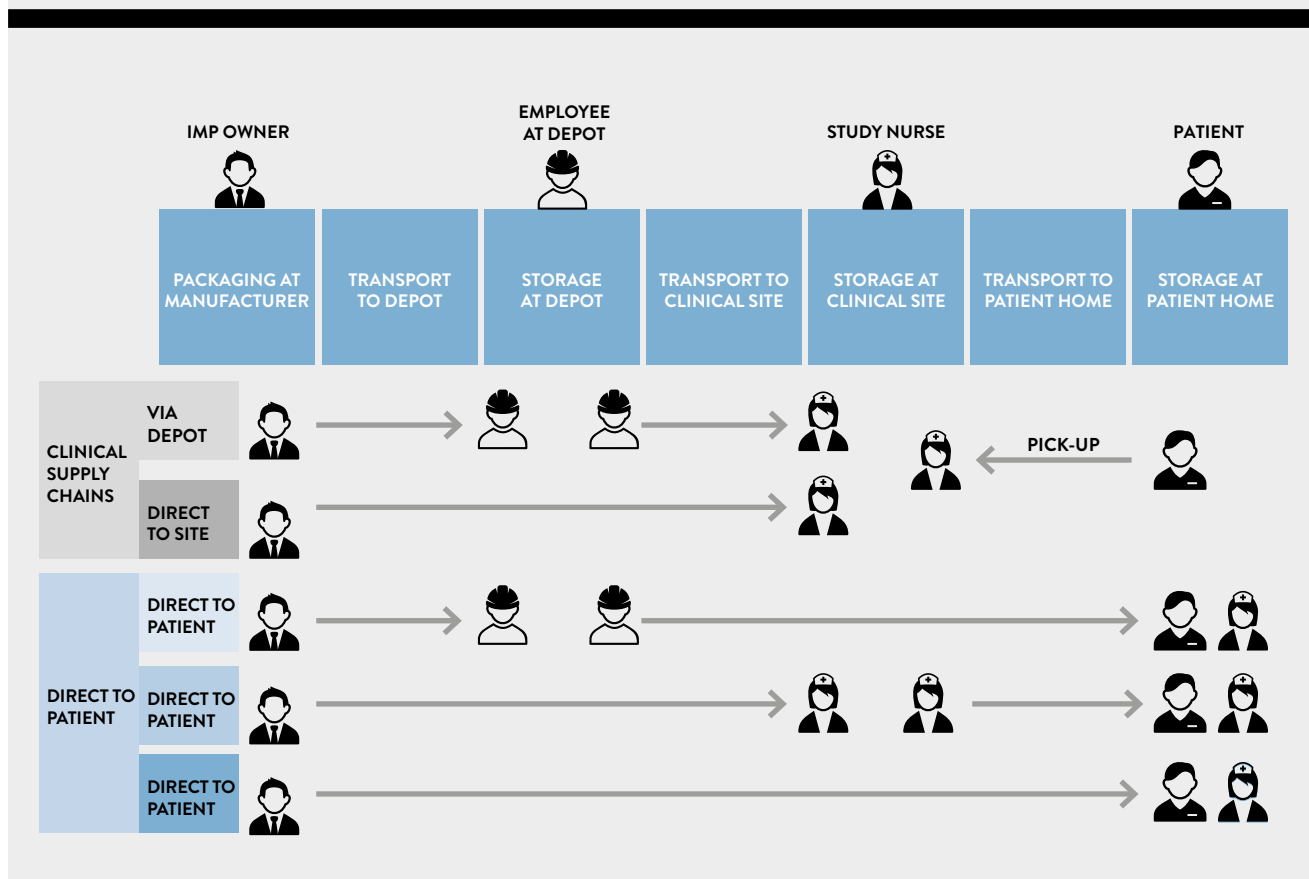
In the past, GMP and GCP responsibilities have typically stopped at the clinical site when the IMP was handed over to the patient. The 'last mile', transportation to the patient's home, was never monitored. Neither was the storage at the patient's home, since the consensus has always been 'you cannot manage the patient'. ICH E6 (R2) 5.13.3 states that 'the investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage'. However, this never was interpreted to include storage at the patient's home.

With an increase in DTP deliveries, the scope of GMP and GCP could shift towards temperature monitoring by the couriers and the patient. Therefore, anything that gives the patient a clear 'OK' or 'not OK' will support compliance and help ensure patient safety.

WHAT IS A STABILITY BUDGET?

The 'stability budget' defines ideal transport and storage conditions and a budget of acceptable excursion hours above and/or below the 'ideal' before a product loses stability. This stability budget has been established over time by the product innovator company through numerous stability studies, combining relevant information from temperature studies with available data from the stability testing to determine the amount of time a product can spend out of its labelled storage conditions without risk to its safety, quality or efficacy.

FIGURE 1. IMP SUPPLY CHAINS



As a product moves through the various phases of clinical supply chain and life cycle, parts of this budget may be used up by small temperature deviations – typically during loading, unloading and transit points, from one step to the next, but also during packaging, manufacturing or storage – small temperature deviations may happen. Such deviations along a clinical supply chain are often called (Total) TOS. If the TOS is deducted from the original stability budget, we can calculate the ‘remaining stability budget’ (RSB). If at the end of a clinical supply chain there is RSB, an IMP is safe to use – at least from a temperature perspective. If there is no RSB, it cannot be dispensed or used. When handing over an IMP to a patient, the healthcare professional must be assured that there is enough RSB to dispense it to the patient. To allow dispensing and hand over to patient, a minimum RSB should be defined by the sponsor. Current practices do not provide this level of detail to clinical sites but if it were available, could also help in decision making in real time if a small temperature excursion has occurred at the site and patients are waiting.

STABILITY BUDGET - TIME-OUT-OF-STORAGE (TOS) = REMAINING STABILITY BUDGET (RSB)

RSB	Status
RSB > 0	OK to use
RSB < 0	Do not Use

OPTIONS OF CLINICAL SUPPLY CHAINS OF IMPs

When supplying IMPs to patients, there are various different ways to define the clinical supply chains (see figure 1).

There are some questions we need to examine and answer about clinical supply chains:

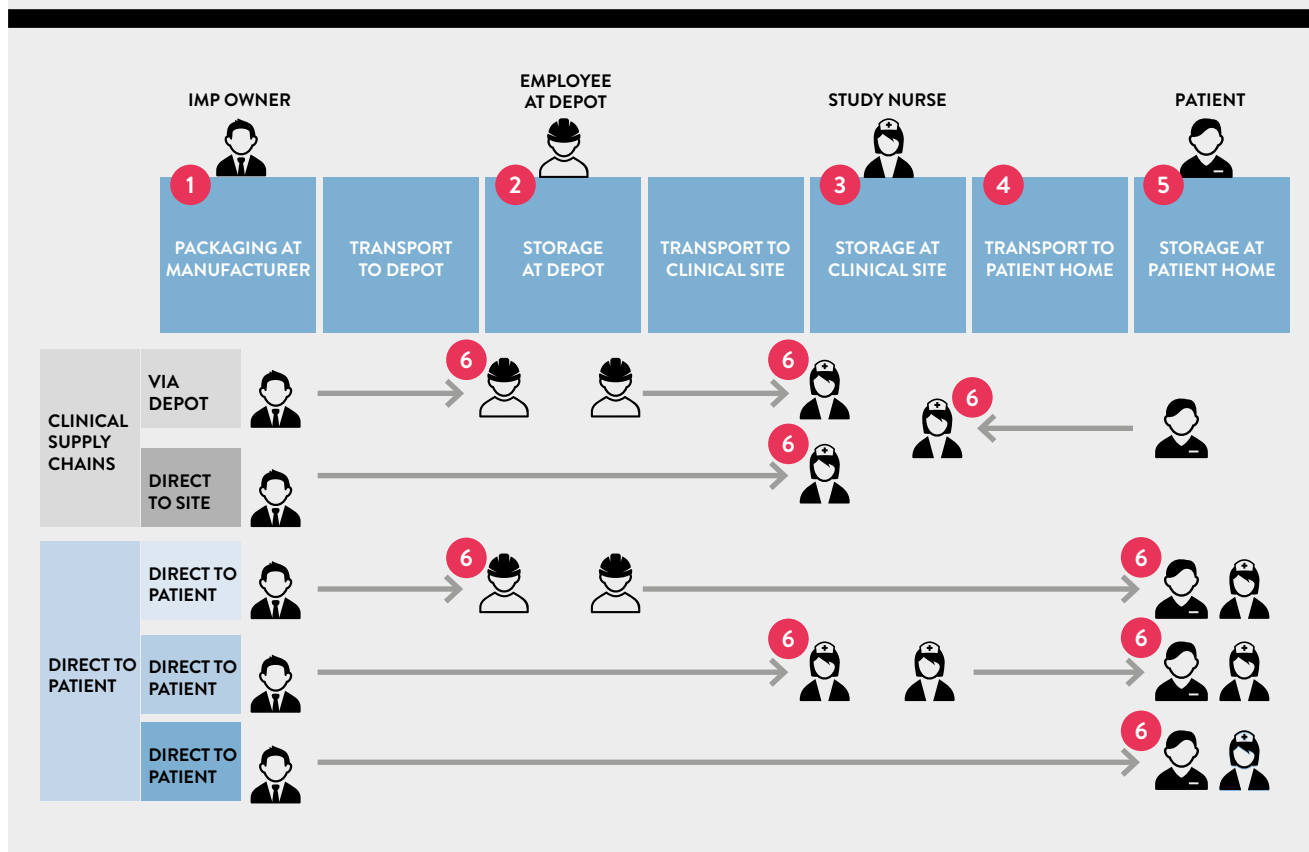
- What are the reasons for different classical clinical supply chains? (why via depot, why direct to site?)
- What are the reasons for DTP shipments?

The design of an appropriate clinical supply chain has to take many factors into account, not least the location and number of countries, number of clinical sites, amount of available product and its shelf life. Sponsor companies may use CMOs to support them as they lack the appropriate manufacturing or packaging capability/expertise or resources. In addition, in order to facilitate the logistics aspects, the sponsor or CMO may also have to consider countries where regional or local depots may be required to accommodate import requirements and to ensure the IMP reaches the clinical site promptly and efficiently without the need to manufacture large quantities of overage.

In the clinical trials marketplace, there is increasing pressure to complete studies in a shortened timeframe to optimise ‘time to market’. Although the regulatory landscape is still developing in this area, various factors have resulted in many studies including an option to ship IMP DTP. The increasing global spread with many studies being undertaken in a growing proportion of third world countries, or in areas of the globe where patients may need to travel long distances to reach the clinical site, is also driving this demand. Additionally, in the developed world, patients are requesting ‘choice’ and can often be time-poor; visiting a clinical site just to receive medication with no study investigations is not something they wish to agree to. The increasing involvement of orphan drugs or customised medicines, coupled with the role of technology and home care, is also playing its part. Some clinical trials have been run remotely or involve the use of study nurses visiting patients’ homes for drug administration or assessment purposes.

However, this patient-centric approach is not without its challenges.

FIGURE 2. MONITORING CHALLENGES AT 'THE LAST MILE'



THE 'TEMPERATURE MONITORING CHALLENGE'

Regardless of which design option is chosen for the clinical supply chain, the challenge of keeping a managed cold chain and/or to continually updating the TOS, remains the same. DTP is emphasising some of the challenges for the last mile (see figure 2).

1. Packaging must comply with GMP requirements and should never be stored outside label conditions. However as part of a well-documented risk-based approach a manufacturer may expose IMP outside label condition during packaging for a limited period. Thus, while packaging clinical kits (which may be partially performed outside the temperature environment), time must be taken into consideration in the RSB.
2. Storage at depot must comply with GMP and GDP requirements. If a temperature deviation happens at a depot or in transit to the depot, how is this time taken into consideration in the remaining stability budget of each single clinical kit affected?
3. During transportation to, and storage at, a clinical (or investigational) site, how is temperature monitored? Are temperature deviations taken into consideration in the RSB of each single clinical kit affected? How are you ensuring the viability of the product when you hand it over to the patient and how is this documented?

4. During transportation to the patient (regardless if performed by a LSP or the patient), is the temperature monitored at all? Has this been risk assessed? Was this risk assessment included in the application to conduct the trial?
5. During storage in the patient's home refrigerator, is the temperature monitored at all? Has this been risk assessed?
6. At the very end of the clinical supply chain, before using an IMP how does the individual know that the IMP is still safe to use? In case of ALARM, who should they contact? How will the sponsor be informed?

It is difficult in 'classical' IMP clinical supply chains to keep track of the RSB. The more handover points, the more risks and the more complexity, it gets more difficult to keep track of the temperature excursions and the RSB. Today this is often performed manually on a paper or an Excel basis: file a batch record, deduct planned temperature excursions and document unplanned excursions. However, once a batch gets split up throughout the clinical supply chain, this manual process is not only time-consuming and expensive, but it is a process which is very fragile, error-prone and puts quality at risk.

This is one benefit DTP offers, as it may reduce the handover points when shipped directly from the depot to the patient or when the transportation to the patient's home is performed by a professional and trained person, taking care of defined transportation conditions and risk assessing the processes.

Consideration of the General Data Protection Regulation 2016/679 (GDPR) and the Health Insurance Portability and Accountability Act (HIPAA) should be included in the review of the feasibility, as the DTP supply will necessitate knowledge of the patient's name and address. How can this be undertaken within the scope of the current legislation and the GCP requirements? The informed consent must contain information on the detail of who will have access to the patient's identifiable information, e.g. the couriers as well as their healthcare professionals.

'It is difficult in 'classical' IMP clinical supply chains to keep track of the RSB.'

IMPACT OF DTP ON THE 'TEMPERATURE MONITORING CHALLENGE'

What is special about shipping, handing over, storing and documenting temperature sensitive IMPs to/at patients' homes?

The typical shipment size of DTP shipments is small (e.g. usually a single or at most a handful of clinical kits) compared to site or depot shipments in the clinical supply chain (e.g. several kits shipped at one time using some form of refrigerated container/cool box or even palletised delivery of multiple cool boxes). Effective data loggers typically used to monitor IMP shipments are built for these larger shipments and are not designed to monitor individual kits.

How is the IMP getting to the patient? Will the study nurse pick up the IMP at the site and bring it to the patient? Will the patient pick up the IMP at a nearby pharmacy? Or will the IMP be delivered to the patient with a courier/logistics provider (and when the study nurse arrives at the patient's home, is the IMP already there)?

When a shipment is handed over to the patient at their homes with some kind of a temperature logger, the temperature status (including the RSB) needs to be documented. The responsibility and process for recording the status of the product on dispatch to, and arrival at, the patient's home needs to be clearly documented and ideally the 'delivery agent' would be trained in these processes.

This step should not be entrusted to patients themselves as most will not have the equipment, training or knowledge on temperature-sensitive shipments. In addition, for some incapacitated patients, they may lack the ability to read classical temperature data loggers or upload information to a database. In the case where a healthcare professional (HCP) is also involved in the patient's home care, the patient may be asked to keep the package containing the IMP until that visit.

Ideally, the HCP has a tool which is intuitive and simple to use. This tool should allow them to document that the IMP is safe to use and still has RSB before handing it over to the patient. Reading a min/max thermometer from a patient's fridge could be an option – but this would not confirm for example that the patient has always kept the IMP inside the fridge. It will be important that whoever is involved in the administration of the IMP has a process for reporting to the sponsor in cases where there is no RSB. Additionally, there would need to be a process for receiving urgent resupply to treat the patient in this scenario.

In today's electronic world, interactive response technology (IRT) plays a key role in managing and monitoring many aspects of the clinical trial process, including the location, availability and status of IMP. Can the IRT be used to monitor DTP supplies? How would it be kept up to date? Is the patient motivated and capable of doing this?

TWO MONITORING OPTIONS

Monitoring temperatures along the clinical supply chain of an IMP up to the patient (and even during storage at patient's home) is important but challenging. There are two fundamentally different options to monitor and keep track of the remaining stability budget: 'measure and puzzle' vs. lifetime/kit-level indicator (see figure 3).

Option A 'measure and puzzle': is what most companies are doing today – at least partly. Depending on the study and depending on the agreements with CRO/CMO's the responsibility of temperature monitoring can be organised in different ways. Depot shipments, but also site shipments, are typically monitored with temperature data loggers – at least to the point where an IMP is handed over at the clinical site or to a patient. However, the challenge with this option is how to put the puzzle pieces together.

Assume that a large quantity of clinical trial kits is shipped in several large containers to a depot. One of these containers experienced a temperature deviation during the shipment. After being repacked and combined with other IMP, one of the kits experienced another deviation in a later clinical supply chain step, when shipped to the clinical site. How can the two deviations be combined? Even if the data loggers from the two shipments are from the same manufacturer, how difficult is it to access the information of which kit has been in which container? Are the two files stored in the same system? Today sponsors often have to put the 'puzzle pieces' together with paperwork or Excel sheets (see figure 4).

FIGURE 3. TWO TEMPERATURE MONITORING OPTIONS FOR CLINICAL SUPPLY CHAINS

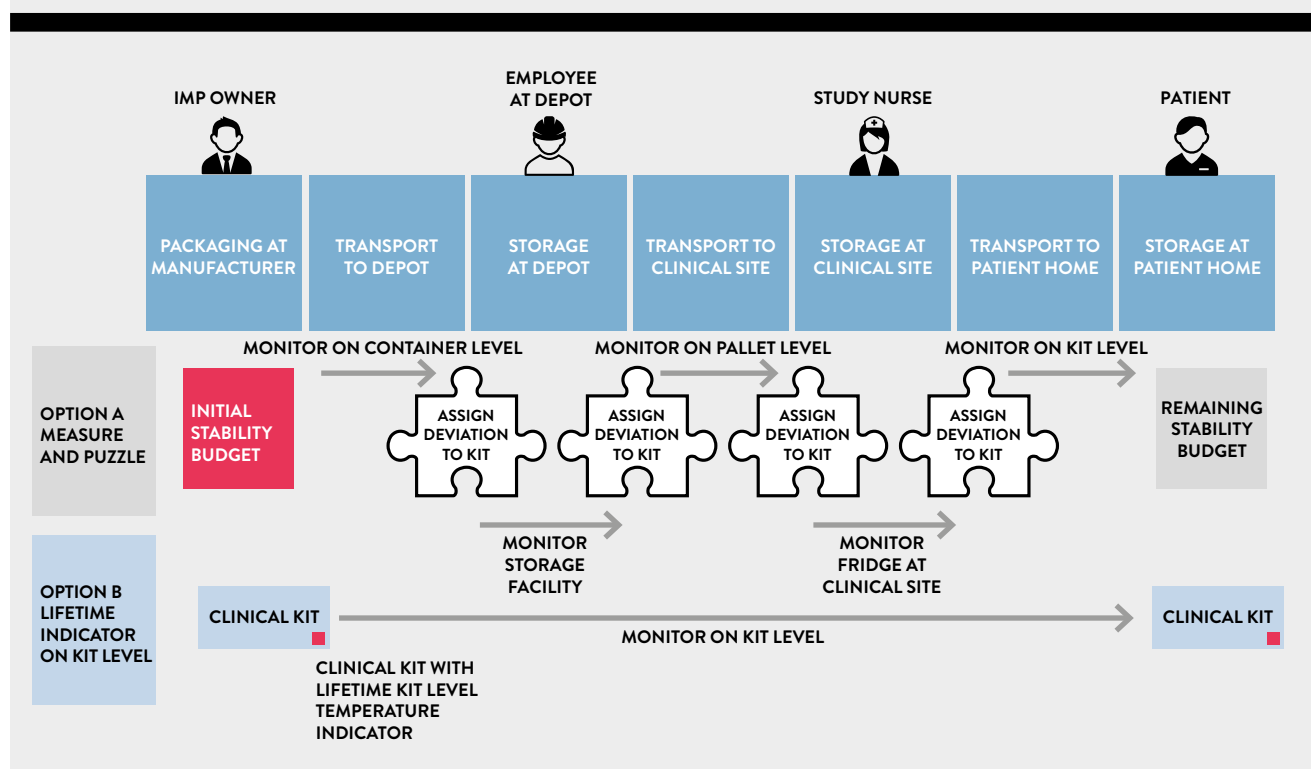
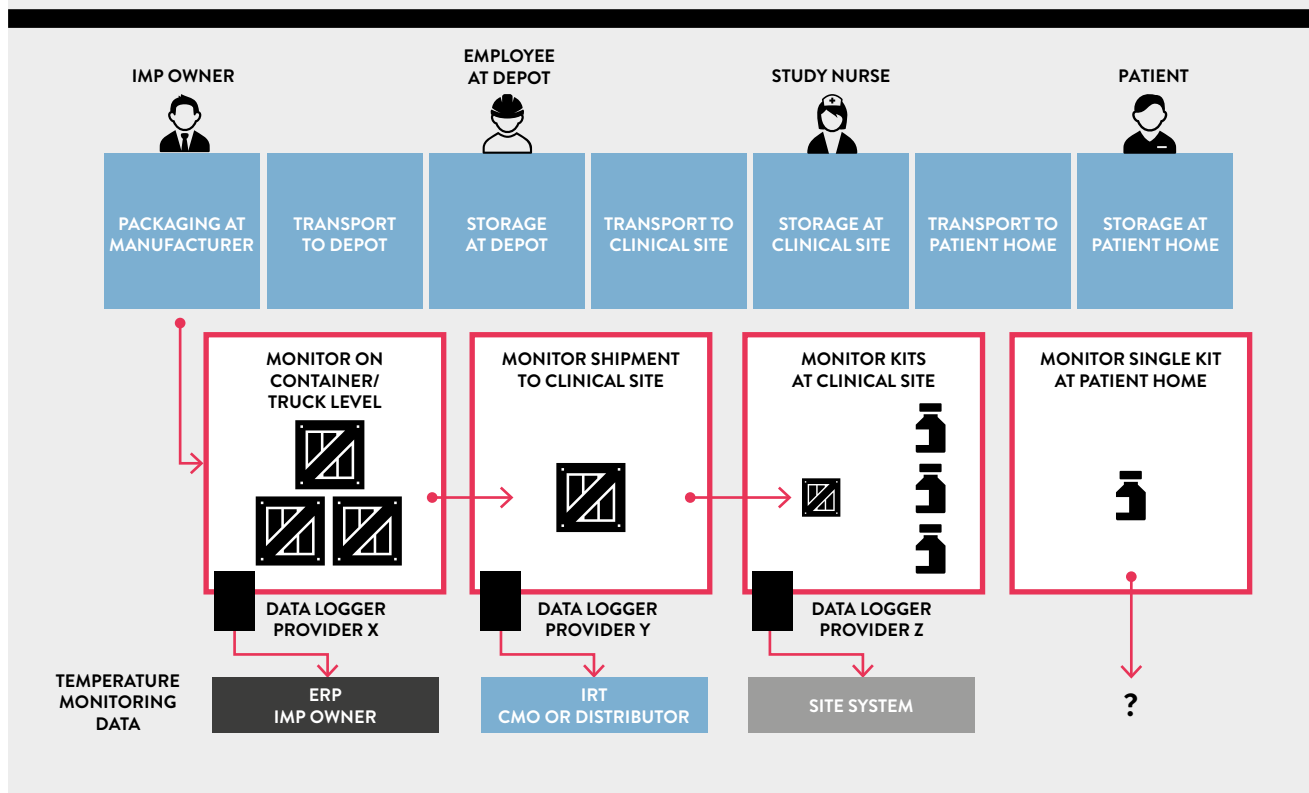


FIGURE 4. DIFFICULTIES IN COMBINING TEMPERATURE DATA



A lifetime/kit-level indicator (option B) is a fundamentally different approach. It equips each clinical kit with an individual visual temperature indicator at a kit-level and monitors temperature during the entire lifetime – from packaging/labelling to the patient's home and final use. It is therefore the obvious choice for several clinical trial scenarios, including DTP shipments, since the transport to the patient – as well as the storage at the patient's home – can be monitored without interruption.

REQUIREMENTS FOR KIT-LEVEL INDICATORS

Monitoring temperatures at kit-level is not new. Chemical indicators which are applied to box level have been available for more than 20 years now. However, they are typically not precise enough for IMPs and are difficult to validate – therefore not considered GxP-compliant (see figure 5).

What are the requirements for an electronic kit-level indicator?

- Must be developed and produced according to GAMP5® guideline and equipped with a unique ID-number to allow traceability
- Must be low cost, since tens of thousands of kits may need to be equipped (e.g. <5 USD)
- Must be thin (<3mm) and small enough for use at the kit-level (< credit card size)
- Can be attached directly to the kit with self-adhesive back

- Monitoring can be started easily without equipment
- Has enough battery capacity to cover the entire lifetime of a typical kit (up to four years)
- Has a calibrated and accurate temperature sensor (with a NIST-traceable calibration certificate)
- Can continuously monitor temperature and keep track of remaining stability budget
- Can easily show status visually (OK to use?) at any time without additional equipment and is also intuitive to use also for HCPs and the patient
- Can document and archive the status in compliant way (no manipulation possible) and allows for easy feedback to sponsor in case the stability budget is used-up (ALARM)
- Keeps track of statistics (time per temperature zone, highest and lowest value) as well as date and time of alarm for further analysis by the sponsor.

To bring all these requirements into one device is not an easy task, in particular since there are conflicting requirements (e.g. extreme long lifetime vs. small and thin). The ultimate dream would be to have everything in a printed label (printed electronics). Unfortunately, this is not possible today since, for example, printed batteries only deliver enough energy for a few days (but not for a few years). However, there are solutions on the market today which cover all those requirements. From a

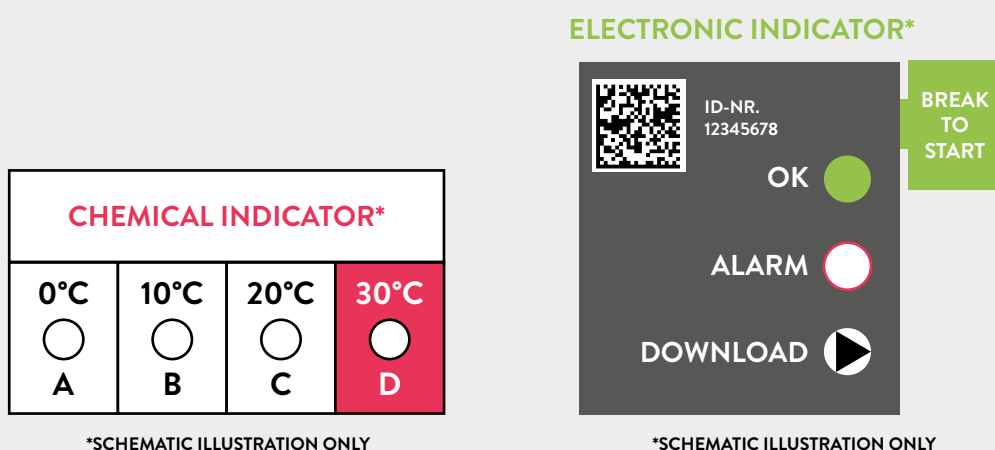
monitoring perspective, such a device could simplify the management of standard clinical supply chains as well as DTP shipments, as these devices fully support patient safety.

ROLE OF IRT

IRT systems ensure randomisation and drug management functions for investigational sites. These systems typically know the status of all clinical kits through the entire clinical supply chain. If a kit is damaged or loses its complete stability budget (= has a temperature ALARM), the status of the kit in the system is changed. Using IRT systems for DTP shipments adds potential difficulties as well as opportunities:

- If no professional personnel are available, shipment and handover-process to the patient must be simple, easy and must be supported by IRT
- Status of clinical kits must be reported back to the sponsor
- IRT allows information about the status of the kit to be available at the point of handover to the patient, (scanning the kit and transferring the data into the system) thus it increases patient safety as it is documented that the kit was within specification when handed over to the patient. Additionally, action can be taken when this is not the case, e.g. trigger another shipment, don't hand out the IMP

FIGURE 5. ILLUSTRATION CHEMICAL VS. ELECTRONIC INDICATOR



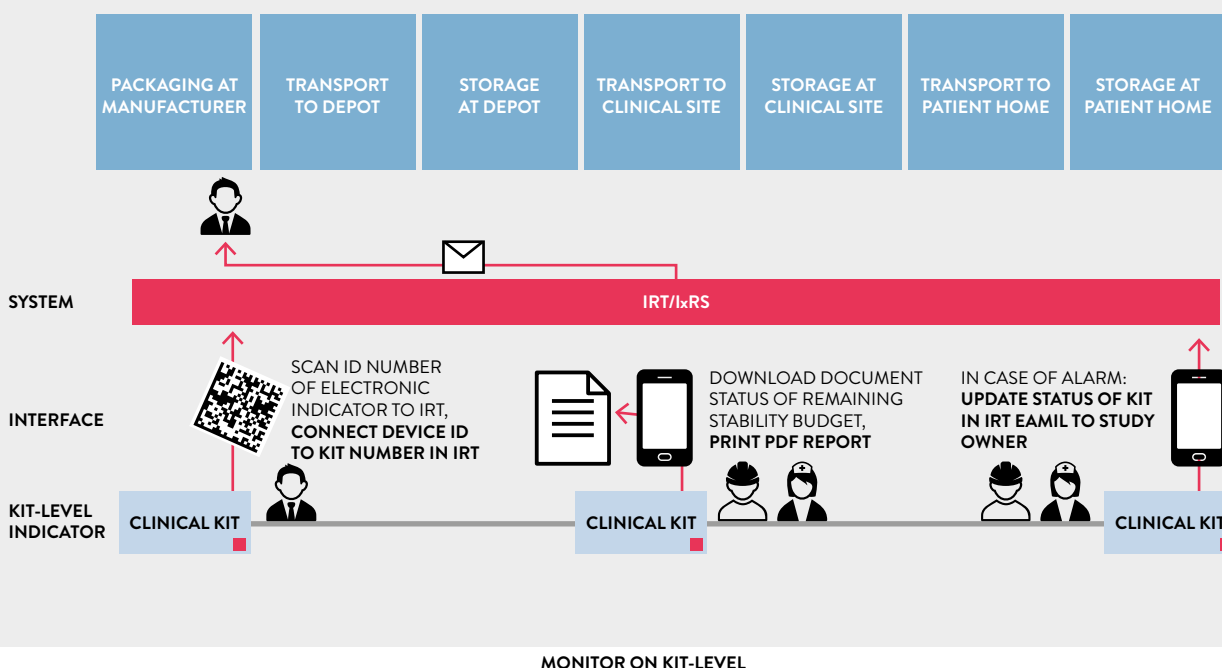
- When the kit is returned it could be scanned and checked if there was a TOS during storage and usage at the patient's home. Depending on the patient and the storage, it might not be possible to store used kits in refrigerated conditions and to transport them back. This would be revealed as early as possible. The scan and data transfer could be performed by the courier or when received by the depot
- The patient could be asked to scan the kit before starting to take the medication, through a specific smartphone app, thus informing the system and enabling notifications as described above, including telling them to stop taking this kit and providing a replacement (automatically through the IRT).

This could also enable better patient compliance calculations about when the patient has started to take/use an IMP kit

- It is possible to scan all kits when the DTP shipment is dispatched, to ensure the shipped kits had no temperature excursion which might not be known yet and provide replacements when required. This will increase patient safety and, as the shipments are relatively small, this should be possible and will act as an additional QC step
- The smartphone app could be used as an extended device to communicate with the patient like an ePRO device, informing patients that a shipment was triggered for them, etc.

Moreover, it is important to keep track of the (temperature) status in the IRT system. To make this feasible, it is imperative to link the device ID of the electronic indicator with the kit ID. As you can see below, this could be done via scanning the data matrix during packaging, labelling or distribution. Once this identification between device and kit is established, it is simple to update its status later in the process without administrative effort. If a download is possible using a standard smartphone app, documentation anytime and anywhere in the process would become possible and enable additional patient safety checks and up to date information for the study team (see figure 6).

FIGURE 6. LINKING AN ELECTRONIC INDICATOR WITH AN IRT



COMPLICATIONS

Complications that need to be considered in using a lifetime/kit-level indicator: (see table 1).

Examples of a ‘worst case consolidation’ of two stability budgets where the products are recommended to be stored at 2°C-8°C.

In Example 1 we have an IMP and a comparator with the same temperature limits but just different numbers of allowed excursion hours in the range between 8°C and 20°C. Defining the worst case is simple: pick the lower number of allowed excursion hours (stability budget).

In Example 2 the IMP has three levels defined up to 30°C while the comparator has fewer hours but a larger range (up to 40°C). The worst case consolidation is to take the highest limit from the IMP (0h > 30°C), the middle range from the IMP (12h at 20°C to 30°C) and take the smaller amount of hours from the comparator in the lower range (36h at 8°C to 20°C).

SUMMARY

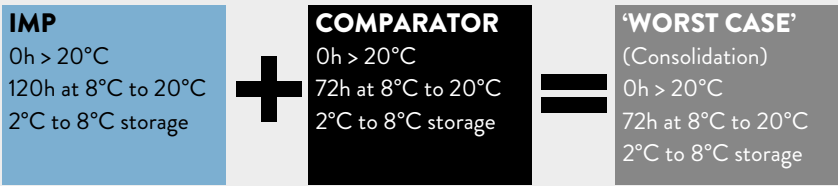
In the past years, the industry has brought the processes of temperature controlled bulk shipments close to perfection, with sophisticated data loggers and validated shipping containers. In this age where patients are much more aware of trials and where we need to go further for patients, we need to think about new ways of bringing IMPs to the patient. Patients are much more technologically aware, which allows the use of modern technologies to facilitate a DTP supply.

The clinical supply chain is long and complex, with DTP adding new challenges but also new opportunities for sponsors, sites and patients. Technologies are available to overcome those challenges and make the benefits accessible – in temperature monitoring and mobile applications as well as in IRTs. However intuitive tools, clear SOPs and training are needed to make the processes safe, efficient and as simple as possible for the users.

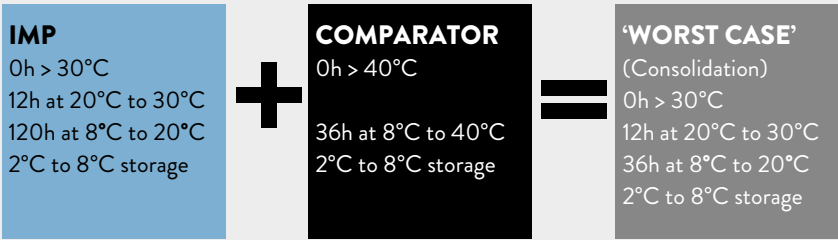
TABLE 1: COMPLICATIONS THAT NEED TO BE CONSIDERED IN USING A LIFETIME/ KIT-LEVEL INDICATOR

COMPLICATION	RECOMMENDATION
Packaging or kit set up does not allow the attachment of one indicator per kit (e.g. for cost or size).	Use a ‘flag-label’ which offers enough place for all required labelling information, as well as the indicator itself.
IMP has unknown stability budget (or stability budget cannot be used) at the time of packaging.	Use the defined storage conditions as strict alarm limits (e.g. 2-8°C). Extending a stability budget on clinical kits of a running study is a complex task that goes beyond the scope of this paper.
Patient does not have access to smartphone technology.	Ensure HCP is available at the home during administration to confirm viability.
In a double blind study a comparator agent has different (or unknown) stability budget to the IMP.	Use the most stringent controls between the products and consolidate the stability budgets to a ‘worst case’ (see examples 1 and 2).

WORST CASE CONSOLIDATION
EXAMPLE 1



EXAMPLE 2



FURTHER READING

The recent report on the ISPE Project Concerning Patient perceptions of IMPs found, that 75% of patients would find it helpful to have their clinical trial medication delivered to their homes

GAMP5® is a well-known development and production guideline for suppliers to the pharmaceutical industry developing and producing electronic equipment and software

NIST is a well-known (US) standard of calibration which is traceable to the (USA) national standard. Other well-known standards are DAkkS (Germany national standard), or SAS (Swiss national accreditation standard)

An electronic patient-reported outcome (ePRO) is a patient-reported outcome that is collected by electronic methods. ePRO methods are most commonly used in clinical trials, but they are also used elsewhere in healthcare. As a function of the regulatory process, a majority of ePRO questionnaires undergo the linguistic validation process (Source: Wikipedia).

SOURCES

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<https://ispe.org/pharmaceutical-engineering>

PROFILES

Based near Manchester, Esther works as Managing Director at SIMPLYESW (Clinical Trial Supply Training and Consultancy), has previously worked with various CROs and has published articles on Direct to Patient shipments highlighting the importance and challenges.

Nimer is CEO at Trial Brain - a Berlin based consulting company for IRT and the surrounding logistics. He is providing training and is specialised on the IT side of clinical trials. Nimer understands how IRT systems are built and why Direct to Patient shipments are even more difficult from a system perspective.

Gary is Global Head of Business Consultancy at the Clinical Trial Supply Unit of Boehringer Ingelheim. He is an active member in the clinical trials community and a pioneer in working with new technologies. Before his time at Boehringer Ingelheim he worked with Wyeth and has been a consultant to the industry for many years.

Samantha works as Lead Pharmacist R&D/Clinical Trials at NHS Greater Glasgow and Clyde (UK National Health Services) where she is also one of the Lead Sponsor Representatives when they act as a non-commercial sponsor of studies. She has many years of experience as a pharmacist, having spent time in different areas of pharmacy including hospital pharmacy and within the private sector working for a large international pharmaceutical company. She has responsibility for and experience and knowledge in the processes and realities of running projects at clinical sites. She has practised as a clinical pharmacist in the areas of oncology, critical care and anaesthetics.

Rebecca currently works as Global Head Compliance and Regulatory Affairs Quality at Novartis Pharma AG. She is responsible for compliance activities across GxPs in the development area and regulatory affairs quality and provides strategic direction to Novartis Pharma Development to ensure patient and public safety and compliance with legislation. Before joining Novartis, Rebecca has been Group Manager Inspections at MHRA.

Martin works for the Swiss-based company ELPRO. He has been working in the cold chain area for almost 20 years and worked for consulting and logistics companies before he put his focus on temperature monitoring. Martin understands the world of temperature controlled shipments and temperature monitoring.



Mario Corrado



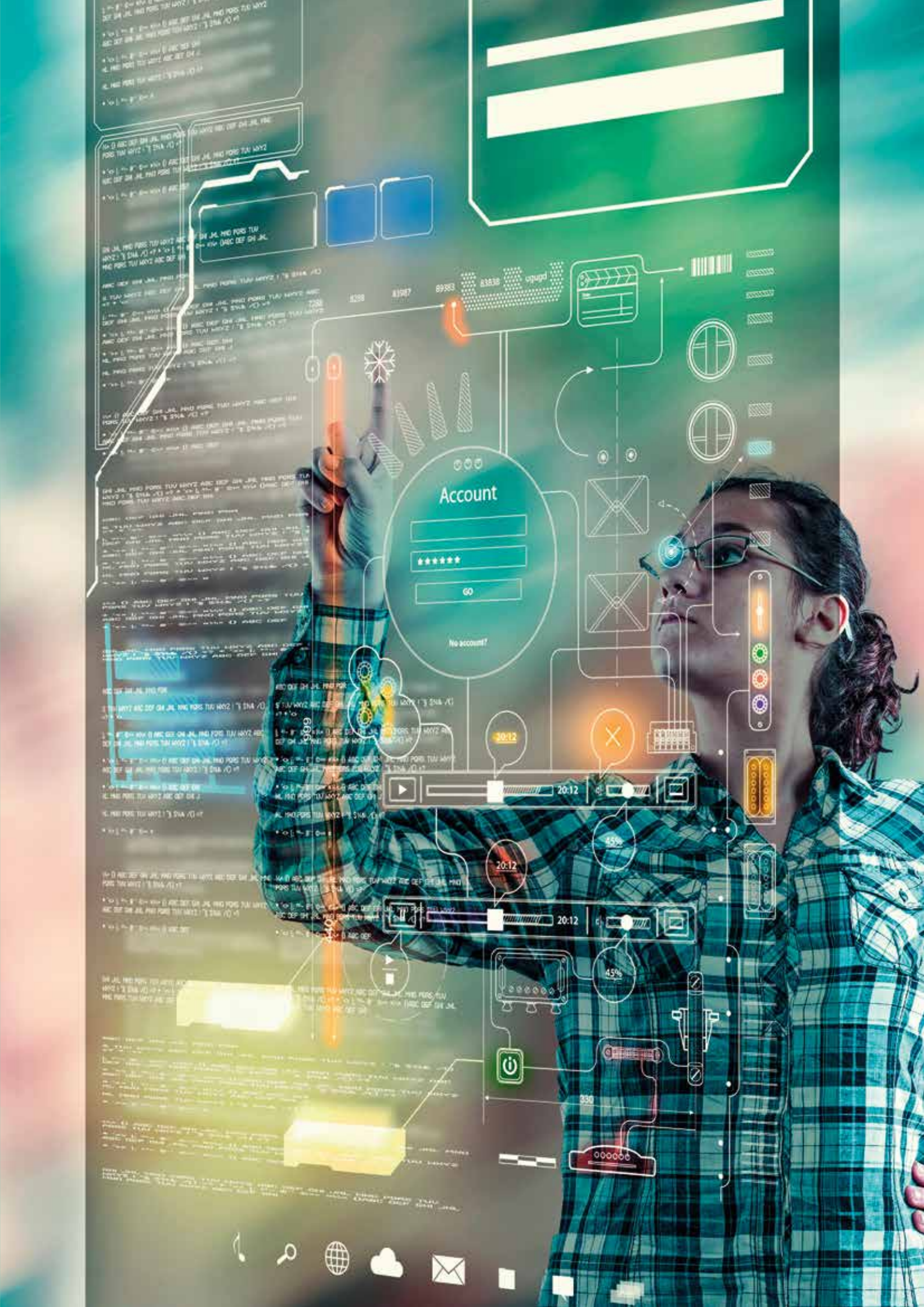
Edoardo Vitali



Giulia Valsecchi

ELECTRONIC PATIENT RECORDS IN THE CONTEXT OF CLINICAL RESEARCH

Medical research is more and more rapidly embracing electronic systems with the purpose of facilitating access to clinical documents. The paper-based records used by clinical sites for documenting patient data, like assessments, visits, medical history, etc. are now frequently replaced by their electronic counterpart, the Electronic Patient Record (EPR), i.e. a software tool that can take the form of a simple database or a complex system interfaced with hospital systems. These tools have great potential, especially when connected with other local, regional or national databases and systems for the management of electronic health records, thus providing an integrated approach to citizen health (eHealth).



This positive innovation is not problem-free, especially when these systems enter the data workflow of a clinical trial. When records of a study are not sourced from the familiar, safe and reassuring context of paper documents, but rather from electronic data, monitors and auditors alike may feel like explorers in a brave new world, sometimes puzzled by operational doubts. Difficulties may arise when concepts and approaches suitable for paper medical records are simply applied as such to the electronic counterpart.

Pursuing the best practical and conceptual approach when these systems are applied in clinical trials is within the focus of the Italian Group of Quality Assurance in Research (GIQAR), part of the Italian Society of Pharmaceutical Medicine (SIMeF, <https://simef.it>). In 2016, a specific team within the GCP workgroup of GIQAR was established with the purpose of investigating the use of electronic patient records (EPRs) in the context of clinical trials, i.e. when some or all data related to subjects participating in medical research are collected by the sites electronically, rather than on paper.

Specifically, the team goals were:

- 1) Review and compare the existing regulations applicable to the management of EPRs.
- 2) Investigate the main difficulties (conceptual and practical) faced by monitors and auditors when monitoring or auditing sites using EPRs, providing advice, guidance and best practices, where possible.

The team, coordinated by Giulia Valsecchi, involved 13 people from pharmaceutical industries and CROs. In order to streamline the work, the team was split into three sub-teams, each working on a specific area, as described below.

METHODS

Two sub-teams analysed existing regulations, either in the local setting (Italy) or internationally (mainly Europe). The initial step for both sub-teams was the definition of those requirements deemed relevant for the EPRs like functionalities, confidentiality, data integrity, validation, documentation, etc. Different types of regulations or reference documents (laws, guidelines, reflection papers, etc.) were reviewed to understand how they, directly or indirectly (i.e. as general guidance), deal with the requirements above.

Reviewed international documents included:

- ICH E6: Good Clinical Practice – (R2) (integrated addendum)¹
- EMA Reflection Paper on Expectations for Electronic Source Data and Data Transcribed to Electronic Data Collection Tools in Clinical Trials (EMA/INS/GCP/454280/2010)²
- SCDM: eSource Implementation in Clinical Research: A Data Management Perspective³
- ACDM/PSI Computer Systems Validation in Clinical Research – A Practical Guide⁴
- PIC/S guidance: Good Practices for Computerised Systems in Regulated ‘GxP’ Environments⁵
- Directive 2007/47/EC on Medical Devices⁶
- EU Data Protection Regulation 2016/679 (GDPR)⁷.

The reviewed national documents are not discussed in this publication.

A third sub-team focused on the most common practical problems related to the use of EPRs in clinical studies. An online survey was launched in March and concluded in July 2016 where monitors and auditors were invited to share, anonymously, their experience with EPRs, to describe the problems they faced, the implemented solutions and the adopted workarounds, if any.

FIGURE 1: COMMON PROBLEMS WITH EPRS IN CLINICAL TRIALS

TECHNOLOGICAL LIMITS

LACK OF AUDIT TRAIL
PARTIAL AUDIT TRAIL
LACK OF SEGREGATION
LONG TERM AVAILABILITY/
ARCHIVING
...

SITE PROCESS LIMITS

LACK OF TRAINING
LACK OF STANDARD
PROCEDURES
SHARED PASSWORDS
HYBRID SYSTEMS
INADEQUATE DOCUMENT
WORKFLOWS
...

MONITORING PROCESS LIMITS

LACK OF TRAINING
INADEQUATE
UNDERSTANDING OF
DOCUMENT WORKFLOWS
INCORRECT IDENTIFICATION
OF SOURCE DOCUMENTS
...

The collected responses were fewer than expected, still, they allowed the identification of common problems linked with EPR adoption in clinical trials. These can be summarised (see figure 1) as:

- Technological limits of the systems (i.e. limits by design, functionalities not implemented or poorly implemented), for example:
 - Lack of specific system access profiles for monitors
 - Lack of audit trails or partial, inadequate audit trails (for example recording only the last data change and not all the changes)
 - Lack of data segregation (i.e. possibility of viewing data for patients beyond the scope of a given trial)
 - Possibility of printing documents before data lock-out when data can still be changed.
- Process implementation limits (i.e. inadequate use of the EPR system by the site), for example:
 - Inadequate use of a properly designed system
 - Lack of knowledge and training on EPR functions
 - Lack of site procedures
 - Shared login/passwords.
- Monitoring errors (i.e. inadequate understanding of the system by the monitor), for example:
 - Inadequate identification of the true source document when both EPRs and paper records are available
 - Inadequate understanding of true document workflow from original to copies (e.g. creation of paper copies of the electronic data and subsequent changes introduced on paper only).

CONCLUSIONS

The analysis of selected guidance allowed the identification of common requirements: e.g. functionalities, confidentiality, security, data integrity, validations, etc. leading to the following considerations:

- There is no single unique document that can be considered as a reference document for the use of EPRs in clinical studies
- According to the reviewed documents, similar concepts and requirements are differently addressed by various documents in different contexts
- As far as it could be investigated, EPR manufacturers do not seem to be bound by specific national or international standards when designing their products.

A traceability matrix between the identified general requirements and how they were specifically addressed by each guidance has been set up and made available on the SIMeF website as a free downloadable spreadsheet. https://simef.it/phocadownload/GIQR/GIQR_GCP/epr-reqs-summary-cross-reference-with-rules-guidance-2-0.pdf

The analysis of the difficulties with EPRs reported by monitors and auditors evidenced that:

- Some of the problems were only apparently linked with EPRs. In fact, these could be more correctly ascribed to conceptual pitfalls in understanding the meaning of 'source document' when moving from the domain of paper records to that of electronic records
- The training of monitors and auditors on data integrity, especially when dealing with electronic records is of paramount importance
- The initial phases of monitoring activities are extremely important and can prevent data integrity and source data verification issues or errors. In particular, a clear understanding and agreement is needed with regards to the available records, their location, how and when data are recorded, how EPRs are used, how these enter in the clinical data workflow and how they are managed
- When discussing the use of EPRs with clinical sites, it is very important to ask the relevant and adequate questions, avoiding technical jargon that can be misunderstood or is inappropriate in the specific context.

The difficulty in retrieving or in obtaining clear information from the sites, which is a common monitor complaint, could be sometimes resolved by asking a few clear, simple but focused and relevant questions. Therefore, in order to leverage a proper collection of information at site, the 'Electronic Patient Records, Guideline for Interview to Site Staff' document has been developed by the team and made available on SIMeF website. https://simef.it/phocadownload/GIQR/GIQR_GCP/epr-site-interview-guideline-v-1-3.pdf

The documents contain a set of 'key questions' aimed to guide and focus the discussion between monitor (and auditor) and site staff in order to facilitate the understanding of how the system works and how it is locally implemented, focusing on the key requirements and avoiding technical jargon. This guideline is not meant to be a 'ready-to-use' checklist but rather a tool to facilitate collection of information about system and processes used by the sites to collect and maintain EPRs.

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- 3 <https://scdm.org/wp-content/uploads/2016/09/SCDM-Mobile-Health-White-Paper.pdf>
- 4 www.acdmglobal.org/resources/books-available/entry/4/
- 5 www.picscheme.org/layout/document.php?id=155
- 6 <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32007L0047>
- 7 <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:3A32016R0679>

PROFILES

Mario has 20 years of experience in clinical research. During his career he has worked as monitor, project leader, quality assurance and auditor. He leads the Quality Assurance Unit of the CROss Alliance Group and he is one of the coordinators of the GCP working group of the Italian Group of Quality Assurance in Research (GIQR).

Edoardo is a QA professional with experience in GCP and GLP areas. He has been working in the QA Department of the pharmaceutical company Angelini since 2011 where he is involved in the maintenance of quality standards according to GCP and GLP and he is expert in auditing (clinical sites, CROs, providers, laboratories, internal system audits, documental audits), in SOP writing and review, training management and computer system validation.

Giulia has over 25 year's of experience in the implementation of quality management systems, auditing, computer system validation and data integrity in the clinical research and pharmacovigilance fields. In 2016 she joined Roche where she leads the clinical research compliance and vendor management units. Such units are responsible for supporting the clinical study conduction in compliance with regulatory requirements and company procedures and to ensure the governance and the oversight of GCP Vendors respectively.

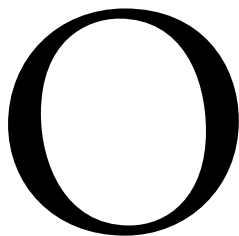


Mark Birse

THE MHRA APPROACH TO DATA INTEGRITY

Over the last five years, the MHRA Inspectorate has been developing its ability to educate as much as it regulates, with the aim of driving a culture of compliance with our stakeholders. When serious non-compliance is identified, it's a painful experience for all; be that for patients with potential disruption to their treatment, for the regulator through the increased workload to ensure patient safety and continued availability of critical medicines and for industry as a result of the reputational and financial impacts.





One key aspect of this work has been the provision of greater clarity around the agency's expectations

regarding data integrity. Readers of the MHRA Inspectorate blog will be well aware of our work in this field and this article outlines our approach and provides examples of anonymised findings that have been identified across all parts of the Inspectorate.

The MHRA Inspectorate is made up of four groups which cover our operational activities, strategy and innovation, as well as overseeing how we operate as a risk-based regulator using science to underpin the decisions we make. The inspectorate employs around 75 inspectors working across five GxP areas: good clinical practice (GCP); good distribution practice (GDP); good laboratory practice (GLP); good manufacturing practice (GMP); and good pharmacovigilance practice (GPvP).

MHRA inspectors are regularly requested by other regulatory agencies to provide specialist data integrity training for their inspectors.

INTRODUCTION TO DATA INTEGRITY WORK UNDERTAKEN BY THE AGENCY

The MHRA's strategy for the education of stakeholders regarding data integrity is multifaceted and cross-agency. The agency had always inspected for data integrity, with each area of the inspectorate developing its own GxP-specific methodologies and expertise.

Our first published data integrity guidance ('MHRA GMP Data Integrity Guidance' in March 2015) was developed following a greater awareness of software vulnerabilities and an increase in high-profile GMP data integrity cases.

Following the successful launch of the GMP Guidance, the 'GMP Data Integrity group' was expanded to encompass all GxPs to facilitate the sharing and collation of the inspectorates' collective experience and knowledge of data integrity issues across the product lifecycle. This then led to an objective to produce a data integrity guidance document that encompassed all GxPs.

The GxP guidance was issued for consultation in July 2016 and more than 1,300 comments were received. A thorough review and re-write then followed with the final version being ready for publication in March 2018. The feedback thus far is that it is well received and we welcome any comments that would help to strengthen it further.

As an agency we are involved in many educational engagement activities relating to data integrity, including engaging with other inspectorates across the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the Organisation for Economic Co-operation and Development (OECD) network. We also engage in the education of external stakeholders. This is supported by the whole inspectorate through promotion and awareness raising of the GxP Data Integrity Guide and presentations at external conferences. Finally, we engage in education of agency staff. This is being coordinated as a joint venture with personnel from across the agency and delivered in a number of ways, such as identification of fraudulent data being received by the agency and mechanisms to detect this, but also with assistance from the Information Management Division, training of each asset manager in the principles of data integrity.

Through all of this engagement work, our aim is to have a harmonised approach to data integrity and mutual understanding across the agency and influence the wider regulatory environment.

There still remains a concern that not all organisations are addressing data integrity appropriately; serious GxP failings with respect to data integrity continue to be discovered by our inspectors and reported to us by the organisations themselves. To highlight this, an inspector from each GxP discusses a recent case from their area in order for readers to pass on any new knowledge to their organisations and hopefully avoid such situations in the future. As with all instances that are serious, we are here to listen and help where we can, our mission is protecting and improving public health which often means supporting industry to ensure medicines are safe and available.

GCP CASE STUDY

A GCP inspection of a clinical trial sponsor identified a large number of errors associated with the documentation of medication batch numbers by patients into an electronic diary system. When this was followed up on inspection, the sponsor did not have oversight of the vendor's process for verification of patient-reported data changes and could not confirm that source data existed to support all changes to participant-reported data and that an

accurate record existed of study drug received by patients.

A critical finding relating to data integrity was given which led to the organisation re-monitoring the affected studies to determine the extent and impact of these to the marketing authorisation Rapporteur. The organisation also committed to enhancing the processes used by data management, monitors and site staff when querying these types of data.

A follow-up inspection was conducted two years later which demonstrated that the revised processes had failed to work, as similar issues were identified in relation to changes to participant-reported data. This led to a second critical finding being raised in relation to data integrity, as it was clear that the issue remained and had not been addressed. This required the sponsor to review the trial data for a further three trials to determine why changes to participant-reported data had been made, whether these changes could be substantiated from the medical records and the reason behind each change (i.e. was it a true correction or was it to amend a trial participant's 'best guess' as to when treatment had been taken). The output of the review was reported to the MHRA inspectors, the MHRA Inspection Action Group (IAG) and marketing authorisation Rapporteur to assess the impact of the issue on the marketing authorisation and to determine whether they had fulfilled their regulatory commitments made in response to the inspection.

Due to the increased level of risk associated with the nature and grading of the findings and the prior inspection history, the organisation will have a shorter inspection frequency and future inspections will continue to include significant focus in these areas. The organisation failed to understand that changes to patient-reported data are potentially high risk to the integrity of the trial, due to the difficulties associated with accurately documenting discussions and subsequent changes to patient-reported data, although there is no actual risk to the patient. This, in turn led to a huge amount of additional work to determine what the impact was on the affected trials and to put in place effective systems which could appropriately manage these types of data changes in the future.

Data integrity issues are often linked to the failing of an established system or process, usually where several opportunities for intervention have been missed. This can then lead to significant inspection findings and additional regulatory workload.

GDP CASE STUDY

During a routine GDP inspection of a medicines distributor, physical stock count was compared to both hard copy and electronic stock records. Hard copy stock records were issued on a free-vend principle and were therefore not reconcilable. These included a stock quantity of Zopiclone, a controlled drug that did not match the physical stock in the warehouse. Electronic Sage records were also inaccurate when compared to physical stock and had been used to trace transactions, monitor stock levels and provided stock data for recall management.

Stock counts were routinely carried out by the account manager and a warehouse operative. These were recorded on a Sage printout of stock quantity and consisted of physically counting all medicine stock lines twice a year. Anomalies occurred frequently, with the December 2017 tally showing 16 out of the total of 43 medicine lines not being accurate. Corrective action consisted of adjusting quantities on Sage with no justification, no root cause assessment, no quality risk assessment or any preventive action. Adjusting discrepancies in this way had become accepted as normal practice. The company did have an operating procedure in place that described data governance, but this was clearly ineffective. A 'major' deficiency was raised that related to ineffective quality risk management, lack of corrective and preventive action planning changes and providing impact analyses and a lack of appropriate oversight by the responsible person (RP). During the inspection, the inspector clarified the MHRA GDP expectations in these areas and emphasised their impact on risk to public health. A recommendation was made that approval of stock adjustments should include a member of the Quality Department and the RP was made fully aware of their responsibility in assessing effectiveness of the quality system and the quality of records.

The company openly accepted the deficiency and the serious implications of having data that could not be trusted, as well as failure of their risk management and deviation management processes. As part of their preventive action plan to the deficiency, the RP reviewed the data governance procedure and trained it out through the whole of the company including the Finance Department.

Due to the weak data integrity standards in some distribution companies, the GDP inspector published an MHRA blog aimed at this sector to supplement the MHRA GxP Data Integrity Guide.

The issuing of a major deficiency increased the risk profile of the company that resulted in a shorter re-inspection interval, which is ultimately costlier to the organisation.

GLP CASE STUDY

The UK's GLP Monitoring Authority (GLPMA) was contacted by a test facility and made aware that its QA Department had discovered data integrity issues that it was investigating. The issues had come to light following a sponsor-requested audit of the test facility's processes and procedures used to generate histopathology slides. The audit was triggered because the sponsor had concerns about the unexpected nature of the results reported for its study. The outcome of the test facility's initial investigation concluded that duplicate slides had been cut from one processed tissue block but labelled as originating from different animals. A total of 26 studies performed for seven clients were affected and all slides affected had been prepared by the same individual.

Some of the studies known to be affected were to support an application to perform clinical trials designed to assess a new manufacturing technology which was to be used to produce critical vaccines.

Following receipt of the test facility report, the GLPMA conducted a 'for cause' inspection. The outcome of the inspection resulted in the following GLP 'critical' deficiency:

Following the identification of serious issues associated with the integrity of data generated for the above studies it is the opinion of the GLPMA that the quality of necropsy data and histopathology sample preparation cannot be assured. Consequently, the GLPMA cannot support claims of GLP compliance for the above studies.

Report amendments must be issued for each study clearly indicating that no claim of GLP compliance is made for the work.

Test facility management should ensure that each report amendment is sent to the study sponsor. The UK GLPMA should be sent written confirmation indicating that each sponsor has acknowledged receipt of the amendments to their studies.

In addition to dealing with the test facility, the GLPMA, in accordance with EU regulations and international convention, notified the GLP working groups of the EU, OECD, EMA and the US FDA informing them of the serious data integrity issue that potentially affected submissions for marketing authorisation and clinical trial applications.

The GLPMA served a warning notice on the GLP operator (the person legally responsible for GLP), because their initial response and actions to the critical deficiency did not address the root cause of why the data integrity issues occurred. The GLPMA inspectors had identified the following serious GLP quality system failings and required the facility to take corrective action:

There was insufficient evidence that the person involved in the data integrity issues had the appropriate training and experience to undertake histopathology assessment. They were involved in the necropsy, tissue processing and slide reading.

The study records indicated that there was a lack of appropriate peer review/QC checking of the block preparation and necropsy phase. There was documentation to show these were checked by the technician but there was no documentary evidence that anyone else was involved.

The histopathology procedures had not been subject to any routine audits.

Several affected studies had to be repeated. Delays were incurred to the development of patient-critical medicines. The GLPMA conducted several follow up inspections to assess the effectiveness of the test facility's corrective and preventative actions.

GMP CASE STUDY

The GMP inspectorate was contacted by a small pharmaceutical company in the UK, disclosing details of an issue the company had identified during a routine mock recall. What it had discovered was that every batch record, dating back for eight years, had been deliberately falsified with respect to the quantities of some excipients added and some batches as far back as 13 years. In total this occurred for 2,621 batches of oral liquid products.

During this time the site had been subject to regular regulatory inspections, customer audits and self-inspections. The fabrication of data was discovered because of the discrepancies found when reconciling a batch of glycerol to the batches of finished product in which it had been used. This led to further investigation to probe deeper and expansion to cover another excipient, maltitol, where discrepancies were also found. When questioned, senior production management admitted to the internal quality group that the quantities of glycerol and maltitol added were not in accordance with the quantities stated on the product batch manufacturing records and that the dispensing/manufacturing operators were systematically trained to record the registered quantities on the batch records. In practice, one drum each of material was added instead of the required amounts (a drum of glycerol was 260kg and for maltitol was 275kg).

Upon discovery of the issue, production was halted at the facility by the investigation team and no further release of the implicated products was performed by the Qualified Persons.

The assigned GMP inspector thanked the site contact for informing us of the issue as it allowed the agency to immediately evaluate the potential impact to patients.

The case review from the MHRA perspective involved multiple divisions to coordinate, advise and take action. This included the Defect Medicines Reporting Centre (DMRC), Licensing Division, the Inspectorate, Enforcement, Inspection Action Group (IAG) and Department of Health and Social Care lawyers and product criticality assessors.

Since any data generated previously could not be relied on, new data were required. The activities that were required to bring the processes and marketing authorisations (MAs) back into compliance included:

- Full process validation on three full scale batches
- Stability data on three new commercial scale batches conducted under ICH conditions with six months' data from ongoing studies included in the variation
- New efficacy of preservative studies covering levels down to 70% nominal levels
- Dissolution data conducted at three pHs
- Uniformity of deliverable mass from multidose containers
- Suspension uniformity.

Some of the consequences included:

- Lots of ongoing communication with the agency
- Any batches that were on hold had to be destroyed
- The cost and time completing the actions required to reinstate the MAs became prohibitive to the company and these were sold on. At this point the MAs were suspended to ensure that post-transfer, these were not simply reinstated in the absence of robust development and stability data
- The resulting outcome was that the company closed.

This last case study is extremely rare in that the non-compliance led to company closure; almost all companies are able to recover from the situation that they face.

GPVP CASE STUDY

The MHRA pharmacovigilance inspectorate carried out an inspection of a large global pharmaceutical company which had recently undergone a series of mergers and acquisitions. As a result of these activities, the inspection placed a high degree of focus on data integrity issues, particularly those relating to data migration and data retrieval. Several data integrity issues were identified, all of which formed part of findings graded as 'critical' or 'major':

- **Critical finding.** For an innovative, potentially high-risk product there was incorrect product name configuration for 45 out of approximately 120 serious clinical trial cases in the Argus safety database. The incorrect configuration led to these 45 cases not being included in database searches and consequently being omitted from both internal signal detection activities and regulatory submissions. The company committed to identifying the full extent of documents from which the cases were missing and on investigation this was found to be periodic safety update reports (PSURs), annual and five-yearly licence reassessments.

The company also corrected the product name in the database so that the cases would be visible on all searches and carried out remedial signal detection activities. Due to the nature of the product, regulatory assessors were informed and the company asked to liaise with them with regard to resubmission of all regulatory documents with erroneous safety data.

- **Major finding 1.** The company used a validated Business Objects report to build cumulative and summary tabulations of adverse events from post-marketing data sources for inclusion in PSURs. On detailed inspection of the search strategy logic it was discovered that the report was retrieving incorrect data: (1) certain types of non-interventional study cases were being incorrectly excluded; (2) unrelated adverse events were being wrongly included; (3) there was potential for incorrect inclusion of partner-sponsored clinical trial cases. It was found that multiple EU PSURs had been submitted with incorrect data. The marketing authorisation holder (MAH) carried out an extensive analysis and committed to an exercise to recode study type descriptors and full re-validation of the search strategy.

- **Major finding 2.** Approximately 300 adverse event cases were found to have incorrect status regarding confirmation by healthcare professionals. This had the potential to affect expedited and aggregate safety reporting to regulatory professionals. There were multiple causes, including incorrect data migration when databases were merged. The MAH committed to recoding of affected cases, staff retraining and additional data validation for future data migrations.

The company accepted the data integrity issues identified during the inspection and carried out appropriate corrective and preventative action in the prescribed timeframe.

CONCLUSION

The MHRA GxP Guideline was produced to assist the stakeholders we regulate. The interpretation given in the guide should afford the reader insight and a stimulus to check internal systems. It should also help in identifying gaps in current processes and offer ways of addressing these. The underlying principles for data integrity are not new but the environments in which they need to be applied continue to change. If when applying the guidance, you identify a serious data integrity issue or you just simply don't know where to begin, pick up the phone, we may be able to help.

ACKNOWLEDGEMENTS

This article was first published in Regulatory Rapporteur Vol. 14, No 9, September 2018. Contributors to the article are members of the agency's GxP Data Integrity drafting group: Jason Wakelin-Smith (Lead Senior GCP Inspector); Terry Madigan (GDP Inspector); Lesley Graham (Lead Senior GLPMA Inspector); Tracy Moore (Senior GMDP Inspector and GMP Operations manager); Dominic Nguyen-Van-Tam (Senior Pharmacovigilance Inspector & RBI Risk Information Manager).

FURTHER READING

1. MHRA Innovation Office – www.gov.uk/government/groups/mhra-innovation-office
2. MHRA Inspectorate blog – <https://mhrainspectorate.blog.gov.uk/>

PROFILE

Mark is the Group Manager of MHRA Devices Safety and Surveillance Group and Devices Software and Apps Group. He is the former Deputy Director of the Inspection, Enforcement and Standards Division and Head of the MHRA Inspectorate and Process Licensing which employs around 75 Inspectors covering GCP, GDP, GLP, GMP and GPvP and the Process Licensing team. Mark joined the MHRA in 2002 as a GMP Inspector having previously worked in the pharmaceutical industry for over 10 years.

Managing digital data from a regulatory perspective

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Healthcare regulatory affairs has always involved managing and interpreting large quantities of data. Digitalisation and the pressure to use big data effectively has added to the complexity. Regulatory professionals are called on to provide guidance to their product teams and senior management about the integration of data from multiple sources using electronic data standards that meet regulatory requirements and the use of advanced analytics in decision-making.

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Joanne Donald

MANAGING COMPUTER SYSTEM VALIDATION CHANGE CONTROLS

Throughout the life cycle of a Validated Computer System, changes will be required to be made to the system. These can range from a minor update to a report, to a major upgrade of the system software or hardware.

Some typical types of changes are:

- Adding new access levels, e.g. allowing QA to have read-only access to a computer system for auditing purposes
- Updating settings e.g. adding a new alarm for a freezer to a data monitoring system (DMS)
- Adding a new process/workflow e.g. adding a new document approval route to a document control system.

WHEN THINGS GO WRONG (EXAMPLES):

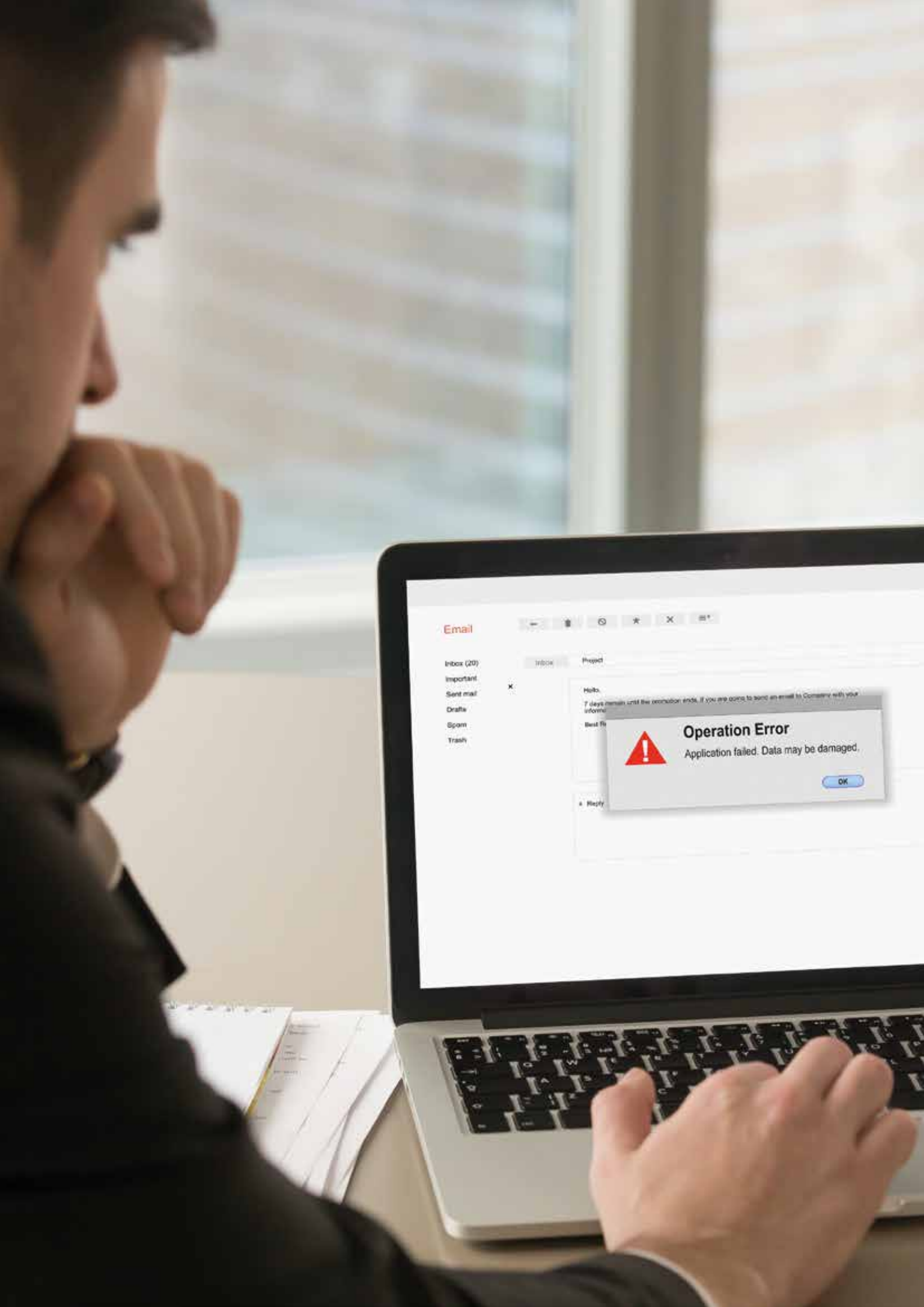
- Vendor on routine visit installs a patch which changes how the system reports data without telling the user department. This means the system is no longer validated and may be reporting inaccurate results
- IT make changes to the system without telling the user, this means the system is no longer validated
- A change control is raised but the risks to changing the system are not adequately assessed. The relevant specifications e.g. user requirement specification are not updated so do not match the live system
- A change control is raised but the risks to changing the system are not adequately assessed. The change is made in the live system without testing in a test system and the live system falls over
- The update to the setting/software is not backed up, this means if the system falls over and is restored at a later date, the old version of the system will be restored
- Not enough evidence of making the change in the form of screen shots, etc. is taken at the time the change is made.

To ensure changes are performed in a controlled manner, the following is required:

STAGE 1 – ASSESS THE CHANGE

All changes must be assessed for the possible impact to the validated system. Key questions to ask are:

1. Does the change require an update to a validation specification/document?
2. Does the change have an impact on functionality? If it does, a functional test will be required.
3. How will it be tested? Ideally it should be tested on a test system before going into the live system.
4. What will be your back out plan to roll back to the previous system version if the change needs to be reversed?
5. How will the system software/settings be updated after the change?
6. How will the change be documented? Would taking a screenshot of a simple setting before and after the change be sufficient or is a detailed report of the change required?



Here are some examples of change controls risk assessments:

- A) Add a new field to an existing report
- B) Updating a data monitoring alarm setting (see figure 1)
- C) Upgrading a chromatography systems software.

For a breakdown on the required actions required for each change, see table 1.

‘The main thing to do is to demonstrate adequate risk assessment of changes in advance of making the change and then to gather the required evidence of the change.’

FIGURE 1: UPDATING A DATA MONITORING ALARM SYSTEM

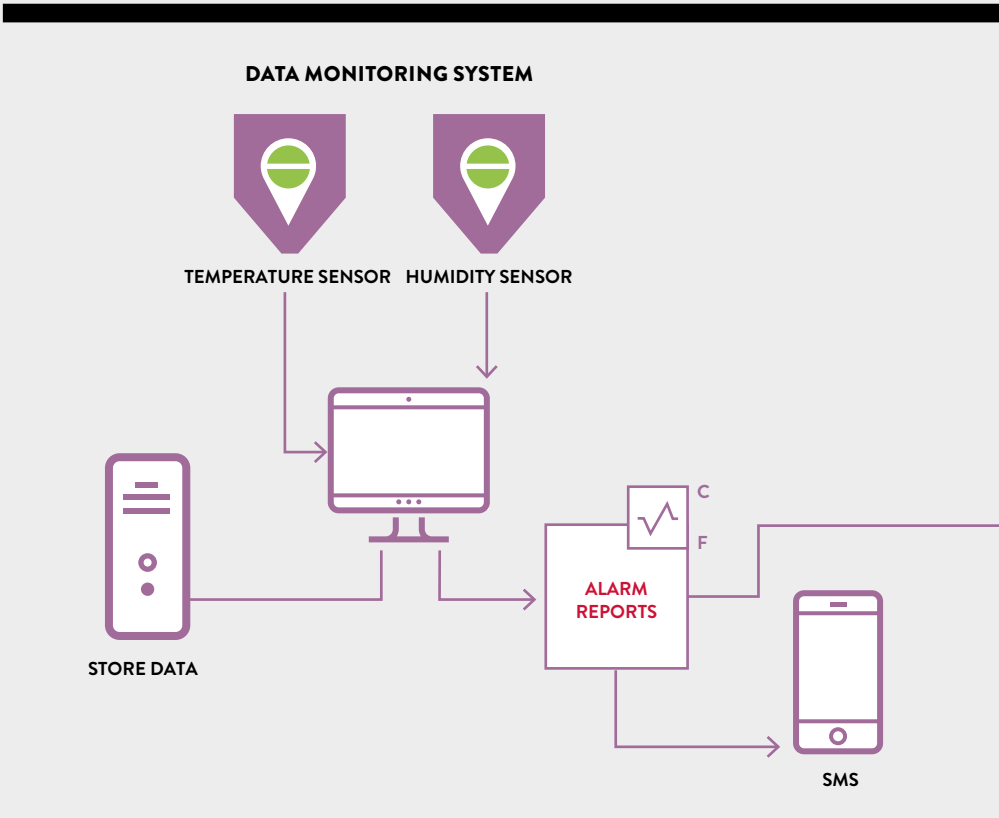


TABLE 1. CHANGE ASSESSMENT TABLE

RISK	A) ADD A NEW FIELD TO AN EXISTING REPORT
Does the change require an update to a validation specification/ document?	Yes. The configuration specification needs to be updated to list the new field.
Does the change have an impact on functionality? If it does, a functional test will be required.	Standard report functionality is not affected by the change so no functional testing is required.
3. How will it be tested? Ideally it should be tested on a test system before going into the live system.	No testing is required. All that is required is that evidence is taken that the change has been made in the live environment.
4. What will be your back out plan to roll back to the previous system version if the change needs to be reversed?	The change will be made at the start of the day when the previous day's full data and system image has been taken. If this is not possible, scheduled downtime will be required to make the change. If any issues arise after the change, the latest system image can be reinstalled on the system.
5. How will the system software/settings be updated after the change?	A system image will be taken after the change to update the system image.
6. How will the change be documented? Would taking screen shot of a simple setting before and after the change be sufficient or is a detailed report of the change required?	A screenshot can be taken pre and post change to document the completion of the change.

STAGE 2 – PERFORM THE CHANGE

The change owner makes the change gathering all the evidence required as listed in the change assessment table, for example a DMS change.

STAGE 3 – CLOSE THE CHANGE

The QA/validation department review the evidence of the change and confirm it meets the requirements listed in the change risk assessment. The required evidence is either attached to the change control or else referred to from the change control. QA/validation then approve the change control for closure.

If all the above requirements are met then the change control will be compliant and will meet the requirements of a regulatory or supplier audit. The main thing to do is to demonstrate adequate risk assessment of changes in advance of making the change and then to gather the required evidence of the change. All of this will demonstrate good control over the validated state of the Computer system.



PROFILE

Joanne originally gained a degree in Applied Biology before embarking on a QA career.

She has worked at Norton Waterford, Viragen Limited at Charles River Laboratories and at Patheon UK. She has a broad range of QA and Validation experience and has worked to GLP, GCP and GMP regulations at different stages over the course of her career.

Joanne is a very experienced computer system auditor, an experienced computer systems vendor auditor and she is a proven expert on GxP computerised systems validation compliance.

Her current role is as a Computer System Validation Manager for a biotechnology company, Porton Biopharma Ltd, where she leads a team and is the subject matter expert for computer systems validation.

She is also a member of the RQA DIGIT Committee.

B) UPDATING A DATA MONITORING ALARM SETTING (DATA MONITORING SYSTEM ALARM)	C) UPGRADING A CHROMATOGRAPHY SYSTEMS SOFTWARE (LARGE CHROMATOGRAPHY SYSTEM)
The user requirement specification and the configuration specification require updates with the new alarm details.	Full validation life cycle documents are required. Starting with a user requirements specification and computer system risk assessment. Also required will be a validation plan detailing the validation strategy for the system.
A new alarm is required to be set up. This will need to be functionally tested to confirm that it works.	The upgrade contains several new design elements and changes the existing features previously validated for the system. As per the approved validation plan, full testing of the new features and detailed regression testing of the existing functionality will be required. Data migration testing of the data previously collected on the system will be required.
The freezer alarm will be tested by means of a preapproved test script, on the live system. There is no test system.	A development environment will be set up to trail the new version of software. A test and live environment will need to be set up and validated to formally test the upgrade.
The system will be backed up prior to the change being made. If any issues arise after the change, the latest system backup can be reinstalled on the system.	The upgrade will be set up and trialled in the development environment, formally tested in the test environment and only then installed into the live environment.
A copy of the updated configuration settings will be taken after the change and submitted to the software archive for storage.	The three development, test and live system environments will be stored on virtual servers that are mirrored across the site. Once the system has been tested and released for use, the final versions will be frozen and access to settings restricted to QA system administrators.
A preapproved test script will detail the update to the alarm and the testing of the alarm. A copy of the audit trail of the change to the alarm will be attached to the test script for review. QA and validation will review the test script evidence and approve the report section of the test script.	A validation summary report will be generated to confirm that all the validation deliverables listed in the validation plan have been produced. It will confirm that all the required validation testing such as installation, operational and data migration testing has been completed as expected and passed and it will list any issues/discrepancies raised together with their resolution details.

The 3rd European QA Conference will take place in Dublin, Ireland between the 6th and 8th November 2019. It is the turn of RQA to organise the conference, following successful events organised in 2013 by the German Quality Management Association (GQMA) and 2016 by the French Quality Assurance Society (SOFAQ).

The venue was secured early on in the planning stage, with the Convention Centre Dublin (CCD) being chosen for its central location and fantastic facilities for delegates and exhibitors alike. The location is ideal for travellers from all over the world, with Dublin Airport handling flights from over 42 countries every year and the bustling city centre is only a 20 minute car journey away. The Programme Committee was formed from the three main organisers (GQMA, RQA and SOFAQ), as well as numerous quality associations from around Europe (including The Netherlands and Spain). The Committee met in early January at the venue in Dublin to discuss all aspects of the programme. This meeting is key to developing a varied and informative programme that will encourage participation from around Europe and the rest of the world.

The starting point is the title of the conference. Whilst this sounds simple, it is crucial to find a title that describes the overall topic that the conference will touch on. From there, the shell of a programme is made based on what this title represents. At this stage, ideas flowed around the table on how to structure the two and a half days, taking into consideration the various GxP's and hot topics that should be discussed, as well as the requirements of potential attendees.

As the two and a half days were filled with potential topics and speakers, it was fantastic to see the various associations and nationalities working together to create a programme that quality professionals will want to be involved in.

After the programme structure was completed, the group were taken on a tour of the facilities. The CCD offers 22 flexible spaces including a 2,000 seat auditorium and Wi-Fi for up to 22,000 devices – more than enough to seat everyone and ensure that everyone can access the Conference App and get involved in asking questions, viewing presentations and networking whilst at the venue.

Following this initial meeting, the group meets by teleconference every two weeks to ensure that speakers have been found and all information is gathered for delegates to potentially book from April. We all hope that the programme interests you enough to join us in Dublin.

Left to Right: Carl Lummis-Blaxell (RQA) Steffen Koenig (GQMA), Kerstin Koenig (GQMA), Angelika Tillmann (RQA), Catherine Liang (SOFAQ), Tony Ward (RQA), Nuria Elisenda Puigoriol (SEGCIB), Salvador Ribas (SEGCIB), Rose Buot (SOFAQ), Marijke Steenvoorde (DARQA), Anthony Wilkinson (RQA)





BOOK REVIEW

A REFRESHED PERSPECTIVE ON THE IMPLEMENTATION OF WELL-ESTABLISHED QUALITY IMPROVEMENT INITIATIVES
BY JENNIFER BELL

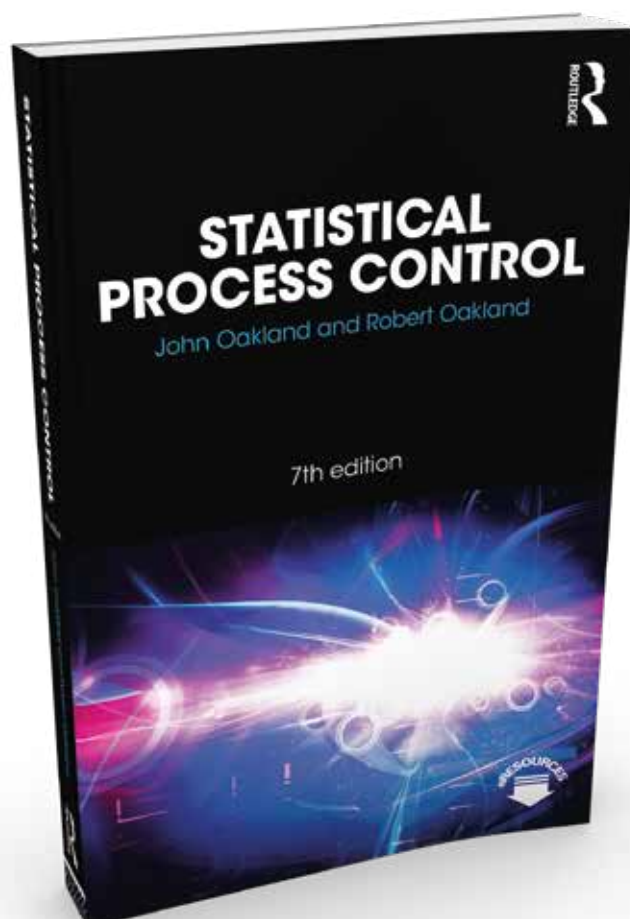
Statistical Process Control (7th Edition) by John Oakland and Robert Oakland applies to industry, academia and the public sector, including drug and medical device development processes. Both authors are consultants with decades of industry experience. Indeed, John Oakland wrote the first edition of this book in the mid-eighties.

Effective implementation of statistical process control contributes to market competitiveness and increased profitability for many successful organisations. For those interested in process control for quality management and process improvement, the book is informative and not intimidating. The content allows for self-instruction by those unfamiliar with statistical process control.

Statistical Process Control gives examples for implementing quality management and business excellence systems and lean and six-sigma initiatives. Each chapter outlines learning objectives at the start, provides case studies and refers to appendices as applicable for supporting information in the body and summarises chapter highlights at the end including references for the reader to follow-up on if desired. Each chapter ends with discussion questions and worked examples to promote group interaction. The appendices, glossary of terms and the index provide further clarity to the reader. Additionally, the publisher's website www.routledge.com provides supporting Excel spreadsheets of data tables and corresponding assessments in the book to ease data transfer into statistical software packages to conduct analyses.

Overall, the book gives a refreshed perspective on the implementation of well-established quality improvement initiatives. It contributes to driving cultural improvement by helping departmental perspectives to blend and align to reach the common goal of producing fit for purpose process outputs. It highlights common behaviour found in companies attempting to manage out-of-control processes, remove waste and redesign business activities.

The book presents questions that ask whether to replace detection strategies with prevention strategies.



In focusing on prevention strategies, the emphasis is on activity at the front end of the process, e.g. quality by design (QbD). This approach saves effort, time and money spent on detection of issues near the end of processing activity.

Statistical Process Control outlines quality design and conformance costs. The described quality costs contribute to understanding approaches for right first time, meeting specifications and avoiding the cost of getting it wrong. As variability decreases, quality and productivity increase and statistical methods of quality control help visualise this at various time points in relation to the whole.

Processes are the central theme running throughout the book; processes require *understanding*, have *variation*, must be *controlled*, have a *capability* and need *improvement* – these form the five sections of this valuable textbook.

In summary, Statistical Process Control presents approaches for those wanting to understand and apply controls to the total quality strategy of their company to enhance profitability.

Statistical Process Control (7th Edition) by John Oakland and Robert Oakland is available from all leading booksellers and online retailers.

PROFILE

Jennifer holds a PhD Molecular Microbiology and an MSc in Pharmaceutical Manufacturing Technology. She has worked in QA roles in medical device and pharmaceutical manufacturing and clinical trial sectors since 2010.



KEEPING YOU POSTED

REGULATIONS AND GUIDELINES

GCP

Angelika Tillmann, GCP Committee

MAIN REGULATORY NEWS

MHRA

In January 2019:

- Legislation has been published which, in the event of the UK leaving the EU with no agreement, will cover the regulation of medicines, medical devices and clinical trials <https://bit.ly/2WjY9s7>
- Guidance for clinical trials in case of a no-deal Brexit <https://bit.ly/2ScDNOs>
- A news story was published as the agency's response to exiting the EU <https://bit.ly/29UYmM2>
- MHRA published a press release about medicines regulators of the UK and Russia and set out key principles to support their collaboration on improving public health <https://bit.ly/2UuGegS>
- MHRA created a new post on the MHRA inspectorate blog 'it pays to be compliant' concerning their plan to apply the office-based assessment (OBA) fee more broadly <https://bit.ly/2XdNSOL>
- MHRA created a new blog post on dose escalations and GCP compliance. <https://bit.ly/2DYRz1V>

EMA

The EMA published an update on their relocation to Amsterdam in March 2019 <https://bit.ly/2E0ahXb>

and some related articles:

- <https://bit.ly/2zFKcwQ>
- <https://bit.ly/2XmsUgO>
- <https://bit.ly/2GAtvGe>

EMA published 'Guideline on the Content, Management and Archiving of the Clinical Trial Master File' <https://bit.ly/2tvnlPd>

Related to this, the EMA Inspector's Working Group has updated their website and added question 12 'What are the expectations for the inspection readiness of trial master file?'

<https://bit.ly/2Xd02HO>

Additionally, the EMA added two new Questions and Answers, numbers 10 (if clinical trials procedures can be performed at home) and 11 (if it is allowed that the sponsor contracts third parties to conduct trial related investigator responsibilities)

<https://bit.ly/2Xd02HO>

AUSTRALIA

The TGA was seeking comments from interested parties on a pilot GCP inspections programme of 12 months duration that will inform a routine GCP inspections programme – the consultation period ended in February but the link still give a good idea on the plans <https://bit.ly/2VRPaOE>

FDA

The US FDA has proposed changes that would allow institutional review boards (IRBs) to waive or alter requirements for obtaining informed consent for certain clinical trials involving minimal risk to participants.

Under current FDA regulations, exceptions for obtaining informed consent can only be made in life-threatening situations or when conditions for emergency research are met. Outside those situations, FDA regulations require that subjects provide informed consent before they can participate in a clinical trial.

In 2017, FDA issued guidance (<https://bit.ly/2NeHaU0>) stating it would not object to IRBs waiving or altering informed consent in line with Cures. FDA now says it plans to withdraw that guidance if the newly proposed rule becomes final.

Once final, FDA says the new rule will harmonise informed consent requirements for studies subject to its and the Department of Health and Human Services' regulations.

But FDA says it is not adding the fifth requirement that was added to the revised Common Rule set to take effect in January 2019 that allows a waiver or alteration of informed consent for research involving identifiable private information or identifiable biospecimens if the research 'could not practicably be carried out without' using identifiable information.

<https://bit.ly/2T2YBMQ>

<https://bit.ly/2NeHaU0>

ANIMAL AND VETERINARY PRODUCTS

Shona Ross, Animal and Veterinary Products Committee

EMA DRAFT GUIDANCE AVAILABLE FOR CONSULTATION

Draft guideline on the quality of water for pharmaceutical use. Reference number: EMA/CHMP/CVMP/QWP/496873/2018. Status: draft consultation open, consultation end date: 15th May 2019.

Draft guideline on data requirements for veterinary medicinal products for the prevention of transmission of vector-borne diseases in dogs and cats. Reference number: EMA/CVMP/EWP/278031/2015. Status: draft consultation open, consultation end date: 31st August 2019.

Draft guideline for the demonstration of efficacy for veterinary medicinal products containing anticoccidial substances. Reference number: EMA/CVMP/EWP/755916/2016. Status: draft consultation open, consultation end date: 31st August 2019.

Draft guideline on requirements for the quality (production and control), safety and efficacy of allergen products for use in horses, dogs and cats. Reference number: EMA/CVMP/IWP/170689/2016. Status: draft consultation open, consultation end date: 31st August 2019.

Draft revised guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market. Reference number: EMA/CVMP/SWP/66781/2005 Rev.2. Status: draft consultation open, consultation end date: 31st August 2019.

Draft reflection paper on risk management requirements for elemental impurities in veterinary medicinal products. Reference number: EMA/CVMP/QWP/153641/2018. Status: draft consultation open, consultation end date: 31st August 2019.

Draft reflection paper on antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products. Reference number: EMA/CVMP/ERA/632109/2014. Status: draft consultation open, consultation end date: 31st August 2019.

Updated draft guideline on manufacture of the veterinary finished dosage form. Reference number: EMA/CVMP/QWP/798401/2015. Status: draft consultation open, consultation end date: 31st August 2019.

Email address for submission of comments:

vet-guidelines@ema.europa.eu

EMA ADOPTED SCIENTIFIC GUIDANCE

Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs. Reference number: EMA/CHMP/CVMP/3Rs/742466/2015. Status: Adopted. Last updated: 7th November 2018.

Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union. Reference number: EMA/CVMP/AWP/237294/2017. Status: Adopted. Last updated: 21st November 2018.

Implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products. Reference number: EMA/CVMP/QWP/631010/2017 Rev.1. Status: Adopted. Effective date: 27th November 2018.

Revised guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD). Reference number: EMA/CVMP/IWP/105506/2007 Rev. 1. Status: Adopted. Effective date: 1st July 2019.

Guideline on the conduct of bioequivalence studies for veterinary medicinal products. Reference number: EMA/CVMP/016/2000 Rev.3. Status: Adopted. Effective date: 1st July 2019.

Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products. Reference number: EMA/CVMP/SWP/377245/2016. Status: Adopted. Effective date: 1st July 2020.

Questions and answers on the CVMP guideline on the 'guideline on veterinary medicinal products controlling Varroa destructor parasitosis in bees'. Reference number: EMA/CVMP/EWP/77872/2018. Last updated: 9th January 2019.

VICH ADOPTED SCIENTIFIC GUIDANCE

GL56, Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods. Status: Adopted. Effective date: 1st June 2019.

MHRA GLP CONSULTATIVE COMMITTEE MEETING 19TH OCTOBER 2018

Unofficial minutes recorded by Lisa Heely and Vanessa Grant, RQA

MHRA UPDATES

PERSONNEL CHANGES

Mark Birse has been seconded to the Medical Devices Division for 18 months as Group Manager of MHRA Devices Safety and Surveillance Group & Devices Software and Apps. Andrew Gray has moved into Mark's previous position as Inspectorate Group Manager. Post meeting note: During this time, Stephen Vinter will take the role of Head of the GLPMA.

BREXIT

There have been no changes yet pending an agreement on the conditions for leaving the EU. Updates will be published in the inspectorate blog and online. It was clarified that as the UK are members of the OECD MAD programme then Brexit does not alter the acceptance of UK GLP data within Europe or on a Global basis.

INSPECTION METRICS

Metrics gathered from deficiencies arising from MHRA GLP inspections in 2017 were published at the end of 2018.

There was a significant jump in critical deficiencies raised (8 in 2016 compared with 16 in 2017). These are mainly in the categories of Study Management and QA, and include such things as:

STUDY MANAGEMENT

- Lack of transparency
- Misleading compliance statements
- Data integrity controls
- Inability to reconstruct the study
- Lack of method validation, but study director has indicated validity of data
- Lack of checking use of non-GLP facilities.

QA

- Insufficient audit coverage
- Critical phases not inspected by study based or process-based inspections
- Failure to identify deficiencies
- Failure to address corrective and preventative actions
- Insufficient QA resource.

On the basis that poor close out of CAPA and QA resourcing are often outside of QA's control, a new finding category of Test Facility Management is being introduced for use where applicable.

There has also been a jump in major deficiencies predominantly in the same areas. Data integrity major deficiencies have risen from 4 to 15 and include issues such as what is the raw data, access rights and audit trail management and review.

The MHRA explained that these deficiencies are not in areas which have been newly introduced by the Data Integrity Guidance but are pre-existing GLP requirements. The inspectorate does not believe that the rise in critical and major deficiencies is due to a shift in the grading of inspection deficiencies, however, a greater understanding of processes and a greater focus on electronic data may be contributing factors. The MHRA stressed that all deficiencies are peer reviewed and there is consistency of deficiency gradings.

The MHRA have updated the definitions of the categories and are now more aligned with GCP definitions by introducing clarity about escalations if they see insufficient CAPA or repeats of deficiencies.

The MHRA indicated that whilst there is no requirement for a formal CAPA system, they do expect organisations to have a mechanism for implementing corrective actions in response to inspection deficiencies.

LABORATORIES SYMPOSIUM

A symposium covering GLP and GCP/GMP laboratories was held on 13th March 2019 at Novotel, Hammersmith. The symposium covered GLP, GCP and GMP facilities. Topics on the draft agenda include data integrity and QA/QC interactions as well as an agency update. The afternoon was split into bioanalytical validation, tired approach and cross GxP quality.

EMAIL ADDRESS

There is a new contact email address for GLP, GCP and GMP labs gxpplab@mhra.gov.uk. The previous email address will continue to work for a period of time and will be monitored during the transition.

FEES

Fees for next year are being reviewed. In the event of a change in fees there will be a consultation period with stakeholders.

GUIDANCE DOCUMENT UPDATE

INTERIM REPORTS

The MHRA have issued a draft position paper on interim reports with GLP compliance claims. As outlined in the laboratories symposium in 2018, the MHRA position and majority EU GLP working party is that interim reports should not include a claim of compliance. There is a problem if compliance is claimed for interim reports where data is significantly incomplete, or where data acquisition methods have not yet been fully validated. In these cases, it is difficult and inappropriate for the study director to indicate validity of the data and therefore a claim of GLP compliance. The MHRA has approached all the UK assessors to understand if they require interim reports to include GLP claims and all have indicated that not only do they not require it, but they they would prefer not to have such claims. However, there are some receiving authorities within the OECD that require compliance statements to be included in interim reports. There is no issue with having QA audits of the interim reports and the inclusion of a QA statement. If a receiving authority does ask for a claim of compliance, it must be supported by a full review of data and a QA audit.

The comments that have been received will be incorporated into the draft position paper before it is circulated for further comment.

USE OF NON-GLP DATA IN GLP STUDIES

The position outlined in the guidance on the use of non-GLP facilities remains unchanged. If the work is critical to a study it should be GLP compliant and any non-GLP data should be clearly excluded from the compliance statement. Conclusions from the study cannot be drawn from non-GLP data. There was some discussion around including non-GLP data as an addendum to the report but this is not widely agreed by receiving authorities. The GLPMA agreed that non-GLP data can be included in the body of the report but it should be unequivocally identified in the report as being 'non-regulatory' data.

An update may be issued by the MHRA to clarify further.

INTERNATIONAL REGULATORY UPDATE

Every year, the MHRA attend an EU GLP Working Group in February and the OECD GLP Working Group in March.

EU GLP

UK and NL are looking at differences in the way OECD GLP Working Group members deal with the fact that there is no routine inspection programme in the US. They are also looking at the way members deal with facilities in third countries which have been inspected by an OECD member country. Focus is on what is allowed under national law with respect to study director claims of compliance. The results of this exercise may be published when it is completed but this would need to be agreed by all Working Group members.

There is an agreed process for audit requests by EMA, EFSA and ECHA of planned inspections so that they can routinely ask for random studies to be reviewed.

OECD GLP

Thailand was subject to assessment late 2018 and the results of the report from the assessment will be discussed at the next OECD Working Group meeting. China remains an observer and there is a lot of effort to engage at OECD level. MOFCOM in China are coordinating with different ministries, but it remains difficult to move forward. It may mean that each ministry will be approached individually.

OECD have set up a drafting group to convert the UK data integrity guidance into an OECD advisory document. Work on this is ongoing. The document will be checked for consistency with OECD Advisory Document 17 and then go out to public consultation once the working group have agreed the draft version. There may be differences from the MHRA document, in which case the OECD document will take precedence.

It was confirmed that QSAR requirements falls outside the scope of GLP.

There is interest to see how much the OECD MAD programme saves industry. As such they are reaching out to industry trade associations.

US FDA CENTRE FOR VETERINARY MEDICINE (CVM) SUBMISSIONS

A question was submitted from RQA regarding the FDA CVM requirement to submit all study raw data and supporting data and whether this undermines OECD MAD. If RQA and SLA put this question in writing, the MHRA will pass to US FDA.

DATA INTEGRITY ON INSPECTION

Major deficiencies are being raised where there appear to be no plans in place to address gaps to meet the Data Integrity Guidance

Document. The inspectors are being pragmatic where there are plans and evidence of progress. Where there is a lack of management commitment then findings will be raised. The expectations for small companies and large companies are the same.

Examples have been found where a risk assessment has been undertaken but the remediation done in the wrong order, with high risks left until last including older systems with paper data. In such cases appropriate checks and balances should be implemented until the system is upgraded.

It is no longer acceptable to define the paper printout as the raw data. If data integrity issues have been identified during an MHRA inspection, the expectation is that they will have been addressed by the next inspection.

QUESTIONS AND ANSWERS

THE GLPMA WILL PUBLISH THEIR RESPONSES TO THE FOLLOWING QUESTIONS IN THE NEAR FUTURE:

Question 1. How should complex mixtures be characterised?

Discussion included that the guidance given in OECD Advisory Document 19 (Management, Characterisation and Use of Test Items) should be followed. This is intended to foster a risk-based approach.

Supplementary question: if a formulated product has not been characterised, what should be reported and how?

Discussion included that the MHRA expect deviations to be reported in the study director's compliance statement and the report. Study director statement should assess the impact. Detailed information on scientific rationale can be elsewhere in the report, i.e. study director statement highlights it and report discusses it.

Question 2. The EMA seems to be moving towards a more pragmatic approach to long-term retention of electronic data. What are the MHRA expectations for migration of data?

Discussion included that a risk-based approach should be adopted. What is the risk of long-term data retention versus the dynamic readability of data. If you have a process to migrate to paper data, the expectation is that you need to have access to the dynamic data for at least three years. Inspectors expect to access the electronic data so it should be available for review at the very least up to the time of marketing authorisation application.

Question 3. How should small companies validate software?

Discussion included that companies should understand what they are buying, its functionality and the vendor support available. Validation should be appropriate i.e. validate only what you will use. Companies do too much and overcomplicate the validation process. Software must be validated and size of company does not influence the validation requirements.

Question 4. How should companies validate cloud-based storage?

Discussion included that a clear, robust contract is required. Facilities should understand the data-flow process and how the data is managed. Advice should be sought from knowledgeable IT people. Security and control are key in a cloud-based system.

Question 5. In what circumstances would inspectors look at QA reports?

Discussion included that inspectors usually only look at inspection dates and the description of what was inspected. QA reports are only inspected if there are concerns regarding whether the QA programme is effective.

ANY OTHER BUSINESS

The MHRA are establishing a StEM for GCP laboratories in May 2019 and will shortly be inviting attendees.

GMP

Philip Butson, GMP Committee

BREXIT

What feels like a long time ago, in a country probably quite close to where you are now...the UK Government has suffered a record defeat in the 'meaningful vote' on the Brexit Withdrawal Agreement, but has narrowly survived a no-confidence vote. The Prime Minister has been tasked with going back to Brussels to obtain a better deal from the EU. However, whilst many different suggestions have been put forward for how the agreement might be changed, none of these seem to have majority support and the EU is insisting that the agreement cannot be re-negotiated. Given that the UK were scheduled to leave the EU at 23:00 GMT on 29th March 2019, the likelihood of a 'no deal' Brexit would appear to have increased, yet both the UK parliament and the EU are keen to avoid this. Will an agreeable way forward be found? Hopefully, by the time you read this in April, you will know the answer to what seems to be an almost impossible question as I write this at the end of the first week in February!

The MHRA created a new webpage at the end of January collating the various documents covering a possible no deal situation.

<https://bit.ly/2T3zp8L>

Amongst this collection are the outcome of the MHRA consultation on no deal legislative proposals and correspondingly updated guidance notes. Contingency legislation has also been created amending the Human Medicines Regulations 2012 and legislation covering both medical devices and clinical trials.

The EU have also updated their 'no deal' preparations and updated their Q&A document on 1st February 2019.

<https://bit.ly/2MXXgkG>

Important elements of the new Q&A document include:

- A revised text for question 11, which states that 'pivotal studies (bioequivalence, in vitro dissolution tests or therapeutic equivalence studies, as appropriate) that have been conducted with a medicinal product sourced in the UK can be used in generic/hybrid marketing authorisation applications only if the marketing authorisation for that application will be granted before 30th March 2019'
- New questions 26 and 27 which relate to third country sites with GMP certificates issued by the UK: GMP certificates issued by the UK MHRA, including those dated before 30th March 2019, will be considered in the same way as information on GMP compliance from any other third country regulatory authority – they will be an input to the EU risk assessment as to whether any further confirmatory action is required to provide assurance that the site operates to the equivalent of EU GMP
- 'As of the withdrawal date, UK authorities will no longer have access to EudraVigilance' (Q&A 35).

FDA DATA INTEGRITY Q&A DOCUMENT FINALISED

Following the publication of a draft document in 2016, FDA has finalised its data integrity Q&A document. <https://bit.ly/2GI2BsV>

The guideline is minimally changed from the draft and is largely aligned with MHRA, WHO and PIC/S documents. Key points that may be of interest include, but are not limited to:

- Additional CFR references have been added to strengthen the tie between the guidance and the base legislation
- Some helpful general questions have been added to the background
- The importance of understanding the full data lifecycle has been stressed
- It has been clarified that 'even if test results are legitimately invalidated on the basis of a scientifically sound investigation, the full CGMP batch record provided to the quality unit would include the original (invalidated) data, along with the investigation report that justifies invalidating the result'
- The requirement for system administrators with any rights to alter files and settings to be independent from those responsible for the record content is more strongly worded
- Whilst stressing that all production and control records, which includes audit trails, must be reviewed and approved by the quality unit, it is clarified that 'the regulations provide flexibility to have some activities reviewed by a person directly supervising or checking information'
- The text on frequency of audit trail reviews (question 8) has been extensively reworded
- Specific text added relating to the control of records in microbiology laboratories (question 10)
- It is noted in question 17 that records such as emails could fall within the scope of CGMP and thus be subject to FDA inspection.

EU-US MUTUAL RECOGNITION AGREEMENT

On 7th February 2019, two further countries, Poland and Slovenia, were added to the twenty already recognised as equivalent by FDA. This now leaves recognition of six Member States to be concluded by 15th July 2019. You can keep track of the progress here:

<https://bit.ly/2Xmz6FA>

PIC/S GUIDANCE ON CLASSIFICATION OF GMP DEFICIENCIES

In January 2019, PIC/S published this guidance 'to provide a tool to support the risk-based classification of GMP deficiencies from inspections and to establish consistency amongst inspectorates'. In addition to enhancing our understanding of the regulatory agencies' approach, this guidance is useful for industry personnel involved in supplier and contractor auditing to help drive consistency.

<https://bit.ly/2Xmz6FA>

PHARMACOVIGILANCE

Raj Bhogal, GPP Committee

NOTE: The information below is a summary and you must refer to the source and local regulatory agency websites for more detailed information. Visit the RQA website for the latest update. www.therqa.com/committees-working-parties/good-pharmacovigilance-practice/regulations-guidelines

COUNTRY	STATUS	DATE	LEGISLATION CHANGE	LINK TO WEBPAGE
Australia	Effective	4th January 2019	Reformatting Product Information: frequently asked questions. FAQs have been updated to include additional content to address common issues found when reviewing reformatted product information (PI). A new PI form was approved on 8th November 2017, with a commencement date of 1st January 2018. From this date, PI documents that must accompany relevant registration applications will need to be prepared in accordance with the format of this new form. The PIs for all marketed products will need to be in the new format by 31 December 2020.	www.tga.gov.au/reformatting-product-information-frequently-asked-questions
Australia	Draft	11th January 2019	GCP Inspections Programme Consultation paper dated December 2018.	www.tga.gov.au/sites/default/files/consultation-good-clinical-practice-inspections-program.pdf
China	Effective	1st January 2019	Reporting requirements for adverse events submissions will change; in addition e2b R3 format reporting will also be implemented (for post marketing cases as well as clinical cases).	
EU	In process	TBC	Set of documents applicable to clinical trials that will be authorised under Regulation EU No 536/2014, once it becomes applicable – Chapter III – Quality, Chapter IV – Inspections, Chapter V – Additional documents and Chapter VI – Legislation.	https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1
Hungary	Effective	14th January 2019	DHPC – submit translation of DHPC even if product not marketed in Hungary. Revised with new content.	www.ogyei.gov.hu/direct_healthcare_professional_communication
Hungary	Effective	25th January 2019	Adverse reaction reporting arising from clinical trials – small updates with no change of content.	www.ogyei.gov.hu/adverse_reaction_reporting_arising_from_clinical_trials
Switzerland	Effective	1st January 2019	Guidance document Drug Safety Signals. Timing for reporting of completion of signal evaluation procedures by foreign authorities from 7 to 15 days.	www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/market-surveillance/pharmacovigilance/instructions-and-information-sheets.html
Switzerland	Effective	1st January 2019	Therapeutic Products Ordinance – Guidance documents for PSUR/PBRER and RMP submissions updated.	www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/market-surveillance/risk-management--psurs--pv-planning-.html



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CALENDAR

OUR ROUND UP OF COURSES, SEMINARS AND FORUMS

MAY

08 | **North Regional Forum**
Manchester, UK

14-16 | **Systems Approach to Good Pharmacovigilance Practice**
Cambridge, UK

16 | **Anglia Regional Forum**
Cambridge, UK

21-22 | **Good Laboratory Practice for Study Directors, Principal Investigators, Study Staff and Management**
Cambridge, UK

21-22 | **Practical Approach to Auditing Systems and Processes**
Cambridge, UK

23 | **Ireland Regional Forum**
Dublin, Ireland

JUNE

4-5 | **Process Mapping and Using Maps in Standard Operating Procedure Writing**
Cambridge, UK

11-12 | **Quality Systems for Research Laboratories**
Cambridge, UK

11-13 | **Practical Pharmacovigilance Auditing**
Cambridge, UK

18-19 | **The Auditing Course**
Cambridge, UK

24-26 | **Good Clinical Practice Auditing – Principles and Practice**
Cambridge, UK

27 | **Good Laboratory Practice Refresher**
Cambridge, UK

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For full details of Courses, Seminars and Regional Forums, see the RQA website www.therqa.com, where all events can be booked online.



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Visit www.therqa.com for guidelines on article submission.