Pharmacy-related challenges of investigator-initiated trials: lessons from Kenya

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The pharmacy role in clinical research is under-appreciated; little is known about the contribution of pharmacists to clinical trials in developing countries and resource-poor settings. International council (formerly conference) for harmonization or ICH sets out guidelines for regulation of clinical research. Kenyan guidelines have assigned onerous responsibilities to the trial pharmacist. In this article, the author shares personal experiences in resolving pharmacy-related challenges in investigator-initiated trials. The clinical research pharmacist role demands continuous learning and constant engagement with science and teamwork. Proactive engagement with industry, regulators and service providers can resolve many pharmacy-related challenges in IIS. Innovative approaches to secure the support of holders of market authorizations in planning and implementing clinical studies are required.

Keywords: clinical trial pharmacist; role of pharmacist; investigator-initiated studies; pharmacy; clinical trial project management

Introduction

The pharmacy and poisons board of Kenya (PPB) formally assumed control of trials in Kenya in 2006 (Patel,2006). In 2017 PPB published its first version of national guidelines for the conduct of clinical trials in Kenya, revising the same in 2020 and 2022(Government of Kenya,2022).

The guidelines spell out pharmacy related requirements for approval of clinical trials. These requirements cover diverse issues- from characterization of the investigational product to its quality, use, procurement, manufacture, import shipment, custody, labelling, relabelling, storage, control, and accountability.

International council (formerly Conference) for harmonization or ICH sets out guidelines for regulation of clinical research. ICH recognises the sponsor, principal investigator, and the study co-ordinator as the focal persons with whom regulators may communicate and interact in respect of a trial. A sponsor may or may not be the manufacturer of the investigational product. Where the sponsor organization is not a manufacturer, it contracts or enters into a collaboration agreement with a manufacturer. In addition, the sponsor may engage a Qualified Person or another Authorised Person to review and certify the quality of the IP for purposes of release for use in the trial. Thus, the sponsor is responsible for the product. This responsibility includes the burden to demonstrate, quality, integrity and efficacy and safety of the product.

In investigator-initiated trials also known as investigator-initiated trials (IIS), the role of the product manufacturer is minimal or non-existent. Ordinarily pharmaceutical firms will support a trial if it feeds into its own Research &Development efforts by providing more safety data or data that can support extension of product indications. Sponsor-investigator (SI) is the name given to the physician or individual who undertakes the IIS. Both ICH guidelines and USFDA regulations hold the investigator responsible for all aspects of the trial that impact on data integrity and patient safety. Assurance of the IP's quality and integrity is one such aspect. The SI must therefore assume responsibility for the quality and integrity of the product. Unlike the sponsor who has access to the product manufacturer's resources, the SI lacks such resources.

Clinical research pharmacy

Little is known about the contribution of pharmacists to the conduct of clinical trials. Traditionally, the role of pharmacists has been to receive, store, control, dispense, account for, and dispose of the product. ICH guidelines allow the investigator to delegate pharmacy roles to any suitable member of the clinical study team. But national regulations and guidelines for conduct of clinical research in Kenya have determined that pharmacy specific responsibilities should be performed by the pharmacist. Further, the guidelines require the clinical trial applicant to provide the name, license details, *curriculum vitae* and training certificates of a pharmacist assigned responsibility for the pharmacy aspects of a proposed trial. The trial pharmacist is expected amongst other things to ensure compliance with law and regulations. The guidelines assert that the pharmacist should be part of the *core study*

*team.*The trial site to covered in this paper follows the said guidelines. This is noteworthy: in the developed world, the clinical trial pharmacist (commonly known as investigational drug service pharmacist) is for all intent and purpose an external service provider with little to do with the daily activities of a clinical trial (Phillips1999; Malson 2015). This article is the author's lived experience of pharmacy-related challenges encountered in the implementation of IIS. In this article, the multifaceted role of clinical research pharmacist in a developing country is highlighted.

Case studies

Case 1: Access to product and product information.

Issue: Batch specific investigational chemistry, manufacturing, and control (CMC) product information can only be provided by the manufacturer; generic manufacturers that are not regulated by a stringent regulatory authority (SRA) usually lack some of the critical CMC data.

In a certain trial a site investigator wanted to use a vaccine BZ (for prevention of disease R) as an immunological probe to profile immune responses to infection with a related disease T. We approached the manufacturer of vaccine BZ to seek documents to support the quality of the product. At this point we were informed that the product was not licensed in Kenya, and information on its efficacy, safety and quality could not be distributed by the local office. We urged the local representatives to contact the head office who in turn made it clear that they could not share any information or donate their product for purposes of our proposed study.

Solution:

We resolved to submit surrogate information: we negotiated with the regulator to allow us to submit a product monograph from the United States food and drug administration (USFDA) website in place of the Investigational Medicinal Product Dossier.

Case 2: Manufacture of IP and matching placebo.

Issues: regulatory approvals for manufacture of placebo, approval to repack a marketed product, role of the owner of the marketed product, arranging contract-manufacturing, and product matching. Placebos match the IP in every aspect except efficacy and possible

toxicity: a placebo should match the IP's form, appearance, texture/feel, smell, and route of administration.

We approached a local manufacturer QRS who had current authorization for oral paediatric suspension of drug MPZ. We requested them to make a placebo for their existing product. The pharmacist advised that they could not match the two products for both taste and appearance as these were attributable to the active pharmaceutical ingredient.

Solution: We resolved to make a placebo for an existing (marketed) active product which was easier to match in terms of colour, flavouring agents, and sedimentation rate. To ensure matching with the placebo we contracted the facility to repack and relabel the marketed product under our supervision. The repacked product was tested for gross microbial contamination.

Case 3: Pharmacy staff shortages.

Issue: Guidelines require that all pharmacy procedures be under the control of a pharmacist.

Solution: we developed a manual of pharmacy operations wherein roles are shared across pharmacists, technologists, and dispensers. Under the guidelines activities are delegated to both technologists and dispensers with the pharmacist retaining overall responsibility. Further, pre-study and in-study activities are shared out between the two pharmacists. For vaccine trials, a dedicated team consisting of a pharmacist (the back-up pharmacist), a pharm-tech and a nurse is in place to run vaccine manufacturing activities for vaccine trials conducted at the site clinic.

We also developed a request for pharmacy resources form which is a planning tool to help research teams to determine what support and input they would require for their projects.

Case 4: Local purchase of investigational products

Issues:

I. Quality assurance of manufactured product.
II. Product release for use
III. Ongoing go/stop decision-making on potency and viability of products
IV. Cold chain rules

V. Brand changes

VI. Stock-outs.

Solutions: For issues (i) to (iv) we have developed a Standard Operating Procedure for Quality Assurance of investigational Products and other Clinical Supplies. The SOP is also applicable to vaccines used for routine medical care.

For issues (v) and (vi) there are several solutions:

a) Purchase all the stock required to complete the study before the study
b) Indicate in the clinical trial protocol all the brands that would be used
c) Make an ad hoc request to the Board to use other available brands

Case 5: Management of temperature excursions.

Issues: The impact of temperature excursion on product viability is cumulative.Thus, in determining viability following temperature excursions one has to consider the impact of all excursions since the product was manufactured and packed. This information is usually held by the manufacturer.

However, many manufacturers, being unable to accept responsibility for temperature deviations occurring once the product has been released into the market, cannot review or comment on temperature excursions for the product which is no longer in their possession. Secondly, there is currently lack of local capacity to analyse biological products for potency. To get around this problem one needs to include Cold Chain Rules for the product either in the protocol or a study specific procedure. Using available data on impact of temperature excursions, the Rules would aim to have narrower tolerances for the product under study.

Case 6: Absence of guidance; lack of clarity on applicable rules and regulations for control of a proposed product or process.

Where a process is not governed by board guidelines, the board is likely to advise applications to apply for exemption from review. But it is also possible for the board, in consultation with the applicant, to elect to adopt a procedure established and used by a stringent regulatory authority (SRA) e.g., WHO or US FDA. Such was the case when we first sought to undertake shelf-life extension of a locally manufactured investigational product.

Case 7: Unsustainable regulatory standards

The national quality control laboratory (NQCL) requires a sample of 100 vials to be submitted whenever a request for analysis of injectable medicines is required. In one case we sought to identify a brand of injectable ceftriaxone that would be appropriate for use in his trial. We targeted to get 4 brands tested.

We realised that sacrificing 100 vials for each of the 4 chosen brands would be wasteful. Therefore, we opted to work with a consultant in UK who had the capacity to conduct chromatographic analysis with a single vial of each product.

Another example is in the process of IP shelf-life extension where applicants are required to supply a certificate of analysis from the NQCL. In our case, where the lab lacked capacity to analyse a new candidate vaccine, we negotiated with the board to accept the manufacturer's own stability data to support a decision to extend the life of the product.

Case 8: Transfer of IP to other purpose.

At the close of a study, unused IP stocks should be destroyed or returned to the sponsor unless study approval has a provision for a post-study patient access programme. This makes sense in the case of a trial using a novel IP (a candidate drug or vaccine) and/or is unlicensed. But this position is untenable where the IP is a licensed product. To make matters worse there may be local shortages of the product due to cost and other barriers.

It would therefore make sense for the applicant to clearly state that unused stocks may be donated for clinical use at the site or at a named health facility. On occasion we have had to write to the regulator to request approval to transfer of an imported IP to a related trial.

Case 9: Use of IP from other stock.

It is a good practice to involve the regulator in this decision: generic substitution of IP, if done without the regulator's knowledge, may constitute a deviation if not a violation. Where this happens without the approval of the regulator, on account of medical necessity, it should be reported post-factum to both the ethics committee and the regulator. The trial team should assure itself, and file evidence, that the substitute product is of a quality that is comparable to that of the substantive IP.

Case 10: Global supply chain disruptions.

Issue:

Global manufacturers (domiciled in the Northern hemisphere) are at liberty to discontinue any of their products, in any market without notice. Such decisions are quite common in the sub-Saharan region whose contribution to global pharma sales is less than 2%. For instance, 2 years into a trial, a nationwide stock out of an imported vaccine was reported. This came as a surprise as local representatives of the company had discounted the possibility of the vaccine being discontinued "in the next few years''. Contacts in UK informed us that the manufacturer had ''ceased production in UK".

Solution:

We approached a UK-based contract research organization (CRO) to help us source the product from Eastern Europe where the global firm had active manufacturing facilities. The CRO in turn, sub-contracted a Germany-based pharmacy to procure supplies from Eastern Europe.

Case 11: Supply chain safety.

Global manufacturers market their products in Kenya through distributors. These distributors may in some cases import the product and hold market authorization for the product. Such distributors are few. This creates a monopoly leading to poor service and lack of responsiveness to customer needs.

In one instance, we received a shipment of vaccines whose temperature record had apparent gaps-the provider had SOPs that provided for shipment of goods without temperature monitoring from the central warehouse in the capital to regional outlets. The provider was adamant that their carrier had been validated, and helped them to cut down on the cost of purchasing and maintaining reusable temperature loggers.

Solution: we offered to provide carriers and temperature loggers for shipment of vaccines to our site. Initially, the provider declined, and we were forced to momentarily suspend their services.

Case 12: Sole suppliers.

A vendor's shipment incurred a temperature excursion during packing as a result a recording lag of the temperature logger.

The source of the product was an importer of vaccines who also provides storage for manufacturers. We discovered that during storage at the importer's facility the vaccine stock had also experienced several temperature deviations that were seemingly reported to the neither the customer nor the regulator. Some repeated non-conformances were neither adequately explained nor discharged.

Solution: we sought information on when vaccines were received at the warehouse and where they were stored within the warehouse. We then proceeded to compute total deviations above or below the temperature tolerances. To make a final determination we had to turn to the market authorization holder -who having reviewed all the data-was able to confirm continued stability of the vaccine stock.

Discussion

Clearly, sponsor-investigators lack the capacity to mitigate the quality risks associated with the use of investigational products. Investigators working in low and middle-income countries are further disadvantaged by *external* barriers to quality medicines such as lack of availability and affordability of products; high prevalence of substandard and counterfeit medicines; and a non-transparent local manufacturing industry.

The foregoing cases illustrate the nature and range of pharmacy-related challenges in IIS. Amongst other things the cases bear out the following important lessons: -

1. clinical research pharmacy requires multiple technical and problem-solving skills. The role demands continuous learning and constant engagement with science and teamwork.
2. On- the-job learning opportunities are few and infrequent; and learning resources are few and are not always quality assured. Further, formal learning courses address only a few categories of knowledge at a time.
3. Pharmacy related decisions are team-based decisions. Pharmacists, being champions of collaborative work, should find fulfilment in this kind of work.

4. Having SOPs helps to *routinize* problem-solving. This helps the pharmacist to delegate work that requires technical skill so that he/she can devote more time to the finer details of the research protocol and other scientific work.
5. Proactive engagement with both regulators and service providers can resolve many pharmacy-related challenges. This requires trust-based relationship building. But this is very uncommon in the developing world where regulators function as law enforcement agencies. For this co-production of research work, agency officials must be committed to the advancement of research, and pharmaceutical science.
6. A pharmacist in this role will frequently draw from his previous work experience and rely on his professional network for information and solutions for challenges.
7. We believe that our efforts to demand quality from our dealers have changed vendor attitudes and practices around quality for the better. As we sought means and ways to achieve the quality required of IPs, we concluded that all our products must be sourced with the same quality in mind. This understanding is now shared across the organization.

Recommendations

1.A change of attitude is required on the part of the manufacturing industry. Industry should support all IIS-by sharing safety and information quality with would-be investigators. What is required is greater flexibility so that investigators can share their results with the owners of the product. This would advance science.

2.Where the refusal of market authorisation holders (MAH) to provide critical information to support approval of IIS threatens the success of the application, applicants may seek the assistance of the regulatory agency. The applicant(s) may:-

I. seek leave of regulator to submit alternative data
II. may request waiver of the requirement to submit given data
III. request the regulator to obtain(demand) or retrieve the data. The regulator may seek the owner's authorisation to share the data with the applicant, or, in the alternative, proceed to review it confidentially for purposes of the proposed trial.
IV. need to sign collaboration agreements and/or institute data sharing mechanisms with manufacturers of interest.

Conclusion

The clinical research pharmacist role demands continuous learning and constant engagement with science and teamwork. Proactive engagement with industry, regulators and service providers can resolve many pharmacy-related challenges in IIS. Innovative approaches to secure the support of holders of market authorizations in planning and implementing clinical studies are required.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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