ROUND TABLE

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What is a reliable source of practical oncology stability data?

hospital pharmacy europe

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Pilar Blasco
Chief Pharmacist, Valencia General Hospital, Spain

Maria Cammarota
Director of Pharmacy, Cardarelli Hospital, Naples, Italy

Agnès Castillon
Pharmacist, Hôpital Privé Saint Martin, Caen, France

Tim Hanlon
Chief Pharmacist and Clinical Director, Guy's and St Thomas', London, UK

Irene Krämer
Head of Pharmacy, University Hospital Mainz, Germany

Belen Marzal
Pharmacist, Gregorio Marañon Hospital, Madrid, Spain

Robert Terkola
Consultant Pharmacist, Vienna, Austria

Johan Vandenbroucke
Head of Production, Gent University Hospital, Belgium

Dr Theresa Saklatvala
Chair, Head of Clinical Content, Cogora

A recent gathering of senior hospital pharmacists from seven European countries reached the consensus that it was time that they became more proactive and more politically minded in their calls for methodologies underpinning extended oncology drug stability data.

What is a reliable source of practical oncology stability data?

Pharmacists' perception of differences between originator and generics companies as regards extended stability data centres on marketing strategy: while not in the commercial best interest of an originator company to publish in its drug's Summary of Product Characteristics (SmPC) a shelf-life of more than the absolute minimum, it is clearly in the commercial interest of a generics company to have published studies that attest to stability extending beyond the SmPC limit.

The only extended stability data that pharmacists are interested in are those that reflect the real conditions in which the drug is going to be used - practical, not theoretical.

It is also clear that they perceive 'extended' stability data to mean everything beyond what is stated in the SmPC, when measured in the pharmacy and not on the ward or any clinical area.

The classical range for concentration of active ingredients is 90-110%. A deviation of 10% is considered reasonable (allowing for additives, degradation products and routes of administration).

It is thought to be regrettable that extended physical and chemical stability data are not required in the SmPC. Manufacturers are obliged to publish clinical data, but you cannot gain good clinical data if you have bad stability data: of what use is it to cite clinical data if the product has, say, only 80% potency? Another way of thinking about it is the active linking of outcomes with product, which is the basis of medicines optimisation: in order to achieve a given outcome, everything in the process (including product stability) has to be aligned to that end.

Sources of extended stability data

The two prominent sources of extended oncology stability data are Stabilis® and the Krämer list (often referred to as the Gelbe list). Stabilis®, now translated widely, ranks all published papers against a checklist of attributes, as an indication of reliability. While supporting methodology/ original papers are often not accessible (eg. if you work in a small hospital without access), Stabilis® is perceived to be a strong, reliable source of stability data. So, too, is the Krämer list, with which there is 90% overlap with Stabilis®. Everything on the Krämer list has been certified in the Pharmacy Department at University Hospital Mainz: physical and chemical stability data for the stock solution and for the diluted preparation. The list does not hold the primary data, but is rather the evidence-based recommendation of what can be used in practice. Supporting data, while not published on the Krämer list, can be distributed via the German Association of Hospital Pharmacists.

Ought a manufacturer to be expected to provide their extended stability data to hospital pharmacists, especially as the analytical equipment required to perform the studies individually are increasingly and prohibitively expensive? The problem with industry-supplied data is that you, as the hospital pharmacist, will have no influence over the types of study done. The manufacturers know their products better than anyone, but are under no obligation to release their methods. And without the methods, the data are of limited use.

"We have the power to enforce these things"

Manufacturers will release extended stability data only insofar as required for product launch. Beyond that, it is the responsibility of the pharmacist. And companies are never enforced by law to provide underpinning methods that would allow a pharmacist to extend the shelf-life. If a pharmacist were to have access to an analytical laboratory, and the analytical method were to be provided by industry, then the work could be repeated under his own conditions. But if the method is now given, it could take as much as two years to develop and validate the data. Who has the resources? Additionally, industry may state that a product is 90-95% stable, without having looked at

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or reported on toxicity of degradation products. To do this yourself, given that the pharmacy may not even know what the breakdown products are, it would take two to three years. Variability in conditions under which extended stability testing is done has made their translation to local environments difficult to impossible. And it is illogical that every hospital pharmacy (even those that have the capabilities) should have to duplicate other people's efforts in performing stability tests for their products. Therefore, it has been the initiative of the European Association of Hospital Pharmacists for some while to have a working group that performs the studies once and for all, reliably and properly. The guideline for the practical framework for stability studies of anti-cancer drugs has been published, but there the initiative has halted, perhaps through lack of finances, or, more probably, lack of leadership.

"We do not do our jobs well in terms of wielding influence"

Whose responsibility?

It is a sign of the professionalism for which hospital pharmacists are held in such high regard that they unsurprisingly assume 100% responsibility for the safety and quality of drugs prepared in their pharmacies, including expiry dates - physicians trust them to provide only stable products.

Responsibility is a critical concept, and two issues arising from its consideration are given here: (1) It may well be 'easy' for a pharmacist in a large teaching hospital to undertake their own stability studies, but a small hospital may have neither the capabilities not the capacity. (2) It will depend on how a hospital buys its products. When purchasing from generics manufacturers, it can be done on a large scale, as part of the procurement framework; in this instance there is power in the hands of the pharmacist to demand extended stability data. But it remains incumbent on the pharmacists in this situation to wield that power.

So where does responsibility sit when outsourcing a preparation? Although the outsourcing unit is responsible for their own in-house processes, it is the pharmacist, as secondary commissioner, who remains responsible for the provision of that medicine.

Learning to be more proactive

The economic climate is driving a trend toward centralised production, toward changes in care settings, to outsourcing and to merging of hospitals. This, in turn, is likely to drive batch production and complex transportation issues, which in turn is likely to drive an accelerating need for extended stability data.

Pharmacists are involved in decision making regarding choice of supplier at varying levels, depending on national and regional variations, and must learn to exercise their purchasing power. An example from Belgium was tabled, in which manufacturers were invited to tender for supply, and if they were not willing to provide, say, external contamination data for the first and last production vials, they were not considered. In this instance, each company provided extended stability data, but none would deliver the methods. And if, as a pharmacist, you need to give input, you will be faced with the task of interpreting – not just accepting data compiled by somebody else.

"If it is prepared in the pharmacy, the pharmacist is responsible"

Pharmacists must learn to be more proactive in leveraging their power. Professional associations rely on volunteer after-hours work. They might want to consider becoming more political, more willing to show their professional teeth. Either by professional subscription, or with funding from industry to support a full-time post to champion whatever action the Association decides appropriate, pharmacists could and, in the opinion of those present, should take the initiative to effect change. It is not inconceivable that, say, the EAHP, led by a full-time champion, and enlisting the services of a team of (analytical) experts, could bring pressure to bear on medicines agencies and local legislators, in the interest of quality of medicines and safety of patients.

An extension of this initiative would be to adopt the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for validation of test methodology, as they have a team of top chemists guiding stability testing.

Options

Pulling together route of administration, batch production and stability data, the following case study was presented. There are instances in which infusion solutions and infusion pumps are normally not used in intensive care

"Never trust the study where you did not see the methods"

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units (ICUs) for continuous infusion, but rather injection pumps, which are more accurate. For adult patients on an ICU, there may be, say, ten injection pumps, and a 50ml syringe is used as the primary container. Each of the five ICUs in that particular hospital was using a different concentration. So a consensus was taken to use the same concentration for the same product, and to dose by volume. And once this was agreed, it became obvious to start preparation in the pharmacy by batch. They started to compound 50ml vials in the correct concentration. So they now have ICU 50ml vials, and nurses have to draw up in a spike and introduce into the injection pump, which is pre-programmed for this concentration – an obvious advantage in safety. And the stability data were obtained internally.

We have the situation where companies may not want to divulge the methods by which their extended stability data are defined. And pharmacists, in turn, do not trust the extended stability data for which methods have not been provided. One work-around may sit with compounding centres, which could provide ready-to-administer products centrally: their stability data, their responsibility. No need to share methods with hospital pharmacists. Although the majority of delegates said they would gladly opt for this strategy, there were two caveats put forward: 1. there was concern that, once a pharmacy foregoes their technical service, it will never get it back, and 2. large teaching hospitals will want to retain control of their own stability testing.

"The trend for the future will be for longer extended stability data"

It was the consensus that clinical trials ought to be undertaken with standard doses rather than with drug concentrations derived from dose per body surface area calculation (in which variations in calculation are bigger than variations in preparation).

There is the appetite for an interface for extended evidence-based data provided by companies with individual compounding software, in which companies would push their data into hospital systems. This would be much more efficient than that which currently happens, assuming that updates and maintenance were provided.
The company who would provide such interrogating, interpretable software would have to create the software that could interface with individual systems, but it is not unreasonable to assume that there would be software solutions to existing information problems- solutions that cannot be found on paper. As a concept, it would doubtless be cost-effective, but pharmacists would need to have 100% confidence in its safety, which would perhaps be hard won.

Preferable would be the construction of one central database, in Europe or worldwide, which housed all the information - the product, the container, whatever – that was here considered to be the absolute solution to the problems. And such a database would be housed on a neutral, high-level source: the European Medicines Agency homepage was proffered as the ideal.

"Stability testing needs to be fit for purpose"

Why should the EMA be receptive to pharmacists' approaches for extended stability date? Two reasons: safety of patients and quality of medicines.
It was at the top of the wishlist of more than one senior hospital pharmacist present that the EMA should require extended chemical and physical stability data in the SmPC.

The roundtable 'Providing hospital pharmacists with practical in-use oncology stability data' was convened in Frankfurt 5th November 2015, with the support of Fresenius Kabi, and was attended by senior hospital pharmacists from the UK, Belgium, Spain, Austria, Italy, France

Wishlist

The creation of one all-inclusive source of oncology extended stability data, accessible from a high-level source, and supervised, controlled and validated by a team of experts.

The creation and housing of a single high-level centralised database of extended chemical and physical oncology stability data.

Access for pharmacists to the parameters, methodologies and specifications underpinning extended stability data, preferably through manufacturers' product SmPCs.

A more proactive, more political hospital pharmacy workforce that uses its power to effect the above.

140 London Wall, London, EC2Y 5DN

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