**Meeting report – Stability requirements**

**Joint Pharmaceutical and Analysis Group meeting: Stability Challenges Part II**

This event examined scientific and implementation challenges regarding the harmonisation of stability requirements. Reported by David Elder, Director, PTS, R&D, GlaxoSmithKline, and JPAG committee member.

**Introduction**

Although considerable progress has been made in harmonising stability requirements for pharmaceutical products, a significant number of scientific and implementation challenges still remain. This Joint Pharmaceutical and Analysis Group (JPAG) symposium provided a timely update on these challenges, particularly stability in support of in-use shelf lives and during transit, and for "specials" products.

Ms Rowland indicated that stability studies are to "establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions (ICH Q1)". Supply chains for medicinal products in the 21st century can be very complex. Compliance issues have been historically seen across the entire supply chain, but transportation is the weak link. The product can be shipped by air, road or sea, the transportation route is not consistent and there are often stopovers on the way.

The MHRA has observed that after product receipt there are often no reviews of temperature/humidity data; temperature excursions are not fully investigated; and there are often delays in downloading data for review. Companies need to better understand their own supply chains, and they need to audit service providers. Stability studies need to be designed to address the events that can likely be predicted within the supply chain.

Ms Rowland indicated that of the three zero good manufacturing practice deficiencies were presented.

In one case, two temperature-controlled containers containing eight batches of drug product arrived at the receiving site. The data loggers showed that the containers had experienced high humidity (maximum of 84.7% RH) excursions during the journey. There was no risk assessment performed based on existing stability data or product knowledge. The company therefore failed to ensure these products were stored and transported appropriately to ensure the maintenance of quality.

In another case, the data loggers for temperature-controlled containers containing several batches of drug product had a functional failure, hence there were no supporting data to demonstrate transportation conditions. No quality risk assessment was undertaken to demonstrate that there was no impact on product quality. The decision to support subsequent batch certification and release was not documented.

In a third case study, the MHRA identified several deficiencies in a company’s action plan to address reported stability failures. The MHRA concluded there was no final report summarising the actions required to address the underlying cause of the failure. There were no plans to address the lack of senior management oversight of the quality control function responsible for stability testing. Lastly, there had been no checks on the raw data of studies that had been completed to demonstrate that the data actually supported the findings.

In conclusion, companies must be able to control all aspects of their supply chain and undertake periodic reviews of their product recall system (including timeliness and reconciliation).

**Stability Requirements and Expectations for Medicinal Products from Manufacturers to Patients**

**Speaker: Vivian Rowland, GMDP Inspector, MHRA.**

Mr Santillo reviewed the problems facing the National Health Service (NHS). The UK has an ageing population with complex health problems. There are initiatives to reduce both resources and costs and this adversely impacts on budgets. More patients are being considered for homecare therapy and remote clinics necessitate longer shelf lives.

Summary of product characteristics (SmPC) information is often neither useful nor practical. Shelf life is often restricted to 24 hours with advice to use immediately due to microbiological considerations. Most high-cost medicines are branded and most products are licensed for single use. The NHS therefore needs to be able to generate extended shelf lives.

In conclusion, companies must be able to control all aspects of their supply chain and undertake periodic reviews of their product recall system (including timeliness and reconciliation).

**Dealing with the Gaps in Stability Data in the NHS**

**Speaker: Mark Santillo, South Devon Healthcare NHS Foundation Trust and JPAG.**

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Responsibility for products available as "specials" in the UK resides with the prescriber and procurement pharmacist. There is a requirement for supporting stability data and an expert review. The NHS is trying to incorporate this review assessment into the contracting process. There are financial pressures to reduce drug contracts resulting in different active pharmaceutical ingredient (API) source or processing, different formulations, and different stability information being developed for the 'same' product.

Historically, many NHS units undertook supporting stability studies; however, coordination and data sharing were relatively poor. However, now the data sharing is much better coordinated and these units are working collaboratively with each other and academia.

The NHSPQA (NHS Pharmaceutical Quality Assurance) has established standard protocols for deriving and assessing the stability of various preparations. For example, the 2011 guidance for aseptic preparations (small molecules) identifies sterile products in pre-filled syringes, infusion bags, infusers, vials and eye drops. It notes the minimum testing protocol and testing; ie, potency, degradation products, colour, clarity and any precipitations (including sub-visible particulates) and pH.
Mr Behets outlined the five-step process for generating in-use stability data. This can be done by adapting already developed methods using the same API, same formulation, etc., or it can be in partnership with the drug manufacturer to access the existing analytical knowledge.

The second stage is method development, ideally identifying the critical attributes affecting the method’s variability. For small molecules, HPLC (assay and related substances), pH and visible and sub-visible particulates are key. For large molecules, a bioassay to assess activity, together with orthogonal methods looking at low molecular weight (MW) degradation products, content (light chains), identity and any chemical changes (capillary gel electrophoresis) and MW distribution to quantify polymer content and aggregates (size exclusion chromatography), as well as pH and visible and sub-visible particles are key.

The standard validation criteria outlined in ICH Q2 are then utilised. The fourth stage of the process is generating in-use stability data. The testing plan should reflect end-user practices and include representative stress factors, ie, transportation, interim storage, sterilisation, temperature and light excursions. The final stage of the process is statistical analysis of the experimental data. This has two main objectives: to determine the “worst case” degradation rate and then to calculate a statistically meaningful shelf life using 95% confidence limits (as per ICH Q1 guidance on evaluation of test data).

Ms Bradford highlighted some practical considerations for stability protocols. Both parties need to assess testing methodology and ask whether enough samples are being stored to complete all of the testing. In addition, the multiples that are being removed from testing need to be assessed, ie, one cannot pull just 50 tablets from a pack of 100 tablets. Are there enough spaces for repeat testing at each time point and are any ad hoc time points likely to be needed? Have the requirements for packaging during storage being described; eg, are the stability samples to be stored in the secondary pack? Importantly, is batch information recorded on all types of packaging, or primary or secondary packs? If the samples require inverted storage, how will this be achieved?

Contingency storage at a second site is a requirement for most disaster recovery strategies. Set-down dates are often not thought through fully, ie, what is the date three, six or nine months hence? Does it clash with major holidays? In addition, for very large stability studies, eg, those to support a marketing authorisation application, it might be important to stagger set-down dates to ensure the available analytical resource can cope. The contract research organisation (CRO) should communicate with the client in the event that things go wrong, ie, out of specification, temperature deviation, etc. Similarly, the client should notify the contract manufacturing organisation (CMO) if changes are required, ie, methods, specifications, extra tests. In summary, a successful outcome is derived from good interaction and communication.

Dr O’Connor reviewed the current state of cold chain storage within the pharmaceutical industry. He indicated that there is an initial assessment of the storage space carried out using multiple sensors, the facility is monitored for several days in the empty state, then simulation of the full state for several days is assessed. This is then followed by periodic reviews, re-mapping the various calibrated sensors, hot and cold spot assessments, operation of both standby and duty alarms, and a review of the alarming capability. Finally, an assessment of any issues and the impact on product quality and a review of maintenance schedules are performed.

Shipping has evolved historically from a state where there was limited knowledge of what had occurred, to the present state where there is forced receipt acknowledgement at the receiving site, a requirement to analyse as per pre-agreed protocol, an awareness of any temperature excursions and a risk assessment of the entire process. The containers have increased in cost and capability, but the impact of failure is also higher. For high-value shipments with complex customs clearance procedures, a detailed risk assessment is required by the courier. At each stage, there will be a contingency plan in case of delays.

Dr O’Connor reflected that most problems occur on reaching the recipient. He indicated that storage at clinical sites is now being monitored more closely, although it is far from perfect. He highlighted a recent case where shipping issues had led to a £1 million loss of a biopharmaceutical from a large pharma company. In another example, a medium-sized pharma company had suffered a £100,000 loss after the product was delayed by US customs and there was no access to controlled temperature storage.

Dr O’Connor then focused on business continuity planning (BCP), or how an organisation will recover and restore interrupted critical operations within a predetermined time period of any disaster scenario. This could be any conceivable disaster, eg, earthquake, hurricane, etc. BCP involves five main elements; people (key contacts along with contact details), premises (recovery operations), process (for returning organisation to minimum service levels), providers (key contacts in the supply chain), and PR (internal and external communications).

Ms Kaye noted the reasons for in-use stability, which is to mimic patient use and demonstrate adequate stability over that period. However, there are many different types of products and in-use scenarios, including repeatedly opening and closing the pack, the impact of removal of the secondary pack and reconstitution of products. There is limited guidance for in-use stability both for registered products and IMPs. The following guidance can be applied: CHMP/QWP/185401 (Guideline on the requirements to the chemical and pharmaceutical
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ICH Q1B specifies that applicants must consider the potential of their compound to photo-degrade. The guideline indicates that forced degradation and confirmatory studies should be performed on both API and drug product. There is a huge difference between artificial lamp light, artificial lamp light/natural light through a window and bright summer sun, in fact there is a 10^4 dynamic range between overcast night (0.0001 lux) through to a sunny day (10^4 lux).

Mr Clapham discussed photo degradation pathways. They are very similar to oxidative pathways, and they often lead to photoinduced hydrolysis, ring opening, isomerisation and polymerisation. Certain structural motifs are sensitive to photo degradation, eg, aryl halides (I>Br>Cl>F), benzylic hydrogens, -hydrogens (adjacent to heteroatom), sulphides, etc.

There are two scenarios for light sources; either option 1 (artificial daylight combining UV/visible light from a xenon or metal halide lamp), or option 2 (exposure to both cool white fluorescent light and near UV fluorescent light). However, the relative spectral power distributions of these lamps can show pronounced differences. Option 1 ≠ option 2 and neither may accurately mimic the sample environment (best to use both). The total exposure should be 1.2 million lux hours and 200Wh/m². From a forced degradation perspective, if the compound is known to be photo stable then apply ca. 2x ICH Q1B recommendations, whereas, if the compound is photo labile, aim for 10–20% photo degradation and ensure the primary photo degradation products are observed.

For solid oral drug products, “samples should be positioned to provide a maximum area of exposure to the light source, eg, tablets should be spread in a single layer (ICH Q1B)”. Mr Clapham presented a flow diagram for photo stability testing of the drug product, highlighting that if degradation is seen with the unprotected samples, then test with the primary pack, followed by testing in the secondary pack. If instability is still seen then it may be necessary to redesign either formulation or packs. However, companies need to remember that the patient won’t necessarily use the pack.

In summary, the guidance is not all-encompassing, and cannot be read in isolation; nor is it easy to interpret. The guideline doesn’t say that options 1 and 2 are equivalent, or how to present samples for testing, how to control temperature effects, or that the samples must be homogenous (surface effects vs bulk effects). Finally, the guideline doesn’t address the control of humidity, the kinetics of photo degradation or how to handle in-use stability testing.

Assigning Shelf Life to Unlicensed Medicines
Speaker: Paul Graham, JPA

Mr Graham said that the Human Medicines Regulation 2012 (Section 167) recognises that some patients have special clinical requirements that are unmet by current licensed drug products. In these circumstances, an unlicensed medicinal product (“special”) is allowable, subject to the following considerations. There must be a bona fide unsolicited order, the product must be formulated to the prescriber’s requirements, and it must be for the specified individual patient.

The MHRA has published a Review of Unlicensed Medicines (RUM), but this has not been updated since 2011. However, the shelf life of unlicensed medicines is not in scope. Secondly, ICH produced Guidance Note 14, The Supply of Unlicensed Medicinal Products (Specials) which states that “when inspecting a specials manufacturing site, an inspector will take into account stability data and justification for expiry dating”. Finally, the MHRA published a Q&A for Specialists’ Manufacturers in September 2013.

Mr Graham explained how a shelf life was assigned to an unlicensed medicine. Initially a literature search is undertaken to see what relevant information can be obtained from the public domain. The second step is that the shelf life of the “specials” cannot be greater than the shelf life of the input product. APIs and excipients are selected to be comfortably within their designated shelf life at the time of manufacture. The shelf life must be justifiable and must include an appropriate margin for safety. A Certificate of Conformity (CoC) is required at the time of release. The MHRA Guidance Note 14 indicates that the manufacture of the product may be carried out in anticipation of receiving the order, ie, batches can be manufactured based on the known future demand of a product. This allows batch manufacturing, which ensures that some economies of scale are achievable, a certificate of analysis (CoA) can be produced and potentially longer shelf lives are achievable.

Some of the challenges inherent in moving from a “one-off” bespoke special to a batch special were outlined. For the latter, the product formulation may require some elements of product development, including an evaluation of the API, forced degradation studies and selection of the most appropriate dosage form, ie, “age appropriate”. The container closure needs to be developed. The batch then requires some elements of validation. This centres on the likelihood that this is indeed the formulation of choice and if the product is likely to be subsequently licensed and the need for a stability indicating analytical method (linked with forced degradation). Finally, stability studies need to be initiated. This may require some initial scouting studies. ICH conditions and time points are likely applicable, as is compliance with existing pharmacopoeial monographs.

In summary, Mr Graham compared the differences between the true bespoke unlicensed medicines, where the shelf life is justified by the literature, periodic reviews are performed in light of any patient complaints or newly emerging information, and a risk assessment is required. In contrast, a batch-manufactured unlicensed product is very similar to a licensed product, where shelf lives are based on actual data, the protocols, storage conditions and testing time points are all ICH-aligned, stability indicating methods are used and periodic stability testing will be performed.