EFPIA LATAM Network
Latin America
Stability Studies – Proposal for Harmonization
May 7, 2015

BACKGROUND

Nowadays pharmaceutical companies are working globally with several manufacturing sites for drug substance and drug products, registering their products globally with different Health Authorities and having complex supply chain structures to ensure the continuous supply of high quality drugs to patients globally.

The pharmaceutical industry and regulators have been working together to streamline and harmonize the process for registering medicinal products from the global perspective, to allow patients faster access to safe and efficacious new medicinal products of high quality worldwide.

Harmonization initiatives have been successful where scientific consensus has been achieved between the industry and regulators, and regulatory agencies have subsequently implemented guidelines and recommendations that largely reflect the consensus. In the 1990s, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) began its work to harmonize regulatory requirements, which helped facilitate global development and expedite the availability of medicines to patients, while maintaining safeguards on quality, safety and efficacy. In Latin America, ANVISA is an observer to ICH.

Regional harmonization activities include the European Community (EC), which in the 1980's, worked to achieve a single oversight regulatory agency for pharmaceutical products. Stability Studies have been the subject of several harmonization efforts. The ICH guideline Q1[1] *"Stability Studies for New Drug Substances and Products*" was implemented very early in the ICH process. ICH stability principles were adopted by a number of regulatory agencies and regions (e.g. Europe, US) and by the WHO[2]. The Association of Southeast Asian Nations (ASEAN) *Guideline on Stability Study of Drug Product* (May/2013) addresses the information to be submitted for registration and variations of drug products in ASEAN Member States.

The implementation of ICH Q1A(R2) - Q1E and WHO guidelines have harmonized the core stability data package for marketing registrations, but there remain some specific LATAM country requirements that are not aligned with ICH or WHO. The paper is intended to identify and discuss these requirements and propose some recommendations to promote further harmonisation.

The scope of this paper is for synthetic drugs (small molecules).

DISCUSSION

Non-stability indicating testing requirements: Examples:

a. Tablet hardness testing for drug product.
b. Endotoxin testing.
c. Microbiological testing of non-sterile dosage forms such as solid oral dosages (tablets).

These quality attributes are typically non-stability indicating and assessment during stability provides no additional assurance of product quality. Tablet hardness testing may be appropriate for certain types of tablets in some types of packaging but should not be an universal requirement. Endotoxin levels would be unlikely to change on stability (unless there was gross contamination) and microbiological testing of solid oral dosage forms during stability studies is also of limited value because the low water activity of such products inhibits microbial growth. Evaluation of these attributes in stability studies is not indicated in the ICH stability guidelines.

Specific formatting requirements: country-specific requirements create complexity without improving the quality of the study or the product. Examples:

a. Specific form for the MOH to be able to find the information requested,
b. All cells or spaces to be completed, tables with blank cells are not accepted,
c. Commonly used expressions of acceptance criteria such as “pass” or “similar” are not accepted.

Signed, notarized, legalized original documents: The requirement for signed or legalized documents does not increase assurance of product quality or veracity of data. Such requirements increase the regulatory burden by adding complexity and delays to the submission process and are not aligned with ICH expectations.

Number of batches / matrixing and bracketing: Examples:

a. Some countries require 3 batches for reconstituted product while ICH indicates 2 batches.
b. To support technical variations, the requirement is for 3 batches, typically not allowing bracketing or reductions in number of lots based on established scientific principles (International guidelines require 1 or 2 batches depending on type of change).
c. Regarding APIs, stability is to be done with 3 full production batches per strength. For example: if there are 2 API sources and 1 strength, a total of 6 batches will have to be placed on stability.

API sources are evaluated and qualified by the manufacturer in the DP manufacturing process to demonstrate equivalency. The requirement to submit 3 batches of DP stability data using each API source is not aligned with ICH expectations. This requirement can delay access to new medicines by requiring specific additional stability studies or, if only one API source is registered, decreases sourcing flexibility with increased potential for drug product shortages.

Matrixing and bracketing in stability studies is permitted by ICH guidelines.

Site specific stability:

Some countries request that the stability study be done in the final packaging site. The requirement for packaging site-specific stability studies is not scientifically justified because the processes, including the packaging operations, are validated and shown to be equivalent, and therefore the location of the packaging operation is not relevant. The primary packaging operation is controlled through adherence to cGMP, and is inspectable,

Stability is a function of the product and primary package. Companies use a matrix of API and final product manufacturing sites to ensure continuity of supply in the event a specific site encounters challenges which may temporarily or permanently inhibit their ability to produce and/or release API and finished products meeting all GMP and quality requirements.
The requirements for non- ICH aligned stability precludes companies manufacturing for a global environment from using the same supply chain flexibility, processes and procedures for all countries.

Local shelf-life stability: ongoing stability has to be done in some countries. Examples:

a. If the primary packaging is done in the country, it will require local stability.
b. The company must perform local stability on the first 3 batches and also submit the batches for verification testing to the authority before marketing of the product.
c. For imported products, either in bulk or in primary package, the follow-up stability studies must be carried out in the country.

As stated above, the requirement for local stability does not add scientific value to the review process since the processes have been validated to be equivalent.

Other product related data/local requirements: Examples:

a. Batch related data for excipients, Certificates of Analysis (CoAs) for excipients that were used in drug product batches under stability studies.
b. Standard deviation for each time point.
c. Dissolution result for each tested sample (individual result) at each tested frequency for each batch.
d. Raw data must be presented
e. Provision of chromatograms, including the chromatograms of the API and reference standard, used for the manufacturing and testing of that DP respectively.
f. Must provide DP sample chromatograms for each of the (e.g.) 3 batches on stability, at each time point or at the starting and final time points.

This information (excipient CoA, standard deviations, individual results, raw data, chromatograms) is available at inspection and inclusion in the dossier adds no value to the review process or increase assurance of product quality. It does increase the documentation burden for both the applicant and the reviewer and these requirements are not aligned with ICH.

Lack of harmonized stability requirements for post-approval changes (PAC): Examples:

a. Require full long term stability data package (all stability timepoints, e.g. 0, 3, 6…months), and will not accept accelerated stability only.
b. Require data for 50% of the proposed shelf-life, e.g. if asking for 24 month expiry date, 12 months of data have to be presented.

This lack of harmonization results in prolonged approval timelines, and companies need to consult widely varied, country- or region-specific guidelines.

RECOMMENDATIONS/PROPOSALS

2. Adoption of **ICH/WHO stability recommendations** across the region. The adoption of internationally accepted, harmonized guidelines in lieu of country-specific stability requirements would facilitate access to new medicinal products.
3. Encourage **science- and risk-based approaches** to stability studies:
    a. Avoid rigid requirements for defined numbers of batches in stability studies and allow matrix and bracketing approaches.
    b. Accept the use of scientifically-based predictive models to statistically justify proposals for adequate shelf-life, including API retest period. This will reduce the need to submit shelve-life extensions and re-labelling and facilitate access to medicinal products.
    c. Adopt flexible approaches to the interpretation of stability requirements need to support the assurance of product quality, instead of employing a standard set of tests for different dosage forms. For example, a science- and risk-based evaluation of the impact of a proposed change to the manufacturing process/synthesis route/formulation/packaging on the stability related quality attributes, (SRQAs) or ideally the shelf-life limiting attributes (a sub-set of the SRQAs) could conclude that no, or limited, stability studies are required. If the changes may potentially affect the SRQAs, then science- and risk-based approaches could be used to determine what testing is needed to assess/ confirm stability performance. (Reference Colgan et.al[3])
    d. Consider aligning the stability requirements to support post-approval changes with those defined in other regulatory frameworks (e.g. EU guidelines[4,5]).
    e. Eliminate or reduce the requirements for site specific stability if none of the stability related quality attributes have changed in batches produced at the new site.

Stability data generated on product manufactured at alternate sites should be considered representative of the drug product, provided that the manufacturing process has been validated for all sites and none of the stability related quality attributes have changed. All validated sites will provide product of the same quality and meeting the same specifications. Therefore, the primary stability batches cover products manufactured at all sites, and stability data do not need to be site specific.

f. Accept the use of appropriate stability data (e.g. accelerated, thermal cycling) or predictive modelling (e.g. Accelerated Stability Assessment Program (ASAP)[6]) to support temperature deviations from the approved label conditions during transport. The company quality system should have procedures to handle such deviations.

g. Encourage dialogue with industry towards timely discussions on new innovative or alternative approaches[5] to establishing product shelf life and storage conditions, to rationalise post approval annual testing commitments and product/ process changes (e.g. statistical approaches, predictive models, etc) to be up to date with scientific developments.

4. Allow quality reviewers the **flexibility** to accept risk-based approaches and alternative stability proposals when scientifically justified, e.g. long term stability for Zone IVb countries at other conditions than 30°C/75%RH with a scientific justification of the proposed shelf-life and labelling. Note that according to WHO, alternative storage conditions can be used if justified.

5. Increase opportunities for **dialogue and collaboration** between industry and regulators across the region and throughout the lifecycle of the product to discuss integrated science and risk based approaches to stability.

   a. encourage industry to propose updates or revisions to guidelines/regulations during the drafting stage, prior to public consultation)Reasonable time for comments should be provided.

REFERENCES

1. ICH, Q1A (R2), Stability Testing of New Drug Substances and Products (Feb/2003) http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

2. World Health Organization, WHO Technical Report Series, No. 953, 2009, Annex 2, Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

   a. Table 2 updated February 2013: http://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditionsTable2UpdatedFeb2013.pdf?ua=1

3. S. T. Colgan, R. J. Timpano, D. Diaz, M. Roberts, R. Weaver, K. Ryan, K. Fields, G. Scrivens, "Opportunities for Lean Stability Strategies" J. Pharm. Innov. 9:259–271 (2014).

4. EU Guideline on various categories of variations (May 2013) http://ec.europa.eu/health/files/eudralex/vol-2/2013_05_16_c2804_en.pdf

5. EMA Guideline on stability testing for applications for variations to a marketing authorisation (March 2014) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500164972.pdf

6. Waterman KC, Carella AJ, Gumkowski MJ, et al. Improved protocol and data analysis for accelerated shelf-life estimation of solid dosage forms. Pharm Res 2007; 24(4):780-9