GLOBAL STABILITY PROGRAM - a long journey to harmonization

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In the current business strategy, pharmaceutical companies must work globally and collaboratively. Drug products are now manufactured in one country and may be marketed in over 100 countries. Therefore, it is imperative to be aware of the global regulations. We must not only understand and comply with these regulations but also the differences among them as well as influences or harmonization efforts. In addition, one also must not lose sights on current industry practices and scientific judgments to develop a global program.

Stability is defined as a Critical Quality Attribute (CQA) in current development process. Stability program provides data to support the expiration dating and storage condition of finished pharmaceutical products. Testing for stability studies are very costly; therefore, drug manufacturers are interested in harmonized guidelines to streamlining testing for global registration of new medicines; unfortunately, the global harmonization of this area has spanned a couple of decades with tireless efforts from several organizations.

The most controversy issue is probably the long-term storage condition. The concept of climatic zones, first introduced by Schumaker in 1972 and Wolfgang Grimm in 1986, has become an established standard in developing pharmaceutical products. In 1993 and subsequently 2006, The International Conference of Harmonization (ICH) has issued a guideline for Zone I and II covering registration in United States, Europe and Japan. Much work has put into defining storage condition to support Zone III and IV from ICH and other international organizations. In 2005, WHO proposed as an option to divide Zone IV into two sub-zones: Hot & Humid (IVa) and Hot & Very Humid (IVb) to accommodate several regions that experience very high temperature and humidity. In 2006, FDA has withdrawn their stability guidance and reference ICH Q1A(R2) for stability testing. Subsequently, ICH withdrew Q1F, which covers studies supporting Zone III and IV, leaving the industry with no guideline for submission of pharmaceutical products to countries in these regions.

In September 2009, the World Health Organization (WHO) has issued the final stability guideline of “Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical products” as the Annex 2 in the WHO Technical Report Series 953, 2009. The scope of this document covers the active pharmaceutical ingredients and pharmaceutical products for marketed and new products. It also includes the transition period recommended for already marketed actives and products. Table 1 lists the climatic zones referenced in the WHO guidelines. WHO guideline also includes a list of long term conditions recommended for marketing authorization in its Member States. This table has assembled from several regional harmonization groups (e.g. ASEAN, ICH and GCC), international conference of Drug Regulatory Authorities (ICDRA) and International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). (1)

Table 1: WHO Stability Testing Conditions

Climatic Zone	Climate	Long Term Condition
I	Temperate	21 °C/ 45% RH
II	Subtropical	25 °C/ 60% RH
III	Hot & Dry	30 °C/ 35% RH
IV a	Hot & Humid	30 °C/ 65% RH
IV b	Hot & Very Humid	30 °C/ 75% RH

In this guideline, WHO recognizes the diversity of global climate, thus recommends three long-term storage conditions depending on the regions (25 °C/60% RH, 30 °C/65% RH, and 30 °C/75% RH.) Many countries have come up with regional guidelines that are in agreement with this international document. However, a few countries (e.g. Canada, Chile, and Afghanistan) list 30 °C/65% RH is the required long-term storage condition, which is different than their climate reality one would expect. These countries have been accepting 25 °C/60% RH stability data for their markets. 30 °C/65% RH is the intermediate condition for ICH, and normally is a hold condition until a significant change is found for testing at accelerated condition. In another case, India lists 30 °C/70% RH as their requirement of long-term study. This condition is not aligned with other countries of the same climatic condition, thus prevent the use of one condition to support registration in all countries of this region. (2) For more information, Zahn has explained the concept of climatic zones and how long-term testing condition should be selected based on actual meteorological data. (3)

Therefore, continuing efforts seem to be needed to fine-tuning this process. However, there is not much activity circling this issue at this point. The WHO indicates that they will update these requirements on their webpage as they receive from national regulatory authorities of their Member States.

As companies continue to tune in to specific requirements from different countries for new product registration, Table 2 lists the recommended conditions and time points that would provide sufficient information for all 4 climatic zones. In essence, 30 °C/75% RH is the most severe condition for long-term study; therefore, many companies have selected this condition to support non-ICH regions and reduce testing at 25 °C/60% RH if the product is found stable.

Table 2: Stability Testing to Support Global Markets

Stability	Testing condition	Time Zero	3 mo	6 mo	9 mo	12 mo	18 mo	24 mo	36 mo
ICH Long-term	25 °C/ 60% RH	X	x	x	x	x	x	x	x
ICH Intermediate	30 °C/ 65% RH		(x)	(x)	(x)	(x)			
Zone IVa Long-term	30 °C/ 65% RH		x	x	x	x	x	x	x
Zone IVb Long-term	30 °C/ 75% RH		x	x	x	x	x	x	x
Accelerated	40 °C/ 75% RH		x	x					
Stress	50 °C/ Ambient		x						

(x) Hold, testing if there is significant change

It has been close to two decades since the harmonization of storage conditions has been discussed; I think we have gone a long way to understand specific needs of different counties shaped by their culture, market and distribution with regard to stability program. To be competitive, company must be aware of the dynamic of global manufacturing and registration to exercise good science-risk based approach. A solid compliance program and collaboration with regulatory authorities are also necessary to understand the regional requirements of the target marketing countries. Although the final destination has not quite been reached as desired, I think it is a successful journey!

References:

(1) S. Kopp, "Update on WHO Stability Guidelines", *Stability Testing to Support Global Markets*, Huynh-Ba (ed.), Springer, New York, 2010, pp. 23-28.

(2) M. Zahn, "WHO Stability Guideline: Remaining Issues", presentation at AAPS Stability Workshop, 25 September 2009, National Harbor, MD.

(3) M. Zahn, "Handbook of Stability Testing in Pharmaceutical Development", Huynh-Ba (ed.), Springer, New York, 2008, pp. 43-91.