Shelf Life Assessment of Drug Product after opening Container for the first time

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***ABSTRACT*: The continued integrity of products in multi-dose containers after the first opening is an important quality issue. The purpose of in-use stability testing is to establish a period of time during which the product in multi-dose container can be used retaining quality within an accepted specification once the container is opened.**

KEYWORDS*: *Multi-dose, container, quality in-use, stability, testing

PREFACE:

The authors of this paper suggest that any approach used to demonstrate in-use stability of medicinal products be science and risk based and that many approaches could be used with justification. A framework for the use of multiple approaches is provided in the following paper, which is intended to shade some light on how in use stability can be performed. This paper provides an approach to address the void created due to absence of regulatory guideline. The authors do not advocate that the following approaches given in this paper be the only way that in-use stability should be assessed. To the contrary, the publication of other approaches that can be used within the framework of this paper is welcomed and encouraged, and it is expected that regulators will consider all science- and risk-based approaches when setting guidance for industry. These other approaches may include various method to assess in-use stability, with justification.

INTRODUCTION:

The continued integrity of products in multidose containers after the first opening is an important quality issue. While this principle is acknowledged in various Guidelines, no specific guidance is available on defining test design and conduct of studies to be undertaken to define in-use shelf life in a uniform fashion. Therefore, this article attempts to define a framework for selection of batches, test design, test storage conditions, test parameters, test procedures etc., taking into consideration the broad range of products concerned. Stability of products is the length of time that they retain their properties and functionality while stored or handled as defined by the manufacture's specifications. During their life span products may change as they age but they are considered to be stable as long as their characteristics remain with the specifications. The change of the performance as products age is called degradation and is usually defined in terms of loss of activity or/and decrease of performance. Stability encompasses several stages of product life; i.e., time and events during transportation of products from manufacturer to the end user, the length of time that products are stored at recommended conditions without being used, time and events while products are being used. The last stage is referred to as in-use stability. The above stages may not be all inclusive and all products may not go through all of them. There are products that are designed for a single use while others are stored in containers that can be used for a period of time after it is opened.

The absence of a detailed and authoritative guideline for the human pharmaceutical sector does not assist in the design and conduct of such studies, and when manufacturers design their own studies it is by no means certain that the regulatory agencies will find the data to be completely acceptable. Furthermore, there are circumstances when the generation of data from specific in-use simulations may not add significantly to the data already generated from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (1CH)-compliant stability studies. There are also situations (e.g. when small multi-dose containers are involved) where it is difficult to conduct meaningful studies due to the limited quantities of residual product on which to perform chemical or microbiological testing.

Modified Approach for the assessment of In-use shelf life for multi dose container after first opening:

Selection of batches:

A minimum of two batches, at least pilot scale batches, should be subjected to the test. At least one of the batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies. The batch number, date of manufacture and size of each batch should be stated. The container and closure of the product and, if present, the medicinal device should be equivalent to that proposed for marketing [2]. Study can also be performed by bracketing the study design on same batch i.e study should be initiated at beginning and at the end of shelf life of the product.

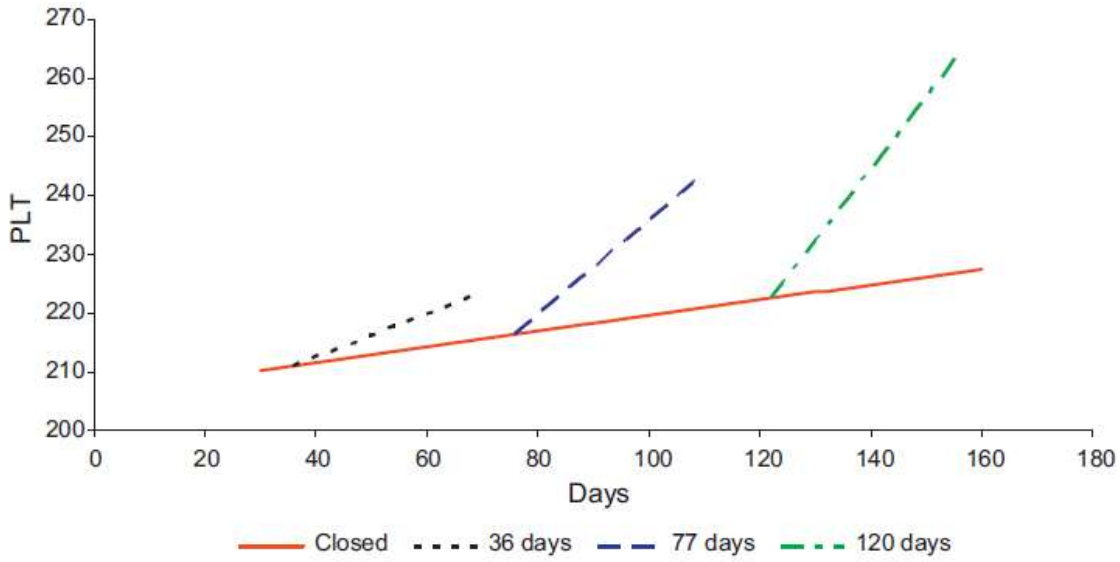
In use period (Design of study):

As far as possible the period to which the in use stability study is to be performed should be design in such a way that it will simulate the use of the product in practice taking into consideration the filling volume of the container and any dilution/reconstitution before

use. The appropriate physical, chemical and microbial properties of the product susceptible to change during storage should be determined over the period of the proposed in-use shelf life.
As per board of pharmacy regulation once dispense the product is given a shelf life of 1 year and if it is approaching its expiry than the number of days reaming for expiration is mentioned. In various guidelines in use stability study for 28 days is recommended for bulk packs but the quantity of units in bulk pack may change and the pack may be used for more than 28 days, so it is also necessary to design the study in such a way that it will simulate the use of product in practise.

The following study was carried out to determine the effect of shelf life period on in use stability of product , Vials of the reagent were stored at recommended storage conditions and tested on a hematology analyzer in 5 replicates at 34, 48, 62, 77, 90, 105, 120, 133, and 146 days after manufacturing. A new vial is opened at each testing time point. This constitutes real time closed container stability testing of the product. The in-use stability testing was performed at three different time points of product's life, 36, 77, and 120 days after manufacturing. Let us denote with tc time of closed container stability, to is time of in-use open container stability, and e events (n is the number of instances that the same vial/container is used). Vials were open at these time points and tested 20 times in duplicates for a maximum of 35 days. Number of platelets (×103 cells/_L) is the measuring parameter in the tests. Estimated degradation patterns of PLT (platelet cells/_L × 103) closed container and in-use open container at three closed times are shown in Fig. 1.

Figure -1: Degradation pattern of closed container and in-use open container



Degradation statistics for in-use open container for the three scenarios, time, events, and both time and events are defining parameter. Drift of in-use stability depends on the age of closed container. Regardless of the way (time, events, time & events) drift is estimated, its magnitude increases as closed container product gets older. Drift of in-use open container for tot = 35 days and et = 20 events is 15.32 × 103 cells/_L at tct = 36 in comparison to 34.56 ×103 cells/_L at tct = 77 and 50.81 × 103 cells/_L at tct = 120. The 95% confidence intervals of these three drift estimates do not overlap providing additional evidence that they are statistically different from each other.
Drift estimate for the time of open container (tot = 35 days) is greater than the drift estimate for the number of events (et = 20 events) when they are considered independently. This indicates that the length of time of open container contributes more to the in-use degradation in comparison to the number of events. Time of open container and events are highly correlated with each other but when considered together multiplicatively the degradation accelerated in comparison to their separate effects. The estimated platelet drift for the multiple effects of time and events is 50.81 × 103 cells/_L at tot = 120 days. This drift is 8.04 × 103 cells/_L greater than the drift for the effect of time of open container and 11.99 × 103 cells/_L greater than the drift of the effect of number of events. In-use degradation drift of open container for 35 days and 20 events is greater that the drift of closed container for 120 days. This evidenced the fact that the majority of degradation occurs during the period that the product is in use[6].
From the following article we can say that the duration to which the container is open for use and the age of container are determining factor for its degradation i.e its stability. So it is necessary to determine the period to carry out in use stability study for different packs as the period may vary as per the pack size.

Number of Counts in each container:
If the product is to be supplied in more than one container size or in different strengths, in use stability test should be applied to the product which presents the greatest susceptibility to change. The choice of the tested product should always be justified [2].

Figure -2: Process flow diagram for assessment of bulk product sample for in use stability for oral product

1. Selection of pack Size:
The question remains the same on which pack the study to be carried out. As there are multiple packs with different pack design which makes each pack individual entity. So is it necessary to carry out study on each pack or to use bracketing. There is no such guideline which sheds light on pack size selection and also each product may act differently as compared to other.
In this case we can use bracketing for various pack size available, it will cover the entire range of pack size.

2. How to determine susceptibility of a pack:
Susceptibility is defined in terms of microenvironment present in the container after first opening of container which increases the degradation rate of product in container. Change in head space due to sampling also accelerates the degradation of product. Presence or absence of canister also affects the microenvironment. We need to consider this condition while selection of pack in term of susceptibility.

3. Dispensing:
Frequency of dispensing and duration to dispense the total medicament need to be considered. There are chances that after tampering the seal the pharmacist may keep the pack till end of its shelf life. There are also chances that pharmacist can open the bulk pack container at the end of its shelf life, as we know that the shelf life is provided only for sealed container and not for open container. So it is necessary to complete the in use study till its shelf life and determine the period to which the product is stable for safe use.

4. Desiccants, Canisters and oxygen scavengers Evaluation:
We need to evaluate wither the canister incorporated in given pack is suitable to withstand the microenvironment after the pack is open at least it should keep the product stable for the duration for which it was evaluated under in use study condition.

5. If we consider 30's pack and 90's packs and further:
If we consider 30's and 90's pack the quantity of tablets will fall short for complete analysis as per finished product specifications. Is it feasible to keep 2 bottles during whole study and pooled sample to be used for analysis purpose? Also what time point to be selected for the study, can it be 15, 30, 60, 90 days for 90's count or it should be directly 90 days. Similar is for 30's count can it be 15, 30 days or directly 30 days.
What would be the time point for 250's count, 500's count, 1000's count and so on?
We can perform in use study for 90 days and if results are within specification it can be stated on label that once open it should be utilize within 90 days or the date till the pack is safe to dispense and consume.

6. Use of controlled sample along with test samples and the condition for controlled samples:
Control samples are sample kept along with test sample at similar condition. Is there any need to keep control sample? Is there any need to open the seal of control sample when the study is initiated? Is there any need to withdraw same amount of sample as that of test at given time point? We usually face these questions when we keep control sample along with test sample, and we don't have any guideline regarding same.
What could be done is to break the seal of container when the study is initiated and then to keep the sample as it is till the end of study. It can act as control sample.

7. Fish bone Blister pack:
If we consider fish bone blister pack once you take out one tablet from the given pack the canister present starts saturating and at some time point it will be no use and degradation of product accelerates.
So it is necessary to determine for what duration the following pack can be utilize after first tablet is taken out from the pack, and also it is necessary to mention it on the label the duration for which the tablet is safe to consume after first tablet is taken out.

Storage condition for test product:
The product should be stored under conditions as recommended in the product literature (PIL) throughout the in-use stability test period. Any other storage conditions should be justified.

1. Sample susceptible to light:
Mostly light sensitive products are coated which acts as an barrier, but in use stability of such products to be performed to evaluate the stability of product once the seal is broken.

2. Sample highly susceptible to moisture:
Mostly moisture sensitive medicaments are coated which acts as an barrier, but in use stability of such products to be performed to evaluate the stability of product once the seal is broken. e.g OROS product are considered to be more susceptible to moisture as they contain salts which may absorb moisture during its storage.

Test to be performed:

The appropriate physical, chemical and microbial properties of the product susceptible to change during use should be monitored. The tests used must be appropriate to individual dosage forms, however, examples of parameter types which may need to be studied are given below:

Physical: Description, colour, clarity, closure integrity, particulate matter, particle size, dissolution.
Chemical: Assay of active substance, degradation product level (impurities), antimicrobial preservative and antioxidant content(s), pH, Water by kf.
Microbial: Total viable count, sterility.

Labelling:
Labelling of primary container: The in-use shelf life should be stated on the label. Manufacture can also provide a space for the user to write the date of opening or the "use-by" date.
Labelling of secondary container: The in-use shelf life should be stated on the label of secondary container.
PIL: The in-use shelf life should also be included in leaflet.

References:

[1] International Conference on Harmonization. Q1E. Evaluation for stability data, Rockville, MD , 2003.
[2] NOTE FOR GUIDANCE ON IN-USE STABILITY TESTING OF HUMAN MEDICINAL PRODUCTS, London, 1 March 2001, CPMP/QWP/2934/99.
[3] Note for guidance on In- use Stability Testing of Veterinary Medicinal Product, (EMEA/CVMP/127/95), March1996; The regulatory Affairs Journal, 1997, 8(1), 29.
[4] Evaluation of "In-Use" Stability Period of Lacidipine Tablets in Multi-dose Plastic Container-Closure, International Journal of Pharmaceutical Sciences and Nanotechnology, Volume 6,Issue 2, July– September 2013.
[5] Note for Guidance on Maximum Shelf –life for Sterile Product after First Opening or following reconstitution (CPMP/QWP/159/96), 28 January 1998; The regulatory Affairs Journal, 1997, 9(5), 340
[6] In-use stability modelling, Robert T. Magari, Elena Afonina, Journal of Pharmaceutical and Biomedical Analysis 56 (2011) 799– 803