

IN-USE STABILITY TESTING: WHAT DATA ARE REQUIRED AND WHEN?

Scott Sutton, Brian Matthews and Danny Dunn discuss the implications of the lack of guidance for human pharmaceuticals in the EEA, and draw attention to some practical limitations

This article considers current guidance on in-use stability testing in the European Economic Area (EEA). It highlights the problems arising from the absence of specific guidance for human medicinal products and illustrates these using two examples of different product types. Finally, a proposal is made for a guideline on in-use stability testing, specifically for human medicinal products.

Current requirements

The European Community (EC) Committee for Veterinary Medicinal Products (CVMP) has recently adopted a guideline for in-use (open-bottle) stability testing¹. There is no equivalent document offering guidance in the European (i.e. the EC and EEA) human medicinal product sector. However, several Committee for Proprietary Medicinal Products (CPMP)/CVMP and International Standards Organisation (ISO) guidelines have recently addressed the need and conditions for performing an in-use stability study as a part of the development process for new medicinal products and medical devices²⁻⁵.

It is clear from these documents that chemical, physical and microbiological data are expected to support the proposed in-use stability period for products designed to be used on more than one occasion. In recent questions from regulatory authorities it has been suggested that in-use stability studies should incorporate removal of the product from the container on a number of occasions under in-use conditions with the product left out of its carton.

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 (ICH)-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.

In-use stability testing: considering the problem

This question will be explored using two different product types. At one end of the spectrum is a bulk pack used in a pharmacy, and packaged in a glass container. At the other end is an ophthalmic medicinal product, packaged in low-density polyethylene (LDPE)⁶.

No guidance on in-use stability testing exists for human medicinal products

Studies designed by manufacturers may not necessarily be acceptable to regulators

Two product types used to illustrate the problems

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Four different aspects of the problem will be addressed:

- **package type:** (a critical parameter) if the container is completely filled and oxygen impermeable then there will be no opportunity for oxygen degradation to become apparent during product development stability studies;
- **susceptibility to oxidation:** if the product, or components of the product, are volatile or oxygen labile then special concern should be reserved for the effects of multiple aerations;
- **in-use period:** if the proposed in-use shelf-life is beyond one month, then the 28-day compendial preservative efficacy test does not provide a satisfactory level of assurance as to the adequacy of the preservative system;
- **how should an in-use test be performed:** significant technical and practical issues exist concerning the design of a test to support in-use stability.

Different aspects to be addressed...

PACKAGE TYPE AND SUSCEPTIBILITY TO OXIDATION

Guidance for in-use preservative testing is described in an EC guideline (EMEA/CVMP/127/95¹) which specifically states that additional testing may be applicable to multi-dose or topical dosage forms if a specific problem (in terms of stability of the product) has been identified after the product has been opened. For example, this situation would apply to a product with an active ingredient that is subject to oxidative degradation and has been packed in a completely filled oxygen-impermeable container (e.g. a pharmacy bulk pack). Its glass package provides a barrier to oxygen so that oxidative stress would not be seen during the normal stability program. The situation would be exacerbated if the active ingredient, the antimicrobial preservative or any other critical formulation component exists in a reduced form. A real concern would exist about the potential for oxidative degradation of the formulated product upon repeated exposure to oxygen during use.

CVMP guidance states that additional tests may be necessary for multi-dose or topical dosage forms

Contrast that situation with the hypothetical ophthalmic eye-drop. The most common container resin for ophthalmic products is LDPE as described in the *European Pharmacopoeia* (Ph Eur)⁶. As discussed before, a primary purpose of in-use stability testing is to establish that the active ingredients or preservative are not degraded by exposure to oxygen while being dispensed. LDPE is known to be readily permeable to oxygen⁷, and ophthalmic containers are intentionally prepared with a 2–5 mL air headspace. This allows the bottle to be more 'squeezable' and helps to ensure that drops are dispensed instead of a 'liquid stream'. In this situation any oxidative degradation of an active ingredient or preservative due to exposure to oxygen would be readily evident during normal stability studies which extend over 36 months or longer at storage conditions of 25 °C, 40 °C and possibly 30 °C, at various humidity conditions. It is not clear what additional stability information the simulation of in-use conditions would provide for this type of product.

IN-USE PERIOD

In these examples, the pharmacy bulk pack may be used for months while the ophthalmic eye-drop normally has a standard in-use period of 28 days or fewer. The eye-drop period of use is in agreement with guidance document CPMP/QWP/159/96² and will be justified by the chemical stability and the preservative efficacy demonstrated during ICH-compliant stability studies. This is noted in the introductory text to the Ph Eur antimicrobial preservative effectiveness test⁸, which declares that the tests provide proof of 'adequate protection from adverse effects that may arise from microbial contamination or proliferation during storage and use of the preparation'. This interpretation seems to be one of the rare instances of agreement among pharmacopoeias on the subject of antimicrobial preservative efficacy testing^{9,10}.

Stability studies conducted in line with ICH requirements should be sufficient

This interpretation is also supported in the scientific literature. Several recent studies have correlated the activity of the preservative system with the performance of the finished product. Two of these articles describe work involving members of the *British Pharmacopoeia* (BP)

Working Party on Antimicrobial Preservative Efficacy Tests. In the first, Davison *et al*¹¹ examined a variety of used ophthalmic products, correlating the level of contamination seen in actual use with the level of antimicrobial efficacy as determined by the compendial test. They found that the BP criteria then in force and the then-proposed Ph Eur 'A' criteria, correlated with low contamination levels in actual consumer use. The second study in this series¹² extended the evaluation to a wide range of medicinal products. It was found that meeting the Ph Eur 'A' criteria provided protection against contamination in actual consumer use in these different dosage forms as well. This correlation has also been observed with personal care products, where products that had more efficacious preservative systems (as determined by compendial tests) were more highly resistant to contamination in a simulated patient abuse study¹³.

Products packaged in large volumes intended for long-term use may require additional testing

A second concern is described by the guidance document CPMP/QWP/155/96⁴ which identifies a need for inclusion of an 'in-use shelf-life' for medicinal products packaged in large volumes and intended for a longer in-use shelf-life (section 3.3.1.1). It is also interesting to note that most veterinary products (covered by EMEA/CVMP/127/95¹, as discussed previously in this article) are packaged in large volumes, and so are likely to be used well beyond the 28 days covered by the compendial antimicrobial preservative effectiveness test.

Guideline on multi-dose preserved contact lens care products gives additional information

Additional light is shed on this topic in a draft ISO standard for the testing of contact lens care products which has been prepared by ISO Technical Committee 172 Subcommittee 7 (ISO/TC 172/SC 7)⁵. Although this is directed to the medical device industry, it discusses the topic of in-use shelf-life to a great extent. The underlying principle is that 'the preparation must meet the requirements for an adequately preserved contact lens care product throughout its intended discard date'. The intended discard dates are given as three months or greater due to the large size of the containers (360 mL).

The hypothetical bulk pharmacy package described earlier, with an extended in-use shelf-life, should require investigation beyond the compendial antimicrobial effectiveness test.

No additional testing should be required for small volume eye-drop preparations meeting the Ph Eur 'A' criteria

However, products intended for only 28 days in-use dating that have acceptable preservative effectiveness (e.g. meeting the 'A' criteria) are a different matter entirely. The compendial preservative efficacy test covers the entire in-use period and is monitored for the storage shelf-life of the product during its development. The level of challenge in such tests is in the order of 10⁶ Colony Forming Units (CFU) of the index organisms per mL: far in excess of what is likely to be encountered in an in-use situation. The Ph Eur indicates that meeting the 'A' criteria is accepted as demonstration that the product has 'adequate protection from adverse effects that may arise from microbial contamination or proliferation during storage and use'. Therefore, for a product that meets the 'A' criteria consistently during testing, the pharmacopoeial experts who devised the preservative efficacy test presumably were content that there was no need for additional testing. Indeed, it is not clear what additional information the simulation of in-use conditions would provide.

Guidance on testing is lacking

HOW SHOULD THE TEST BE PERFORMED?

There is no guidance on the performance of this type of testing for the human medicinal product industry. Two guidance documents do provide some direction, and these will be considered. The CVMP¹ and ISO⁵ documents, one for veterinary products and the other a draft standard for medical devices (contact lens care products), are consistent in their approach. The investigator is to dispense the product in a manner similar to its use and then test the chemical/physical properties and preservative effectiveness at the end of the in-use period. Is this approach appropriate for medicinal products?

CVMP and ISO guidance may be applied to pharmacy bulk pack products, but not ophthalmic eye-drops

In the first case, that of the pharmacy bulk pack, this is a reasonable approach. The container may be entered repeatedly during a period of several months and can be expected to provide a suitable volume of product for testing after the proposed in-use stability period. The second case, the ophthalmic eye-drop, is not so simple.

The frequency of use for ophthalmic eye-drops is generally given as two to four times a day. Presumably, therefore, the simulated in-use test should cover the worst case. There is potential for microbial contamination each time the product is opened and used, as well as potential for oxidative degradation.

Consider the potential for oxidative degradation. Does chemical/physical testing need to be done on drops removed from the container as the test proceeds, or is it sufficient to perform chemical/physical testing on the small amount of sample remaining at the end of simulated in-use study? In either case, it will be a significant technical challenge to analyse the small volumes available with appropriate precision and accuracy.

Consider the challenge to the preservative system. How great a challenge will there be? Should this test be designed (as suggested by CVMP and ISO guidance) to simulate normal use, and then challenged using current compendial preservative testing? If that is to be the case, then a significant logistical issue arises: as the product is intentionally packaged in a volume sufficient for only 28 days of use (generally 5 mL/unit), at the end of the 28 days there is very little left to test. This makes performing the test extremely challenging as the preservative test normally requires approximately 100 mL of sample.

One option for testing the preservative system might be to perform a test *in vitro* to simulate repeated microbial challenges. Such a test has been described by Urban *et al*¹⁴. They suggest a repeated challenge, using a battery of challenge organisms, which would provide a model for a simulated in-use testing. By this method, the sample is challenged repeatedly over the 28-day in-use shelf-life with a low level (10^2 – 10^3 CFU/mL) of each organism, and the efficacy of the preservative system is evaluated under this simulated abuse situation. This approach has the advantage of simulating consumer abuse of the product, and may be designed to monitor the entire in-use shelf-life. It also allows for pooling of small volume medicinal products to increase the sample size. This method has some drawbacks, however, as it would be impractical to use the same inoculation level as that employed in the preservative efficacy test if this was to be introduced four times a day over 28 days. Therefore, some compromises must be made as the container is too small to hold that much product and inocula (and the dilution effects on the product's preservation system would become significant anyway).

Additional questions concerning in-use stability testing protocols include:

- is it sufficient to in-use test only one lot or should multiple lots be tested;
- if the product is sold in multiple sizes, do all sizes need to be in-use tested; *and*
- should in-use testing be performed on fresh samples or on samples at the end of their shelf-life?

Regulatory guidance

As indicated previously, there are regulatory guideline requirements (stated or implied) for in-use stability testing, but there is no regulatory guidance on how to conduct this test in the human medicinal product sector. It would be of great assistance to manufacturers if the regulators would consult on proposed guidance, propose data that they would like to see and define the type of studies that they would find acceptable. However, in devising the guidelines it is essential that due consideration be given to the practicalities of actually conducting the test. In particular, the restrictions on conducting such tests with small-volume liquid dosage forms should be taken into account. In these cases, the availability of sufficient product for testing is severely limited, especially if the recommended frequency of dosing is relatively high.

There should also be guidance on situations where in-use testing would not be considered necessary. For example, products packaged in containers permeable to oxygen with an intentional head-space should be excluded from in-use testing as any potential for the oxidative degradation of an active ingredient or preservative would be readily evident during normal stability studies. It is also suggested that fuller account should be taken of the Ph Eur's preservative efficacy test results: no additional preservation testing should be required for

Small volume of product and container poses problems

Other questions arise...

Consultation on any proposed guidance would be welcomed by manufacturers...

... and consideration given to cases where in-use testing is not necessary

products which are shown to meet the Ph Eur's 'A' criteria in the normal stability tests. If regulators consider that such tests are required, there is a special need for advice on how they would wish the test to be conducted (e.g. the types of organism to be used, the inoculum level and whether or not the testing should be conducted in the container).

Summary

There are situations where studies designed to address the question of in-use shelf-life are desirable and necessary. Current regulatory documents from the veterinary pharmaceutical and medical device sectors provide guidance on how to perform this test. There is no equivalent detailed advice in the human pharmaceutical sector. We suggest that there are two conditions that would prompt this investigation:

Situations where testing would be necessary

- **if the container is completely filled and oxygen impermeable:** there will be no opportunity for oxygen degradation to become apparent during product development stability studies; if there is an ingredient in the product that is oxidation sensitive, then the opening of the pack will provide the first challenge to the product; *and*
- **where the intended in-use shelf-life exceeds one month:** if the proposed in-use shelf-life is beyond one month, then the 28-day compendial preservative efficacy test should be supplemented with a simulated in-use test that lasts the duration of the intended in-use shelf-life; this would be the case for large volume, multiple-use products with an in-use shelf-life of several months.

The need for guidance specifically on human medicinal products is emphasised

Finally, the absence of a detailed guideline for the human medicinal product sector adds confusion to an already uncertain topic. Significant technical issues prohibit the use of the CVMP-based approach in small volume liquid medicinal products since little or no sample remains at the end of a simulated consumer-use study. There is a definite and urgent need for additional guidance from the European regulatory agencies.

Proposal

The following proposal is put forward as the basis for a specific guideline for in-use stability in the human medicinal product sector.

Before considering the provision of in-use stability data, due account should be taken of the available information from conventional stability studies. However, results from in-use stability testing should be supplied as part of a marketing authorisation application for a human medicinal product in the following circumstances, where:

In-use stability testing should be required where...

- the manufacturer's recommended period of use is longer than that recommended in the relevant monograph of the Ph Eur;
- there is a *prima facie* case for chemical and/or physical testing being relevant (e.g. in cases where the head-space gas in the container has been replaced with an inert gas and where interchange with atmospheric oxygen is possible);
- there is a *prima facie* case for antimicrobial preservative efficacy testing (e.g. in cases where the antimicrobial preservation efficacy test data for the product suggest that it will not consistently meet the 'A' criteria of the Ph Eur test); *and*
- it is physically possible to simulate use of the product and have sufficient left to allow analytical tests and/or antimicrobial preservative efficacy tests to be conducted on the remainder.

Where the first three of the points given *above* do not apply to a particular product, no additional testing should be required. When one or both of the second and third conditions apply, two representative batches of the product should be tested, at least one of them being towards the end of its shelf-life. As far as possible the test conditions should simulate the practical use of the product (volume of product removed and frequency of removal according to the instructions for use). The actual tests to be applied should relate only to those factors which might be of concern

(e.g. a product which is not liable to oxidation, but which has a borderline preservative efficacy, would be tested for the ability to cope with appropriate preservative challenge tests, but not for chemical stability).

Where different pack sizes are available, the in-use stability test should be applied to the presentation which offers the greatest potential challenge to the product (e.g. in the case of an oral liquid product which has borderline preservative efficacy, this should be the largest product; for a product in a semi-permeable container with inert gas head-space and a potential for oxidative degradation, this should be the smallest pack as it is likely to offer the greatest potential for gaseous interchange with atmospheric oxygen).

Choice of pack size is critical

In the case of preservative efficacy tests, clarification should be provided on the type of testing required. It should be sufficient to provide data from multiple low-level challenges on the product as a development test to demonstrate the adequacy of the preservative system throughout the proposed in-use shelf-life.

Guidance on type of test is required

As indicated earlier in this paper, different concepts may need to be applied to different products because of the practical limitation of applying a meaningful simulation (e.g. the same protocol can not be applied to a large container of an oral product and to a 5 mL eye-drop container). Special consideration will need to be given to the type of testing to be applied to small-volume containers.

In many cases the amount of product involved is not sufficient to allow for chemical or physical analysis of the material dispensed as part of simulation of use, and there would be too little product remaining in the container at the end of the study for this to be analysed. Allowance will need to be made for such situations in any guidance document. The use of alternative approaches will need to be allowed for where special limitations apply, although applicants should present a reasoned justification for the lack of need for such tests or for the design of the studies applied.

Guidance should also consider...

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