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REVIEW

Regulatory and safe-use considerations related to stability after opening of nonsterile dosage forms

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Abstract

Background The stability test after opening is conducted to establish an appropriate storage period during which the quality is maintained of multidose drug products that are opened and used repeatedly. While some of the regulatory agencies have provided guidelines for in-use stability study design, detailed guidelines covering various formulations are not provided. So, the guidelines are necessary to help the industry both understand and conduct stability studies. In addition, health-care professionals are required to provide patients or patient caregivers with information regarding the storage of medicines after opening. Furthermore, unless otherwise stated in marketing authorization, if the safety, efficacy, and quality of products are susceptible to inappropriate storage, then it is also necessary to prepare the related safe use guidelines.

Area covered In this paper, trends in the stability after opening guidelines of international organizations and competent regulatory agencies were investigated. The safe use guidelines, such as storage period after opening for nonsterile preparations, were also reviewed.

Expert opinion As a result of the study, regulatory guidelines for the formulation (product), target batch and testing time point, container closure system, and sample storage conditions of the in-use stability test are presented. Additionally, from the perspective of the safe use of pharmaceuticals, stability information to be recommended to patients and storage period after opening for each dosage form are also presented. Based on these presentations, we intend to prepare guidelines that pharmaceutical industry and health-care professionals can refer to in the field.

Keywords In-use stability · Beyond-use dates · Nonsterile dosage forms · Stability guidance

Introduction

The stability test of a drug provides the basis for how the quality changes over time under the influence of environmental factors such as temperature, humidity, and light. The stability test also defines the retest period of the drug substance or its shelf life of the drug product and recommended storage conditions (ICH 2003).

To obtain the marketing authorization for a drug, the applicant conducts the stability tests to secure the evidence to establish the storage conditions, such as storage temperature and storage period. In general, the drug product should be evaluated under storage conditions (with appropriate tolerances) that can be tested for thermal stability, and where applicable, humidity, sensitivity, or potential loss of solvent. The storage conditions and test period should be selected to be appropriate in consideration of storage, transportation, and subsequent use, and should be carried out on formulations (including secondary packaging and container labels, if applicable) that have been packaged with the container closure system as suggested for sale (ICH 2003).

After approval of the drug, the marketing authorization holder is obliged to conduct on-going stability tests, which includes checking the product over its shelf life to verify that the quality of the product is or will be maintained in accordance with specifications under the labeled storage conditions. In general, the tests should be conducted on at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability program (PIC/S 2021).

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Unlike premarketing and post marketing stability tests that check the possibility of product change over time in the unopened state of the container closure system, the in-use stability test is conducted for pharmaceuticals where there are concerns about quality deterioration, such as decomposition of ingredients or mixing and proliferation of microorganisms. It is carried out to establish the period (if applicable) during which a multidose drug product can be used repeatedly while maintaining its quality within the permitted specification after opening (EMA 2001). The in-use stability test is also used independently to set the shelf life after opening for marketing authorization of the drug product. The marketing authorization holder may submit to the regulatory authority based on stability test data after opening or equivalent valid data.

In this regard, European Medicines Agency (EMA 2001) and MFDS (MFDS 2016) provide guidelines for basic considerations when designing stability tests to set the shelf life after opening. Examples of simulation design covering various formulations are not presented in detail, but detailed considerations and scientific evidence that the pharmaceutical industry can refer to when conducting stability tests are needed. For this purpose, it is necessary to conduct the stability study after opening for each dosage form.

For reference, according to a study by Brian R. Matthews (Matthews 1999), the type of drug instability should generally be considered as follows: physical changes (appearance, product uniformity, disintegration, dissolution, etc.), chemical changes (generation of degradation products, loss of active ingredients and excipients), and microbial changes (whether or not microorganisms multiply and change in preservation efficacy). In the case of nonsterile formulations, it is mentioned that excipients (antimicrobial preservatives, antioxidants) should be considered in addition to the types of change mentioned above, if applicable. Stability data must be submitted for all types of products that require to approval.

On the other hand, in terms of the drug use, in the United States, Japan, and Korea, pharmacists are required to provide information and education including proper storage to those who purchase drugs (MHLW 1960; MHLW 1961; USC 2008; MFDS 2015; MFDS 2015; MFDS 2016). If there is a storage condition after opening in the marketing authorization, the pharmacist can check and provide the proper storage management for the drug after opening and provide medication guidance for patients or patient caregivers. Unless otherwise specified in the marketing authorization, the safety, efficacy, and quality of medicines may deteriorate due to inappropriate storage by pharmacists and consumers (patients or caregivers) because of a lack of accurate information. Therefore, it is necessary to prepare guidelines for health-care personnel engaged in hospitals and pharmacies for safe use related to the storage of medicines after opening based on the scientific evidence.

By reviewing the current status of regulations, such as stability after opening regulations and guidelines for nonsterile preparations and safe-use guidelines presented by health-care associations, we intend to present guidelines for the safe use of after opening storage conditions. We intend that these guidelines can be used in the medical field by health-care personnel as well as considerations for stability after opening of nonsterile preparations that the pharmaceutical industry can use for reference.

International regulatory and guideline trends: international organizations

International conference on harmonisation (ICH)

According to '2.2.7. Storage conditions' of ICH Q1A(R2), published in 2003 (ICH 2003), stability studies of the drug product after reconstitution or dilution should be provided on the drug label giving information on preparation, storage conditions, and in-use shelf life. It is recommended that this information should be obtained during the intended use period for primary batches of reconstituted or diluted drug products as part of formal stability studies. In addition, the tests should be conducted at the initial time point and the last time point. If there is no complete long-term stability data covering the proposed shelf life before submission, the test should be conducted at 12 months or at the last time point when test data can be obtained. Generally, it is recommended that there is no need for repetition on commitment batches. In addition, in the guidelines for photostability testing of new drugs (ICH Q1B), published in 1996 (ICH 1996), in '3. According to Drug Product' section, it is appropriate to conduct the test to prove photostability during use for some products, such as infusions or dermal creams. The extent of this testing is determined according to the directions for use, and it is recommended that applicants choose arbitrarily.

In this regard, 'P.8.1 Stability Summary and Conclusion' is included in the 'Quality Assessor's Guideline – Pharmaceuticals' (IPRP 2020) published in 2020 by the Quality Working Group (QWG) within the International Pharmaceutical Regulators Program (IPRP). According to this article, the considerations of the quality assessor relating to the stability test after opening the drug product are described in detail. It states that the stability testing after opening should be performed for sterile multidose pharmaceuticals, solid oral products in bulk packages (e.g., hospital dispensing packs containing hygroscopic or moisture-sensitive APIs), and products with a specific expiration date after opening on the label. In addition, testing that supports shelf life should be performed at appropriate intervals and should be

performed on two batches, including batches close to the end of the proposed shelf life for a particular drug product. Where this is not possible, data supporting the in-use shelf life should be provided and a commitment to repeat these studies on batches close to the end of shelf life should be provided. In addition, the shelf life after opening should be justified by data, where applicable, consistent with the product labeling, and should show that the container is representative of use in the study. For example, the drug container should be opened daily, and several tablets (1–3) should be extracted each time it is opened. When the product does not require analysis after opening, the product can be immediately returned to the container for later analysis. In the case of smaller bottle size, a sufficient number of tablets for analysis should be taken when the test is performed (e.g., 0, 15, 30, and 60 days).

World Health Organization (WHO)

According to '2.2.11 In-use and hold-time stability' among the guidelines for drug substance and drug stability testing (WHO 2018) published by the WHO in 2018, the purpose of in-use stability testing is to provide information for labeling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution, or dilution of a solution. For example, on a moisture-sensitive or hygroscopic solid oral drug product in a large format multidose container (e.g., high-density polyethylene (HDPE) bottle of 500 tablets), it is stated that in-use shelf life of 30 days is normally considered acceptable without further supporting data. In addition, as far as practicable, tests should be designed to simulate actual drug product use, taking into account the filling volume of the container and dilution or reconstitution prior to use. It is stated that adequate amounts should be removed at intervals by withdrawal methods commonly used and described in the product literature. In addition, the physical, chemical, and microbial properties of the drug product, which are prone to change during storage, should be determined during the proposed shelf life after opening. If possible, it is recommended that the final amount of the drug product should be tested at the midpoint and at the end of the proposed in-use shelf life. For example, for liquid and semisolid formulations, specific parameters such as the content and effectiveness of preservatives should be studied. In addition, testing should be performed on at least two batches, at least pilot scale batches, as a minimum one of which should be selected at the end of the shelf life. It is stated that if these results are not available, one batch should be tested at the end of the submitted stability study. Finally, this study should be performed on initial batches of drug products reconstituted or diluted or solid oral dosage forms for the proposed shelf life as part of the stability study at the initial and final time points, and data should include the shelf life at the time of submission. If this is not possible, the 12-month time point or the last time data are available may apply, and it is generally stated that this study does not need to be repeated in the commitment batch.

International regulatory and guideline trends: regulatory authorities

Food and drug administration (FDA)

Regarding the submission of stability test data in the guidelines for abbreviated new drug applications, published by the FDA in 2019 (FDA 2019), it states that, if applicable, the information and data of one-time in-use stability studies for oral solutions and other dosage forms (e.g., solutions used within a certain period of time after the container has been opened according to labeling instructions, compatibility systems with droppers if provided as part of the container closure) can be included.

In addition, in response to the question of when post-opening stability studies are required, in the guideline for abbreviated new drug applications submission Q&A published by the FDA in 2014 (FDA 2014), it states that 'ICH Q1A (R2), sections II, B, 7, storage conditions (2.2.7)' should be followed for all three batches. In these studies should be performed when the drug product is labeled for reconstitution or dilution.

Additionally, the guidance for stability testing of new drugs and generic drugs (FDA 2003, 2013) is reflected in the same way as the abovementioned ICH Q1A (R2) guidelines regarding stability after opening.

U.S. Pharmacopeial Convention (USPC)

According to USP43/NF38 (USPC 2018; USPC 2020; USPC 2020) 'General Chapter < 7 > Labeling, the Beyond-use date (BUD)' is the date or time at which the drug prepared in the pharmacy should be discarded. It is defined that this date or time is determined from the date of preparation. In addition, according to 'General Chapter < 795 > Pharmaceutical compounding—Nonsterile preparation,' if there is no separate stability information, BUD is generally divided into three types for nonsterile preparations. For nonaqueous formulations, the BUD is not later than the time remaining until the earliest expiration date of any API, or 6 months. For oral formulations containing water, the BUD is not later than 14 days when stored at controlled cold temperatures, and for water-containing topical/dermal and mucosal liquid and semisolid formulations, the BUD is within 30 days. These maximum BUDs are recommended for nonsterile pharmaceuticals for which there is no applicable stability information for a specific drug or dosage form, and it is stated that the BUD should not be later than the expiration

date on the container of any component (Table 1). It is also noted that for drugs or chemicals known to be unstable, it is necessary to apply a shorter BUD than the abovementioned recommendations.

Moreover, 'General Chapter < 1191 > Stability Considerations in dispensing practice' refers to stability that pharmacists must consider first when dispensing drugs. The types of stability are divided into 5(chemical, physical, microbiological, therapeutic, and toxicological), and each acceptance criterion is presented. In addition, major formulation factors affecting drug stability include particle size (especially emulsions and suspensions), pH, solvent system composition (e.g., "free" moisture % and overall polarity), compatibility of cations and anions, solution ionic strength, primary container, specific chemical additive, and molecular binding and diffusion of drugs and excipients. The reactions such as hydrolysis, epimerization, decarboxylation, dehydration, oxidation, photochemical decomposition, ionic strength, pH effect interionic (Ion^{N+}-Ion^{N-}) compatibility, solid state stability, and temperature are mentioned as the cause of the loss of active ingredient content in dosage forms. Additionally, pharmacists are obliged to provide patients with information on appropriate storage conditions (e.g., in a cool, dry place–excluding bathrooms) for prescription and over-the-counter medicines, and to suggest a reasonable estimate of the time after which the medication should be discarded. As well, it mentioned when applying BUD, pharmacists should emphasize to the patient that BUD application is only possible under appropriate storage conditions, and it is noted that patients should be encouraged to clean the drug storage cabinets cyclically.

European medicines agency (EMA)

According to the 'note for guidance on development pharmaceutics' (EMA 1998) published by the EMA in 1998, antimicrobial preservatives may generally need to be added to multidose products with respect to the composition of liquid and semisolid formulation. It is recommended that the testing program should be established for allocating the "in-use shelf life" for products that will later appear in the product literature. It also states that the level of antioxidants should be justified and supported by appropriate experimental data to ensure that sufficient activity is maintained throughout the proposed shelf life of the product, including the in-use period.

Furthermore, according to the 'note for guidance on in-use stability testing of human medicinal products' (EMA 2001) published by the EMA in 2001, it is mentioned that the registration dossier for multidose products should be contained either in the data on stability after opening on which the in-use shelf life is based, or a justification for why post-opening stability testing is not established. The guidelines for batch selection, study design, test storage conditions, test parameters, analytical procedures, etc., is also mentioned.

Last, the guidance for stability testing of new drugs and generic drugs (EMA 2003, 2004) is reflected in the same way as the abovementioned ICH Q1A(R2) guidelines regarding stability after opening.

Pharmaceuticals and Medical Devices Agency (PMDA)

The stability test guideline (PMDA 2006) published by PMDA in Japan in 2001 reflects the same content as the abovementioned ICH Q1A(R2) guideline regarding stability after opening.

Therapeutic Goods Administration (TGA)

According to '14.2.4 In-use stability testing on medicines for multidose use' in the stability testing of prescription medicines (TGA 2017) published by the TGA in 2017, iterative approaches (e.g., opening and closing) for multidose drugs should provide evidence that it does not affect the physical, chemical, or microbiological quality of the medicinal product, and in the case of bottles containing solid dosage units (e.g., capsules) that are to be refrigerated, it is recommended that information or justification should be provided to explain the possibility of moisture condensation after repeated openings and closings of the bottle and the effect of the condensation on the drug.

Table 1 General Guidelines for Setting Beyond-Use Dates [General Chapter < 795 >]

Type of formulation	BUD[a]
For Nonaqueous Formulations	Not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier
For Water-Containing Oral Formulations	Not later than 14 days when stored at controlled cold temperatures
For Water-Containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations	Not later than 30 days

[a]These maximum BUDs are recommended for nonsterile compounded drug preparations in the absence of stability information that is applicable to a specific drug or preparation. The BUD shall not be later than the expiration date on the container of any component

International regulatory and guideline trends: health-care associations

American Society of Health-System Pharmacists (ASHP)

According to the paragraph 'Stability, Expiration, and Beyond-Use Dating' in the ASHP technical assistance bulletin on compounding nonsterile products in pharmacies (ASHP 1994) published by the American Society of Hospital Pharmacists (ASHP), the stability can be affected by the following factors: the characteristics of each ingredient (regardless of therapeutic activity or inactivity); the environmental factors such as temperature, radiation, light, humidity, and air; particle size; pH; the properties of water and other solvents employed; the nature of containers; and the presence of other substances resulting from contamination or instability. In addition, it is advised that determination of the shelf life of a drug after dispensing should be based on available stability information and reasonable patient requirements for the intended drug therapy. The paragraph, 'General Compounding Considerations' refers to considerations of pharmacists to provide patients with the most stable drug. First, the pharmacist should closely observe whether there are any signs of instability in the prepared drug. These observations should be made during drug dispensing and during storage periods prior to dispensing the drug to the patient. The dispensed drug should be labeled with appropriate BUD and storage instructions.

National Health Service (NHS)

According to 'the storage, stability and in-use shelf-life guidelines for nonsterile medicines' published in 2001 by NHS Specialist Pharmacy Services (NHS 2001), it is recommended that, in the case of solid oral dosage forms, it is appropriate to set the in-use shelf life to a date of 1 year from the first opening date or the manufacturer's expiry date, whichever is shorter. It also states that this setting has been supported by studies of repackaged drugs in various container types. In the case of tablets that are susceptible to atmospheric moisture (e.g., Co-amoxiclav, Dipyridamole MR) or tablets with physical instability (e.g., GTN volatility), the in-use shelf life should be set shorter. This information can be obtained from the package insert of the drug, though it is not usually noticeable or by the presence of a desiccant in the container. If the drug is provided in unit dose forms, such as blister packaging rather than large-capacity packaging, unless the package contains a desiccant (e.g., Nicorandil), the manufacturer's expiry date should be applied for the in-use expiry. When opening the blister strip for the first time, it is explained that the medication is a course of treatment and patients must take all the doses (e.g., 1–2 weeks), which will be the in-use shelf life.

Similarly, in the case of liquid drugs, the guidelines mentioned that the labels should distinguish between external and internal drugs, and whether the liquid contains preservatives. Moreover, for approved liquid drugs, the marketing authorization holder must specify the storage conditions and any requirements as to the in-use shelf life. For example, reconstituted antibiotics have the storage and in-use shelf-life information specifically defined on the label. However, the guidelines stated that for all liquids containing preservatives, the manufacturer's shelf life is not specified because it has been confirmed that shelf life is covered in normal in-use conditions. In this guideline, when it is expected that the bottle will be opened and used continuously (e.g., chronic disease) or used when necessary depending on the situation (e.g., pain relief), it states that the degree of judgment that may be necessary is when the discontinuation of the drug is expected. It also recommends that the in-use shelf life of liquid medicines containing preservatives is generally appropriate for a period of 6 months. The shelf life of topical semisolid drugs after opening is determined by factors such as the packaging format, the presence of preservatives, whether it is cream or ointment, and any dilution of the original base. Creams, usually oil in water emulsions, are much more susceptible to microbial contamination because the continuous aqueous phase is a much more favorable medium for microbial growth than the fatty continuous phase of the ointment base. It mentioned that even if the preservatives are included, the shelf life after opening of the cream should be shorter than that of the ointment. For licensed products, the ointments packaged in tubes are generally recommended to have a shelf life of 6 months unless otherwise recommended by the manufacturer, the creams packaged in tubes are recommended for 3 months, and the ointments and creams packaged in jars and pots are recommended for 3 months and 1 month, respectively (Table 2).

In this regard, a subgroup within the NHS guidelines related to the in-use expiry dates has been published. First, according to the guideline for expiry date of medications after opening (NHS 2021a, b) published in 2021 by the NHS Telford and Wrekin Clinical Commissioning Group, it is suggested that the expiry date from date of opening is 1 month for cream/ointment in tubs, 1 month for creams/ointments in tubs decanted from a bulk container, 3 months for creams/ointments in tubes, manufacturer's shelf life for creams/ointments in pump dispenser packs, 6 months from date of dispensing for tablets/capsules/liquids decanted into a pharmacy bottle, 8 weeks from date of dispensing for tablets/capsules in monitored dosage systems, 6 months for oral liquid formulations in the original container (if the label is not clear, check with community pharmacist for antibiotics), 6 months from opening or manufacturer's recommendation where shorter for external liquids (e.g., lotions, shampoos

Table 2 The shelf life after opening by formulation

Formulation (Class)	Formulation (Sub-class)	The shelf life after opening
Tablets and Capsules	Bulk packs	1-year from date of opening or the manufacturer's expiry is less (Exceptions: Products susceptible to atmospheric moisture, GTN)
Liquids	Preserved	6-Months (Internal and External) (local policy may direct 3-months for internal liquids)
Creams	Packed in Tubes	3-months (local policy may direct 1-Month for Unpreserved creams)
	Packed in Jars/Pots	1-month
Ointments	Packed in Tubes	6-months
	Packed in Jars/Pots	3-months

and bath oils), and 1 month for drops/ointments applied to the ears and nose.

Second, according to the guidance on the expiry dates and storage of medicines in care homes (with or without nursing) (NHS 2014) published in 2014 by the NHS Oxfordshire Clinical Commissioning Group, as a general rule for drug use and storage, all of the pharmaceuticals should avoid direct sunlight and store in a cool (below 25 °C) and dry place. It is recommended that some medicines need to be refrigerated at a temperature of 2–8 °C, and that care homes should have a policy to monitor the temperature of fridges and places where medicines are stored. In addition, it states that the use of expired products may result in product changes that may cause patient discomfort, such as reduced active ingredients or safety risks due to pH changes or microbial contamination. Furthermore, in relation to the shelf life of medicines after opening, there are recommended expiry dates as follows: 2 months for tablets and capsules packaged in monitored dosage systems; manufacturer's expiry date for tablets and capsules in their original blister/foil packs (e.g., prn medicines); 6 months from the dispensing date or manufacturer's recommendation where shorter for tablets and capsules bottled by pharmacy; 6 months after opening or the manufacturer's recommendation, whichever is shorter; for internal and external solutions, 6 months after opening or the manufacturer's recommendation, whichever is shorter; for ointments/creams in tubes or with a pump dispenser, 3 months after opening or as recommended by the manufacturer, whichever is shorter; for ointments/creams in tubs with a lid, manufacturer's expiry date for suppositories/pessaries /rectal tubes/patches and inhalants; and 3 months after opening, unless manufacturer advises otherwise, for ear/nose drops and spray.

Third, according to the good practice guidance on expiry dates of medicines (NHS 2019) published in 2019 by the NHS Rotherham Clinical Commissioning Group, the expiry date after opening is mentioned separately, presenting not only the in-use shelf life for the specific product, but also that for each general formulation. There are recommended expiry dates, as follows: 8 weeks from dispensing date for tablets and capsules packaged in monitored dosage systems; in-use shelf life needing advice for community pharmacies after expired date for tablets/capsules/liquids decanted into pharmacy bottle; 1 month or seeking community pharmacy advice for tubs of creams/ointment decanted from bulk container; 3 months for tubes of creams/ointments (when closed container, contents not openly exposed to the environment); 1 month for tubs of creams/ointments (when the contents are exposed and can become contaminated); manufacturer's expiry date for pump of flexi dispenser packs of creams/ointment and inhalers; 6 months unless otherwise specified by manufacturer for oral liquids in original container; and 1 month for ear and nose drops/ointments.

Fourth, in the guidelines for care homes–good practice guidance expiry dates for medication (NHS 2021a, b) published in 2021 by NHS Gloucestershire Health and Care, recommended expiry dates are given as follows: 8 weeks from dispensing date for monitored dosage systems/blister packs; 6 months after opening, unless manufacturer's recommendation, for original bottles of liquids (internal), usually 7 or 14 days once reconstituted for liquids (internal) containing antibiotics; 1 month once opened for creams/ointments in tubs; manufacturer's expiry date for creams/ointments in pump dispensers; 3 months after opening, unless manufacturer advises otherwise; for creams/ointments in tubes, 6 months once opened, unless manufacturer advises otherwise for liquids/lotions (topical preparations); 1 month after opened, unless manufacturer's recommendation otherwise, for ear and nose drops or ointments; and manufacturer's expiry date for inhalers.

Finally, in the good practice guidance–understanding expiry dates and storage of medicines in care homes (NHS 2017) published in 2017 by the NHS Isle of Wight Clinical Commissioning Group, the expiry dates are recommended as follows: 2 months (unless stated otherwise by pharmacy) for tablets and capsules packed in an monitored dosage system; manufacturer's expiry date for tablets and capsules in original blister/foil pack (e.g., prn medicines); 6 months from dispensing date or manufacturer's recommendation, whichever is shorter, for tablets and capsules dispensed into a bottle by pharmacy; 6 months from dispensing date or manufacturer's recommendation, whichever is shorter, for

internal and external liquids; 6 months from dispensing date or manufacturer's recommendation, whichever is shorter, for emollients in tubes or with a pump dispenser; 3 months from dispensing date or manufacturer's recommendation, whichever is shorter, for emollients in tubs with a lid; 1 month from opening or manufacturer's recommendation, whichever is shorter, for medicated creams/ointments (e.g., clotrimazole/hydrocortisone); manufacturer's expiry date for suppositories/pessaries/rectal tubes/patches/inhalers; and 3 months after opening unless manufacturer advises otherwise for ear/nose drops and sprays (Table 3).

French society of clinical pharmacy (SFCP)

According to 'Methodological guidelines (Part 1: liquids) for the stability studies of hospital formulations' published by the French Society of Clinical Pharmacy (SFCP) and GERPAC (Evaluation and Research Group on Protection in Controlled Atmosphere) (SFCP 2013), the instability is broadly classified into three categories: chemical, physical, and microbiological, and the factors that affect the formulation stability are classified into pH, surfactants, temperature, oxygen, light, and packaging materials, and suggested general stability test methods (including test method validation).

Conclusion

Regulatory perspective

When regulatory agencies present guidelines for conducting in-use stability test to the industry, it is necessary to consider the following. First, if it is confirmed that the drug substance is unstable to temperature, humidity, light, and pH if applicable, it is necessary to recommend performing in-use stability test for the subject (formulation). It is expected the stability test will be conducted after opening, because the drug is expected to be more vulnerable in the storage conditions after opening than before opening. Examples of such formulations include finished products that are reconstituted or diluted from the dosage of the product, as well as multidose large-capacity formulations (e.g., HDPE bottles containing 500 tablets), oral solid preparations (e.g., hygroscopic or moisture-sensitive APIs), multidose liquid and semisolid formulations containing preservatives (e.g., antibacterial preservatives, antioxidants), and oral solid formulations (e.g., capsules) that require refrigeration. Additionally, as discussed at the AAPS workshop in 2017 (Khan et al. 2018), regarding photostability, finished drug products containing active ingredients sensitive to light or topical drug products applied to the human body surface may also be included in the test subject.

Second, when a batch of the in-use stability test is carried out for the drug products, it should be recommended to select at least a minimum of two batches of pilot size including at least one batch close to the end of the proposed shelf life of the product. If the batch close to the end of the proposed shelf life is not available, the applicant or marketing authorization holder is asked to submit additional test data for one batch at the end point of the stability study, or they should be encouraged to submit together with supporting data for the in-use shelf life and a commitment to repeat these studies on batches close to the end of the proposed shelf life. In addition, in the case of drug products or solid oral dosage forms either reconstituted or diluted, it should be recommended that the tests be performed as part of the stability study at the initial point and end point of the test on initial batches during the proposed shelf-life period. If data including the shelf life cannot be submitted at the time of data submission, the 12-months timepoint or the end point data may be applied, and it may be recommended that there is no need to repeat in commitment batches. Moreover, the product used for the stability test should have the same prescription, formulation, and container (including closure) as the commercially available product. If items consist of more than one product packaging material, packaging unit, or quantity of active ingredient(s), the applicant or marketing authorization holder may select the product with the packaging material, packaging unit, or content expected to be most susceptible to changes after opening. In this case, it may be recommended to present a justifiable reason for the selection of the product to be tested. In addition, for products requiring in-use photostability testing, applicants or marketing authorization holders can generally apply the ICH Q1B guideline to test one batch of drug product. If the results of the confirmatory study are uncertain, it may be recommended to conduct additional tests on up to two batches.

Third, the storage conditions of the samples in the stability test after opening should be stored according to the storage conditions permitted during the test period. In the case of storage under other storage conditions, a justifiable reason should be presented, and it can be recommended to include the effect of temperature, humidity, and, if applicable, light and pH in consideration of the storage environment after opening the medicines. If the proposed storage temperature of the product is 1–30 ℃, considering the storage location, the applicant or marketing authorization holder can refer to the ICH Q1A guideline and it can be tested for room temperature conditions (25 ± 2 ℃/60 ± 5% relative humidity [RH] or 30 ± 2 ℃/65 ± 5% RH) and refrigeration conditions (5 ± 3 ℃) within the storage temperature range. If there are differences in the drug storage locations by country (e.g., shelves in bathrooms), it may be more appropriate to select and store them under conditions similar to the actual storage environment in consideration of such cases. Moreover, if the

Table 3 In-use shelf life by formulation in detail

Formulation (Class)	Formulation (sub-class)	Expiry date after opening	Reference
Tablets and Capsules	Packed in monitored Dosage System	2 months (unless stated otherwise by pharmacy)	(NHS 2014, 2017)
		8 weeks from dispensing date	(NHS 2019; NHS 2021a, b; NHS 2021a, b)
	In original pack	Manufacturer's expiry date	(NHS 2014, 2017; NHS 2021a, b)
	Loose i.e. dispensed into a bottle by pharmacy	6 months from dispensing date or manufacturers recommendation whichever is shorter	(NHS 2014, 2017; NHS 2021a, b)
		Seek Community Pharmacy advice if not stated on label	(NHS 2019; NHS 2021a, b)
Liquid (internal)	Original bottles	6 months from dispensing date or manufacturers recommendation whichever is shorter	(NHS 2014, 2017, 2019; NHS 2021a, b)
	Liquid decanted into pharmacy bottle	Seek Community Pharmacy advice if not stated on label	(NHS 2021a, b)
	Antibiotics	Usually 7 or 14 days once reconstituted. Check Pharmacy label	(NHS 2021a, b)
Topical preparations	Creams/ointments (Tubs)	1 month once opened	(NHS 2019; NHS 2021a, b; NHS 2021a, b)
		3 months from date of opening or manufacturer's recommendation where shorter. For unopened creams follow the manufacturer's expiry date	(NHS 2014, 2019)
	Creams/ointments (Tubs) decanted from bulk container	1 month or seek community pharmacy advice	(NHS 2019; NHS 2021a, b)
	Creams/ointments (Pump or flexi dispensers)	Manufacturer's expiry date	(NHS 2019; NHS 2021a, b; NHS 2021a, b)
		6 months from date of opening or manufacturer's recommendation where shorter. For unopened creams follow the manufacturer's expiry date	(NHS 2014)
	Creams/ointments (Tubes)	3 months once opened unless manufacturer advices otherwise	(NHS 2021a, b; NHS 2021a, b)
		6 months from date of opening or manufacturer's recommendation where shorter. For unopened creams follow the manufacturer's expiry date	(NHS 2014)
	Liquid (external) in original container	6 months from dispensing date or manufacturers recommendation whichever is shorter	(NHS 2014, 2017; NHS 2021a, b)
	Liquid (external) decanted into pharmacy bottle	6 months from date of dispensing unless otherwise informed by Community pharmacist	(NHS 2021a, b)

Table 3 (continued)

Formulation (Class)	Formulation (sub-class)	Expiry date after opening	Reference
	Emollients in tubes or with a pump dispenser	6 months from dispensing date or manufacturers recommendation whichever is shorter (For unopened creams follow the manufacturer's recommendation)	(NHS 2017)
	Emollients in tubs with a lid	3 months from date of opening or manufacturers recommendation whichever is shorter. (For unopened creams follow the manufacturer's recommendation)	(NHS 2017)
	Lotions	6 months from opening or manufacturer's recommendation where shorter	(NHS 2021a, b; NHS 2021a, b)
	Shampoos & bath oils	6 months from opening or manufacturer's recommendation where shorter	(NHS 2021a, b)
Medicated creams/oint-ment i.e. Clotrimazole/hydrocortiso-ne		1 month from opening or manufacturers recommendation whichever is shorter (For unopened creams follow the manufacturer's expiry date)	(NHS 2017)
Suppositories/Pessaries/R-ectal tube/Patches		Manufacturer's expiry date	(NHS 2014, 2017)
Rectal Diazepam		Individual foil wrapped tubules Manufacturer's expiry date Non-foil wrapped 6 months from date of opening	(NHS 2021a, b)
Inhalers		Manufacturer's expiry date	(NHS 2014, 2017, 2019; NHS 2021a, b; NHS 2021a, b)
Ear/Nose	drops	Discard 3 months after opening unless manufacturer advises otherwise	(NHS 2017, 2019)
		1 month once opened unless manufacturer advices otherwise	(NHS 2019; NHS 2021a, b; NHS 2021a, b)
	sprays	Discard 3 months after opening unless manufacturer advises otherwise	(NHS 2014, 2017)
	ointments	1 months once opened unless manufacturer advices otherwise	(NHS 2014, 2019; NHS 2021a, b; NHS 2021a, b)

Monitored Dosage Systems (Blister packs) (NHS 2017): It is recommended that medicines dispensed in a MDS are discarded after 8 weeks if they have not been used
Please note not all medicines are suitable for inclusion in MDS for example: Medicines that may be harmful when handled, e.g. cytotoxic products like methotrexate, Medicines that are sensitive to moisture, e.g. effervescent tablets, Light-sensitive medicines, e.g. chlorpromazine, Medicines that should only be dispensed in glass bottles, e.g. glyceryl trinitrate s/l tablets (GTN), Medicines that should only be taken when required (prn), e.g. painkillers, Medicines whose dose may vary depending on test results, e.g. warfarin

actual in-use storage temperature exceeds the approved storage conditions due to rapid extreme weather conditions, it can be recommended to set additional worst-case scenarios such as accelerated test conditions (40 ± 2 ℃/75 ± 5% RH) reflecting this weather.

Finally, if the applicant or marketing authorization holder sets the in-use shelf life of a product, it is necessary to recommend them to submit the in-use stability data or other equivalent valid data as evidence at the time of submission for appropriate evaluation.

Perspective of safe use of the medicines

It is necessary to consider the following when regulatory agencies present guidelines for the safe use of drugs on in-use stability for health-care professionals.

First, as mentioned above, in addition to environmental factors such as temperature, light, and humidity, factors such as the characteristics of each component may affect the stability. Thus, general information on drug stability and additional information on drugs vulnerable to specific changes (refer to information from drug development studies by the marketing authorization holder, literature, etc.) should be provided so that the relevant personnel can refer to it when prescribing, dispensing, and storing. Considering this information and the treatment period comprehensively, it can be recommended to define an appropriate storage period and observe whether there are the signs of drug instability.

Second, pharmacists should provide the relevant information, such as in-use storage method and its storage period of the medicine dispensed, to patients and their caregiver. This information needs to include appropriate storage conditions (e.g., a cool and dry place), the expiry date after opening (including justification), and recommendations to keep the storage area of medicines clean.

Third, when determining the in-use shelf life for each dosage form, it is supposed that it is possible to set the expiry date after opening according to the presence of moisture (in the case of liquid, it is necessary to distinguish between external and internal preparations, and whether or not it contains preservatives) and the application site.

However, in the case of the in-use shelf life, we found that the recommended standards are different for each country. For example, in the United States (US), for nonaqueous formulations, the date remaining is from the earliest expiry date of the API used or 6 months, whichever is earlier. On the other hand, in the United Kingdom (UK), it is recommended to set the shorter date of 1 year from the date of initial opening or the manufacturer's expiry date for solid oral dosage forms, whichever is shorter, based on related studies. If a conservative approach is applied to the criteria, the US guidelines for expiry date after opening can be consulted. In addition, in the US, 14 days (controlled cold temperature) and 30 days are recommended for water-containing topical preparations (internal and external), and semisolid formulations, respectively. There are no additional guidelines for other formulations. In the UK, the expiry date after opening is individually set in consideration of the storage container and specific ingredients for each detailed formulation, such as tablets/capsules, liquids (internal and external), topical preparations (creams, ointments, lotions, etc.), and inhalants, etc. UK guidance may be consulted for more comprehensive information. However, it is considered that additional studies on the in-use stability for various formulations to support this advice are needed.

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Declarations

Conflict of interest All authors (H.S. Lee, M.K. Jin, W.J. Jeon, H.U. Kim, M.W. Jung, H.L. Yoo, J.H Won and C.W. Cho) declare that they have no conflict of interest.

Research involving human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

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