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REVIEW ARTICLE

Stability Storage and Testing of Ophthalmic Products for Global Registration

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ABSTRACT

Regulatory stability testing requirements for various types of ophthalmic products, including eyedrops, eye ointments, ophthalmic inserts, injections, irrigating solutions, lens washes, and lenses, are not always straightforward. The International Conference on Harmonisation (ICH) guidelines do not completely address all of the stability conditions required for these types of pharmaceutical products and medical devices; regulatory agencies around the world still differ on the exact data requirements, storage conditions (especially temperature and humidity conditions), and certain testing methods. These uncertainties make the development of a global ophthalmic product very difficult. This article reviews many of the appropriate, internationally recognized, regulatory guidelines and many of the important points to consider in stability studies for new ophthalmic products. Discussions of regulatory experiences and Expert Reports provide insight to common questions frequently asked by regulatory agencies on these types of products.
Key Words: *Ocular; Ophthalmic; Stability; Storage.*

INTRODUCTION

There is a wide range of products used in connection with the treatment of ophthalmic medical conditions; hence, there is no single guide available for stability testing and storage requirements for these products. Ophthalmic products include eyedrops intended for use on one occasion (and usually unpreserved) or for multiple use (preserved solutions, suspensions, gels, modified-release products, products that gel in the eye, etc.), eye ointments, ophthalmic inserts designed to release drug into the eye, injections to be used at various ocular sites, con-

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tact lenses, intraocular lenses, surgical sutures, dressings packs, and more. Some of these products, such as eyedrops, are obviously pharmaceuticals; others, such as contact lenses and intraocular lenses, are obviously medical devices. Some ophthalmic products reside at the border between pharmaceuticals and medical devices, dual-nature in a regulatory sense, because they may be viewed as a pharmaceutical in one country and as a medical device in another. These dual-nature products include, for example, those used in the care of contact lenses and viscoelastic products used during cataract removal surgery.

The range of uses of ophthalmic products is broad: therapy for glaucoma using β-blockers, α-adrenergics, prostaglandins, mydriatics, miotics, and so on; therapy for ocular infections; local anesthesia of the eye (e.g., during diagnostic procedures or for removal of a foreign body from the eye); tear replacements (e.g., for dry eye syndrome); topical antihistamines; topical mast cell stabilizing drugs; diagnostic tests for ocular injury, abnormality, or disease; vision defect correction; cataract correction through replacement of the diseased lens by an intraocular lens with the use of associated products, such as intraocular irrigation solutions and viscoelastics; ocular proteolytic enzyme preparations; prevention of postsurgical peaks in intraocular pressure using intraocular therapeutic agents such as acetylcholine and carbachol and postsurgical medication such as apraclonidine, nonsteroidal anti-inflammatory drugs, topical steroids; contact lens cleaning, hydration, disinfection, comfort drops, and more. A fuller listing of the different types of products used in ophthalmic care is given in Table 1.

The regulatory expectations for ophthalmic pharmaceutical products have always been among the most demanding (1). Products to be used in the eye are expected to be biocompatible with its sensitive tissues (including being at a suitable pH), isotonic with the relevant fluids (unless otherwise justified), and sterile until the container has been opened. If the product is intended to be used on more than one occasion, it should be preserved adequately. For some therapeutic uses, such as use while the eye is opened during surgical interventions, it is usually required that the product should be sterile, single use, and contain no antimicrobial preservatives and a minimum of other additives.

Many ophthalmic pharmaceutical products are intended to be used for a long period by the patients themselves (e.g., in the treatment of glaucoma) and are often presented in plastic containers as an aid to the safe and effective administration of the product and to promote patient compliance. However, the use of plastic containers may preclude the use of terminal sterilization in the manufacturing process (because the plastic may melt/deform). The use of sterile filtration processes and aseptic assembly into presterilized containers is preferred, but often requires additional process validation and justification in regulatory submissions.

Ophthalmic products are expected to meet relevant pharmacopoeial requirements (e.g., the *United States Pharmacopeia* [USP], the *European Pharmacopoeia* [Ph. Eur.], or the *Japanese Pharmacopoeia* [JP]), including general monograph requirements such as the application of a sterility test, defined potency, and purity standards. Regulatory agencies tend to have additional expectations in terms of product specifications over those of the pharmacopoeial authorities. Pharmacopoeias allow the use of purified water in the manufacture of aqueous eyedrops, but water for injection(s) might be considered more appropriate for larger volume products, such as irrigation solutions.

In this paper, particular attention is paid to the global stability testing and storage requirements for new drug

Table 1

Product Types Used in Ophthalmic Care

Pharmaceuticals	Medical Devices	Dual-Nature Products[a]
Eyedrops	Contact lenses	Contact lens care products
Solutions	Phacoemulsifiers	Ocular irrigations
Suspensions	Lasers	Tear replacements
Eye ointments	Intraocular lenses	Viscoelastic products
Eye gels		
Enzyme preparations		
Other inserts		

[a] Dual-nature products are those that may be classified as pharmaceuticals in some regulatory arenas and as medical devices in others.

applications (NDAs) (in the United States or Japan) or marketing authorization applications (MAAs) (in Europe) applying to ophthalmic products that are pharmaceuticals or are on the pharmaceutical–medical device interface. Other reviews on ophthalmic pharmaceutical product design and development (1,2), international pharmaceutical registration (3–5), and regulatory aspects of stability testing in Europe (6) may be of interest.

SOURCES OF REGULATORY REQUIREMENTS FOR STABILITY STORAGE AND TESTING

General stability requirements for ophthalmic pharmaceuticals (e.g., eyedrops and eye ointments), other than humidity conditions and specific tests, are similar to other pharmaceuticals. Stability testing requirements for drug products are being harmonized via the International Conference on Harmonisation (ICH) process among the United States, Europe, and Japan, involving input from the European Agency for the Evaluation of Medicinal Products (EMEA) (including the Committee for Proprietary Medicinal Products [CPMP] and the Quality Working Party [QWP]), the U.S. Food and Drug Administration (FDA), and the Japanese Ministry of Health. But, even after harmonization becomes complete and official, some countries will still have their own particular requirements for certain products; therefore, companies should continually maintain a dialogue with agencies to assess the regulatory climate for their products.

There are relevant guidelines available on topics such as stability tests, impurities, and analytical validation. Many of the guidelines current at the time of writing had been developed within the ICH process and therefore are gaining global acceptability. These documents are general in nature and often do not take into account the specific nature of ophthalmic products. Some of the relevant documents (with brief summaries) at the time of writing include the following:

- European Council Directive 65/65/EEC Articles 1, 4, and 4a (7): Define a medicinal product in Article 1 and describe overall requirements for application for a new drug product in European Union (EU) member countries that includes shelf life after opening or reconstitution in Articles 4 and 4a
- European Commission Directive 75/318/EEC as amended by Directive 91/507/EEC (8): The agreed EU member state requirements for documents and particulars for new pharmaceutical products are included in the Annex
- CPMP/ICH, *Note for Guidance on Stability Testing of New Drug Substances and Products* (9), and sister FDA publication, ''Guideline on Stability Testing New Drug Substances and Products'' (10): Both describe stability requirements for new drug substances and products with suggested storage conditions of 25°C ± 2°C/60% ± 5% relative humidity (RH) long term and 40°C ± 2°C/75% ± 5% RH accelerated or (if 40°C fails) 30°C ± 2°C/60% ± 5% RH with the stipulation that low relative humidity (10% to 20% RH) conditions should be evaluated for products in semipermeable containers
- ICH draft consensus guideline, *Stability Testing of New Drug Substances and Products*: Expands on current guidelines, for instance, for liquids in semipermeable containers, long-term stability at 25°C ± 2°C/40% ± 5% RH, accelerated condition of 40°C ± 2°C/not more than 25% RH, and intermediate condition (if 40°C fails) of 30°C ± 2°C/60% ± 5% RH, or the alternative of allowing studies at other humidity conditions and the application of stated ''ratios'' to derive water loss at the stated humidity conditions by calculation (11)
- FDA draft (not for implementation) guidance document, *Stability Testing of Drug Substances and Drug Products* (12): Expands on the ICH guideline, suggesting for liquids in semipermeable containers, long-term stability at 25°C ± 2°C/40% ± 5% RH, accelerated condition of 40°C ± 2°C/15% ± 5% RH, and intermediate accelerated condition (if 40°C fails) of 30°C ± 2°C/40% ± 5% RH
- CPMP/ICH, *Note for Guidance on Quality of Biotechnological Products*: *Stability Testing of Biotechnological/Biological Products* (13), and sister FDA publication, ''Final Guideline on Stability Testing of Biotechnological/Biological Products'' (14): Biotechnological product stability studies may be confined to the proposed storage temperature; moisture protectant containers obviate the need for studying at controlled humidity conditions; controlled humidity, accelerated, light, and reconstitution studies are conducted as appropriate
- CPMP/ICH guideline, *Note for Guidance on Stability Testing: Requirements for New Dosage Forms* (15), and sister FDA publication, ''Guideline on Stability Testing for New Dosage Forms'' (16): Stability requirements for a new dosage form of a previously approved active substance must follow the parent stability guideline in principle, but only

6 months of (accelerated and long-term) data are needed at time of submission

CPMP Guideline, *Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products* (17): Describes requirements for drug substance and finished products; for liquids in semipermeable containers, suggested storage conditions are 25°C ± 2°C/60% ± 5% RH long term and 40°C ± 2°C/15% ± 5% RH accelerated with an intermediate condition (if 40°C fails) of 30°C ± 2°C/40% ± 5% RH; also discusses changes in manufacturing process of active substance, composition, and immediate packaging of finished product

CPMP/ICH guideline, *Note for Guidance on the Photostability Testing of New Active Substances and Medicinal Products* (18), and sister FDA publication, ''Guideline for the Photostability Testing of New Drug Substances'' (19): Specifies a minimum exposure of 1.2 million lux hours of visible light and 200 watt hours/m^2 of near-UV light

CPMP guideline, *Reduced Stability Testing Plan—Bracketing and Matrixing* (20): Describes the use of bracketing and matrixing as options to reduce stability testing protocols and gives examples of each

CPMP/ICH guideline, *Note for Guidance on Impurities in New Medicinal Products* (21), and sister FDA publication, ''Guideline on Impurities in New Drug Products'' (22): Discusses all aspects of degradation products in drug products

CPMP, *Note for Guidance on Maximum Shelf Life for Sterile Products for Human Use After First Opening or Following Reconstitution* (23): User information text should include the following: for sterile products, chemical and physical in-use stability has been demonstrated for *x* hours/days at *y*°C; for sterile unpreserved products, from a microbiological point of view, the product should be used immediately or should be stored no longer than 24 hours at 2°C to 8°C; for an aqueous preserved sterile product, once opened, the product may be stored for a maximum of *z* days at *t*°C

CPMP, *Note for Guidance on Declaration of Storage Conditions for Medicinal Products in the Products Particulars* (24): Labeling statements needed: if product is stable at 25°C ± 2°C/60% ± 5% RH long term and 40°C ± 2°C/75% ± 5% RH accelerated, none (unless unstable to refrigeration or freezing); if stable only up to 30°C ± 2°C/60% ± 5% RH, label precludes storage above 30°C; if stable only at 25°C ± 2°C/60% ± 5% RH long term, label precludes storage above 25°C; if stable only at 5°C ± 3°C long term, label specifies storage at 2°C to 8°C and no freezing; if only below zero, label specifies storage in a freezer; other statements may clarify sensitivity to light or moisture

WHO, *Guidelines on Stability Testing of Pharmaceutical Products Containing Well-Established Drug Substances in Conventional Dosage Forms* (25): Four climatic zones are defined for worldwide stability testing based on mean climate conditions: zone I, temperate, 21°C/45% RH; zone II, subtropical with possible high humidity, 25°C/60% RH; zone III, hot/dry, 30°C/35% RH; and zone IV, hot/humid, 30°C/70% RH; also includes a WHO stability testing summary sheet and a WHO ''essential'' drug checklist

CPMP/ICH, *Note for Guidance on Validation of Analytical Procedures; Methodology* (26), and sister FDA publication, ''Guideline on Validation of Analytical Procedures'' (27): Discusses aspects of analytical procedure validation

United States Pharmacopeia (USP 23) guidelines on stability testing of new drug substances and products (28, p. 1959): Based on the ICH guidelines, for instance, 25°C/60% RH long-term condition and 40°C/75% RH accelerated condition, but does not specifically address liquids in semipermeable containers or light exposure

Japanese Pharmacopoeia (29): Particular attention is paid to qualification of plastic containers used for drug products with regard to leachables, transparency, and the like and Japanese official stability testing guidelines (Japan is gradually adopting ICH guidelines) (30,31)

An important issue at the time of writing of this paper is that of the stability conditions for liquid products in semipermeable containers, especially for the long-term condition. The current ICH guideline (9,10) addresses aqueous products in plastic containers as follows:

> For products such as solution suspensions etc., contained in packs designed to provide a permanent barrier to water loss, specific storage under conditions of high relative humidity is not necessary but the same range of temperatures should be applied. Low relative humidity (e.g., 10–20 percent RH) can adversely affect products packed in semi-permeable containers (e.g. solutions in plastic bags, nose drops in small plastic containers etc.) and consideration should be given to appropriate testing under such conditions. (9, p. 6)

Table 2

Proposed[a] Stability Storage Conditions for Liquids in Semipermeable Containers

Storage Condition	Temperature	Humidity
Long-term stability	25°C ± 2°C	40% ± 5% RH[a]
Intermediate accelerated condition (if 40°C fails)	30°C ± 2°C	40% ± 5% RH[b]
Accelerated condition	40°C ± 2°C	15% ± 5% RH[c]

[a] See Refs. 11 and 12.
[b] 60% ± 5% RH, Ref. 11; 40% ± 5% RH, Ref. 12.
[c] Not more than 25% RH, Ref. 11; 15% ± 5% RH, Ref. 12.

The proceedings of an ICH working meeting (32) reflected agreement on a more stringent long-term condition of 25°C ± 2°C/not more than 40% ± 5% RH for liquids in semipermeable containers. Therefore, if the current trend continues, as evidenced by the most recent ICH (11) and FDA (12) draft guidance document, we may soon have a harmonized guideline with stability conditions for liquids in semipermeable containers (see Table 2). A significant difference between the ICH (11) and FDA (12) draft guidelines is the humidity at the intermediate condition (30°C ± 2°C). The ICH document specifies 60% ± 5%, whereas the FDA document specifies 40% ± 5%. However, the ICH guideline offers the possibility of conducting studies at other humidities and deriving the water loss at the reference condition by calculation. This flexibility should be of considerable assistance to laboratories not equipped for low-humidity studies.

The need to use validated analytical methods is clearly required on a global basis (26,27). Although there are some differences in local requirements concerning the number of replicate analyses and statistical treatment of results from validation studies, it is possible to develop a global package of information. It is also noteworthy that statistical analysis of stability data is a common requirement.

For products that are on the pharmaceutical–medical device borderline, the source of regulatory requirements is different. In Europe, some of these products have transferred from the pharmaceuticals regulatory regime to the medical device regime; others have moved in the opposite direction. In individual countries, this might represent the introduction of regulatory controls for the first time. In others, it will represent a transfer from one system to another. The timetable for this change involved a considerable period of notice: The relevant Directive 93/42/EEC was adopted in 1993, and the transition period extended to June 1998. However, the regulatory regimes are very different, and a considerable amount of effort is required of affected manufacturers in accommodating the necessary changes.

For medical devices, the primary regulatory demands are in the essential requirements included in Annex I to the European Union's Medical Device Directive 93/42/EEC (33). However, these requirements are worded in a very general way, and for more specific guidance, it is necessary to refer to other sources of information. In practice, it is necessary to look to a series of International Organization for Standardization (ISO) or European Standardization Committee (CEN) drafts or adopted standards to find detailed suggestions on stability data requirements. For contact lenses, contact lens care products, and intraocular lenses, some of the more relevant documents at the time of writing (August 1999) were (DIS = Draft International Standard; FDIS = Final Draft International Standard; BS = British Standard):

- *ISO 19811: 1999 (E) Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Determination of Physical Compatibility of Contact Lens Care Products with Contact Lenses* (34)
- *ISO/FDIS 11986: 1999 (E) Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Guidelines for Determination of Preservative Uptake and Release* (35)
- *ISO/FDIS 11987: 1997 (E) Ophthalmic Optics—Contact Lenses—Methods for Determination of Shelf Life* (36)
- *BS EN ISO 13212: 1999 (BS 7208-20:1999) Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Guidelines for the Determination of Shelf Life* (37)
- *ISO 14534: 1997 (E) Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Fundamental Requirement* (38)
- *ISO/DIS 14729 Ophthalmic Optics—Contact Lens Care Products—Microbiological Requirements and Test Methods for Products and Regimens for Hygienic Management of Contact Lenses* (39)
- *ISO/DIS 14730 Ophthalmic Optics—Contact Lens Care Products—Antimicrobial Preservative Efficacy Testing and Guidance on Determining Discard Testing* (40)
- *ISO/DIS 11979-6 Ophthalmic Implants—Intraocular Lenses—Part 6: Shelf Life and Transport Stability* (41)

For medical devices, the usual method of premarket approval of products does not apply in the same way as for pharmaceuticals. The need for data to support a product does not change, but the nature of the data and the need for their reference to third parties does.

For medical devices required to be sterile, there will always be some third-party involvement (usually a Notified Body selected by the ''manufacturer'' concerned, i.e., the person placing the product on the market). The extent of that involvement will depend on whether the manufacturer has a Quality System approval based on EN ISO 9001 or EN ISO 9002 (and the additional requirements derived from the Medical Devices Directive). The content and format of the ISO 9000 series of standards is under revision at present. The final impact of the proposed changes, which are extensive, will not be known for some time.

In Japan, the registration of contact lenses and related products is controlled by the Japan Contact Lens Association (JCLA; Hongo Seimei Bldg., 2-31-24 Yushima, Bunkyo-ku, Tokyo 113-0034). At the time of writing, the JCLA was drafting standards for stability storage and testing for contact lens cleaning and disinfecting solutions.

Also in Japan, intraocular lens standards are being finalized. At the time of writing, the draft guidelines cross-referred to ISO/DIS 11979-6.

STABILITY TESTING FOR OPHTHALMIC PHARMACEUTICALS

Primary stability data for inclusion in a new product application should relate to the formulation and container/closure system that it is intended to market. Data for related formulations or a different container/closure system are not considered adequate for approval on their own.

The testing requirements for active ingredients used in ophthalmic products will not normally differ from those used in other types of product; therefore, they are not dealt with in detail here. Discussion is restricted to the products (dosage forms) themselves. However, because of the limited systemic exposure arising from the ocular route of administration, there may be some relaxation in the amount of data required for drugs administered by this route in some other sections of the application.

In this section, consideration is given to the stability testing expectations for ophthalmic pharmaceuticals such as eyedrops, eye ointments, and tear replacement products (''artificial tears''). Many aspects will be the same for products on the pharmaceutical–medical device interface, such as irrigation products, or will need little amendment. The specific aspects of stability testing relating to products that are considered to be medical devices in Europe are not considered further.

A number of aspects of the design of ophthalmic products are also addressed in the development pharmaceutics section of a marketing authorization application in Europe; many of these may have an impact on the design and conduct of stability trials. These aspects include

- Justification for the package type chosen and for the volume of product in the container (in terms of a reasonable period of use, taking into account the intended use for the product, and taking into account any relevant practice or regulatory guidelines)
- Product-container compatibility studies (adhesive, label, and container leaching, extraction, and adsorption)
- Biocompatibility with and nonirritancy of the formulation to the eye and the surrounding issues
- Uniformity of dosage for suspension products (including content uniformity and particle size distribution)
- Preservative efficacy of multidose products (especially aqueous products, although the U.S. authorities also appear to require such data for nonaqueous preparations such as eye ointments)
- The need for an overage of the active ingredient or a key excipient in the product and its justification
- The results from simulated in-use stability trials (with a focus on oxidation/degradation of components as well as preservative efficacy issues)
- Freeze-thaw cycling of drug product (to ensure shipping integrity)
- Effects of light exposure
- Any special performance characteristics required for a particular product (rheological characteristics, release characteristics, gelling characteristics)

The test for preservative efficacy is currently being considered for international harmonization. At the time of writing, the methodology of the USP 23, Ph. Eur., and JP 13 for preservative efficacy testing were well on their way to such harmonization. Unfortunately, the same is not true for the requirements for preservative efficacy for various types of products (e.g., USP is equivalent to JP, but is less stringent than Ph. Eur A and Ph. Eur. B requirements). The sampling times used in the USP method have also been criticized recently by the Australian Therapeutic Goods Administration. For the foreseeable future, it will be necessary to generate preservative efficacy data and to justify the adequacy of performance for each regulatory region.

The use of intermediate point stability data (i.e., not just initial test results and results at the end of the stability program) from stability lots may be useful in supporting

a shelf life extension for products before real-time data become available, especially in Europe, where a general rule allows twice the real-time stability study duration as a shelf life if supported by accelerated study data.

Depending on the development pharmaceutics results, it may be appropriate to add some tests to the stability program. Cross-references between the development section of the dossier and the section containing the stability data are often appropriate. For the European MAA, discussion of relevant issues in the Pharmaceutical Expert Report is also most important (see below).

An area that has received little attention is that of stability storage facilities. Facilities are becoming increasingly more difficult to manage with the addition of humidity- and light-monitoring requirements to that of traditional temperature monitoring. Computer systems are of great help, but issues of validation must be addressed. Low-humidity conditions impart significant implications for the types of stability test facilities required. For many solid dosage products, it is adequate to have test cabinets that are capable only of humidification. To meet low-humidity requirements, it is also necessary to have the capacity for dehumidification (especially when the ambient conditions are likely to exceed the storage conditions). Such facilities are considerably more expensive to purchase and maintain.

EYEDROPS

Most eyedrops are presented in a semi-permeable plastics container system. The volume of product in a single-use product is commonly less than 0.5 ml, and for multiuse products, it is usually between 3 ml and 15 ml.

Table 3

Typical Tests for Inclusion in a Stability Program for Eyedrops

Suitability Test	Comments
Potency	Active ingredient; possibly key excipients
Assay of degradation products/interaction products between the active ingredient and the container system and critical excipients (e.g., preservatives, preservative aids, antioxidants)	ICH guidelines apply
Appearance	Physical form
pH	
Osmolality	
Tonicity	
Weight change	Especially critical for smaller volume products in plastic containers
Uniformity of dosage	Homogeneity of suspensions, gels
Resuspendability	Suspensions
Particle shape, size, and distribution	Suspensions
Particulates	For solutions, the U.S. FDA has frequently requested such data at least at the beginning and end of shelf life
Clarity and color of solution	Clarity and color are readily assessed using Ph.Eur. clarity and color reference solutions; USP and JP also have reference color solutions, but are less categorized compared with Ph.Eur. JP requires that containers for ophthalmic solutions must not interfere with the visual test for foreign insoluble matter (29)
Rheological characteristics	Viscosity; getting tests when applicable
Package integrity	Usually visual appearance and function
Sterility	Shelf life
Preservative efficacy	Shelf life testing for multidose products and in-use testing when applicable

Other ophthalmic dosage forms, such as eye washes and irrigation solutions, may be much larger in volume (e.g., up to 500 ml or occasionally more). While other formulation approaches may be used, most eyedrops are simple aqueous solutions, aqueous suspensions, or aqueous solubilized systems that may contain surfactants, gelling agents, or the like. There are relatively few nonaqueous eyedrops.

The combination of small volume and aqueous medium for many ophthalmic products can result in particular challenges when the generally accepted stability test conditions (Table 2) are applied. This is one example of a specific requirement that can have a significant impact on the shelf life claimed for a pharmaceutical product. Storage under such low humidity is not likely to be met during normal storage or use of the products. Humidity as low as 10–20%, as proposed for stability testing, can significantly reduce the shelf life that can be justified because of a significant increase in the rate of moisture loss from the plastic container.

When testing the stability of eyedrops, a variety of chemical, physical, and microbiological characteristics of the product should be considered, especially those listed in Table 3. The ICH recommended testing intervals are usually applicable to ophthalmic products without amendment.

Solution products are expected to be essentially free from particulate matter. The apparent concern seems to be injury to the eye, but there is no scientific evidence to suggest that the levels of particulates in currently available ophthalmic products cause any patients to experience even subtle adverse medical events. A recent USP proposal to extend the small volume injection particulate controls to eyedrop solutions seems extreme considering that the eye is constantly exposed to particulates from the atmosphere. Furthermore, there are numerous eyedrop suspension products that contain up to 1% insoluble material that have been used safely by patients for treating both acute and chronic conditions.

In the case of large-volume products used in ocular surgery, the pharmacopoeial requirements for particulate controls applied to large-volume parenteral products may also be applicable. The formation of particulates in these products should be monitored during stability trials.

Particle shape and size have been subjects of considerable discussion for ophthalmic products. There are control tests included in the Ph. Eur. for the numbers of particles over specified sizes (25 μm, 50 μm, and 90 μm) in a specific weight of suspended material from the product (42). While other methods of determination may be used, the Ph. Eur. method should also be applied to European products since the pharmacopoeial requirement can be applied at any time during the shelf life of the marketed product by an independent testing laboratory.

EYE OINTMENTS

Eye ointments offer one way in which the dwell time of materials in the eye can be increased. Eye ointments are generally nonaqueous, being formulated with inert components such as paraffin oils and jellies and possibly other components, such as lanolin or similar materials.

Particle size of suspended solids in eye ointments should be monitored for stability; there is a Ph. Eur. test applicable to such products (42). Depending on the type of container (e.g., metal or plastic tube) and the regulatory authorities involved, tests for the absence of metallic particles may be relevant, with both USP (28, p. 1806) and JP (29) requiring tests for the absence of metal particles in ophthalmic ointments. The JP has a special requirement that ophthalmic ointments and suspensions (actually referred to in the pharmacopoeia as solutions) should not contain particles greater than 75 μm (29).

One of the specific aspects of stability of eye ointments that may require attention is the physical stability of the product. For many ointments, accelerated storage temperatures adversely affect physical stability. It is fairly common for the lighter components of the base to separate on storage (called bleeding). Such separation is unlikely to present a problem in the field unless it interferes with the performance of the product.

INJECTIONS FOR USE IN OR AROUND THE EYE

The stability test requirements for such products are not likely to differ from those applied to other injection products.

INTRAOCULAR IRRIGATION SOLUTIONS

Intraocular irrigation solutions are usually large-volume products, and they will gain access to the interior of the eye during ocular surgical procedures. They are used to maintain the structure of the eye, to remove surgical debris (from the phacoemulsification of the lens during a cataract removal) and, depending on the formulation, to enhance the viability of the cells within the ocular tissues (especially the endothelial cells of the cornea) or

control inflammatory reactions. Such products would normally be subject to the same type of stability program applicable to large-volume injectable products, including monitoring of particulates, ion concentrations, and the like.

MODIFIED-RELEASE PRODUCTS

Products such as drug-impregnated plastics systems, in-eye gelling products, products based on ion-exchange resin, solid delivery systems designed to dissolve in the eye, and the like will need to have stability tests designed to determine the stability of the ocular release or retention mechanism with time as well as the measurement of stability of the active ingredients and so on. Since the characteristics of the product will vary, the design of the specific stability studies should be justified in the Pharmaceutical Expert Report for applications submitted in Europe.

PHARMACEUTICAL EXPERT REPORTS

Expert Reports are a European requirement for MAAs (3). However, they are also used by a manufacturer to explain why the product should be allowed onto the market. In the Pharmaceutical Expert Report, there can be a discussion of a number of critical development, control, and stability issues. When there are debatable results in one or more of these areas, the manufacturer may be able to put forward explanations and justifications for apparent difficulties in the Expert Report.

Some of the aspects of the stability section of the dossier that may need to be discussed in the application are

- the relevance of the information included in the file to the product intended for the market
- potential effects related to the manufacturing processes on the stability of the ingredients or the product
- justification for the stability trials design and the tests conducted
- the results obtained in the stability trials
- a commentary on any inconsistencies in the data
- a discussion of any interbatch variations in the results obtained
- an explanation of any calculations used to estimate an extrapolated shelf life from the reported data
- a justification for any overages of ingredients included in the formulated product (both in terms of the pharmaceutical [e.g., loss in manufacturing or on stability] and the toxicological and/or medical justification for their inclusion and the potential effects of any resulting degradation products)
- a discussion of any in-use stability data provided and justification for any shelf life or use period suggested after the product has been opened, reconstituted, or diluted
- a justification for the release and shelf life specifications, including consideration of the qualification of any degradation products allowed

From other sections of the application, the Expert Report might discuss issues such as the compatibility of the active ingredients and excipients, the significance of the chosen pH in terms of product suitability and stability, and/or the potential for product-container system interactions.

REGULATORY EXPERIENCE

Manufacturers are usually most successful in gaining approval if all international, regional, and local requirements and guidelines have been met and if relevant issues relating to the intended use of the product have been taken into account. A suitable stability study protocol should be approved before the stability study is initiated. The elements of a stability protocol have been proposed (12). An approved stability protocol is requested frequently during regulatory inspections.

Stability-indicating methods should have been used for assaying the active ingredient, degradation products, and critical excipients (e.g., antimicrobial preservatives and antioxidants). In the case of novel excipients, the data requirements are often similar to those for new drugs, including full characterization, raw material stability, and the like.

An explanation for the basis of the choice of the test program components often helps avoid regulatory questions for products that have particular aspects needing special attention (e.g., modified-release products). Differences of interpretation of reported data between regulatory agencies (e.g., for predicted shelf life from limited real-time data), however, are not uncommon.

It is also possible that a company might wish to extend its marketing of an older product to new markets. Depending on age of the product data, this can become a challenge. It is often necessary to use supplementary stability studies to support new applications for old products since the original data would probably not have been generated according to current standards. The use of the rou-

tine stability data from manufacturing plants may be sufficient for this purpose provided that correct storage conditions and appropriate methodology have been used. Analytical validation studies may also require some updating.

Apparent differences sometimes arise in comparing stability data generated by a dedicated stability-testing group versus stability data generated by a general quality assurance/quality control group. Stability trials should be carried out in a strictly controlled stability testing environment with specialized training and retesting guidelines that produce very reliable data. After this technology is transferred to a manufacturing setting in which stability testing is less important than product release, the same tight control of the results is not always maintained. Unfortunately, retesting in a manufacturing setting is more likely frowned on and viewed as ''testing into compliance.'' Therefore, an efficient technology transfer from research and development to the manufacturing site is becoming an important step in preparing to market a new product. Even this can be addressed in the Pharmaceutical Expert Report for European submissions.

CONCLUSIONS

Ophthalmic care products present a rich diversity of therapeutic uses and dosage forms. This diversity sometimes complicates regulatory requirements for stability testing because these products may require unique tests outside existing guidelines, those usually reserved for small- and large-volume parenterals or even solid dosage forms. A manufacturer wishing to minimize its time to market for a new ophthalmic product should first confirm that regulatory agencies would accept its stability protocol strategy, particularly relating to the use of low-humidity test conditions or microbiological and other testing requirements prior to initiating these labor-intensive and often very long-term studies.

REFERENCES

1. G. Hecht, R. E. Roehrs, J. C. Lang, D. P. Rodheaver, and M. A. Chowhan, Design and evaluation of ophthalmic pharmaceutical products, in *Modern Pharmaceutics*, 3rd ed. (G. S. Banker and C. T. Rhodes, Eds.), Marcel Dekker, New York, 1996, pp. 489–546.
2. K. M. Bapatla and O. J. Lorenzetti, Development of ophthalmic formulations, in *Pharmaceutical Dosage Forms Parenteral Medications*, Volume 2, 2nd ed. (K. E. Avis, H. A. Lieberman, and L. Lachman, Eds.), Marcel Dekker, New York, 1993, pp. 541–581.
3. A. C. Cartwright and B. R. Matthews (Eds.), *Pharmaceutical Product Licensing Requirements for Europe*, Taylor and Francis, New York, 1991.
4. A. C. Cartwright and B. R. Matthews (Eds.), *International Pharmaceutical Product Registration Aspects of Quality, Safety and Efficacy*, Taylor and Francis, New York, 1994.
5. B. R. Matthews, European aspects of the regulation of drug products, in *Modern Pharmaceutics*, 3rd ed. (G. S. Banker and C. T. Rhodes, Eds.), Marcel Dekker, New York, 1996, p. 773.
6. B. R. Matthews, Regulatory aspects of stability testing in Europe, Drug Dev. Ind. Pharm., 25(7), 831–856 (1999).
7. Council Directive on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (65/65/EEC), Articles 4 and 4a, Official J. Eur. Communities, L 147/13:65ff (1965).
8. Commission Directive modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (91/507/EEC), *Official Journal of the European Communities*, No L 270/32, 1991, p. 193ff
9. CPMP/ICH/380/95, *Note for Guidance on Stability Testing of New Drug Substances and Products*. Available on line at: http://www.eudra.org/humandocs/humans/ich.htm
10. International Conference on Harmonisation, Guideline on Stability Testing of New Drug Substances and Products, *Fed. Reg*., 59(183), 48754–48759 (1994).
11. ICH draft consensus guideline, Stability testing of new drug substances and products, released at Step 2 of the ICH process on October 7, 1999, by the ICH Steering Committee. Available on line at: http://www.ifpma.org/ich5q.html
12. *Guidance for Industry, Stability Testing of Drug Substances and Drug Products*, FDA Draft (not for implementation). Available on line at: http://www.fda.gov/cder/guidance/index.htm
13. CPMP/ICH/138/95, *Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*. Available on line at: http://www.eudra.org/humandocs/humans/ich.htm
14. International Conference on Harmonisation, Final guideline on stability testing of biotechnological/biological products, Fed. Reg., 61(133), 36466–36469 (1996).
15. CPMP/ICH/280/95, *Note for Guidance on Stability Testing: Requirements for New Dosage Forms*. Available on line at: http://www.eudra.org/humandocs/humans/ich.htm

16. International Conference on Harmonisation, Guideline on stability testing for new dosage forms, Fed. Reg., 62(90), 25634–256735 (1997).
17. CPMP/QWP/556/96, *Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products*. Available on line at: http://www.eudra.org/humandocs/humans/QWP.htm
18. CPMP/ICH/279/95, *Note for Guidance on the Photostability Testing of New Active Substances and Medicinal Products*. Available on line at: http://www.eudra.org/humandocs/humans/ich.htm
19. International Conference on Harmonisation, Guideline for the photostability testing of new drug substances, Fed. Reg., 62(95), 27116–27120 (1997).
20. CPMP/QWP/157/96, *Reduced Stability Testing Plan—Bracketing and Matrixing; Annex to Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products*. Available on line at: http://www.eudra.org/humandocs/humans/QWP.htm
21. CPMP/ICH/282/95, *Note for Guidance on Impurities in New Medicinal Products*. Available on line at: http://www.eudra.org/humandocs/humans/ich.htm
22. International Conference on Harmonisation, Guideline on impurities in new drug products, Fed. Reg., 62(96), 27454–27461 (1997).
23. CPMP/QWP/159/96, *Note for Guidance on Maximum Shelf Life for Sterile Products for Human Use After First Opening or Following Reconstitution*. Available on line at: http://www.eudra.org/humandocs/humans/QWP.htm
24. CPMP/QWP/609/96, *Note for Guidance on Declaration of Storage Conditions for Medicinal Products in the Products Particulars*. Available on line at: http://www.eudra.org/humandocs/humans/QWP.htm
25. World Health Organization, *Annex 5 Guidelines on Stability Testing of Pharmaceutical Products Containing Well-Established Drug Substances in Conventional Dosage Forms*, WHO Technical Report Series, No. 863, WHO, Geneva, Switzerland, 1996.
26. CPMP/ICH/281/95, *Note for Guidance on Validation of Analytical Procedures; Methodology*. Available on line at: http://www.eudra.org/humandocs/humans/ich.htm
27. International Conference on Harmonisation, Guideline on validation of analytical procedures, Fed. Reg., 62(96), 27464–27467 (1997).
28. U.S. Pharmacopeial Convention, *United States Pharmacopeia*, 23rd ed., Author, Rockville, MD, 1994.
29. Society of Japanese Pharmacopoeia, *The Japanese Pharmacopoeia*, 13th ed., distributed by Yakuji Nippo, Kanda Izumicho, Chiyodoku, Tokyo, 1996.
30. *Drug Approval and Licensing Procedures in Japan 1994*, Yakugyo Jiho, Kanda Jimbo-cho, Chiyoda-ku, Tokyo, 1995, pp. 134–139.
31. *Japanese Stability Testing Guidelines Incorporating ICH Guidelines*, Yakushinyaku No. 30, Osaka Medications Association, Chuo-ku, Osaka-shi, April 21, 1994.
32. Food and Drug Administration, Potential approaches for discussion on four ICH Q1A-related issues, based on the Preliminary Position Paper dated September 13, 1996, distributed for comment purposes only, not for implementation, FDA, CDER HFD-003, Author, Rockville, MD, released for comment October 28, 1996.
33. Annex I to the Medical Device Directive (93/42/EEC), Official J. Eur. Communities, L 169:1–43 (1993).
34. *ISO 19811:1999 (E) Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Determination of Physical Compatibility Of Contact Lens Care Products with Contact Lenses*.
35. *ISO/FDIS 11986: 1999 (E) Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Guidelines for Determination of Preservative Uptake and Release*.
36. *ISO/FDIS 11987: 1997 (E) Ophthalmic Optics—Contact Lenses—Methods for Determination of Shelf Life.*
37. *BS EN ISO 13212: 1999 (BS 7208-20:1999) Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Guidelines for the Determination of Shelf Life*.
38. *ISO 14534: 1997 (E) Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Fundamental Requirements*.
39. *ISO/DIS 14729 Ophthalmic Optics—Contact Lens Care Products—Microbiological Requirements and Test Methods for Products and Regimens for Hygienic Management of Contact Lenses*.
40. *ISO/DIS 14730 Ophthalmic Optics—Contact Lens Care Products—Antimicrobial Preservative Efficacy Testing and Guidance on Determining Discard Testing*.
41. *ISO/DIS 11979-6 Ophthalmic Implants—Intraocular Lenses—Part 6: Shelf Life and Transport Stability*.
42. Council of Europe, Eye Preparations, Ocularia, in *European Pharmacopoeia*, 3rd ed., Author, pp. 1761–1763.