CASE STUDY

Visual Inspection of Topical Ophthalmic Formulations Packaged in Opaque and Semi-Transparent Containers: Working Towards Alignment with USP<790> Visible Particulates in Injections

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ABSTRACT: Topical ophthalmic solutions, suspensions, and emulsions are typically packaged in opaque or semi-transparent plastic dropper bottles. This packaging provides resistance to breakage and the controlled drop size needed in ophthalmic container systems. Recent changes to USP <771> *Ophthalmic Products—Quality Tests* have impacted the particulate and foreign matter testing requirements for ophthalmic products dosed via topical application. The USP <771> chapter instructs that topical products undergo visual inspection for particulate matter as described in USP <790> *Visible Particulates in Injections*. Visual inspection for particulates in the filled unit is not feasible due to the lack of package transparency, and therefore alternative test strategies are needed to evaluate the acceptability of the batch. Aspects of this visual inspection approach include: a statistically based sampling plan for the batch, a destructive testing process, and acceptance limits based on manufacturing process capability supported with benchmark testing of competitor products to confirm manufacturing performance. Overall, the visual inspection program should include: historical trending; process monitoring; and upstream life cycle controls for facilities, raw materials, components, and product contact equipment to meet current regulatory expectations and good manufacturing practices.

KEYWORDS: Visual inspection, Particulate matter, Topical ophthalmic formulations, Opaque containers.

Introduction

Ophthalmic products are required to meet the particulate matter requirements described in USP <771> *Ophthalmic Products-Quality Tests* (1). The products are diverse and are supplied in a variety of dosage forms to access the ocular tissues through various routes of administration. USP <771> includes a table that specifies what USP particulate matter chapter applies based on the ophthalmic product's route of administration.

For ophthalmic solutions delivered via a topical route of administration (eye drop), USP <771> instructs that the product must comply with USP <790> *Visible Particulates in Injections* (2). A draft FDA Guidance *Quality Considerations for Topical Ophthalmic Drug Products—Guidance for Industry* published in 2023 also discusses the expectation that finished product be tested for visible particulate matter (3). Visual inspection poses some unique challenges for many ophthalmic products due to the nature of the container-closure systems, which allow limited capability for inspection of the total contents. The lack of package transparency makes 100% in-process inspection for particulates during manufacture not feasible and necessitates alternative supplemental inspection strategies involving destructive testing approaches (4). The general informational chapter, USP <1790>, is an excellent resource for guidance in practices for visual inspection. This case study describes a visual inspection process intended to comply with the compendia and regulatory expectations of a difficult-to-inspect product type.

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Destructive Testing Approach for Inspection of Topical Formulations

Examples of container-closure systems used to package topical ophthalmic products include opaque dropper

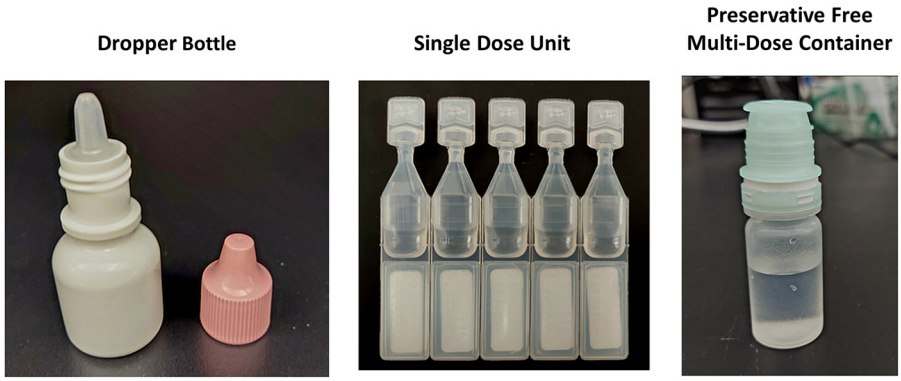

Figure 1

Examples of container types used to package topical ophthalmic products.

bottles, semi-transparent single-dose units, and semi-transparent ophthalmic squeeze dispensers for preservative-free solutions (Figure 1). Machine vision systems are utilized on the filling lines to 100% inspect units for container-closure defects such as missing or misaligned dropper tips, missing closures, and missing container labels. Defective units are rejected from the batch during processing.

However, direct 100% visual inspection for particulates is impossible in the case of opaque containers containing pigments such as TiO_2 and difficult in polyethylene packaging lacking a colorant (natural). To thoroughly inspect the product contents, a destructive testing approach is necessary.

Destructive testing requires the product package to be opened and the contents processed to visually inspect for particulates. The finished product handling activities should take place in a Class 100 HEPA laminar flow hood. The analyst should be properly gowned with powder free gloves and Tyvek sleeve protectors. A stainless-steel pressure vessel with an attached dispenser equipped with a 0.2 µm filter cartridge is used to dispense particle-free water. The product packaging should be cleaned before opening through a rinse of the exterior packaging surfaces using pressurized 0.2 µm filtered water. Clean room manipulation practices that minimize background particulates during processing are essential.

Product Transfer to a Transparent Inspection Container

A clear glass container capable of holding sufficient volume plus additional headspace for mixing is used to accommodate the transferred ophthalmic solution. Prior to transfer of the drug product, the receiving container and closure should be cleaned with 0.2 µm filtered water, and its cleanliness should be confirmed through a background particulate matter check showing no visible particulates present. Inspection containers should be dedicated, reused after cleaning, and stored in a laminar flow Class 100 hood when not in use. Particle free, transparent, disposable inspection containers can be used provided the containers have passed a background particulate matter check before use.

The drug product samples are opened in a manner that minimizes particulate generation and decanted into the visual inspection container. The inspection container should be gently swirled to create movement; however, since many ophthalmic formulations contain high levels of surfactants, gentle mixing is important to avoid bubble formation. Normal visual inspection methodology and conditions as described in USP <790> should be followed, including specified light intensity, use of black and white backgrounds, and a consistent inspection pace.

Destructive Testing of Ophthalmic Suspensions

Ophthalmic suspensions can be clarified by using an appropriate 0.2 µm filtered solvent to dissolve suspended drug particles. The solvent choice should also consider the solubility of formulation excipients such as polymeric viscosity modifiers so that agglomeration or precipitation of an excipient does not occur when dissolving the drug. If sample filtration will be used after the drug particles are dissolved, then compatibility of the solvent with the filter membrane material must also be considered.

Destructive Testing of Ophthalmic Emulsions

Ophthalmic emulsions, in some cases, can be destabilized using ionic strength or sedimentation to separate the aqueous and oil phases. The separate phases, if either or both are transparent, can then undergo visual inspection using a qualified method.

Use of Membrane Filtration and Microscopy for Determination of Visible Particulates

After clarification, ophthalmic emulsions and suspensions can be filtered through a filter membrane of appropriate pore size. The retained solid particulates are then examined and sized microscopically using methodology (5) described in Method 2 of USP <1788.2>. As the membrane surface is scanned under the microscope, the primary focus during enumeration is particulates in the visible size range (≥ 100 µm). Since visible particulates are the primary interest, a larger porosity membrane filter (≥ 30 µm) could be justified for use. Filter membranes having larger porosity may also be useful for filtering ophthalmic products with high viscosity. Viscous gels can be diluted with 0.2 µm filtered water followed by membrane filtration and particle enumeration using microscopy.

Results

Evaluating the Contribution of the Container-Closure System to the Particulate Matter Burden

One aspect of a control strategy for limiting unwanted particulates involves an evaluation of packaging components for incoming particulate matter burden. For new product development, this involves developing quality attributes for components early on with ongoing acceptance testing of components during commercialization.

To support life cycle management objectives, a comprehensive evaluation of the particulate matter burden for a typical dropper bottle, dropper tip, and cap as received from the plastic packaging supplier was designed and executed. In the study, 400 sterilized components were sampled from the shipping cartons at different depths within the cartons as received from the supplier. Groups of 10-25 parts (dropper tips or caps) were rinsed multiple times using particulate-free water with gentle agitation to remove loosely adhered particulates from the packaging component. In the case of dropper bottles, each bottle was filled with particulate-free water and inverted to dislodge particulate matter. Each bottle was rinsed three consecutive times, and the rinsates were collected for particle counting analysis.

All manipulations for the study were conducted in a HEPA Class 100 clean hood using containers that previously passed a cleanliness check. After component washing, the rinsates were pooled and filtered through a 0.8 µm porosity mixed cellulose ester membrane. The retained particulates ≥ 100 µm were microscopically sized and counted. The total particulate matter count was expressed as particulates per packaging component by dividing the total count by the number of components rinsed to create the pooled sample. The results are shown as a boxplot in Figure 2. The evaluation showed that packaging components having direct contact with the product fill (bottle and dropper tip) had very low particulate matter burden, ≤ 0.4 particulates per packaging component. The particulate level from the cap closure was more variable and had a slightly higher contribution; however, the count per part was still less than 1 particulate per part. The results of this study provided confidence that the packaging components from the supplier were not a significant source of particulate burden to the overall manufacturing process. Conducting this type of study on an annual or semi-annual basis with historical trending of the results provides an important component of an overall life cycle control process.

Review of Historical Visual Inspection Data Across Manufacturing Sites and Packaging Configurations

Visual inspection data trending is important to ensure that manufacturing processes are in control and to support continuous process improvement efforts. Toward that goal, a comprehensive review and analysis of visual inspection results generated over several years and across multiple packaging configurations and manufacturing sites was conducted. The finished products included in the analysis are well established and have not exhibited product stability issues, such as particulates arising from container interactions or precipitates due to degradation products or drug-excipient interactions. The review was intended to allow trending of particulate numbers so that issues with certain container types or manufacturing sites could be identified. The majority of the visual inspection testing was conducted by a single trained analyst thus minimizing concerns about inspector-to-inspector variability in the data sets. The results are summarized in the histograms shown in Figure 3A-C. On average, 93% of the visual inspection results revealed zero particulates in the inspection sample across different package types and

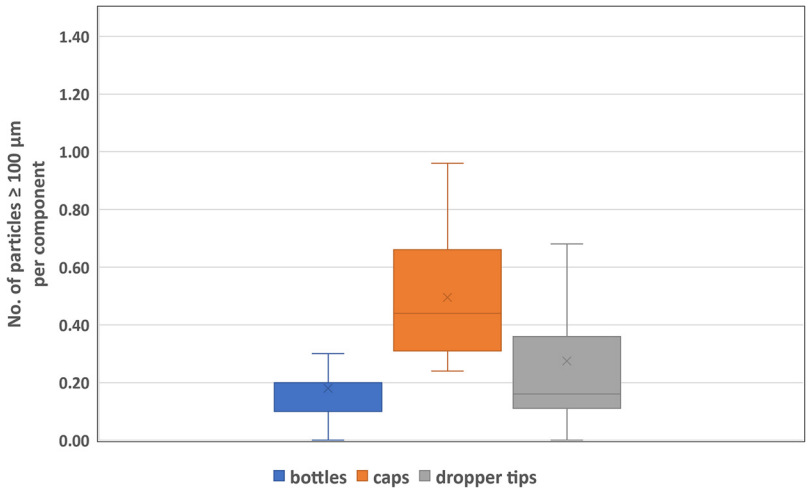

Figure 2

Particulate matter burden of incoming packaging components: dropper bottle (blue), dropper tip (gray), and cap closure (orange).

manufacturing sites. Results inclusive of zero, one, and two visible particulates observed in the inspection sample provided coverage for 99% of the test results.

Statistical analysis approaches were also considered to evaluate the data across different product formulations, packaging configurations, and manufacturing sites. Particulate count data from 305 visual inspection tests were used in the analysis. The assumptions in the analysis were: visible particulates, if present, were randomly distributed in filled units throughout the batch and the number of visible particulates did not change during storage on stability.

The particulate counts generated using manual visual inspection testing are discrete, whole number values with many results of "0". This type of count data is best analyzed using a generalized linear model such as Poisson regression or negative binomial regression. The rationale for using statistical analysis to evaluate the data set was to potentially develop a specification or acceptance limit for visible particulates based on manufacturing process capability that could apply across several product types.

Historical visible inspection data from two product families were evaluated. The first product family was formulated and packaged at one manufacturing site in 10 mL low-density polyethylene (LDPE) dropper bottles with three different solution fill sizes (2.5 mL, 5 mL, and 7.5 mL). The second product family was packaged into two different package configurations: a 1 mL single-dose unit (SDU) LDPE container with a 0.3 mL fill, and a 10 mL preservative-free multidose LDPE container with two fill volumes (7.5 mL and 10 mL). Furthermore, the SDU product was manufactured and filled at two different manufacturing sites.

Models were fit to the data to determine if there were statistical differences between product attributes, such as between fill sizes within a single container type, different container types, or the manufacturing site for the product. For example, an ophthalmic solution filled into an SDU through a blow/fill/seal process might have a lower particulate matter burden compared to the same ophthalmic solution filled into a 10 mL multidose container manufactured on a high-speed filling line. The blow/fill/seal process forms the "unit container" immediately before filling, which decreases the opportunity for introduction of particulate matter. The visual inspection results for the SDU and multidose container are shown as a histogram in Figure 4. The visual inspection results for both product types show overdispersion due to the high number of "0 particulates" observed in the data sets. Data sets that exhibit overdispersion are best evaluated using negative binomial regression analysis. The analysis showed no statistical difference between the SDU and multidose container results (Figure 4); however, it is interesting that the visible particulate counts for the SDU sample set showed up to 3-4 particulates in a few instances. The reason for the higher counts for SDUs is likely due to increased product handling during the test procedure, since many SDUs (~ 60 units) must be opened and pooled to achieve an appropriate volume for the visual

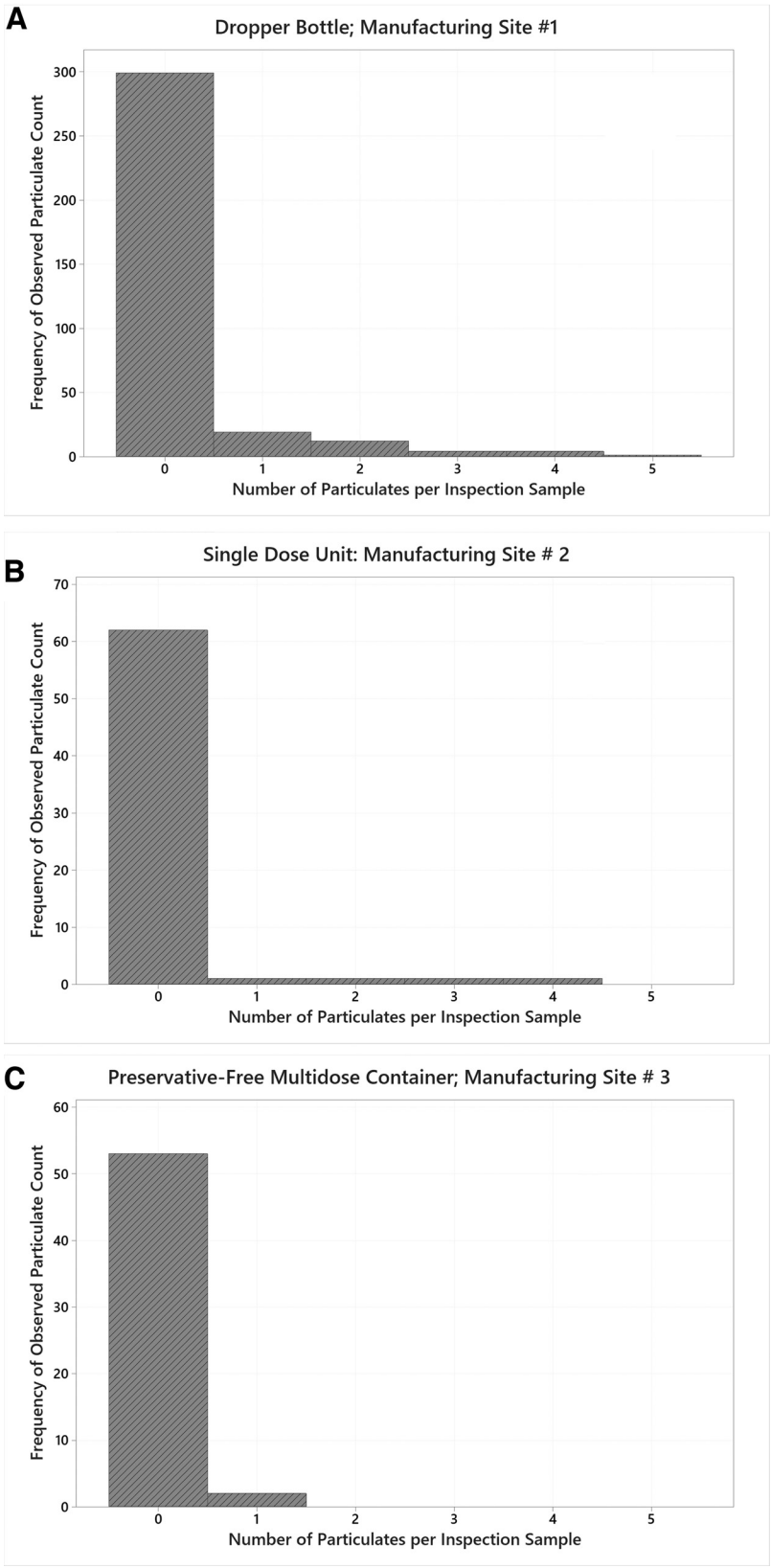

Figure 3

Histograms of visual inspection test results. (A) White opaque dropper bottle, Manufacturing site #1; B) LDPE single dose unit, Manufacturing site #2; C) LDPE preservative-free multidose container, Manufacturing site #3.

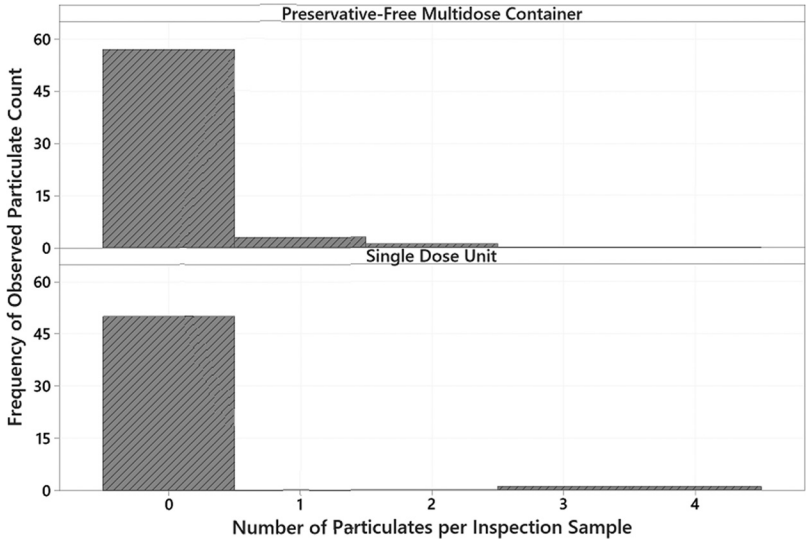

Figure 4

Histograms of visible inspection test results for the same formulation filled into preservative-free multidose containers and single-dose units.

inspection test. Consult with a statistician to determine the best way to model particulate counts from visible inspection testing. If the results are similar within product families or between products themselves, then data pooling may be possible to develop a global specification or acceptance limit for visible particulate testing.

Competitor Product Benchmarking

Performing visual inspection on competitor products is a way to benchmark a company's manufacturing capability against other ophthalmic product manufacturers. The use of manufacturing capability to help establish acceptance criteria for visible particulates requires supportive data to ensure the limits are consistent with industry standards. To illustrate, several prescription ophthalmic solutions as well as over-the-counter (OTC) solution eyedrops were obtained through pharmacies. A 25 mL sample pooled from multiple product units was inspected by a single trained analyst. The visual inspection results are shown in Table I. The results reveal that the majority of the products had zero observed visible particulates in the test sample.

In a few cases, for both prescription and OTC products, 2-3 visible particulates were observed in the inspection sample. The observation that some products had visible particulates in finished units suggests that "essentially free" may be defined by some manufacturers as not zero particulates but rather as a low number (1 or 2) of visible particulates potentially distributed within the batch. Nevertheless, the goal should be to minimize particulate occurrence as much as possible throughout the finished batch by implementing controls in each of the upstream materials and process steps.

Discussion

USP <789> *Particulate Matter in Ophthalmic Solutions* has historically described the requirements for subvisible and visible particulates in ophthalmic products. The text of USP <789> has included the following statement since 2004, when the chapter first appeared in a supplement to USP 27–NF 22: "Ophthalmic solutions should be essentially free from particles that can be observed on visual inspection". Based on this statement, there has been an expectation (before the USP <771> December 2022 revision) that ophthalmic solutions should comply with **both** subvisible and visible particulate matter requirements.

Our organization has been conducting visual inspection of ophthalmic solutions in alignment with USP <789> since the general chapter became official. As a result, our organization has an extensive historical data set of visual inspection test results collected at release and during stability studies for products made across our drug product manufacturing network, including external manufacturing sites. Periodic review of historical visual inspection data helps support a life cycle management approach for maintaining control of particulate matter burden in finished products.

TABLE I
Visual Inspection of Competitor Products

Product Type	Product Name	Fill Volume (mL)	No. Containers Pooled	Visible Particulates (No.)
Prescription	Acular™ (ketorolac tromethamine 0.5%)	5	5	0
	Zymar™ (gatifloxacin 0.3%)	5	5	0
	Quixin™ (levofloxacin 0.5%)	5	5	0
	Vigamox™ (moxifloxacin HCl 0.5%)	3	9	2
	Voltaren™ (diclofenac Na 0.1%)	5	5	3
	Trusopt™ (dorzolamide HCl 2%)	10	3	0
	Cosopt™ (dorzolamide HCl-timolol maleate)	10	3	0
	Xalatan™ (latanoprost 0.005%)	2.5	10	0
Over the Counter	Visine™	15	2	0.3 ± 0.6 [A]
	Thera Tears™	15	2	0 [A]
	Dry eye product, brand name redacted	15	2	2.3 ± 0.6 [A]

[A] = average of 3 replicates; OTC products were tested in triplicate due to availability and ease of product acquisition.

A life cycle approach to visual inspection works to ensure that a robust quality system provides reliable production of finished products with low particulate burden. This is especially important for difficult-to-inspect products and is achieved through good process and product design early in development, environmental control during manufacture, and establishment of quality attributes of incoming components as well as in-process product filling and equipment controls.

Acceptance Sample Size of the Batch and Acceptance Criteria

USP <790> permits supplemental acceptance sampling and testing when the "nature of the contents or the container–closure system permits only limited capability for inspection of the total contents, the 100% inspection of a batch shall be supplemented with the inspection of constituted (for example, dried) or withdrawn (for example, dark amber container, suspensions, highly colored liquids) contents of a sample of containers from the batch". Plastic ophthalmic containers typically lack 100% transparency; therefore, our interpretation of the preceding statement permits a supplemental sampling plan for batch acceptance.

Sampling plans for supplemental testing can be found in the special sampling plans S-3 and S-4 of the Quality Standard ANSI/ASQ Z1.4 (6). For batch sizes between 200 and 100,000 units, the plans specify a sample size of 20 units. Most full-scale batches produced by ophthalmic drug manufacturers should fall within this 200-100,000 finished unit range; therefore, a minimum sample size of 20 units for visual inspection testing should be appropriate.

The acceptance sample group should include units taken from the beginning, middle, and end of the filling process for a minimum total of 20 units so that the batch is assessed across the entire filling operation. Pooling of the finished units before inspection is recommended to minimize excessive sample handling and manipulation of individual units. The fill volume for some ophthalmic products, such as SDUs, can be less than 1 mL. In the case of low fill volume, pooling more than 20 units may be necessary to achieve a minimum sample volume for appropriate visual inspection. As discussed in USP <790>, a batch is deemed acceptable if it is "essentially free of visible particulates". The term "essentially free" is not defined within the compendia and requires a Quality Assurance department to develop a definition based on the product's dosing route, patient risk, process capability, and evaluation of similar competitor products through benchmark testing.

Safety Risks of Particulates in Ophthalmic Products

There is limited scientific literature involving safety studies to assess the potential effects of particulates in the visible size range on the ocular surface (7, 8). One

example is a study conducted with rabbits in which the potential effects of 2-3 plastic particulates (either polyethylene terephthalate or polyethylene) instilled on the eye were evaluated. The particulates ranged from 150-500 µm in size and were dispersed within a saline + 0.01% Tween 80 solution. The suspended particulates were instilled on rabbit eyes followed immediately by induced blinking. The rabbit corneas were examined after treatment and revealed no irritation response and no lasting corneal injuries after installation (7).

As discussed in USP <1790> under the "Plastic Containers" section, the risk profile related to particulate matter in a topical ophthalmic product should be viewed as reduced relative to a parenteral injectable product. The use of an Acceptable Quality Limit (AQL) value of <0.65% with an accept number of 0 for batch acceptability may not be appropriate for topical ophthalmic dosage forms. Another approach for setting acceptance limits for visible particulates is to use manufacturing process capability as established during product development to set a limit for the number of visible particles that would be allowed in the batch. As manufacturing experience develops for a product and the number of manufactured batches increases, statistical analysis of visible inspection results can be used to set Alert and Action limits. USP <1790> also suggests evaluating competitor products to benchmark the capability of a manufacturing process against industry standards.

There should be ongoing monitoring and trending of the particulate burden of finished topical drug products as well as the contribution of the container-closures received from suppliers. Development of a reasonable life cycle control strategy is also essential for continuous product improvement.

During the development of new products, any observed visible particulates should be characterized and identified for potential source(s), and mitigation strategies should be developed. If, for example, particulates are observed and the investigation determines that they are due to an interaction between formulation constituents (precipitation event), then the issue should be resolved in development. In this case, specific studies should be conducted to evaluate the phenomenon and steps should be taken to modify the formulation, the container-closure system, or other factor to avoid the formation of the particulates within the anticipated shelf life of the product. Similar scenarios should be evaluated during the process development phase of the project. This might include the use of multiple resin source lots for plastic containers if a leachable precipitate is a concern, multiple API and/or excipient raw material batches, and multiple manufacturing conditions (e.g., filling line speed) to make sure process capability across the entire operation is understood.

Stability Considerations

During new product development, it is recommended that visible particulates be monitored and trended to identify any stability indicating intrinsic particulate formation events (e.g., precipitation). A thorough evaluation of multiple lots during development and into initial commercialization should set the stage for performing a more limited evaluation of the product after commercial launch. After a well-developed product has been commercialized for a period of time and a thorough understanding has been established for the manufacturing process, a release evaluation for visual particulates should be adequate. This test sample can be taken at any point post filling and filtration, final capping and closure, but does not have to include final packaging (secondary carton) and labeling as these are not expected to be contributors to particulate matter burden.

Conclusion

The purpose of this report is to share experience with visual inspection of ophthalmic products packaged in opaque or semitransparent containers. The overall goal is to develop and maintain processes, procedures, and practices that comply with USP requirements for this difficult-to-inspect product type. The approach utilizes destructive testing to visually inspect a statistically valid number of finished units. Controlling upstream process steps such as the particulate matter load of incoming container-closure components is important to minimize foreign particulates in finished product. Ongoing historical trending of visual inspection results is a key component of the approach to ensure a robust life cycle control strategy. Statistical analysis of historical data may be useful when determining the definition of "essentially free of visible particulates" for specific product(s) in question.

Acknowledgments

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Conflict of Interest Declaration

The authors declare that they have no conflicts of interest.

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