Enquiry

Specification for Sub-visible Particles in Eye Drops and Eye Lotions

Currently the Ph. Eur. monograph *Eye preparations* (1163) doesn't set requirements/limits for sub-visible particles in eye preparations. In other regions of the world (e.g. USA and Japan), such requirements are considered very important for patient safety when eye preparations are administered to an injured eye. Furthermore, sub-visible particles are a reflection of the quality of the manufacturing process and may indicate a risk of microbial contamination. Even if the eye is subjected to particles in everyday life, this is not considered a valid reason to tolerate sub-visible particles in medicines beyond a certain limit.

Therefore the Ph. Eur. Commission is currently considering updating this monograph to add a specification for particulate contamination for eye drops and eye lotions that are solutions. The article in the annex below provides a background to the subject and proposes specifications for eye drops and eye lotions based on data obtained from batch preparations made by hospital pharmacies in the Netherlands. The batch data in the article suggest that the proposed specifications can be met in most cases. However, these data derive from only one member state.

The Ph. Eur. Commission would therefore like to obtain further information supported by actual data from stakeholders in the field (manufacturers, regulatory authorities and other users). Based on the responses received the final decision will be taken as to whether a specification is appropriate, and if so, a proposal (revised draft) will be formulated for publication in Pharmeuropa.

The Ph. Eur. Commission invites responses to the following questions.

1. Is such a specification necessary?
2. If not, why not?
3. If so, why, and what should the specification be?

*Users are asked to send feedback before 30 June 2015 to the Ph. Eur. Secretariat by e-mail at the following address: eye-preparations@edqm.eu. Any information will be treated confidentially and only considered within Group 12 and by the Ph. Eur. Secretariat.*
INTRODUCTION

Since 1983 the meanwhile certified Laboratory of Dutch Pharmacists (LNA) performs examinations of particulate load in injection fluids. The LNA has played an important role in the development of measurement methods and in establishing the final Pharmacopoeial standards [1-3]. Standards in this field presently apply world wide.

For parenterals with a volume < 100 ml (so-called Small Volume Parenterals, SVP's) the maximum admissible particulate load is respectively 6000 particles ≥ 10 µm and 600 particles ≥ 25 µm per package unit. For larger volumes a standard applies per millilitre fluid, i.e. ≤ 25 particles / ml for particles ≥ 10 µm and ≤ 3 particles / ml for particles ≥ 25 µm. Internationally discussions are ongoing that might result in a tightening of these standards by a factor 10.

The standardized, countrywide approach of measuring particulate load and the anonymized feedback of data to all participants facilitates the mutual comparison of the results per product. This approach has contributed strongly to the quality of parenterals prepared in hospitals.

Since 2002 LNA has also started the measurement of particulate load in eye drops. In this field no specific European standards apply.

Only the Japanese Pharmacopoeia and the USP lay down a standard in the field of particulate load in eye drops. The Japanese Pharmacopoeia requires that, after filtration and examination with a microscope, a maximum of 1 particle of 300 µm or larger is allowed. The USP lays down a substantially more stringent standard. Chapter 789 (Particulate Matter in Ophthalmic Solutions) states that a maximum of 50 particles ≥ 10 µm and a maximum of 5 particles ≥ 25 µm per ml eye drop fluid is admissible. Until shortly LNA has used the USP standard as a reference to assess the measurement data.

Although the announcement of a European standard has been expected [4] the Expert group (12) of the European Pharmacopoeia has chosen in 2004 not to lay down any standard, in the first place because it is difficult to assess what risks are involved with any presence of particles in eye drops. In general those risks may be assessed as being minor to absent which for instance can be underpinned by the fact that sometimes also suspension eye drops are utilized. In the second place there should be no need for any specific standard in this field. The expert group judged the American standard as too stringent for all eye drops.
The USP standard reportedly has been based upon two understandings: On the one hand the maximum admissible particulate load was said to be based upon the idea that the application of the eye drop might take place in an injured eye or even as an intravitreal or intracameral injection, in which case the presence of any particles was seen as absolutely intolerable. However any research to substantiate such a judgement is lacking. On the other hand the standard reportedly was derived from what is practically achievable in the pharmaceutical industry using the so-called Blow-Fill-Seal (BFS) production process. (In the Blow-Fill-Seal production process manufacturing is realized by creating the synthetic package (the ‘blowing’), filling it with product substance and sealing the filled package to an airtight unit all in one combined mechanical stroke.)

So the standard doesn’t seem to be based upon the necessity to mitigate any apparent clinical risk. However the standard does incite systematic monitoring and trending of the data of particulate loads in BFS eye drops and early signalling of any deviations in the production process that might give rise to elevated particulate loads.

In the Netherlands eye drops are being compounded regularly in qualified (hospital-) pharmacies. Eye drops are always being filtered through a 0,2 µm membrane filter. For those small scale compounded eye drops only a limited number of packaging types are available on the market. The BFS process is not eligible because of its scale. Usually eye drops are being dispensed in so-called Gemo vials and sometimes in so-called minims. Due to the required minimum volume of 30 ml for one measurement the assessment of particulate load is practically only feasible for eye drops packed in Gemo vials.

As with injection fluids it is possible to realize a substantial quality improvement, with eye drops measurement data since 2002 not showing a clear trend in spite of several improvements of the outer packaging of empty eye drop vials, improved cleaning procedures preceding the filling process and improvements of the filling process itself. Still compliance with the USP standard for BFS products usually fails in practice.

Actually there are large differences in the rate results are exceeding the standard and indeed there are sometimes results that do comply with the USP standard. Those differences suggest that factors in the formula, e.g. the preservative, might play an additional role.

In practice Gemo vials containing eye drops are being dispensed, even if they do not comply with the USP standard. Dispensing such non compliant products can be justified in the first place by arguing that the USP standard is not specifically developed for this type of product and in the second place by the acknowledgement that declining from the dispensing in case of a justified pharmacotherapeutic prescription in principle will constitute a greater risk for the patient than accepting the non-demonstrable risk of non compliance with the particulate load standard.

Therefore it is justified to question the use of the USP standard for Gemo vials and other non-BFS products.

From this discussion and from the need to facilitate product quality review against some meaningful standard the proposal for a field standard for the particulate load in eye drops produced at a small scale as described below has emerged.

**FUNDAMENTALS FOR A FIELD STANDARD**

For the design of a field standard for particle load in a pharmaceutical product three different perspectives can be discerned in the following decreasing order of importance:
A. Precluding any clinical risks.

The risk of particles in (intravenous) parenterals is well documented [5-7]. In particular the risk of phlebitis or emboli’s is known to increase in relation to the particulate load in injection fluids. But what about eye drops? For the intact eye we can state that the risk of any particles in general is extremely small, although it is conceivable that particles with specific physical or chemical characteristics indeed might yield a relevant risk, such as glass particles (e.g. in the preparation of glass ampoules) and particles with aggressive or allergic properties. However for the damaged or diseased eye matters are more complex. The natural barrier is broken and there is a real possibility that particles will reach the inner eye. However we could not find any specific literature discussing the risks of intraocularly deposited foreign particles. Ontologically the inner eye is related to nerve tissue. The specific risks of particles inside blood vessels are not applicable. As injection fluids are not only injected into blood vessels but into other tissues as well, including nerve tissue (e.g. epidural injections), no clinical urge emerges for an a priori more stringent standard for the particle load in eye drops as compared to injection fluids. Additionally in practice fluids designed for injection are frequently being applied as eye drops, even in a diseased or damaged eye.

B. Standardising and controlling the production process.

A quite different perspective is about controlling the production process. Based on historical results statistical research can be executed. From that the mean particle load of eye drop preparations in Gemo vials can be derived. The Scientific Institute of Dutch Pharmacists also has executed blank runs with eye drop vials filled with particle free water. In this way a standard could be derived for the mean and its standard deviation $\sigma$ (sigma) based upon historical measurements.

We might even assign an alert level at the mean plus $\sigma$ and an action level (or standard) at the mean plus $3\sigma$.

In production processes the so called ‘six sigma’ principle is chosen more and more frequently. With this principle the risk of deviations and consequently disturbances of the production process is minimized by assigning the standard at the mean plus $6\sigma$. Of course such a standard should never exceed any clinically relevant standard. Table 1 shows the mean (historical) particle loads for several eye preparations and what alert ($n + \sigma$) and action level i.e. standard ($n + 6\sigma$) can be derived from this.

C. Product appearance (“cosmetic requirements”).

Even if a clinical standard would turn out to be very liberal and the practice with available eye drop packages would not result in a more stringent standard, it still might be relevant from a cosmetic perspective to assign a (supplementary) standard that is that no particles or fouling should be visible.

DERIVING A FIELD STANDARD

When proposing a standard for the particle load in eye preparations it is important to take all three perspectives into account in the given order of importance.

From the clinical perspective the application area plays an important role. It can be stated that all eye drops prepared in (hospital) pharmacies packed in Gemo vials or mimims are meant for external application at the eye, intact or otherwise. Any intravitreal and / or intracameral injection using these package forms is out of the question. Therefore it is worthwhile to distinguish intravitreal / intracameral applications on the one hand from external applications on the other hand.
Nevertheless, if we assume external application in a damaged / diseased eye, it is rational to start from the premise that the particle load of the eye drop should never exceed the particle load of an injection fluid.

For eye washing / rinsing fluids even the comparison with other sterile washes is rather obvious, although no specific requirements apply for its particle load, even when those fluids are being applied internally in practice e.g. in an operation wound.

If nevertheless a connection with the requirements of injection fluids is sought it should be borne in mind in the first place that for SVP’s a standard applies per package unit while for eye drops until now a standard per millilitre has prevailed.

The background of a standard per package unit instead of per millilitre is that most SVP’s are used as a package for non-recurrent application (unit dose). Thus the standard determines the maximum number of particles to be injected per application. Additionally SVP’s share the property that the primary package itself has a relatively large impact on the final number of particles in the fluid after filtration, because of the relatively large ratio between the internal surface area of the package and the volume of its contents [8]. A standard for a particle load per millilitre therefore would have to be partly dependent on the volume of the injection fluid which is rather irrelevant as compared to a standard per dose / package.

So if this standard for the particle load in SVP’s shall be related to a design for a standard for eye drops, the applied volume of eye drop fluid per dose should be taken into account. In most cases this is only one drop, so approximately 0.05 ml. Sometimes more drops are applied at the same time, however, the volume applied per eye at a time, hardly ever will exceed 0.25 ml. In addition the conjunctival pocket can not accommodate much more than 50 µl, so a larger volume will run away over the cheeks.

The particle load standard for injection fluids, cautiously calculating with a unit dose volume of 0.25 ml thus would, if applied to eye drop fluids, result in a maximum of 24,000 particles ≥ 10 µm and 2400 particle ≥ 25 µm per millilitre.

If additionally the possible future tightening of the standard for injection fluids with a factor 10 is taken into consideration a standard for eye drop fluids would emerge from the clinical perspective of max. 2400 particles ≥ 10 µm and 240 particles ≥ 25 µm per millilitre.

If a field standard should be derived from the perspective of production process control, based on the mean of historical measurements plus 6σ (six sigma principle), it can be seen in table 1 (see the green boxes in the column below Standard Proposal) that for most preparations a standard of max. 1000 particles/ml ≥ 10 µm and 100 particles/ml of ≥ 25 µm is well achievable. This is slightly more stringent than a standard from the clinical perspective and still stays liberally outside the historic values plus 6σ.

Only with a few preparations some “problems” remain to be dealt with, i.e. acetylcysteine, ceftazidime, phenylephrine, povidon iodinated en vancomycin (see table 1). The topic of clinical justification is outside the scope of this paper. However apart from this the following can be observed.

The historical data of phenylephrine eye drops almost exclusively originated from only one entrant. Meanwhile this entrant has communicated that he has improved the formulation of the preparation. This is expected to result in a lower future particle load. Povidon iodinated is a fluid containing itself an intrinsically insoluble component (the povidon matrix) which can account for the higher particle burden.

Vancomycin, ceftazidime and acetylcysteine remain to be discussed. The first two substances are being applied in cases of an acute eye infection, in which case the barrier of the internal eye might be affected. These antibiotics in practice are being prepared from licensed injection
products. It is a well known feature of reconstituted fluids from lyophilized products to be encumbered with an increased particle burden [1, 9].

In practice reconstituted preparations are being applied as an eye preparation possibly even without being filtered. It is even conceivable that an increased primary particle burden will result in an increased value in the filtrate. Also in the filtrate new particles might emerge as a consequence of available excipients. A further decrease of particulate load for these preparations is to be recommended.

The results for acetylcysteine require further investigation. Possibly the sensitivity to oxygen and/or aggregation due to disulfide bond formation might be involved.

Kept outside of the table, but worth to be mentioned, is the still rather frequently used combination preparation oxybuprocaine - fluoresceine containing chemically incompatible components (precipitate of the complexed compound). Therefore this product will not only always inevitably exceed any particle load standard but is itself unacceptable on the basis of this incompatibility.

Completely separate from the above mentioned perspectives (clinical and control of production process point of view) we should not lose sight of the “cosmetic” perspective. This is also recognizable in the Japanese standard. This standard determines, as said before, that not more than 1 particle of over 300 µm per ml may be found. In the view of the authors it is entirely clear that this standard always should be applicable as a supplementary standard, especially as for this standard there is no relation to any specific preparation process as is the case for the USP standard.

For eye washing / rinsing fluids already the comparison has been drawn with more general sterile rinsing fluids. However, clinically the functional connection to eye drops is more relevant and therefore it is sensible to relate the requirements with respect to particle load to injection fluids. Thus for eye washing / rinsing fluids application of the standard for SVP’s or LVP’s is most logical.

CONCLUSION

Based on the preceding considerations a field standard for the particle load of small scale eye drop preparations, intended to be applied to the external eye is proposed as follows:

Max 1000 particles/ml ≥ 10 µm and 100 particles/ml ≥ 25 µm; no visible particles at observational examination or max 1 particle of ≥ 300 µm per ml if determined by means of the filtration method according to the Japanese Pharmacopoeia.

This standard applies as yet for eye drop preparations in which all components are dissolved (molecularly dispersed). Emulsions, colloidal solutions or liposomal preparations probably will not comply with this standard.

For eye washing / rinsing solutions the standard for LVP’s (volume > 100 ml) or SVP’s (volume ≤ 100 ml), depending on the container volume is proposed.

ACKNOWLEDGEMENTS

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REFERENCES


Table 1 – Aggregated historic data of eye drop preparations in relation to the postulated norm

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<thead>
<tr>
<th>Preparation</th>
<th>Number of batches (n)</th>
<th>mean n</th>
<th>σ</th>
<th>3 σ</th>
<th>6 σ</th>
<th>norm proposal ≤ 1000 mean n</th>
<th>σ</th>
<th>3 σ</th>
<th>6 σ</th>
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