Japanese Pharmacopeia (JP) and United States Pharmacopeia (USP) Developments in Visual Inspection for Foreign Particulate Matter

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Abstract: Visual inspection continues to be an important control method to ensure consistent product quality and patient safety. The desire to detect and remove low numbers of non-conforming units from production batches has resulted in the need to perform 100% visual inspection. The uncertainty of inspection results has been made more complicated by ambiguous compendial and regulatory expectations. It has been difficult to translate requirements to be “essentially free from visible particulates” or “free from readily detectable foreign matter” into quantitative terms that can be applied to batch acceptance and release. This is further complicated by incomplete descriptions of inspection conditions, without which the term visible has no meaning. A definition of reference inspection conditions, which include the critical parameters of light intensity, background and time are necessary to define what is visible under these conditions. This paper discusses the revision of reference inspection conditions in Section 6.06 of the Japanese Pharmacopeia (JP) and the development of new chapters (790) and (1790) in the United States Pharmacopeia (USP) to define both reference inspection conditions and acceptance criteria. Work by both organizations is helping to harmonize inspection methods and expectations as described herein in support of the global pharmaceutical industry and the patients it serves.

Key word: Japanese Pharmacopeia (JP), United States Pharmacopeia (USP), Visual Inspection, Foreign Particulate Matter, JP Section 6.06, USP General Chapter (790), USP Information Chapter (1790)

1.0 INTRODUCTION

Visual inspection continues to be an important control method to ensure consistent product quality and patient safety. The desire to detect and remove low numbers of non-conforming units from production batches has resulted in the need to perform 100% visual inspection. This is necessary to detect and remove foreign particulate matter, as well as units in which container integrity has been compromised, such as those with visible cracks. The Parenteral Drug Association (PDA) assembled a team of industry physicians and inspection experts to assess the risk to patients from inadvertent injection of foreign particulate matter [1]. This paper provides useful guidance in assessing such risk for various types of particles, routes of administration and patient populations. It supports the conclusion that “… notwithstanding high risk clinical circumstances and acknowledging there are limitations to reporting clinical events to particle infusion, the existing data suggest the overall risk to patients is generally low and the benefit of these treatments is generally significant”.

Many studies have demonstrated the probabilistic nature of the inspection process and show that 100% inspection does not result in 100% detection [2]. For foreign particulate matter, particles of decreasing size often have a lower probability of detection (PoD). The actual PoD achieved will depend on the specific product formulation and container, as well as characteristics of the particle itself; however it is common to see less than 100% PoD for particles smaller than 200 μm in diameter and there is a general consensus that the visible range of detection, where visible particles are readily detectable, begins above 100 μm [3].

The uncertainty of inspection results has also been made more complicated by ambiguous compendial and regulato-
ry expectations. It has been difficult to translate requirements to be “essentially free from visible particulates” or “free from readily detectable foreign matter” into quantitative terms that can be applied to batch acceptance and release. This is further complicated by incomplete descriptions of inspection conditions, without which the term visible has no meaning. A definition of reference inspection conditions, which include the critical parameters of light intensity, background and time are necessary to define what is visible under these conditions.

In this paper we are pleased to share significant advances in the Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP) to address these concerns.

2.0 JAPANESE PHARMACOPEIA (JP)

2.1 Introduction

The Japanese market is special for manufacturers of injections because it demands the absence of foreign insoluble matter in injections with extreme severity. On the other hand, the test conditions specified under the Section 6.06 “Foreign Insoluble Matter Test for Injections” in JP (JP method) are very simple, apparently showing a gap from the severity of the market. Let’s look at the description of JP method in the Supplement II to the JP16. Two methods are presented here. Method 1 is applied to solutions including emulsions, and specifies that solutions must be free from “readily” detectable matter when visually inspected at a light intensity of 1,000 lux. For plastic containers, the light intensity is specified to be set higher at 8,000 to 10,000 lux, in consideration of the ease of seeing through containers. Method 2 is applied to solid injections to be dissolved before use, and specifies that injections must be free from “clearly” detectable matter at a light intensity of 1,000 lux. Large differences of JP method from the USP (790) method (USP method) and European Pharmacopoeia 2.9.20 method (EP method) include the followings: USP method and EP method (hereinafter referred to USP method) specify a light intensity of 2,000~3,750 lux while JP method specifies a lower light intensity of 1,000 lux, and JP method does not have specifications for inspection time, inspection environment such as the use of a background of black and white, or motions such as lightly swirling and inverting.

(1) How long is the inspection time per container?
Answer: 15 companies, 20 cases
The majority is no restrictions.

(2) What is the illuminance intensity? Answer: 14 companies, 18 cases
The majority is 1000 lx but EP method is also used in Japan.

According to a survey conducted by the Sterile Product GMP Work Group in the PDA Japan (JPDA WG) in pharmaceutical companies in 2010, the light intensity and time used for visual inspection in QC test for release varied as shown in Fig. 1, showing that there was no standardized application of JP method [4]. More specifically, in addition to 1,000 lux, light intensities of 2,000~3,750 lux, which is the same as that of USP method, and 5,000 lux were used. Moreover, some companies specified an inspection time of 3 seconds, while most companies (14 of 20 companies) replied that they had “no time specifications” as in JP method. This suggests that JP method, which is supposed to show quality standards required in Japan, is very
Fig. 2 The Key Factors Thought to Affect the Possibility of Detection (PoD) of a Detectable Foreign Matter

The combination of three key factors gives higher repeatability and reproducibility than a single factor.

For this purpose, the JPDA WG examined suitable conditions for the test method of JP with an aim to establish more reliable conditions for the pharmacopeial test method, and made a proposal for revision. Details are explained in the following sections.

2.2 The History of the JP Revision of “Visual Inspection” with the Discussion based on a Survey by PDA Japan; diversified application in each plant

The JP method was published in JP6 (1951). Afterwards some minor parts were changed regarding the condition of method 1 and 2. Now the condition of JP method is planned to be revised in the next JP Seventeenth Edition scheduled in April 2016. The JP released a draft revision [5] in September 2014; in short, it was decided to be revised to a similar method as USP method. This can be simply seen as the harmonization effort of adjusting the conditions of the test method to match those of USP method. In reality, however, the revision was made very cautiously after a number of discussions were held over two years and data from experiments in Japan alone were assembled by several companies. This section explains the essential points of the discussions and how the draft revision was finalized.

The JPDA WG proposed a revision of JP method in a journal article in 2010 and 2011 as a harmonization with USP and EP [4, 6]. It then made a formal proposal to the JP in 2012, resulting in the start of discussion on the necessity of revision. Based on differences in the test method of JP and USP, JP method seems to be able to detect only large foreign matter because it uses a low light intensity. However, since JP method has no time specifications, some inspectors may achieve a high PoD due to a long inspection time. Therefore, JPDA WG studied the relationship among the light intensity, inspection time, and PoD in trained Japanese inspectors in a research report [7] in 2013. They showed that when the inspection time is 5 seconds, the PoD is higher at a light intensity of 2,000 lux than at 1,000 lux, but not largely different from 2,000 lux up to 5,000 lux, and when the light intensity was 3,000 lux, the PoD is higher at an inspection time of 5 seconds than at 2 seconds, but not largely different from 5 seconds up to 10 seconds. The PoD at a light intensity of 1,000 lux is close to that at 3,000 lux for 5 seconds when the inspection time is 10 seconds or more, but inferior to that when the inspection time is 5 seconds or less. These findings indicate that depending on the type of foreign matter, JP method with a higher light intensity could provide a similar PoD to that of USP method if the inspection time is 10 seconds or more, but could be inferior to USP method if the inspection time is short.

Here a discussion occurred as to whether higher PoD is really required for the JP. More specifically, the reproducibility when a single inspector repeats inspection is important, but in addition to this, a test method with smaller variability when various inspectors perform inspection is also required. Even if the same test method is used, whether minute particles of 100 or 50 μm in size can be
Fig. 3 Distribution of Detection Rate under 1,000 lx vs 3,000 lx/Total Data
Depends on the inspectors, the detection ratio PoD is variable. The condition of 3,000 lx and 5 secants gives the least variability $CV = 27.1\%$. The higher light intensity 3,000 lx gives higher PoD than the 1,000 lx condition in case of a 5 secants inspection time.

In this research conducted by JPDA WG, inter-company and inter-inspector variability data were processed together to select the conditions that could minimize the variability. The conditions of 1,000 lux for 5 seconds showed large variability, and the conditions of 1,000 lux for 10 seconds and 3,000 lux for 5 seconds were not largely different although the latter showed slightly smaller variability and was superior [8] (Fig. 3).

Based on the above background and findings, the JP reached the conclusion that it could establish its own conditions for the pharmacopeial test method in Japan, but it would be more appropriate to use the same conditions as those of the USP and EP method if similar results could be expected, in the current environment where harmonization was underway.

### 2.3 The Change of the Visual Inspection Conditions in JP; equivalent to EP and USP

From the results of discussions with the JPDA WG, the JP decided to change the current test conditions and adopt the equivalent test conditions as those in USP and EP. More specifically, the light intensity is 2,000–3,750 lux from a white light source, the inspection environment is a background of black and white, and the inspection time is 5 seconds each against black and white backgrounds. On the other hand, descriptions about operating methods, such as lightly swirling and inverting motions, were not included. These descriptions, of course, should be used as references, but the JPDA WG determined that it was difficult to decide on uniform operation. In addition, the JP allows the extension of time if it is difficult to observe foreign matter. This extension of time is not intended to increase the PoD for injections in general, but is prescribed for the situation where it is obviously impossible to operate in 5 seconds, in consideration of suspensions, emulsions, containers of various shapes, and volumes that were added previously. Moreover, the time cannot be shortened. Sampling and PoD for lot assurance, which are discussed in USP method, are not included in JP method because the discussion
between the JP and JPDA WG has not been completed. Furthermore, the issue of the detection skill of inspectors and reference standards, which was discussed in the previous section, is left as a future subject because the JPDA WG has not reached conclusions.

If the revision is implemented as planned, compatibility with the USP and EP method will be increased. Actual manufacturing quality will not change, and there will be future issues such as the method of lot assurance by sampling test and standardization of inspector qualification using reference standards; however, this revision will have the positive impacts that it can standardize test procedures among global companies, and reduce excessive nonconformity results in quality testing and substantial efforts to take actions against such nonconformity.

### 2.4 The Problem of “Visible” Definition

The criteria of “visible” for JP use the expression of “readily” detectable or “clearly” detectable. Even trained visual inspectors have a low PoD for particles of 100 \(\mu\text{m}\) or less in size, and according to the survey report [7, 8], the PoD for particles of 50 \(\mu\text{m}\) in size is 60\% or less under the conditions of USP method. Foreign matter of this size is not readily detectable, and much less, it is hard to be described as a clearly present foreign matter. However, the test method should determine that the matter is visible regardless of the size if the inspector can see it, and if the inspector cannot see it, it passes the test. If Japanese inspectors perform 100\% unit inspection again for products sent to Japan after overseas 100\% visual inspection, they may detect minute foreign matter, possibly resulting in an increase in the defect rate by up to several percent. In other words, if this batch is tested by the current JP method without performing 100\% unit inspection again in Japan, it may pass the test on some occasions and fail the test on the other occasions. In most of such cases, however, detected minute foreign matter is of 50 to 150 \(\mu\text{m}\) in size, suggesting that critical risks on intrinsic quality are not increased or decreased. Nonetheless, corporate decisions on whether the product should be released to the market may be complicated by the severity of sentiment of the Japanese market against foreign matter.

How should we think the difference in the skill of Japanese and non-Japanese inspectors and the foreign matter-free quality required for products? The following three perspectives should be discussed here: safety, technique, and sentiment.

For the first, safety, it is explained in detail in PDA Review [1] and USP \(\langle 1790\rangle\) that the safety of a very slight amount of minute foreign matter is not significant as described in Section 1.0. This is the groundbreaking reference information that clarifies the traditional ambiguousness regarding the risk of a slight amount of minute foreign matter in the market.

For the next, technique, 200 \(\mu\text{m}\) or more is generally regarded as the size that can be detected with nearly 100\% probability as described in Section 1.0, and as mentioned earlier, the detection of minute foreign matter of 100 \(\mu\text{m}\) or less in size is difficult. Even trained inspectors do not always reach 100\% when the experiment is repeated, even though it is qualified or validated. This is also evident from the fact that USP \(\langle 1790\rangle\) adopts 95\% for the criteria to assess inspector qualification in the detection of minute foreign matter. Results may also differ according to the type or color of foreign matter. It is thus difficult to define “readily” or “clearly” with measurable values such as size and area.

Readily or clearly detectable foreign matter is not as small as the one that can only be detected by top-level inspectors highly skilled in the detection of minute foreign matter. In contrast, foreign matter of the size that can be accidentally found by untrained users in the market can be regarded to be readily detectable.

At last but not least the Japanese users have specific sentiment and high expectation on visual appearance of products [9]. What kind of risk does potentially overlooked foreign matter have on the market? If patients, nurses, or physicians detect minute foreign matter, they will not be satisfied even if such information is provided. They will have the sentiment of rejection to visible matter entering the body. Japanese people have the national characteristic that they tend to find and question minute foreign matter of 50 to 100 \(\mu\text{m}\) in size. Such issues of sentiment cannot be ignored. There is no choice but to acknowledge that it is impossible to standardize such issues derived from the characteristics of detection ability of the people forming groups, such as regions and national
characteristics.

From the information explained so far, standard samples of approximately 200 μm in size are recognized as those of the size that should be detected in the United States and Europe, and if these can be eliminated by the USP method, and if it is understood in Japan that even foreign matter of approximately 200 μm in size cannot always be detected with PoD 100%, “clearly” detectable foreign matter required in pharmacopeias can be assessed based on whether it is visible when inspected by the pharmacopeial test method under the same conditions, rather than being expressed with size or area. If it is visible in process sampling test or release assessment inspection for QC reference test, for example, an assessment may be made by determining whether it is critical as compared with the reference standard. In this case, the reference standard, such as a mimic sample of 200 μm in size, may be chosen at the discretion of each company. Further contamination risks with minute foreign matter of 50 to 150 μm in size are the risks for market sentiment, and should be cared properly to avoid fear of patients; however it is not safety risk.

2.5 The Future Plan of PDA Japan to Propose a Further Revision in JP; introduce an in line sampling test method instead of a QC sampling test

There is another issue that we should question for quality assurance to be sure a batch is free of visual foreign matter. A statistical risk assessment of it in releasing products by an acceptance test should replace a QC release testing of a few samples by a diversified inspector. In this regard JP could learn from USP a lot. The currently proposed draft revision of the JP assumes to take samples from an entire batch to be released and use them for QC reference test. According to the above-mentioned survey [4], the number of samples collected per lot was 10 or less in 12 of 20 cases. This method is very unlikely to detect foreign matter with a low contamination rate from the small number of samples. And if a test detects a single contaminated unit by chance, the result would not correctly justify the non-conformity of the entire batch.

In contrast, the assurance system for manufactured lots is well-organized under USP 〈790〉 and 〈1790〉 as explained in the later section. More specifically, after 100% inspection in the visual inspection process, a statistically meaningful number of samples based on AQL or other criteria is collected for process test and visually inspected by the method specified under 〈790〉, and if it passes the test, it is transferred to the next packaging process. The assessment criteria have upper limits of contamination rate for critical, major, and minor categories according to the size and type of foreign matter. In addition, the method of qualification assessment for inspectors who perform inspection is specified, and assessment criteria for the UQL are also defined. This reduces the risk of finding or overlooking foreign matter by chance, allowing determination of the intrinsic quality assurance level for each lot. These two chapters of the USP are very excellent and can serve as useful references in Japan. However, the Japanese industry often disagree with the acceptance level of AQL in USP due to the social characteristic to pay special attention to a small visible foreign particle.

The JPDA WG examined the assurance method for release lots in Japan and once it made a proposal [4, 5], and the scheme for performing AQL inspections in process before release is similar to USP 〈790〉. For AQL assessment criteria, there are wide ranges of practices among the Japanese factories. As USP provided flexible and reasonable criteria in it, JP may establish its own criteria suitable for the Japanese society within its similar range. However there should be again a study to be convinced. The JPDA WG challenges to make a proposal to the JP again by organizing its knowledge through exchange of information with the USP professionals and devising a method that can assure quality in a more logical and well-defined manner, without having a negative impact on the current quality assurance level in Japan.

3.0 UNITED STATES PHARMACOPEIA (USP)

3.1 Introduction

It was noted in the general introduction at the beginning of this paper, the word “visible” has no meaning unless the viewing conditions are specified. The USP has provided such information in its history but this has been absent in recent years. The development of a new chapter, USP General Chapter 〈790〉 Visible Particulates in Injections was undertaken to address this gap. An Information Chapter 〈1790〉 Visual Inspection of Injections was also prepared to
provide further guidance in this area. Before describing the history and contents of these chapters it is important to remember the following about any USP chapter. General Chapters, those with numbers below 1000, are enforceable by the FDA and compliance is expected. Information Chapters, with numbers of 1000 and above, are meant as guidance and are written to support successful implementation of General Chapters. General Notice 3.10 states that units tested must meet the acceptance criteria at any time during the life of the product (from production to expiration) and that test results apply only to the units tested. Such tests are generally not intended to infer acceptance of a larger group of units (e.g. batch release). A test can become a batch release test however, when included in a regulatory filing and subsequently approved by the FDA. General Notice 6.30 allows the use of alternative methods, when shown to be equivalent or better than the method provided in the General Chapter.

3.2 History of USP Visual Inspection Requirements

As with any standard, the methods and acceptance criteria evolve with changes in our understanding of risk as well as advancements in inspection and manufacturing technologies. A complete history of the evolution of visual inspection requirements, as found in the USP, can be found in the Stimulus Article published in 2009 [10]. A brief summary of that history follows. The first reference to visual appearance can be found in USP IX (1915) which described the need for injectable compounds to be true solutions. The first appearance of "solution clarity" and freedom from contaminants for parenterals occurred in 1936 in NF VI. A requirement for clarity of solutions specified, "Aqueous ampule solutions are to be clear; i.e., when observed over a bright light, they shall be substantially free from precipitate, cloudiness or turbidity, specks or flecks, fibers or cotton hairs, or any undissolved material."

The first description of inspection conditions can be found in NF VII and USP XII (1942). Here, it stated that "substantially free shall be construed to mean a preparation which is free from foreign bodies that would be readily discernable by the unaided eye when viewed through a light reflected from a 100 watt Mazda lamp using as a median a ground glass and a background of black and white".

In USP XIII (1947) the inspection conditions were further defined for clarity of solutions. "Clarity of Solutions—Water for Injection, pharmacopeial Injections or pharmacopeial Solutions of medicament, intended for parenteral administration, unless exempted by individual monographs, must be substantially free of any turbidity or undisolved material which can be detected readily without accessory magnification (except for such optical correction as may be required to establish normal vision), when the solution is examined against a black background and against a light which at a point ten inches below the source provides an intensity of illumination not less than 100 and not more than 350 foot candles. This intensity of illumination may be obtained from a 100 watt, inside frosted incandescent lamp operating at rated voltage, or from fluorescent lamps, or from any equivalent source of light."

During the period 1955 through 1970, USP XV through XVIII provided for the visual inspection of injections. USP XV: "Every care should be exercised in the preparation of injections to prevent contamination with micro-organisms and foreign material. Good pharmaceutical practice also requires that each Injection, in its final container, be subjected individually to visible inspection." USP XVI and XVII: "Every care should be exercised in the preparation of injections to prevent contamination with micro-organisms and foreign material. Good pharmaceutical practice also requires that each Injection, in its final container, be subjected individually to visible inspection whenever the nature of the container permits."

In 1980, USP XX continued the philosophical requirement for a zero-defect quality standard for foreign matter and particles initiated in USP XIX, 1st Supplement. Under "General Requirements for Tests and Assays," p. 861, 〈1〉 Injections, "Every care should be exercised in the preparation of injections to prevent contamination. Good pharmaceutical practice also requires that each injection, in its final container, be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents show evidence of contamination with visible foreign material be rejected."

In 1995, USP XXIII repeated the philosophical requirement for a zero-defect quality standard for foreign matter
and particles. “Every care should be exercised in the preparation of all products intended for injection, to prevent contamination with microorganisms and foreign material.” This revision returned to the view expressed in USP XIX Revision 1 that the response to particle contamination in injectable fluids must be a graded one. Only one phrase was changed: the previous use of the term “substantially free” was replaced by the term “essentially free.”

General Chapter 〈1〉 Injections starting in USP 31 (2008), states “Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed “visible particulates”) in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates.” No inspection method was specified.

### 3.3 History of the Development of USP 〈790〉

The development of a chapter specific to visible particles for the USP began with the publication of a Stimulus to the Revision Process in 2009 [10]. This paper described the current state, the risk to patients and recommended adopting the inspection conditions found in the European Pharmacopeia (EP) and an acceptance criterion based on widely used acceptance sampling methods and industry benchmarking. It suggested a change to USP General Chapter 〈1〉 Injections where the other requirements for visual inspection for particles were found.

After publication of the Stimulus, a Stakeholder’s Forum was held on May 13, 2010 to encourage public discussion of the proposal. This was followed by a meeting with the Food and Drug Administration (FDA) on March 28, 2011. After subsequent discussion with the USP, the decision was made to create a new chapter dedicated to inspection for visible particulates. Draft versions of USP General Chapter 〈790〉 Visible Particulates in Injections were published in the USP Pharmacopeial Forum [11, 12]. The development of the chapter benefited from the public comments received and a final version was published in USP 37, 1st Supplement, March 1, 2014 and became official on August 1, 2014.

### 3.4 Current Contents of USP 〈790〉

USP General Chapter 〈790〉 Visible Particulates in Injections defines a set of reference inspection conditions based on those found in EP 2.9.20 Particulate Contamination: Visible Particles. The intent was to move towards a global standard to define what is visible by defining a common set of inspection conditions. These conditions include a light intensity of 2,000–3,750 lux with inspection for 5 seconds each against black and white backgrounds. The container should be swirled or inverted to induce particle movement and no magnification is specified. The chapter notes that it applies to extrinsic (coming from outside of the process) and intrinsic (coming from processing equipment and the primary package) particles. Inherent particles, such as protein agglomerates, must be addressed in individual monographs or approved regulatory filings.

The previous acceptance criterion that the batch be “essentially free” of visible particulates is further defined through the use of acceptance sampling. At the time of batch release, after 100% inspection, a sample of inspected product is reinspected using a General Level II sampling plan from the ANSI/ASQ Z1.4 standard with an AQL of 0.65%. The ISO 2859 and JIS Z9015 standards provide equivalent sampling plans and results. For product in distribution, such as when responding to a complaint, a smaller sample of 20 units may be examined and if no further evidence of visible particulates is found the batch continues to meet the expectation to be “essentially free” of visible particulates. Examining a larger sample will provide increased sensitivity in this assessment and multiple complaints from the same batch should not be treated as isolated events.

This chapter has also repeated the information previously found in USP General Chapter 〈1〉 injection for supplemental testing to be applied to those products where the nature of the product or package limits effective inspection. Examples include lyophilized cakes and powders, suspension, dark colored solutions or containers and non-transparent plastic containers. Destructive testing of a small sample is recommended to better assess the risk of particle in the batch in addition to 100% inspection for defects which may be visible. This might include reconstitution of a dried product or transfer of the container contents to a
clear container for improved inspection. The Special sampling plans found in the ANSI/ASQ standard are recommended for selecting an appropriate number of units to test.

3.5 Contents and Status of USP 〈1790〉

General Chapters in the USP are intended to be concise, providing a description of the test method and acceptance criteria as appropriate. It is often useful to have additional supporting information to better implement these tests. For this purpose, the USP has Information Chapters. These provide guidance on good practices when implementing a test method. To support the implementation of USP General Chapter 〈790〉 Visible Particulates in Injections, USP Information Chapter 〈1790〉 Visual Inspection of Injections was written. A draft of this chapter was published in the Pharmacopeial Forum in January of 2015 [13]. The comment period has closed and the Expert Panel has addressed the comments received. A revised draft will be published in the PF later in 2015.

The scope of this USP Information Chapter includes manual particle inspection. It also extends to other visible defects, such as container integrity and other inspection methods, such as semi-automated and automated systems. It also emphasizes the importance of defect prevention as well as inspection and removal.

This chapter provides a more detailed discussion on the risk of particles to patients. It goes on to discuss the probabilistic nature of the inspection process and typical inspection performance. It provides an overview of the normal flow of the inspection process and the acceptance sampling or AQL inspection after 100% inspection. It introduces the concepts of the Inspection Lifecycle to help identify particle type and source with the goal of continuous process improvement for defect prevention.

It provides recommendations and methods on the preparation of test sets to assess manual inspection performance and to qualify inspectors. These can also be applied to the qualification and validation of semi-automated and automated inspection methods.

The goal in writing this chapter was to provide practical guidance in developing and executing a robust inspection process.

3.6 Brief Summary of other Current and Planned Particle Related USP chapters

The USP has a number of other chapters besides those discussed above that provide requirements and useful guidance on particles. These include the following:

〈787〉 Subvisible Particulate Matter in Therapeutic Protein Injections
〈788〉 Particulate Matter in Injections
〈789〉 Particulate Matter in Ophthalmic Solutions
〈1787〉 Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections (DRAFT)
〈1788〉 Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions

As can be seen from the titles of these chapters, they apply to other dosage forms and to sub-visible particles.

4.0 CONCLUSIONS

The work at the JP and USP are helping to move our industry to a common set of inspection conditions to better define what is visible. The methods described in the chapters discussed here can achieve the level of sensitivity necessary to provide safe medicines for patients. Until recently the guidance found in the pharmacopeias was ambiguous but progress is being made to provide more information to develop and implement effective routine inspection processes. Zero defects should always be our goal when manufacturing sterile pharmaceutical products; however this is not always a practical limit when inspecting such products for visible particles. It is important to base such limits on an assessment of the risk to the patient as well as manufacturing and inspection process capability. And finally, visual inspection should always be done within a system of continuous process improvement.

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