Author: Tim Sandle

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WHAT THE EYE CAN SEE: VISION REQUIREMENTS FOR PERSONNEL WHO INSPECT INJECTABLE PHARMACEUTICALS

INTRODUCTION

Regulators require pharmaceutical products that are injected into the human body (which are by inference sterile products) to be free of visible particulates (1). This is because the presence of visible particulates in injectable products may affect patient safety. There are various controls that need to be built into the manufacturing process to minimize the possibility of particle and particulate formation. These controls will begin with product development and proceed to manufacturing controls. In terms of 'testing,' this is based on visual inspection techniques, conducted as part of batch release and for stability samples (and retained samples in the event of a customer complaint). Any identified particulates need to be identified, investigated, and corrected. Following this, a preventative action should be put in place to prevent recurrence.

In some cases, automated inspection methods are used (either completely automated or semi-automated involving personnel inspections); in other cases, all inspections are performed by personnel; and sometimes a combination approach is used. The inspection process falls under the general definition of non-destructive testing. While automated inspection machines can be used, these are not always reliable. Additionally, automated technologies need to be validated to show that they meet or surpass human inspection capabilities.

The focus in this paper is with personnel. This paper looks at the 'testing' element – the visual inspection of products by people and considers the nature of eye tests required to ensure that personnel are able to detect particulates that could be spotted by another person with acceptable vision under ideal inspection conditions (2). Acceptable vision is taken to be 'near normal visual acuity' (3), which is not so much 'normal vision' but rather a rating of an examinee's ability to recognize small details with precision.

This article does not refer to subvisible particulates (that is those that cannot be seen with the naked eye and examined using the Light Obscuration Particle Count Test or the Microscopic Particle Count Test) (4). The focus is with visible particles and particulates, which are any mobile, undissolved matter other than gas bubbles unintentionally present in an injectable medicine.

PARTICLES AND PARTICULATES

Particles and particulates can only be prescribed a general meaning with any exact definition not currently part of a scientific consensus. A particle is a small, localized object to which has a measurable volume, density, or mass (volume and area are direct measurements of a particle, whereas weight and aerodynamic drag are indirect measures) (5). Particles can be subatomic particles (such as an electron), microscopic, or macroscopic (that is, visible to the naked eye and of concern to this paper). Sometimes fibers (2-dimensional) and differentiated from particles (3-dimensional), although this becomes more a matter of interest in the investigation as to the origins of the impurity than with the detection. It is also necessary to mention the pharmacologic properties of drugs, where the particle size of a drug can affect its release from dosage forms that are administered orally, parenterally, rectally, and topically. While of interest, this is area of micromeritics is outside of the scope of this paper) (6).

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A particulate is something composed of two or more particles, which can be unrelated or a related aggregation of particles of the same origin. For visible assessments when inspecting pharmaceuticals, 'particulate' tends to be used given that a particle, given the potential origins, is unlikely to be an object that can viewed with the naked eye.

Particulates in pharmaceutical products are typically categorized into three groups (with reference to USP Chapter <1> and USP Chapter <787>) (7, 8):

1. Inherent particulates: Particulates that are an innate product characteristic. Examples include: Proteinaceous particles, silicone droplets, inorganic precipitates such as barium sulfate or aluminum sulfate, fatty acid particles from the degradation of polysorbates, and glass lamellae.
2. Intrinsic particulates: Particulates that are derived from the manufacturing equipment, product formulation, or container system, such as cellulose.
3. Extrinsic particulates are particulates that originate from the manufacturing environment and are foreign to the manufacturing process, such as might arise from a cleaning validation failure. Other examples are: Fibers, glass, paint flakes, hair, and insect parts.

With these categories, we can also differentiate between solid particles (flecks), liquid particles (droplets), or gaseous particles (bubbles). Particles will vary according to product formulation, particle characteristics, and package design, and in relation to quantity, size, shape, color, density, and reflectivity.

The potential impacts upon patients should particulates be present are varied and medical reports indicate the concerns relate to infection and venous and arterial emboli; emboli, abscesses, and granulomas in visceral organs; and phlebitis, inflammatory reactions, granulomas, and infections at injection sites (9). The severity will relate to the numbers, sizes, and types of particulates; the individual patient; and the number of injections performed over a given time period.

VISUAL ACUITY

We detect objects using our eyes as part of the sensory nervous system. Central to this process are the presence of photoreceptive cells in the retina (rods and cones) which detect visible light and convey this information to the brain. Through the eyes the brain interprets the perception of color, shape, depth, movement, and other features (10). The ability to do this varies among people and alters with age. For these reasons, assessing 'good vision' needs to be part of the pharmaceutical assessment for those undertaking close vision work. While this needs to include an assessment of 'mocked up' product vials containing representative particles (such as product agglomerants and hairs) the individuals also need to be assessed for their vision, or more accurately, their visual acuity.

Visual acuity refers to the ability to discern the shapes and details of the things that a person sees (or simply 'the ability to distinguish fine detail'). It is one factor in what constitutes overall vision. Other factors include color vision, peripheral vision, and depth perception. In relation to assessing pharmaceutical products, each of these is important, although the requirements have tended to single out visual acuity alone (which while important, this author considers to be a weakness with current regulatory expectations and instead a wider assessment of vision is required).

In terms of how small a person can see; this is based on an eye's resolution. That is how close two objects can become before they blur into one. Some people can resolve two lines about 0.01 degrees apart: a 0.026-millimeter gap, 15 centimeters from their faces. For those deemed to have very good eyes, objects 0.04 millimeters wide (the width of a fine human hair) are just about distinguishable. However, for the typical population deemed to have 'good eyes,' the objects discernable tend to be 0.1 millimeters (the accuracy of a measurement ranges from 0.1 to 0.3 mm), unaided (11). This is dependent upon (12):

- The viewing distance (400 mm away from the object).
- Lighting conditions (1000 lumens).
- The viewing angle ~ 35 degrees).
- The angular size of the object (which needs to be 1 arc minute = 1/60 degrees = 0.0003 radians.

According to a conference paper (referenced in USP <1790>) "the detection threshold for routine, reliable detection (≥70% probability) of a single spherical particle in a clear solution contained in a 10-mL vial utilizing diffuse illumination between 2,000 and 3,000 lux is often near 150 µm in diameter (13)." Putting these elements together, to reach ≥90% probability of detection particles needs to be 200 µm in diameter.

Central to visual acuity are the cone cells of the retina. Cone cells respond differently to light of different wavelengths (there are three different types of cone cells for this purpose). These cells are responsible for color vision, and function best in relatively bright light, differing to rod cells, which work better in dim light. There are six to seven million cones in a human eye, concentrated towards the macula (14). Visual acuity is not static, and it declines with age, from middle age onwards and it accelerates in those aged over 70 years (15).

Visual acuity is assessed by angular resolution (considering by how much an eye can differentiate one object from another in terms of visual angles). This is typically measured using bar charts (black text on a white background). The types of eye tests that provide a measurement of visual acuity of the eye are discussed below. An important determinant is the distance at which the visual acuity is assessed.

FACTORS AFFECTING VISUAL ACUITY WITH PHARMACEUTICAL PRODUCTS

A factor that is difficult to capture in testing but one that needs to be acknowledged is the behavior of particles in liquids, which differ from solids. In liquids, particles are quite close together and move with random motion throughout a container. Particles move rapidly in all directions but collide with each other frequently due to shorter distances between particles. It also stands that particles have the same mass then they will move with the same speed. The dynamics of particle movement in liquids can make them difficult to discern; for this reason, the inspection process should contain a fixed time for the observation, such aa ten seconds per pharmaceutical container. Regular breaks must also be taken to ensure the operator can continue to inspect successfully. Recommendations vary but a good 'rule of thumb' is a break away from the workstation for 8 minutes every hour. If inspections are performed at night (such as where 24/7 working is in place), breaks may need to be more frequent given the body's natural responses to being awake when naturally the person should be asleep.

It is also important that inspections do not begin immediately the operator enters the workplace (16). This is because it takes a period of time for the eye to adapt to new conditions. For example, if the inspector just stepped

in from the outdoors on a sunny day, he would be significantly less sensitive to the inspection task as opposed to having been in a dimly illuminated waiting room, before performing the inspection. Generally, 5 minutes at the workstation should be sufficient in terms of delay before the inspection process begins.

It is also important that the pharmaceutical vial or bottle is swirled and inverted. This is necessary to address cohesion and adhesion. Cohesion is the tendency for the same kind of particles to be attracted to one another and such particles are more strongly attracted to each other than they are to the particles surrounding them. These forces of attraction are relatively strong. Adhesion occurs when forces of attraction exist between different types of particles. Particles of a liquid will not only be attracted to one another, but they are generally attracted to the particles that make up the container holding the liquid. The combination of cohesive and adhesive forces means that a slight concave curve, known as the meniscus, exists at the surface of most liquids. For an accurate assessment of particles, the meniscus needs to be disrupted (17).

A further variant is with the viscosity of the pharmaceutical product, the measure of how much a liquid resist flowing freely. A liquid that flows very slowly is more viscous than a liquid that flows easily and quickly. The degree of viscosity can affect the movement of particles and influence how easily they can be detected.

COLOR VISION

Color vision relates to the ability to distinguish lights of different spectral qualities, generally between wavelengths of 400 and 700 nm (18). The ability to see a range of colors, as indicated above, is a product of cone cells. Cone cells contain different forms of opsin – a pigment protein – that have different spectral sensitivities enabling trichromatic color vision (19). The peak response of human cone cells varies between people (20). Given that some particles may vary in color only subtly differently to the color of the product, assessing the color vision of operators, such as differentiating between yellows and greens, is an additional requirement. Some individuals are color blind. This is typically an inherited issue affecting the development of one or more of the three sets cone cells. Males are more likely to be color blind than females, as the genes responsible for the most common forms of color blindness are on the X chromosome (21). Rates of color blindness vary among different populations. In the U.S. and the U.K., the proportion of males with color blindness is somewhere between 5 and 7% (22).

PERIPHERAL VISION

Peripheral vision refers to part of sight outside of a person's central field of vision and allows them to see objects to the side without having to move their eyes or head. The visual field of the healthy human eye spans approximately 120 degrees of an arc. However, to the extremes peripheral vision is weak, especially at distinguishing detail, color, and shape (hence defining the field of vision for pharmaceutical inspection process is important) (23), as indicated in Figure 1. Most of the field of vision arc is formed of peripheral vision. There are different degrees of peripheral vision with different levels of acuity achieved, as represented by:

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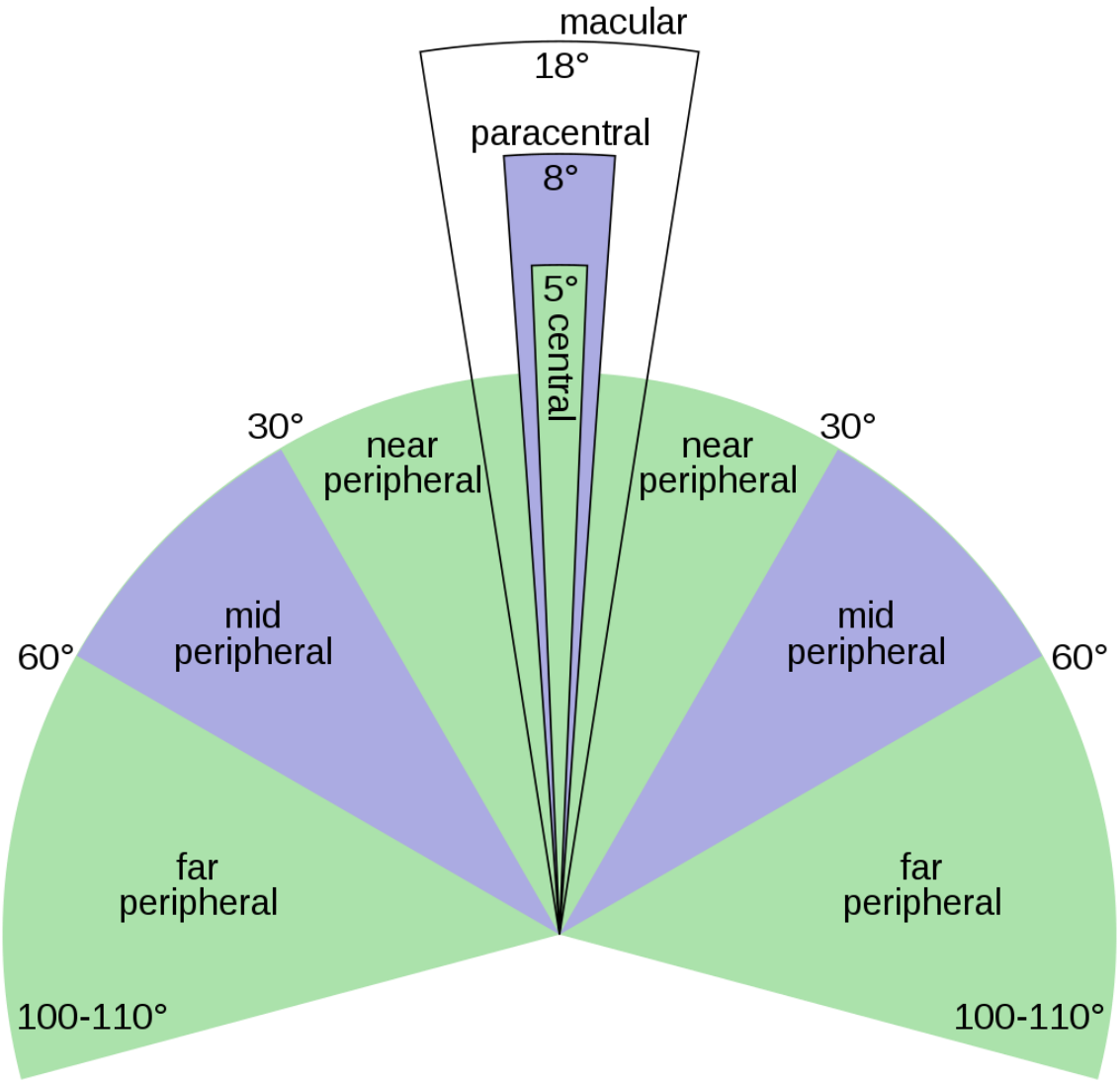

Figure 1: Peripheral vision of the human eye. Image by Zyxwv99. Creative Commons-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=37052186

Hence assessing the field of vision represents an important consideration when assessing close inspection vision (as per Figure 1). This leads to two considerations:

1. Ensuring, as far as possible, the person undertaking an inspection is using their central vision.
2. Assessing peripheral vision and designing workstations to avoid the need for far peripheral vision.

This is because peripheral vision can be lost. This generally arises as a side effect of medical conditions, such as glaucoma (the buildup of fluid and pressure in the eye) and retinitis pigmentosa (a genetic condition) (24).

TESTS FOR VISUAL INSPECTION

Tests for those undertaking visual inspections are commonplace across different industrial sectors, although they vary considerably in terms of their scope and acceptance criteria (25-27). Visual testing is a non-destructive testing method by which reflected or transmitted light from a test object is imaged with the human eye. Some forms of visual testing allow the use of assistance through the use of imaging and light sensitive devices (28).

No unaided visual inspection process can be completely effective (29). Although ensuring the correct conditions and through training considerably reduces the rate of error and helps to overcome subjectivity. Given that the distinction between what would be considered changes in material properties and what would be considered a defect is not distinct, the inspection process can inevitably miss defects and produce false calls (30) (although the later should undergo verification by a second, independent person).

Pharmaceutical standards and GMPs make reference to visual inspection tests as part of quality control. These can be defined as the means to detect and remove units of a pharmaceutical product with predefined defects in a reproducible manner in a controlled process the next section review these.

SETTING THE STANDARDS: CGMP REQUIREMENTS

As indicated above, close visual inspection is a requirement for pharmaceutical product release and a 100% inspection process should be in place. Such examinations need to cover:

- Underfill
- Overfill
- Metal particles
- Glass particles
- Fibers
- Turbidity, as with microbial growth
- Flocculation, as with microbial growth
- Scratches to the container
- Cracks in the container
- Missing flip off caps
- Spots on rubber closures
- Damaged closure components
- Precipitation
- Dirty containers

While each of these elements is important, the topic at hand is particulates. In terms of standards and compendia, the following are of relevance:

- USP General Chapter <1> Injections and Implanted Drug Products (Parenterals)—Product Quality Tests
- USP General Chapter <790> Visible Particulates in Injections (this chapter describes inspection procedures used to demonstrate that injectable products are essentially free from particulates).
- United States Pharmacopeia General Chapter <1790> Visual Inspection of Injections (this informational chapter that provides recommendations on inspection programs for visible particulates covering the injectable product life cycle).
- US FDA Inspection of Injectable Products for Visible Particulates Guidance for Industry (Draft, 2021): https://www.fda.gov/media/154868/download
- CFR 211.160(b) and 211.110(c) and (d)
- European Pharmacopeia 2.9.20. Particulate contamination: Visible Particles, 01/2020:20920

- European Pharmacopeia 5.17.2. Recommendations on Testing of Particulate Contamination: Visible Particles, 01/2021:51702
- Chinese Pharmacopeia 0904 "Test for Visible Particles". (Officially: The Pharmacopoeia of the People's Republic of China). 10th edition. 2015
- ISO standards. There are three ISO standards that relate to non-destructive testing:

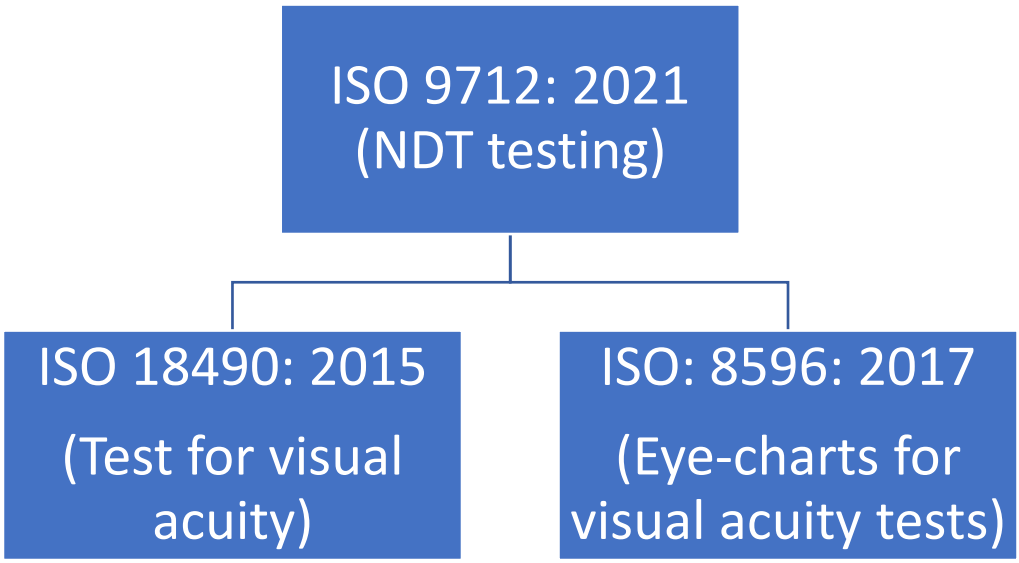

Figure 2: Relevant ISO standards for visual inspection

Of the above, the most recent guidance for visual inspections emerged in December 2021, in the form of a draft document from the US FDA. This sets out the requirements for the examination of visible particulates in parenteral products contains guidance for the training and assessment for those who engage in product inspection activities. The guidance states:

"Inspector candidates should be trained in the relevant CGMP requirements and should have normal near visual acuity (with or without the use of corrective lenses) and no impairment of color vision."

But what form should this assessment take and what do other GMPs, and compendia require? The following table (Table 1) provides a comparison and a checklist, which will be useful for those setting up or wishing to review their visual inspection test criteria.

Table 1: Comparison of international standards and regulations

Topic	Document structure / requirement	Further rationale (if applicable)	Source	Position (where standards and compendia differ)
Policy requirements				
Aim of the inspection	The **inspection process** should be designed and qualified to ensure that every lot of all	To avoid patient harm	USP Chapter 1; USP <790>	Noted

	parenteral preparations is essentially free from visible particulates.			
Training (general)	The inspection must use trained and qualified personnel. Training must be 'in depth'.		FDA Guidance, 2021 Ph.Eur.5.17.2	Personnel must be trained and assessed.
Training (detail)	Threshold studies should be conducted to determine the size of visible particulates that can be reproducibly detected by trained personnel with near normal visual acuity.	Visual detection of a particulate is a probabilistic process that depends on, among other things, the product and the size and shape of the particulate.	FDA Guidance, 2021	Visual acuity test must be assessed prior to training against inspection bottles.
Training (frequency)	Visual assessment must be annual. [Note: This changes to 'at least annually' in the current draft of the revised EU GMP Annex 1] Where problems are noted, examinations should be revised to 3 monthlies. An increased frequency may need to be implemented as personnel age e.g., every six-months.		EU GMP Annex 1 (current) USP <1790> USP <1790>	
Practice				
Training (general)	Only certified inspectors and qualified equipment should be used to inspect injectable products for visible particulates.	N/A	FDA Guidance	Noted
Training (general)	Personnel conducting inspections (100% inspection and AQL inspection) must be adequately trained.	N/A	FDA Guidance	Noted

Training (retraining)	Personnel must be subject to periodic retraining or requalification.	Noted	FDA Guidance	As per EU GMP, this is at least annually.
Training (eye test)	Operators must be able to detect particles within the 'visible size range'.	The eye-test must be appropriate.	CFR 211.160(b) and 211.110(c) and (d)	Details of the eye test are below.
Training (process)	Formalized training and qualification programs promote consistent performance…and help minimize variability among different inspectors. A mixture of good injectable product units and defective units containing visible particulates should be used.	Noted	FDA Guidance	Guidance on training sets.
Training (process)	Manufacturers must…provide a visual description (e.g., photographs or drawings of typical defects) to be used for training purposes.	N/A	FDA Guidance	Requirement for SOP.
Inspection process & link to training (background)	The inspection station should have a backdrop of one or more solid colours (e.g., black, and white). The specific backdrop and light intensity selected for manual inspection stations should be qualified. Inspected units must be free of visible particulates when examined without magnification (except for optical correction as may be required to establish normal vision)	This is to provide adequate contrast and to allow maximum visibility of product contents.	FDA Guidance USP <790> and Ph. Eur. 2.9.20.	To meet the requirements both a black and a white background must be used.

	against a black background and against a white background.			
Inspection process & link to training (light intensity)	The light intensity of the inspection station is critical to achieving maximum visibility. Lighting should also be qualified to allow for accurate human detection of defective products. Illumination at the inspection point is maintained at a minimum intensity between 2000 and 3750 lux. Minimum light intensity is 3750 Variable light intensity depending on the product type: 1000-1500 lux for colourless solutions; 2000 to 3000 lux for coloured solutions	The appropriate light intensity needs to be determined by the manufacturer based on: Container colour, size, and shape together with product characteristics.	FDA Guidance USP <790> Ph. Eur. 2.9.20; Ph.Eur.5.17.2 Chinese Pharmacopeia 0904	It is not possible to set a lux rating that meets all compendia. The majority of compendia require high light intensity Minimum light intensity must be 3700 lux.
Inspection process & link to training (minimum observation time)	Inspection times are to be more than 5 seconds for the white panel and again for the black panel.		Ph. Eur. 2.9.20; Ph.Eur.5.17.2	Inspection time is a minimum of 10 seconds (five for white panel, 5 seconds for black panel).
Training (process)	Training should take place according to written procedures		FDA Guidance.	
Qualification				
Training (process)	The methods used for inspection must be qualified.	This includes the qualification of operators	CFR 211.160(b) and 211.110(c) and (d)	Noted
Training (process)	The programme can include a combination of training materials, standard operating procedures (SOPs), on-	N/A	FDA Guidance EU GMP Annex 1 (current)	Noted

	the-job training, and testing.			
Training (eye tests)	Consideration of eyesight checks	N/A	EU GMP Annex 1 (current)	FDA, USP and Ph. Eur. Require eyesight tests so this 'consideration' needs to become mandatory.
Training (eye tests – visual acuity)	Inspectors should have normal near visual acuity (with or without the use of corrective lenses – if corrective lenses are worn, these must be worn during practice and for any assessment). Near normal visual acuity, is not 'normal vision' but more precisely a rather a rating of an examinee's ability to recognize small details with precision.		FDA Guidance and FDA Guidance cited literature[1]. EU GMP Annex 1 (current)	Eyesight tests must be enables to assess near vision.
Training (eye tests – colour blindness)	Inspectors should have no impairment of colour vision.	Mentioned by FDA and Chinese Pharmacopoeia.	FDA Guidance Chinese Pharmacopeia 0904	No impairment of colour vision should be permitted.
Training (eye test content)	Eye tests	This is the international standard for eye tests	ISO 18490: 2015	N/A
	Eye tests should assess for concerns leading to poor visual acuity: • Refractive error (ametropia) or errors in how the light is refracted in the eyeball.	Good visual acuity is the product of: • The sharpness of the retinal image within the eye. • The health and functioning of the retina.	ISO 18490: 2015	N/A

[1] Ricci, F, C Cedrone, and L Cerulli, 1998, Standardized Measurement of Visual Acuity, Ophthalmic Epidemiol, 5(1):41–53

	• Errors in how the retinal image is interpreted by the brain. • Astigmatism or more complex corneal irregularities. Snellen charts should be used, such as optotype with different orientations of the letter 'E'.	• The sensitivity of the interpretative faculty of the brain. Snellen charts measure far vision. An alternative is a logMAR chart (Logarithm of the Minimum Angle of Resolution). To pass the Snellen chart, the first 9 rows must be read correctly.		
Eye tests requirements – USP & Chinese Pharmacopeia	Near-vision performance should be the equivalent of 20/20 with no impairment of colour vision. Eye tests must be annual (along with other inspection training).	N/A	USP <1790>	Colour vision and near close vision assessment.
	Snellen charts should be used.	Snellen charts measure far vision. For the USP, as pass is defined as being able to read the 9th row. This represents 6/6 or 20/20 vision. For the Chinese Pharmacopeia, a pass is defined as 4.9 (or 5.0 with corrected vision).	USP <1790> Chinese Pharmacopeia 0904	Far vision assessment required. The USP standard is the highest and should be adopted.
	Jaeger charts should be used.	Jaeger charts measure near vision. The type scale on a modern Jaeger eye chart usually ranges from J10 (approximately 14-point type for Times	USP <1790>	Near vision assessment required.

		New Roman font) to J1 (approximately 3-point type, Times New Roman). For close visual assessment, a pass is defined as being able to read row J1 (3-point font). Chinese pharmacopeia mentions a near vision test, but this is not defined.	Chinese Pharmacopeia 0904	
Eye test failures	In the event of a training failure, only one repeat is permitted.		USP <1790>	

ASSESSING VISUAL ACUITY

In looking at the implications from the above review of standards (Table 1), it needs to be acknowledged that there will be some particulates with low probability of detection because they are of a size approaching the visible detection limit. This aside, there are tests that are required across the different standards. Foremost, the regulations and standards call for an assessment of "visual acuity" at a level that is "near normal." This is not so much a reference to the clarity of vision, but more precisely it is a reference to an examination that assesses an examinee's ability to recognize small details with precision. Visual acuity is the product of optical and neural factors (31):

- The sharpness of the retinal image within the eye.
- The health and functioning of the retina.
- The sensitivity of the interpretative faculty of the brain.

The more common issues (and reasons for failing the eye examination) include:

- Hyperopia (farsightedness).
- Myopia (nearsightedness).
- Astigmatism (irregular curvature of the cornea).

Causes of poor visual acuity include (32):

- Refractive error (ametropia) or errors in how the light is refracted in the eyeball.
- Errors in how the retinal image is interpreted by the brain. This can arise from a detached retina; macular degeneration; amblyopia; brain damage, such as from traumatic brain injury or stroke.
- Astigmatism or more complex corneal irregularities.

Medical assessments of visual acuity need to be measured while the eye is fixating, that is as a measure of central (or foveal) vision (33) together with an assessment of peripheral vision (34). A sign of declining acuity normally begins first at the periphery, with the decline following a hyperbola. Common form of measurement is using

optotypes, such as white charts with black, stylized letters of different sizes, such as a Snellen chart or a variant of this using the letter 'E' at different orientations (35), as per Figure 4. This chart measures far vision acuity. Here, 'normal' is defined as the ability to separate contours that are approximately 1.75 milometers apart. This is set out in ISO 8596 (36). In countries using the metric system, normal vision is expressed as 6/6 and in the U.S., where Imperial units are used, normal vision is 20/20. This based on being able to discern a line designated 6/6 (or 20/20), which is the smallest line that a person with normal acuity can read at a distance of 6 meters or 20 feet. Other acuities are expressed as ratios with a numerator of 6 or 20. It is incorrect to refer to 6/6 or 20/20 visual acuity as "perfect" vision. This is because 6/6 or 20/20 is the visual acuity needed to discriminate two contours separated by 1 arc minute (1.75 mm at 6 meters). As an example, for a 6/6 or 20/20 letter, such as the letter 'E', this should have three limbs and two spaces in between them, providing 5 different detailed areas that the person undergoing an eye examination should be able to discern.

In addition, tests should include the Jaeger chart (Figure 3), as recommended in USP Chapter <1790> (37). This is an eye chart for testing near vision acuity. The test consists of a card on which paragraphs of text are printed, with the text sizes increasing from 0.37 mm to 2.5 mm. This card is held at a pre-determined distance from the eye, dependent on the J size being read (38). The type scale on a modern Jaeger eye chart usually ranges from J10 (approximately 14-point type for Times New Roman font) to J1 (approximately 3-point type, Times New Roman). A pass, for near vision assessments, is defined as being able to read the J1 row (3-point font) (39).

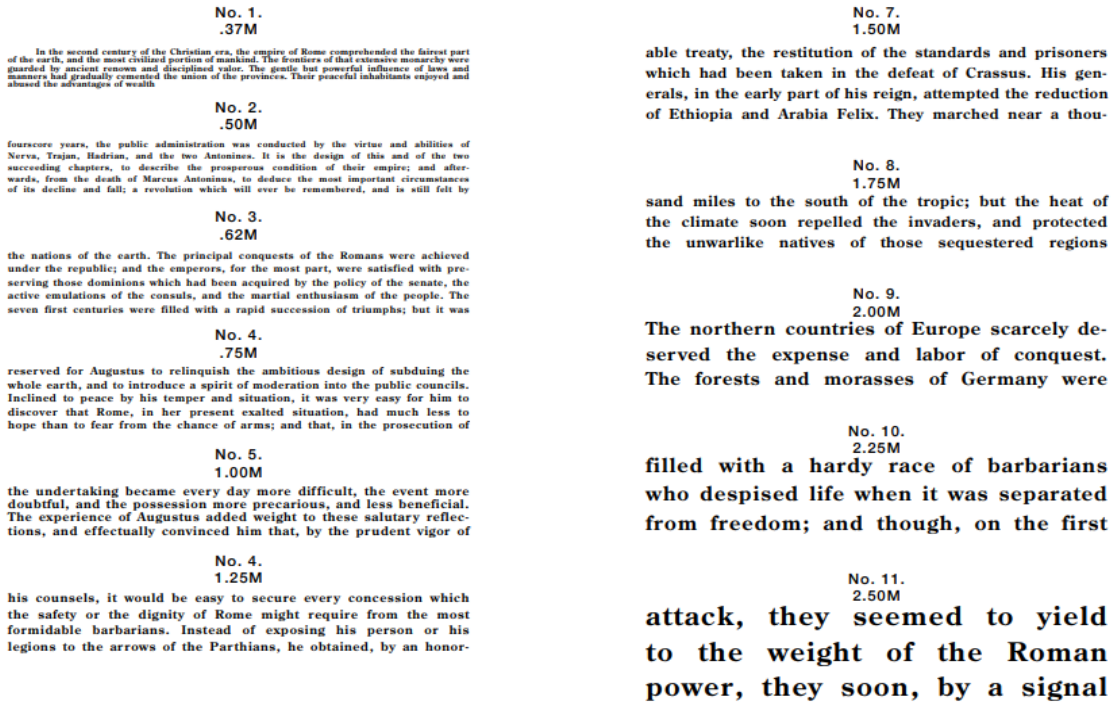

Figure 3: An example of a Jaeger chart, designed to be read 14 inches away. Source: All About Vision (https://cdn.allaboutvision.com/images/jaeger-chart.pdf)

Such tests must be carried out under similar conditions to the inspection light source and at a similar near distance. For daylight vision (photopic vision) visual acuity is better compared with low-light conditions (scotopic

vision). This is because of the activation of cone receptor cells during daylight, and these have high spatial density (and this allows improved acuity unlike low-light where cones do not have sufficient sensitivity and vision is subserved by rods. For this aspect, the lux rating of the lighting conditions during the inspection must be known and replicated in the eye examinations. In terms of undertaking the assessment, ISO 18490 has been developed for a for those who perform a non-destructive test (NDT) (40) (as recommended in the overall standard for NDT, which is ISO 9712) (41). For this, the standard distance must be known. Importantly, the ISO 18490 test is not medical in nature and instead it is intended to objectively ensure adequate near vision perception without reliance on reading ability or text identification.

The ISO 18490 test requires:

- The use of charts printed in black ink on white paper, comprising of two blocks each having 10 lines of 5 optotypes of specified height and width. These are formed of 'E' shapes according to different rotations. An example is provided in Figure 4.
- The body administering the eye test much make sure the printed charts are of a suitable quality. Here, the annotated 250 mm distance between the defined marks shall be measured and cannot be less than 245 mm nor be more than 255 mm.
- Visible, white light, minimum 500 lx, maximum 750 lx is used to evenly illuminate the chart using a calibrated visible light meter.
- The chart is positioned perpendicular to the line of sight on a flat surface and the candidate should view the chart at a test distance of 400 ± 25 mm (and no closer). The distance should be verified by measuring.
- Candidates must wear the same eyewear, if any, as used during routine NDT inspection.
- Where corrective lenses are necessary to achieve the required level of near vision acuity, this must be specifically recorded as part of the results of the test.
- Both eyes must be used at the same time when performing the test.
- The candidate needs to read the chart from left to right, until the candidate reaches the limit of their capability. While not mentioned in the standard, there is a one in four chance that the person undergoing the eye-test can guess the direction; therefore, it is recommended that the patient should correctly indicate the orientation of most letters of the same size, such as four out of five or five out of six.
- Near vision acuity is considered acceptable where the candidate correctly identifies all the individual optotypes, 5 out of 5 on each line, for lines 1 to 9 inclusive. This constitutes a 'pass.' Incomplete lines can be added to the last complete line. For instance, 6/12+3, indicating that the examinee has read the '12' line at 6 meters and gained three of the letters on the '9' line.
- If the result is a "failure,' the candidate can repeat the test using assisted vision.

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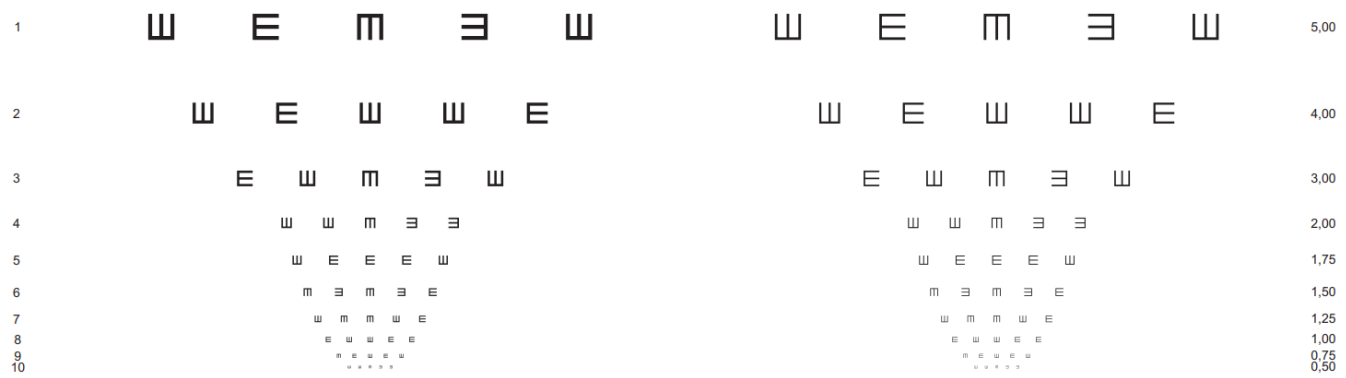

Figure 4: ISO 18490: 2015 chart (or a Snellen chart).

WHAT IS MISSING FROM THE REGULATIONS?

Notably missing from the regulations is any reference to the visual field test (as relating to peripheral vision). The visual field assesses the field of vision, or what can be seen when the eyes are focused on a single point (that is, visual field is how wide of an area the eye can see when a person focuses on a central point). In addition to what can be seen straight ahead, the visual field includes what can be seen above, below, and to either side of the point the eyes are focused on. Vision is typically the sharpest in the middle of the visual field. Assessing the visual field helps to determine where a person's side vision (peripheral vision) begins and ends and how well they can see objects in your peripheral vision. Diseases such as glaucoma, ptosis and droopy eyelids will affect the peripheral vision (42). Methods of assessment include: Confrontational visual field exam, tangent screen test, and automated perimetry exam (43). Interpreting the visual field test depends on the method used. If the Visual Field Index is used, 100% is an indication of perfect vision and 0% would indicate no vision. For visual inspections, the score should be ≥85%.

Another important test is the refraction test. The purpose of this test is to determine whether light bends correctly when it passes through an individual's lens or if a person has a refractive error, such as nearsightedness. During the refraction test, a device with different lenses will be used to view an eye chart 6 meters (20 feet) away. A further test is a dilation test, which examines the pupil; an assessment of eye muscles; and stereopsis (which looks at three-dimensional vision) (44).

Other eye examination tests include:

- An examination of the pupils with a light to see if they respond properly.
- An examination of the retina, at the back of the eye, with a lighted magnifying lens to see the health of blood vessels and of the optic nerve.
- A slit lamp exam, which uses another lighted magnifying device to check various parts of the eye, including the:
    - eyelid
    - iris, the colored part of the eye
    - cornea, the transparent dome that covers the front of the eye

- conjunctiva, the thin membrane covering the whites of the eyes (sclera)

- A colorblindness test, in which the examinee looks at circles of multicolored dots with numbers, symbols, or shapes in them.
- Tonometry, a glaucoma test in which the practitioner uses an instrument to make contact with or blow a painless puff of air at the eye (this helps them measure the pressure of the fluid within the eye).

Considering the above, each would seem to be of importance for the close inspection of pharmaceutical product, such as the ability to differentiate between shapes and structures and to differentiate different colors (such as detecting particulates of a different coloration to the finished product). The most common test for color blindness is the Ishihara color test (as shown in Figure 5). The test uses a number of Ishihara plates, each of which depicts a solid circle of colored dots appearing randomized in color and size. Within the pattern are dots which form a number or shape clearly visible to those with normal color vision, and invisible, or difficult to see, to those with a color vision defect. The acceptance criterion for a pass should be 100%.

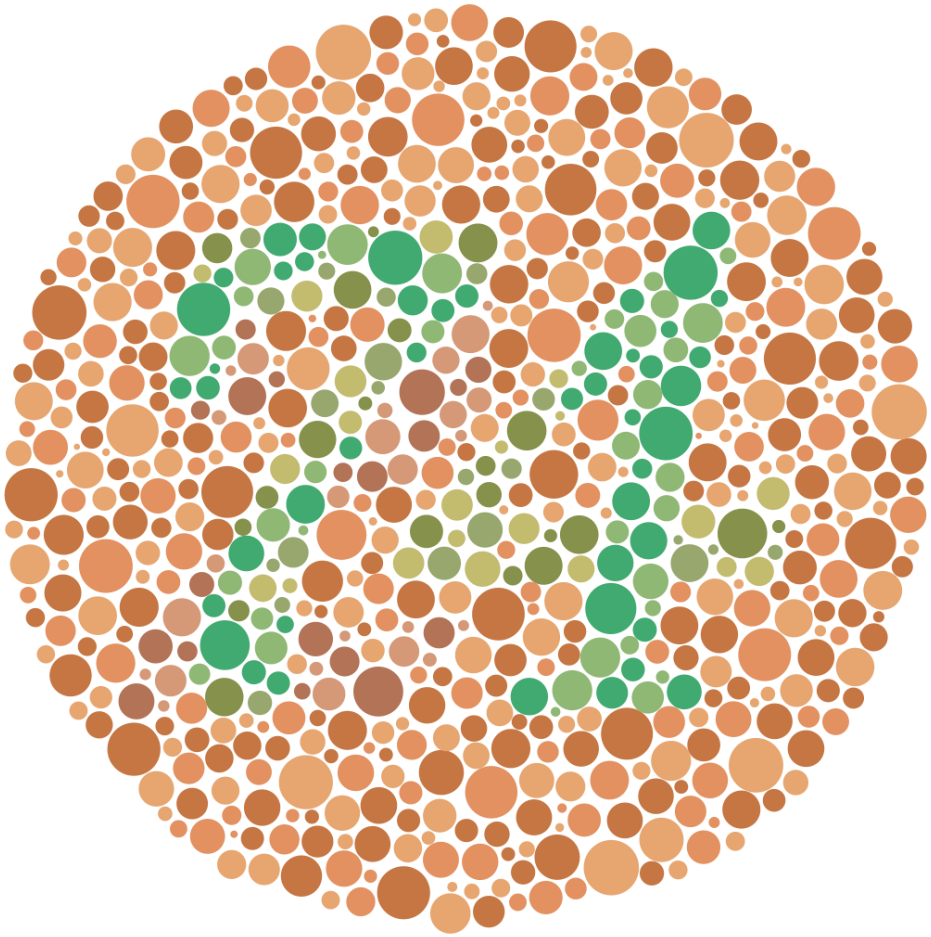

Figure 5: An example of an Ishihara color test plate. The number "74" should be clearly visible to viewers with normal color vision. Viewers with red-green color blindness will read it as "21", and viewers with monochromacy may see nothing. Image by Shinobu Ishihara Public Domain, https://commons.wikimedia.org/w/index.php?curid=104034287

In summary, additional tests (along with the required tests discussed above) to consider are presented in Table 2.

Table 2: Eye examination tests for close visual inspection

Test	Reason for inclusion
Eye examination: Far vision	Snellen chart or equivalent to be used. To show evidence of normal vision at a distance. Acceptance criteria: 6/6 (equivalent to U.S. 20/20) vision. For this, the first 9 rows must be read correctly.
Eye examination: Near vision	Jaeger chart is used. To show evidence of normal vision at close up. Acceptance criteria: To pass, the examinee must be able to correctly read the letters displayed in font point 3.
Visual field / peripheral vision	To ensure the same level of acuity exists across the span of the product being inspected.
Refraction test	To assess nearsightedness, which may affect the position of a person to the product being inspected.
Color blindness	To determine that the individual can differentiate colored particles against the product background.

It may also be important, given the indication above that visual acuity decreases with age (45), to increase the frequency of eye examinations in those aged 50 and over who undertake final product inspections. Here, a six-monthly assessment would be prudent.

CONCLUSION

The process of close visual inspection of pharmaceutical products is an important pat of pharmaceutical quality control and it is necessary to safeguard patient safety so that products with visible particulates are not released into the market. Operators performing visual inspections must be appropriately trained, supported by well-written operating procedures, and be able to differentiate visible particles of different sizes, colors, and dimensions. The training process needs to be supported by eye tests. Care and thought must be given to the eye examination and the specific tests required (which may differ from an everyday eye test). Moreover, the eye tests mentioned in regulatory standards may not be sufficient for an accurate assessment of a person's vision. The frequency of the eye test should also increase as the operator ages past 50 years old. This paper has made reference to additional tests that can be considered and has made recommendations as to the frequency of examinations as the inspector ages.

Note: For readers interested in visual inspection for microbiology laboratories the following paper may also be of interest from the *Journal of Validation Technology*: "Ready for The Count? Back-To-Basics Review of Microbial Colony Counting" (46).

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