Reliability of Operators performing the Visual Inspection of Parenteral Drug Products

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Abstract – *The visual inspection of parenteral product filled vials is performed to assure that any damaged or defective unit is detected and removed prior to packaging. This investigation evaluated the visual inspection process of parenteral products with manual handling to enhance actual process and reduce regulatory exposure. It challenged the probabilistic inspection results due to variability within operators and inspection time. A total of three (3) different standard sets of 100 vials each were evaluated by three (3) inspectors of high, medium and low experience level. The study concluded with a 95% confidence level that there is no significant difference between the results obtained at forty (40) and fifty (50) seconds inspection time neither between the interaction of inspectors and inspection time but that there is significant difference between operators. Consequently, initial and continuous training are essential elements for the quality assurance of the visual inspection process.*

Key Terms – *analysis of variance, operators reliability, parenteral products, visual inspection*

BACKGROUND

The manufacture of parenteral products typically consists of the following key processes: formulation, sterile filtration, aseptic filling, sealing, inspection, labeling and final packaging. Sterile products have several unique dosage form properties, such as freedom from microorganisms, freedom from pyrogens, freedom from particulates, and extremely important high standards of purity and quality; however the ultimate goal in the manufacture of a sterile product is absolute absence of microbial contamination [1]. The inspection process for particulate contamination was the focal point of this study. Particulate matter is an intrinsic element of the manufacturing process.

The European Pharmacopoeia states that visual inspection of drugs for parenteral administration is mandatory. Inspection procedures fall into two categories: 100% inspection or inspection of a statistical sample. Obviously, inspecting a statistical sample does not give absolute assurance that each unit produced will meet specifications. For a given level of defects and a given sampling plan, the probability of a defective item not being discovered can be calculated. Even 100% inspection may not be better. Yet research shows that, even in 100% inspection, up to 15% of defective items are not detected. An example of the fact that we cannot inspect quality into a product is that 100% inspection of parenterals for visible particulates has not resulted in particulate-free products on the market [2]. The results of such inspections are strongly dependent on the performance of human operators. Thus, the reliability of human controls has been demonstrated to be no higher than 85% [3]. Pharmaceutical parenteral preparations must be sterile and free from endotoxins; when examined under suitable conditions of visibility, they should be clear and practically free from particles.

The European Pharmacopoeia defines particle contamination as "extraneous, mobile non-dissolved particles, other than gas bubbles, unintentionally present in the solution".

Visual inspection is one of the quality evaluation tests of parenteral preparations. It is driven by the need to minimize the introduction of unintended particulate matter to patients during the deliverable of injectable medications. Such inspection also offers the opportunity to reject non-conforming units, such as those with cracks or incomplete seals that pose a risk to the sterility of the product [4].

Automatic or manual visual inspection is a complex task that can present an important variability in the results. In fact, it is a subjective control that is not precisely measurable. The detection of particles depends on numerous factors such as the nature and the size of the particles, the type and the intensity of the light used for the inspection, the inspection duration and the length of break between two inspection sets, the time of day of the inspection, the performances of the staff involved with visual inspection, the training of the inspectors and also psychological factors that could affect inspectors and their degree of fatigue. In fact, tiredness is an important parameter, created by inspecting vials over many hours. The confusion between a gas bubble and a particle is a most frequent inspection error. The inspection method can create some bubbles or micro-bubbles which can be confused with particles, and induce a number of false-positive vials resulting in the rejection of vials that conform to the accepted standard [3]. Visible particles (those greater than approximately 50μm) in finished products are normally detected through visual inspection of the end-product by trained operators under controlled conditions.

Most industrial pharmaceutical companies practice manual inspection and have standard operating procedures that describe the training of inspectors and norms for their visual performance. There are some standard reference sets for visible particle contamination, but these sets do not represent all the many different particles contaminating pharmaceutical products; they are also expensive to buy. Nevertheless, they offer an interesting tool to determine operators' visual accuracy [3].

Human reliability could be defined as "the probability that a person has a natural disposition to accomplish a mission in defined conditions in a given time". In the field of visual inspection, reliability is a parameter that is hard to reach because human activity cannot be without failure, even if only occasionally. Individual human performances can vary with time. Thus, when a batch is inspected by different operators, there is a significant fluctuation in the number of rejected vials from one to another. The detection of visible contaminating particles is probabilistic with a high number of units inspected.

When a batch of vials is inspected by two different inspectors or when one single operator inspects the same batch on two different occasions, in both cases, the rate of rejected vials is almost the same between first and second inspections, but rejected vials are not strictly identical. It is possible to see that there is inter/intra-individual variability.

Human beings never act twice in an identical way. This variability is connected to the complexity of sensory, mental and physical processes that are needed to accomplish tasks. It results in some actions being performed outside tolerable parameters; such a situation can become a source of errors. The efficiency of inspectors acting as controls or their capacity to detect substandard products has been studied, particularly in the industrial sector. Human controls are not without fault. In fact, most experts say that efficiency is estimated to be 85% at best. It means that 15% of faults are not detected [3].

When human beings are involved in any process, they can make some errors, even without taking into consideration their competence, experience and level of training.

Visual inspection is a repetitive activity and an inspector performing it could be diverted totally from the process. Thus, there is a loss of vigilance and as a consequence an error could occur. It is important to improve and to reinforce the inspector's training and to continue it regularly. The European Pharmacopoeia states that: "Solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles". "Practically" does not mean "totally" and the interpretation is open. Actually, it is statistically impossible to assure a quality level where no particle is present.

Recognizing the importance of the visual inspection of parenteral products, the objective of this study was to challenge the probabilistic

inspection results due to variability within operators and inspection time with the purpose of identifying an adequate setting for consistent inspection results and a well defined program for the certification of operators responsible for performing the parenteral product visual inspection.

METHODOLOGY

Most inspections today are performed by any of three general techniques:

- Visible inspection with manual handling
- Visible inspection with automated handling
- Automated inspection

Since most industries do not have automatic devices to perform this operation, results are therefore strongly dependent on the performance of human operators.

This investigation appraised the visual inspection process of parenteral products with manual handling to enhance actual process and reduce regulatory exposure.

The visual inspection process in this study involves inspecting vials in dark room underneath fluorescent bulbs inside an inspection station. Vials are inspected by taking a vial at a time, inverting slowly over a period of approximately 40 to 50 seconds against a white and black background. During the inspection process, vials were inspected for appearance, volume, particles, lint, poor seals, defective stoppers, and cracked and scratched container. Inspection operators were required to take a minimum of ten (10) minutes break every fifty (50) minutes of inspection. The light intensity was also controlled to 100-500 foot candle to reduce the number of variables affecting inspection results.

For this study a total of four (4) different parenteral products were evaluated and will be hereafter referred as products A, B, C and D. First of all, the product presentation most difficult to inspect (worst case scenario) was determined. For that purpose, the study considered those characteristics that could directly impact the capacity to identify defects in the parenteral product

vials. Specifically, the following characteristics were identified as the ones increasing visual inspection difficulty:

- Vial size: inspection difficulty is higher in smaller vials' sizes
- Vial type: inspection is more difficult to be performed in molded vials than in tubing vials
- Vial color: amber vials are also most difficult to inspect when compared to clear vials
- Product type: viscous product is most difficult to inspect than aqueous solutions

Table 1
Product Critical Characteristics

Product	Product Type	Vial Size (cc)	Vial Color	Vial Type
A	viscous	5	clear	tubing
		5	clear	molded
		8.2	clear	tubing
		20	clear	molded
		30	clear	molded
		60	clear	molded
B	viscous	8.2	clear	tubing
		30	clear	molded
		60	clear	molded
C	viscous	6	clear	molded
		20	clear	molded
		102	clear	molded
		102	clear	molded
D	aqueous	102	amber	molded
		102	amber	molded

Table 1 summarizes the attributes that were assessed to determine which product combination represents the worst case condition in terms of visual inspection.

Products A and D were identified as the ones having the characteristics most difficult to inspect.

Specifically, product A is one of the worst case scenarios given it is a viscous product filled in molded 5cc vial (smallest vial size). Product A covers all products with the exemption of product D which was also identified as a worst case scenario given it is filled in amber color vial.

This study assessed the reliability of inspectors using product A standard samples. Inspectors shall be capable to classify test samples according to the following categories: critical, major and minor defects as well as to distinguish between good and defective units.

The following table summarizes the inspection criteria categories and the types of defects under each category.

Table 2
Defects Inspection Criteria Categories

Critical	Major	Minor
Visible particles	Cracks	Stains
Volume difference	Deformed vial	Particles of more than 1/16"
Component mix up	Defective stopper	Bubbles of more than 1/16"
Lack of Stopper	Defective seal	Bruises of more than 1/16"
Lack of Seal	Poor seal	
Product Appearance	Component with sharp surface	Damage on aluminum seal but functional
Empty Vial		Deep marks of more than 1/4"

SAMPLES PREPARATION

After identifying the worst case scenario in terms of difficulty for the visual inspection process, then the required samples sets were prepared considering all types of vials defects (non-conforming units) as well as good units (conforming units).

A total of three (3) different standard sets of 100 vials each were prepared for the worst case scenario (product A) as follows:
- 55 Conforming units or good vials
- 45 Non-conforming units or vials with defects; 20 units with critical defects, 15 units with major defects and, 10 units with minor defects

For each sample set, three (3) different visual inspection operators of different level of experience (high, average and low) performed the 100% inspection process.

TRAINING OF VISUAL INSPECTION OPERATORS

First of all, each visual inspection operator had to visit the Infirmary Center in order to assess his/her visual acuity. After a successful visual examination test, each operator followed a training program for visual inspection. Everyone received eight (8) hours of theoretical training in the standard operating procedures and related documents explaining the theoretical aspects of visual inspection.

Practical training, by learning to identify diverse types of defects that could be found in injectable products, was followed. The first part of the practical training was the familiarization with vials resenting the defects that could be found in injectable solutions. During this process, the operators knew the defect present in the vial and they had to be able to identify it. After this step completion, the operators were submitted to a pre-test by means of the identification of defects as well as good vials. For that purpose a standard set of 100 units was prepared (55 good and 45 with defects). The findings were recorded by the trainer. Acceptance limits of 85/100 were fixed to be able to start the evaluation (certification) process.

The three (3) operators used for the execution of this study were subjected to the training process regardless their level of expertise or experience conducting visual inspection process.

CERTIFICATION PROCESS

The certification process was performed using the three (3) different standard sets of samples. Each standard set was inspected for forty (40) and fifty (50) seconds by each operator for a total of six (6) inspections by operator. For the test, one (1) vial was inspected at the same time in a dark room underneath fluorescent bulbs inside an inspection station. Vials were inspected against a white and black background and having ten (10) minutes break every fifty (50) minutes of inspection. The findings were recorded to then use to assess operators' reliability for conducting visual inspection.

OPERATORS' RELIABILITY EVALUATION

The performance of the operators during this study was estimated by the calculation of the following factors, varying between the values of 0 and 1. The calculation of these factors permits the evaluation of an accuracy score (AS) with variations between 0-400 [3].

Sensitivity (Se): Detection of non-conforming units

$$Se = TP / (TP + FN) \qquad (1)$$

Specificity (Sp): Detection of conforming units

$$Sp = TN / (TN + FP) \qquad (2)$$

Positive Predictive Value (PPV): Probability that a detected non-conformity is true

$$PPV = TP / (TP + FP) \qquad (3)$$

Negative Predictive Value (NPV): Probability that a conformity is true

$$NPV = TN / (TN + FN) \qquad (4)$$

Accuracy Score (AS): Sum of the four (4) values X 100

$$AS = (Se + Sp + PPV + NPV) \text{ X } 100 \qquad (5)$$

Where,

TP = True Positive (45 Non-conforming vials from each sample set)

TN = True Negative (55 Conforming vials from each sample set)

FP = False Positive (Conforming vials identified as non-conforming by the visual inspection operators) and,

FN = False Negative (Non-conforming vials identified as conforming by the visual inspection operators.

The inspection results by the inspectors were then analyzed for any significant difference between the inspection time (40 and 50 seconds) and the operators' expertise based on years of experience (low, average and high).

The sensitivity and specificity results obtained were analyzed by means of an Analysis of Variance between groups (Two-way ANOVA Test) to determine if there was significant difference between inspectors and inspection times' results.

RESULTS AND DISCUSSION

The sensitivity, specificity, positive predictive value, negative predictive value and the accuracy score of each inspector for each set of sample set inspected at 40 and 50 seconds time requirement were calculated.

Being sensitivity and specificity the most relevant factors evaluated as part of this study these values were all put together to determine if there was any significant difference between inspection time and operators' expertise.

Sensitivity Results Analysis

Tables 3 and 4 summarize the sensitivity results (ability for the detection of non-conforming), obtained by each operator for each sample set at 40 and 50 seconds inspection time respectively.

Table 3
Sensitivity Results at 40 Seconds Inspection Time

Inspector	Set 1	Set 2	Set 3	Average	Std dev.
1	0.82	0.88	0.79	0.83	0.05
2	0.84	0.70	0.59	0.71	0.13
3	0.74	0.76	0.64	0.71	0.06

The average sensitivity result was higher for inspector 1 than for inspectors 2 and 3. Thus, inspector 1 with high experience level better identified non-conforming units.

Table 4
Sensitivity Results at 50 Seconds Inspection Time

Inspector	Set 1	Set 2	Set 3	Average	Std dev.
1	0.97	0.89	0.80	0.89	0.09
2	0.83	0.80	0.70	0.78	0.07
3	0.79	0.76	0.66	0.74	0.07

The average sensitivity result was higher for inspector 1 than for inspectors 2 and 3 consistent with the results at 40 seconds inspection time. Thus, inspector 1, with high experience level, better identified non-conforming units. Improved results were also obtained at 50 seconds inspection time.

Based on the aforementioned results, the ability to detect non-conforming units seems to improve with the level of experience of the inspectors and also with the inspection time.

This conclusion was challenged by evaluating sensitivity results obtained at 40 and 50 seconds inspection time using an Analysis of Variance between groups (Two-way ANOVA Test). The following Tables summarize the data evaluated as well as the test results.

Table 5
Sensitivity Results Summary

Time	Inspector		
	1	**2**	**3**
1	0.82	0.84	0.74
	0.88	0.70	0.76
	0.79	0.59	0.64
2	0.97	0.83	0.79
	0.89	0.80	0.76
	0.80	0.70	0.66

Table 6
Two-way ANOVA: Sensitivity versus Inspector and Time

Source	DF	SS	MS	F	P
Inspector	2	0.0627	0.03134	4.89	0.028
Time	1	0.0108	0.01076	1.68	0.219
Interaction	2	0.0015	0.00077	0.12	0.887
Error	12	0.0769	0.00641		
Total	17	0.1518			
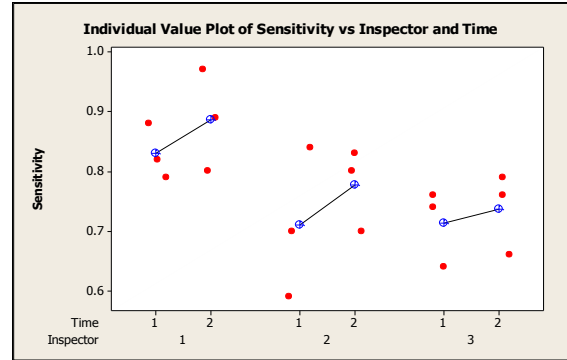
Figure 1
Individual Value Plot of Sensitivity vs. Inspector & Time
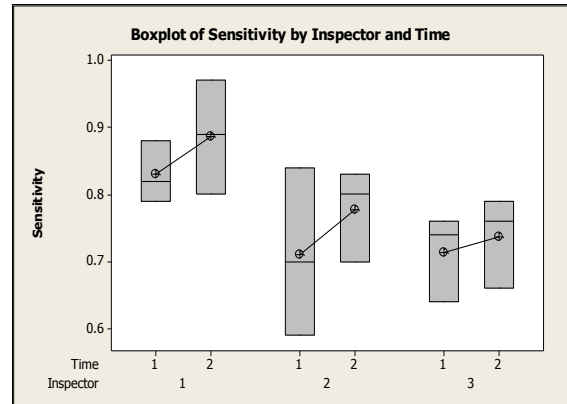
Figure 2
Boxplot of Sensitivity vs. Inspector & Time

Based on the results of the two-way ANOVA test it is concluded with a 95% confidence level that:

- There is a significant difference between operators since the P value obtained was 0.028 which is less than 0.05. In addition, the experimental F value for the operators was 4.89 which is more than the critical F value of 3.89.

- There is no significant difference between inspection times since the P value obtained was 0.219 which is more than 0.05. In addition, the experimental F value for the times was 1.68 which is less than the critical F value of 4.75.

- There is no significant difference between the interaction of inspectors and inspection times since the P value obtained was 0.887 which is more than 0.05. In addition, the experimental F value obtained was 0.12 which is less than the critical F value of 3.89.

Specificity Results Analysis

Specificity results were also evaluated to determine if there was significant difference between inspection time and operators' expertise for the detection of conforming units. Tables 7 and 8 summarize the specificity results obtained by each operator for each sample set at 40 and 50 seconds inspection time respectively.

Table 7
Specificity Results at 40 Seconds Inspection Time

Inspector	Set 1	Set 2	Set 3	Average	Std dev.
1	0.67	0.89	0.87	0.81	0.12
2	0.89	0.91	0.96	0.92	0.04
3	0.93	1.00	0.94	0.96	0.04

The average specificity result was higher for inspector 3 than for inspectors 1 and 2. Thus, inspector 3, with low experience level, better identified conforming units.

Table 8
Specificity Results at 50 Seconds Inspection Time

Inspector	Set 1	Set 2	Set 3	Average	Std dev.
1	0.62	0.73	0.93	0.76	0.16
2	0.85	0.91	0.89	0.88	0.03
3	0.96	0.98	0.85	0.93	0.07

The average specificity result was higher for inspector 3 than for inspectors 1 and 2 consistent with the results at 40 seconds inspection time. Thus, inspector 3, with low experience level, better identified conforming units. Improved results were not obtained at 50 seconds inspection time. Based on the above, the ability to detect conforming units does not seem to be related to the level of experience of the inspectors neither with the inspection time. This conclusion was challenged by analyzing specificity results obtained at 40 and 50 seconds inspection time using an Analysis of Variance between groups (Two – way ANOVA Test). The following Table summarizes the data evaluated as well as the Two- way ANOVA test results.
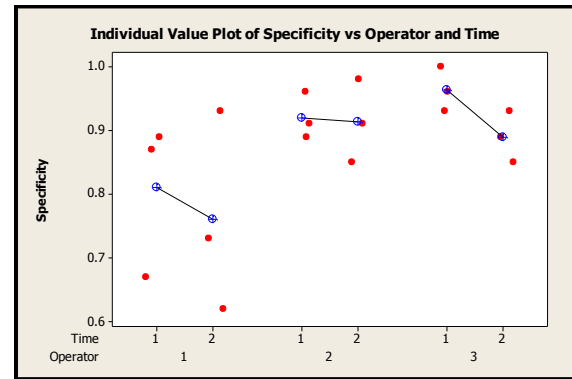
**Table 9**
Specificity Results Summary

Time	Inspector		
	1	2	3
1	0.67	0.89	0.93
	0.89	0.91	1.00
	0.87	0.96	0.96
2	0.62	0.88	0.93
	0.73	0.91	0.89
	0.93	0.98	0.85

Table 10
Two-way ANOVA: Specificity vs. Inspector & Time

Source	DF	SS	MS	F	P
Inspector	2	0.0750	0.03751	4.70	0.031
Time	1	0.0085	0.00845	1.06	0.324
Interaction	2	0.0034	0.00172	0.22	0.809
Error	12	0.0957	0.00798		
Total	17	0.1826			

Figure 3
Individual Value Plot of Specificity vs. Operator & Time
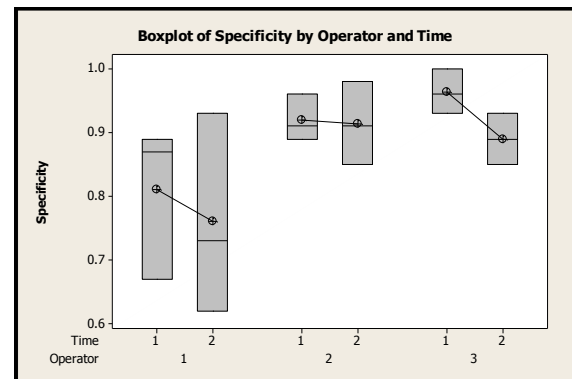
Figure 4
Boxplot of Specificity vs. Operator & Time

Based on the results obtained in the two-way ANOVA test it is concluded with a 95% confidence level that:

- There is a significant difference between operators since the P value obtained was 0.031 which is less than 0.05. In addition, the experimental F value for the operators was 4.70 which is more than the critical F value of 3.89.
- There is no significant difference between the two inspection times since the P value obtained was 0.324 which is more than 0.05. In addition, the experimental F value for the times was 1.06 which is less than the critical F value of 4.75.
- There is no significant difference between the interaction of inspectors and inspection times since the P value obtained was 0.809 which is more than 0.05. In addition, the experimental F value obtained was 0.22 which is less than the critical F value of 3.89.

Accuracy Scores Evaluation

Lastly, accuracy scores were also put together for each sample set to evaluate overall the results obtained at different inspection time and with different level of operators' expertise.

Table 11
Accuracy Results at 40 Seconds Inspection Time

Inspector	Set 1	Set 2	Set 3	Average	Std dev.
1	297	355	332	328	29
2	346	325	323	331	13
3	338	360	326	341	17

Table 12
Accuracy Score Results at 50 Seconds Inspection Time

Inspector	Set 1	Set 2	Set 3	Average	Std dev.
1	321	323	348	331	15
2	337	344	321	334	12
3	355	355	306	339	28

No result reported by any inspector was identical to those of the others. This fact indicates that there is an important inter-individual variability between inspectors' visual detection capacities. In fact, when one inspector identified a vial as defective, a second inspector accepted it as a conforming unit.

The accuracy score being a value resulting from the calculation of the specificity and sensitivity, it represents a mean value of them. For all operators, an acceptable reliability was observed.

CONCLUSION

Humans have a limited reliability, which is probably reinforced in this study by the particulars of the studied task: repetitive activity, necessity for high concentration and particle sizes approaching the limits of visual performance.

The study concluded with a 95% confidence level that there is no significant difference between the results obtained at forty (40) and fifty (50) seconds inspection time neither between the interaction of inspectors and inspection time.

On the other hand, it was demonstrated with a 95% confidence level that there is significant difference between operators.

Experienced operators in the study had better results than beginners in the identification of non-conforming units while beginners demonstrated better performance in the identification of conforming vials. Based on that it is concluded that the experience level of the operators help them in better identifying non-conforming units. For example, experienced operators can better distinguish between a gas bubble and a particle which is the most frequent inspection error. They had more number of false-positive which is the rejection of vials that conform to the accepted standard. Thus, they were more conservative in terms of rejecting those units in question than beginners.

On the contrary, beginners had better performance in identifying conforming units but

were not that accurate in identifying non-conforming units. They had more false negative results in where non-conforming vials were identified as conforming units. This could result in releasing defective units to the field.

In terms of the accuracy scores they were very similar regardless the experience of the operators since experienced operators had better performance identifying non-conforming units and beginners had better performance identifying conforming units. Nonetheless, when evaluating the significance of the results of this study it is concluded that the operators' experience is an important factor for better inspection results and for minimizing compliance and patient risk. Consequently, initial and continuous training are essential elements for the quality assurance of the visual inspection process.

REFERENCES

[1] Berry, Ira R., et al., *Pharmaceutical Process Validation*, second edition, 1993, pp 25.

[2] Agalloco, James P., et al., Validation of Pharmaceutical Processes, second edition, 1999, pp 11.

[3] Sadeghipour, Farshid, et al., "The Reliability of Operators when visually inspecting parenteral drugs", Journal of the European Association of Hospital Pharmacists (EAHP), Volume 13, 2007, pp 41-45.

[4] Madsen, Russell E., et al. "Visible Particles in Injections – A History and a Proposal to revise USP General Chapter Injections", Pharmacopeia Forum, Volume 35, 2009, pp 1383-1387.