The reliability of operators when visually inspecting parenteral drugs

Authors: Farshid Sadeghipour, PhD, Alexandra Bugmann, MSc, Victor Herrera, Pharmacy Technician, Pascal Bonnabry, PhD

Abstract

Objective: To develop training and validation kits for staff in a hospital pharmacy who are involved with inspecting parenteral drugs prepared in the department; to assess the reliability of staff in carrying out the procedure.

Methods: A visual inspection validation kit was developed (90 negative vials with no particulate contamination and 10 positive vials containing particles) and the performance of operators during validation was estimated by calculation of the following parameters from their results grid: sensitivity (detection of products that did not conform), specificity (detecting only those vials that conformed to the standard), positive predictive value (probability that a detected non-conformity is a true one), negative predictive value (probability that a vial actually conforms) and the accuracy score (sum of the four values x 100).

Results: Eleven different operators have used the validation kit. The results showed a high variability between the operators for the different calculated values. This is probably reinforced by the particulars of the studied task (repetitive activity, necessity of giving the task high concentration, particle size approaching the lower limit of detection by vision).

Conclusion: This study also confirmed that experienced operators who took part in the experiment have better results than beginners, and that initial and continual training are essential elements for the quality assurance of visual inspection.

Keywords

Visual inspection, human reliability, validation, parenteral drugs

Introduction

The European Pharmacopoeia states that visual inspection of drugs for parenteral administration is mandatory. However, the results of such inspections are strongly dependent on the performance of human operators. The reliability of human controls has been demonstrated in other fields to be no higher than 85%, but no data regarding visual inspection specifically exist in the literature.

Pharmaceutical parenteral preparations are usually made up in isotonic solutions; they must be sterile and free from endotoxins; when examined under suitable conditions of visibility, they should be clear and practically free from particles [1].

The presence of particles in injectable solutions could have serious consequences for patients' health. In fact, cases of thrombosis, embolism, infarction, cerebral vascular accident and even death are assigned to the presence of particulate contamination [2]. So, the importance of visual inspection becomes obvious, particularly when the medicine is prepared for paediatric use.

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 [3].

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 [4]. Because the number of detected particles increases with the improvement of the inspection method, no control can be considered theoretically as an absolute one [5]. Moreover, performed in industrial practices, i.e. with a high number of units inspected, the detection of visible contaminating particles is probabilistic (based on probability).

In hospital pharmacies, visual inspection is performed manually by qualified inspectors, observing each vial, one by one, with specific equipment, as described in the European Pharmacopoeia.

Contact for correspondence:

Dr Farshid Sadeghipour
Pharmacy of the University Hospitals of Geneva
24 Micheli-du-Crest
CH-1211 Geneva 14, Switzerland
Tel: +41 22 382 39 79
Fax: +41 22 382 39 70
farshid.sadeghipour@hcuge.ch

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 [6].

The confusion between a gas bubble and a particle is a most frequent inspection error [7]. 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 [7-9].

Human visual acuity can detect particles larger than 50 μm, but to ensure reproducibility of the inspection, it was better to fix the limit of detection at 100 μm. Most industrial pharmaceutical companies practise manual inspection and have standard operating procedures that describe the training of inspectors and norms for their visual performance [9].

There are some standard reference sets for visible particle contamination [10], but these sets do not represent all the many different particles contaminating pharmaceutical products in a hospital pharmacy; they are also expensive to buy. Nevertheless, they offer an interesting tool to determine operators' visual accuracy.

Reliability of human controls

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" [11].

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 significantly with time [7, 8]. Thus, when a batch is inspected by different operators, there is a significant fluctuation in the number of rejected vials from one to another [9].

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 [12-14].

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 [4, 11]. The efficiency of inspectors acting as controls or their capacity to detect substandard products has been studied, particularly in the industrial sector [11, 15]. 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 [4, 15]. 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 [15].

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 [11]. 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.

The objective of our study was to evaluate the reliability of our visual inspection operators and to verify their ability to identify particles in parenteral solutions, but also to determine the main parameters affecting their performance.

Methods

Training and validation kits

The training kit (kit A) contained 30 positive (contaminated) units (vials and ampoules) issued from our parenteral solutions production unit. This kit permitted the operators to learn to distinguish different kinds of positive vials and to identify the contaminating elements.

A validation kit was assembled, consisting of units that conformed to the standard and were not contaminated, as well as others that were contaminated. This kit, which validated the inspectors' performance, was developed with 90 negative (conforming) and 10 positive (non-conforming) vials. Negative and positive units were chosen from conforming and non-conforming samples from our parenteral solutions production unit, containing different kinds of particles encountered in injectable drugs (e.g. stopper, glass or fibre fragments). Each non-conforming unit contained one or two particles of different kinds with particle sizes of 100-500 μm.

Three different validation kits were set up (kits B, C or D). These kits had the same quantity of negative and positive units but not in the same configuration, i.e. the non-conforming units could

be a different container, placed and numbered differently in the kit. The units chosen for the training and validation kits represented different sizes and types of containers: 1 mL to 20 mL ampoules and 5 mL to 100 mL vials or bottles.

Training and validation were performed using a visual inspection table in accordance with the European Pharmacopoeia specifications, with a neon light intensity of 3,000 lux.

Training of Geneva University Hospitals pharmacy inspectors and validation of their performance

First of all, each visual inspection operator had to visit the hospital's Staff Medical Officer Service in order to assess his/her visual acuity. The visual acuity had to be greater than 80% (this norm is also applied in the aviation industry) to be considered as operational. Each trainee followed a training programme for visual inspection. Everyone received a standard operating procedure explaining the theoretical aspects and clinical justification. Practical training, by learning to identify diverse types of particles that could be found in injectable products, and adhering to pharmacopoeia recommendations, were followed. The first part of practical training was the inspection of 30 contaminated vials (kit A). Each inspector had to identify the different types of particles and the number of particles present in each vial. The findings were recorded and checked by the trainer. Acceptance limits (27/30) were fixed to validate each trainee inspector.

The validation test was performed twice with two of the three validation kits (kits B, C or D). For this test, inspectors had 60 minutes (with a five-minute break every 15 minutes) to inspect a total of 100 vials and to report their comments on a checklist. The validation of each inspector was approved if he/she could detect 80% of positive vials or ampoules from each kit. This validation had to be set over two days: the first day, in the morning, between 8 and 9 am and the second day, in the afternoon, between 3 and 4 pm.

Operators' reliability evaluation

The checklists completed by the inspectors were analysed to verify any significant difference between morning and afternoon results (intra-individual variability). The performance of operators during validation was estimated by the calculation of the following parameters from their results grid:

- True positive (TP): 10 positive (non-conforming) vials of the validation kit
- True negative (TN): 90 negative (conforming) vials of the validation kit
- False positive (FP): conforming vials identified visually as non-conforming by the inspector
- False negative (FN): non-conforming vials identified visually as conforming by the inspector

These parameters were used to calculate the following factors, varying between the values 0 and 1, according to the formulae presented in Table 1:

- Sensitivity (Se) representing the detection of non-conformity
- Specificity (Sp) representing only the detection of conforming vials
- Positive predictive value (PPV) being the probability that a detected non-conformity is true
- Negative predictive value (NPV) being the probability that a conformity result is true

Table 1: Formulae for the calculation of factors to evalute reliability of operators

Parameter	Formula
Specificity (Sp)	$Sp = \frac{TN}{TN + FP}$
Sensitivity (Se)	$Se = \frac{TP}{TP + FN}$
Positive predictive value (PPV)	$PPV = \frac{TP}{TP + FP}$
Negative predictive value (NPV)	$NPV = \frac{TN}{TN + FN}$
Accuracy score (AS)	$AS = (Se + Sp + PPV + NPV) \times 100$

Key: TN: true negative, FP: false positive, TP: true positive, FN: false negative

The calculation of these four factors permits the evaluation of an accuracy score (AS) (variations between 0-400).

Validation test of the expert inspectors of the pharmaceutical industry

We also acceded to the methodology and the results of validation tests of five expert visual inspectors of the pharmaceutical industry in our region.

Each inspector tested the entire validation kit of 250 glass syringes, containing 80 non-conforming products, 10 consecutive times. The results of these tests were analysed by the same method as above and the different reliability factors were calculated. The mean results were calculated over 50 inspections of this validation kit (12,500 syringes inspected)

Results and discussion

Training and validation of the inspectors from the pharmacy department of Geneva University Hospitals

The validation sets are small in number, but it is important to take into consideration the small number of medicines that are produced in hospital pharmacies. It should be easy to implement these sets in every hospital pharmacy.

Table 2: Results for three of the inspectors in the pharmacy department of Geneva University Hospitals

Inspector	Assessment	True positive	False positive	Sensibility	Sensitivity	Accuracy score
1	Sensitive and specific	8	2	0.800	0.978	356
4	Very sensitive but less specific	10	17	1.000	0.811	318
11	Neither sensitive nor specific	3	14	0.300	0.844	224

Eleven operators followed the training programme and they had successful eye tests. They all passed the training test with an average score of 92.3%. While four operators passed the validations successfully, two of them succeeded in only one of the two validations and five failed both tests. Between the four operators who were successful with the two validation kits, only one of them had never had experience of visual inspection. The other three were the most experienced inspectors in the pharmacy.

There is no real correlation between the number of false positive vials and the experience of inspectors regarding visual inspection.

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 the inspectors' visual detection capacities. In fact, when one inspector identified a vial as contaminated, a second inspector accepted it as conforming to the standard.

Even if inspectors felt more tired in the afternoon, there was no significant difference between morning and afternoon inspections, indicating no significant intra-individual variability.

Table 2 illustrates the results from some of the inspectors. The best results obtained (from inspector 1) identified eight contaminated vials out of 10 and only two false-positives. It represents a sensitive and specific inspector, and has a good accuracy score. Inspector 4 is very sensitive but less specific than inspector 1, because he found 17 false-positive vials in addition to the 10 contaminated vials found. The last of the 11 inspectors was assessed as the worst. He was neither sensitive nor specific, and his accuracy score was very low.

The same test was performed by the four most experienced inspectors with polarised light. With this method, we could see some particles which are not seen under neon light. Actually, polarised light is preferred for ampoule inspection but not for vials, because there are less gas bubbles in ampoules.

Table 3: Results showing the reliability of the tested inspectors in the pharmacy department of Geneva University Hospitals (n=11)

Parameter	Mean value	Minimum	Maximum	Relative standard deviation
Sensitivity	0.650	0.300	1.000	32.0 %
Specificity	0.930	0.811	1.000	5.6 %
Positive predictive value	0.560	0.180	1.000	37.0 %
Negative predictive value	0.960	0.920	1.000	2.3 %
Accuracy score	310	224	378	12.0 %

Reliability of the inspectors from the pharmacy department of Geneva University Hospitals

The results presented in Table 3 show a high variability between the operators for the different calculated values. Indeed, the sensitivity of the operators with a quite mediocre score has also a very high variation (relative standard deviation [RSD] of 32%). It is principally because so few vials were non-conforming and their identification was more difficult than the recognition of conforming vials. Consequently, the specificity value had a higher mean value and much lower RSD. These results are confirmed by the calculated values of positive and negative predictive values, also showing the same trends. The accuracy score being a value resulting from calculation of these values, it represents a mean value between specificity and sensitivity. For a small majority of the tested operators, an acceptable reliability was observed.

Validation test of the expert inspectors of the pharmaceutical industry

The results presented in Table 4 are most interesting. We can see that these expert visual inspectors from the pharmaceutical indus-

Table 4: Results showing the reliability of tested expert inspectors in the pharmaceutical industry (n=5)

Parameter	Mean value	Minimum	Maximum	Relative standard deviation
Sensitivity	0.620	0.558	0.658	7.2 %
Specificity	0.895	0.891	0.925	2.5 %
Positive predictive value	0.741	0.641	0.805	7.5 %
Negative predictive value	0.834	0.807	0.855	2.2 %
Accuracy score	309	286	321	4.5 %

try had quite similar mean values regarding sensitivity and specificity, but with much lower RSDs. This shows a better homogeneity in their appreciation faculties and reliability potential. Nevertheless, higher positive predictive values (PPV) demonstrate that they are more reliable in detecting non-conforming vials. The overall results represented by the accuracy score (AS) show similar mean values but always with less variability for the industry inspectors.

General discussion

In the medical field, important variability in interpretation of a situation is not unique. In 1994 and in 2005 [16, 17], two studies were published on the variability in interpretation of mammograms by radiologists. These studies were based on the cancer detection capacities both in healthy women and in women who presented with some signs of tumour. Results are surprising. For example, the 1994 study [16] selected 150 mammograms and among them, 27 cases presented a histopathology of breast cancer and the other 123 presented no signs of cancer after three years of medical examination. Then 10 radiologists examined all 150 mammograms. Results show that for the same mammography, radiologists proposed several diagnoses. In one case in particular, two radiologists did not agree with the localisation of the cancer (left breast or right breast).

For the other study [17], the interpretation experience of the radiologists was examined. In fact, the radiologists with less experience showed less satisfying results than radiologists who practised interpretation of mammograms on a daily basis.

Conclusion

Referring to the two radiological studies above [16, 17] and the results of the validation of the visual inspection in the pharmacy department of the University Hospitals of Geneva, it appears that experience and regular training are essential parameters to maintain satisfactory human control of visual inspection of parenteral preparations.

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 particles sizes approaching the limits of vision performance.

Even if experienced operators in the study had better results than beginners, a systematic evaluation approach determines their real reliability (sensitivity, specificity, positive predictive value, negative predictive value and accuracy score), and this is particularly well demonstrated with the homogeneous results of the expert inspectors from the pharmaceutical industry. Consequently, initial and continuous training are essential elements for the quality assurance of visual inspection.

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