

Introduction into test sets for the visual inspection of parenterals

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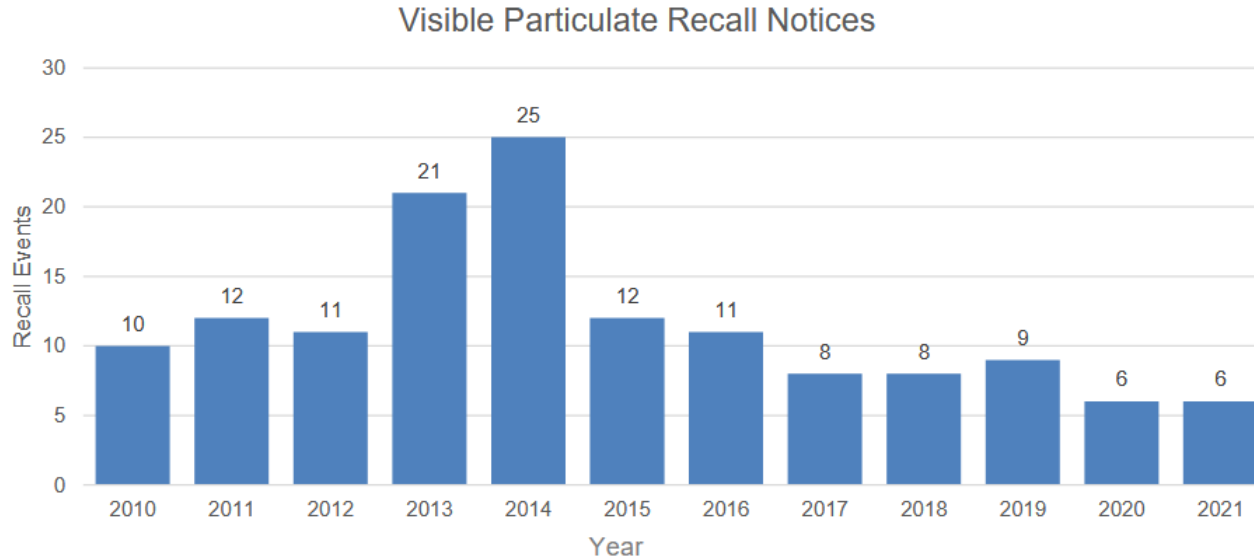
PDA
TRAINING

Why do we use visual inspection?

- 100 percent inspection of injectable products is required by regulatory bodies like EMA and FDA
- All main pharmacopeias (EP, USP and JP) require visual inspection of parenteral products
- Regulations on the acceptable size or number of found particles and testing procedures for parenterals are also described, however an implementation guidance of the process is missing

Why do we use visual inspection?

Recall events for particulates



Source: <https://www.fda.gov/Safety/Recalls/default.html>

What is in principle a test set?

- **Principle**

„A group of defect standards combined with good or blank units used to evaluate the probability of detection in visual inspection or testing system performance. Test sets can be used for inspector training, validation of automated systems, or other special studies as needed” – PDA TR79



What is in principle a test set?

- **Contents of a Reference Standard Test Set**
 - Defect free containers
 - Containers that each have one particle in a known size
 - If needed, additional defects like scratches, cracks, defects of the cap, underfilling and overfilling...
- **Quantity**
 - Enough to cover the entire range of known defects (customer specific)
 - Percentage of defective containers less than 10 % in the manual inspection

Why do we use reference standards in visual inspection?

- **Quality control of the manual inspection**
 - Training the testing staff
 - Qualification / Requalification for the testing staff
 - Establishing baseline
- **Quality control of the automated inspection**
 - Validation and qualification of the inspection process
 - Control of the machine setup
 - Inspection following a format change

Why do we use reference standards in visual inspection?

- **Monitoring routine performance of the inspection process**
 - Over a long period of time
 - Functional test at the beginning / end of a batch
- **Producers of inspection machines**
 - Improvements
 - New developments
 - New product / camera and tool setup
- **Comparison of inspection techniques**
 - Manual vs. Automatic (Knapp Test)
 - New product

Different test kits

- Test sets are composed differently, depending on the desired usage of the kit
- Test sets should be customized considering different aspects:
 - Container type
 - Size
 - Fill volume
 - Product characteristics
 - Manufacturing conditions
 - Inspection parameters



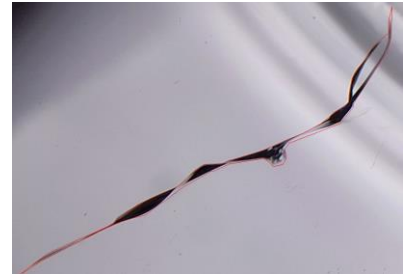
When should you create a test kit ?

A test kit should be created for every product family and each container type (please, see phase-appropriate approaches discussion later)

- Bracketing approaches may be applicable, based on assessment
- Test kits are needed to qualify VI operations (prove that inspectors/ machines are trained/ qualified)
- Different test kits fulfil different roles:
 - Introduction/training
 - Challenge – qualification and periodic re-qualification
 - Baseline e.g. across a multi-site network
 - Evaluation of machine manufacturers

Different kinds of test kits (based on preparation)

- When creating a test set you have the possibility to use selected defects from your production or recreated defects from a controlled laboratory environment
- Using defects from production
 - Advantages: Low cost, most realistic defects
 - Disadvantages:
 - Hard to find enough samples for rare defects
 - Polymorphism
 - Defect characterization of particles in size and material



Different kinds of test kits (based on preparation)

- Using recreated defects in the test set:
 - Advantages:
 - Polymorphism ensured
 - Recreation of defects possible
 - Same test sets across different sites
 - Specific size ranges available
 - Disadvantages:
 - Expensive
 - Risk of deviation from actual defects

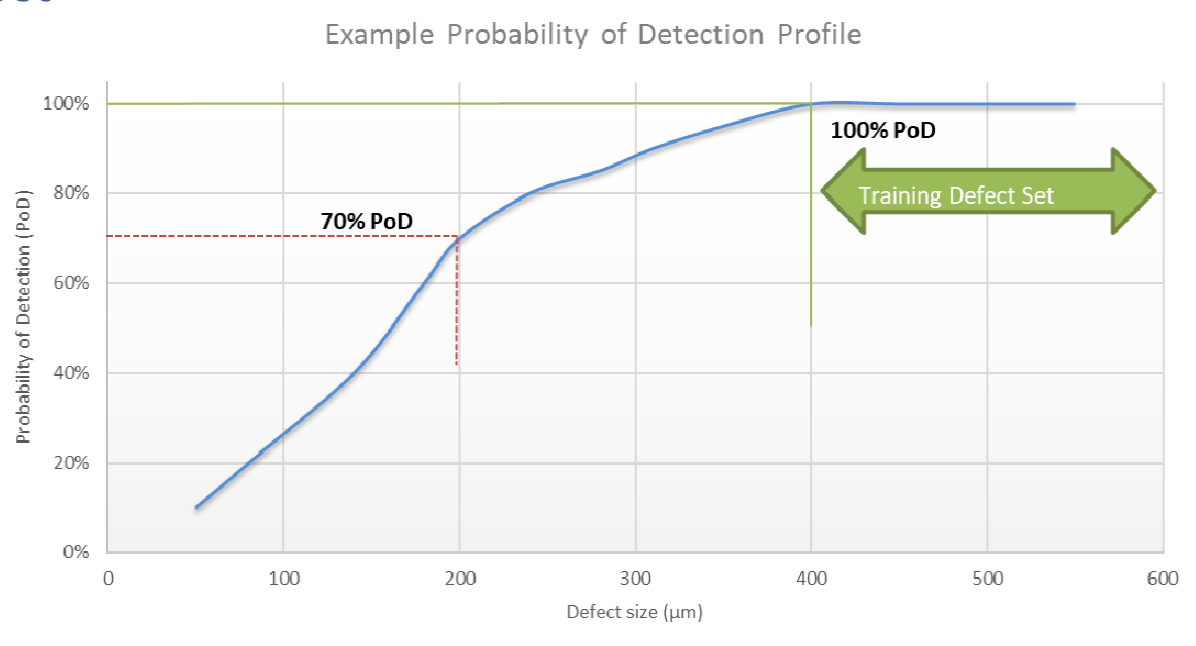
Different kinds of test kits (based on composition)

- **Training set**

- Set utilized to familiarize and train inspectors on the full range of possible defects
- Small size
- Typically, easy to detect defects, but can include also challenging defects
- Primary goal: Familiarize inspectors with the appearance of acceptable products, common and critical defects

Different kinds of test kits (based on composition)

- Training set



Different kinds of test kits

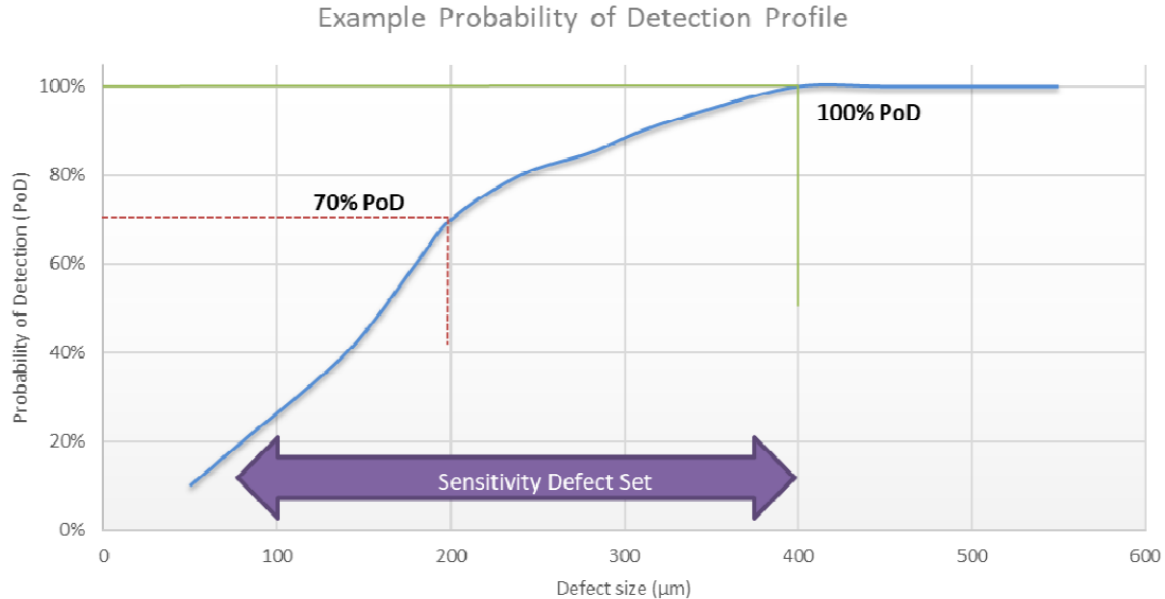
- **Knapp kit**

Incorporates a variety of defect types and densities that are typically found in the manufacturing environment

- Broad size range of particles
- Used to determine the baseline for a specific product/container combination -> results in an average PoD calculation for each defect type
- Contains all defect ranges
- Incorporates a variety of particle types and presentation defects
- Used to challenge inspectors and AVI machines

Different kinds of test kits

- Knapp Test Set/Sensitivity Test Set



Different kinds of test kits

- **Evaluation Defect Set for new VI machine**
 - For e.g. green field project
 - Best VI Inspection machine for the inspection of the product should be found -> comparison between different manufacturers
 - Contains all defect ranges
 - Incorporates a variety of particle types and presentation defects

Different kinds of test kits

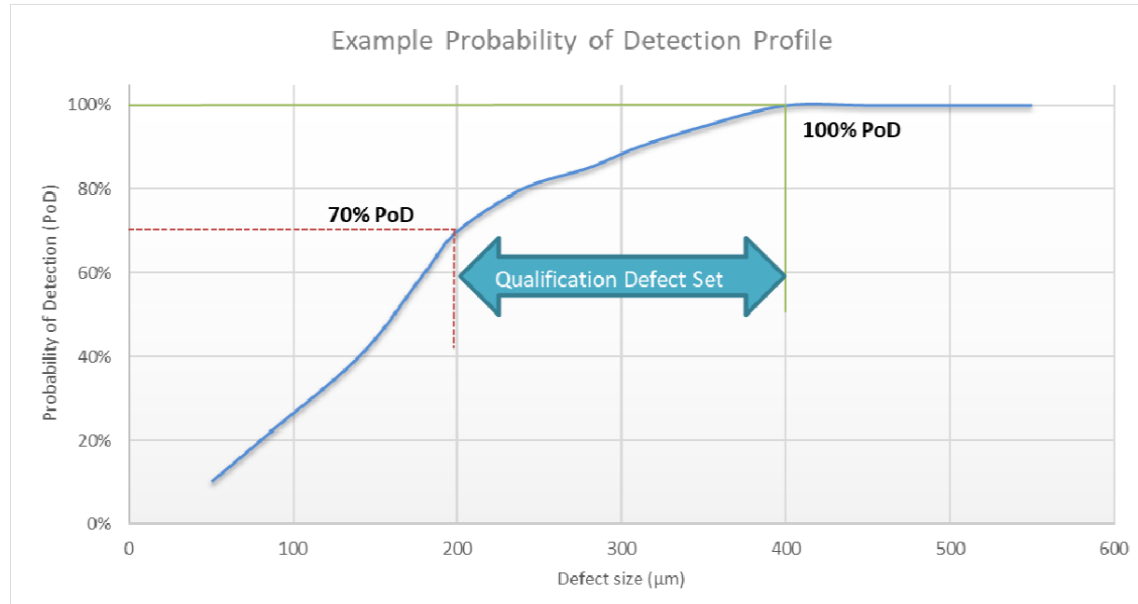
- **Qualification Test Set**

- Standards, production defects, customized standards
- Initial validation and re-validation of machines
- Qualification and requalification of manual operators
- Includes a specific range of defects (POD >70%)
- Defect distribution towards critical defects

A qualification set serves as a reference standard within the qualification process and can vary in its composition and size depending on its use (MVI, SAVI, AVI)

Different kinds of test kits

- Qualification Test Set



Different kinds of test kits

- **Production Defect Set**

- Actual production defects – represents the actual product and defects
- Expiry is short
- Only defects that are found at the site will be regarded
- Need a shorter interval between inspections
- Defects should be reproducible for building new sets
 - > easier if the defects are manufactured

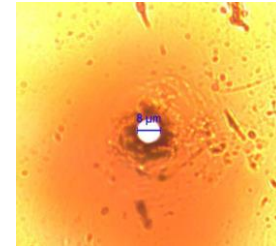
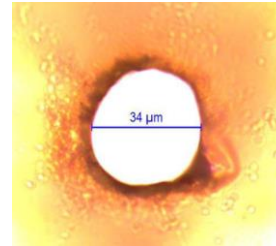
Different kinds of test kits

- **Daily test sets (AVI)**
 - Test sets for the functionality check of AVI machines
 - Only defects to simulate the ejection process
 - Vision system test
 - “The performance of equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch” – Annex 1 revision

CAUTION!

Different uses, different test sets

- Test sets for the visual inspection differ a lot from test sets for Container Closure Integrity testing
 - CCIT test sets include leak test samples e.g. pinholes, cracks or defects that might impact the container closure and the sterility of the product
 - Visual inspection alone is not enough to evaluate container integrity (Annex 1 revision)



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