Particles, defects and the defect library

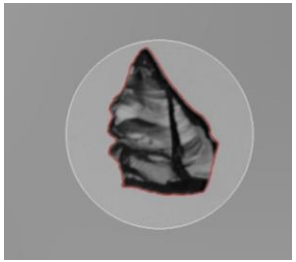
PDA Parenteral Drug Association

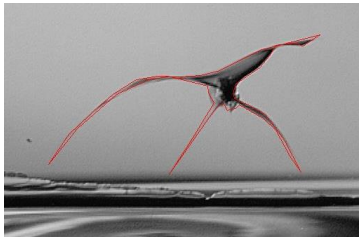
PDA TRAINING

Particles, defects and the defect library

- Test kits are composed differently depending on a multitude of different factors, including the production line, the materials in use, the container format and the physical properties of the solution

- In general a test kit consists of
  - Defect free containers
  - Containers that each have one particle from known material and in a known size
  - Additional defects like scratches, cracks, defects of the cap, stopper, product, filling level…





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Definitions

- Defect sets consist of different defect types or defect families
  - E.g. particles, glass defects, stopper defects…
- Each defect type or defect family includes different defect subtypes
  - E.g. cracks at the bottom, cracks at the shoulder…
- Each defect subtype should be included multiple times in different defect replicates (polymorphism)
  - E.g. horizontal cracks at the shoulder, vertical cracks…

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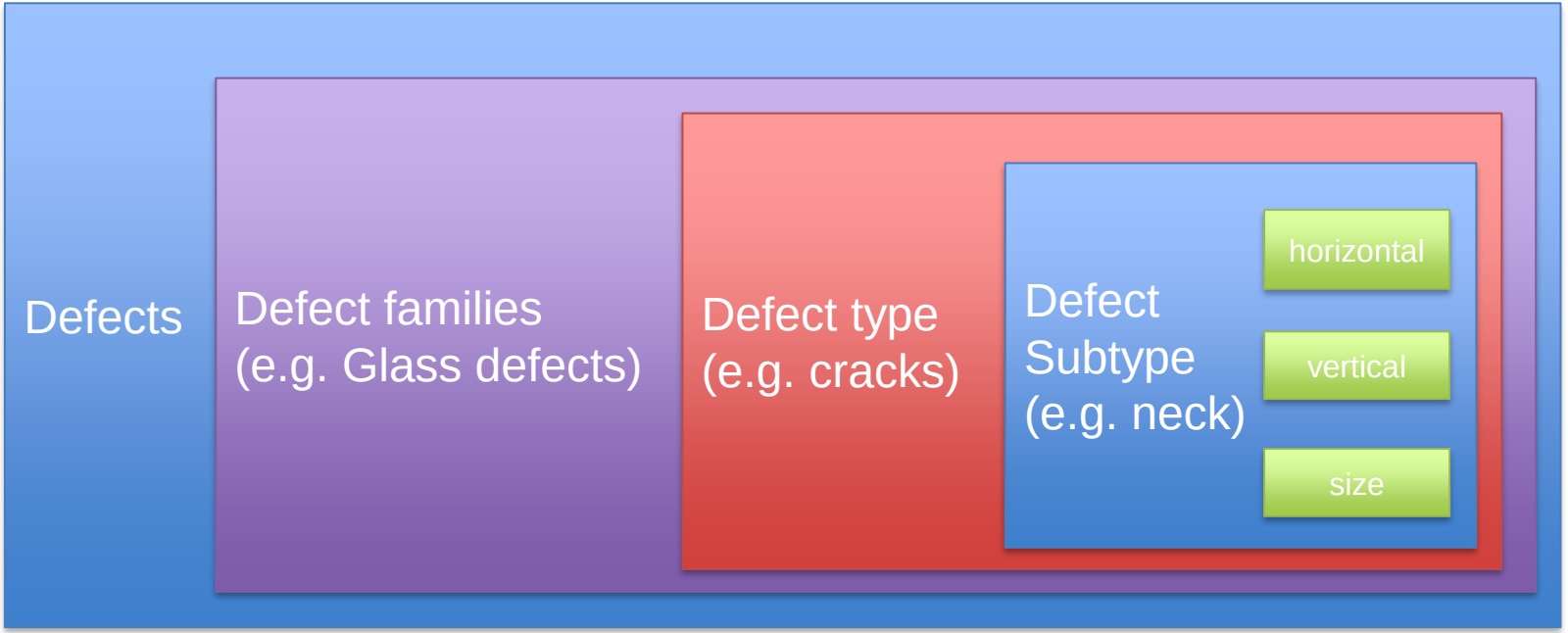
Definitions



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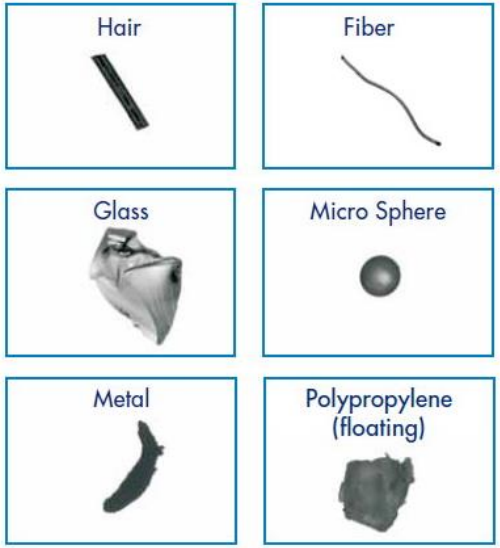
Particle samples

- Particle samples are included in nearly every standard reference test kit
- One container is prepared to contain (one) particle in a specific size (range) without any other defect visible
- Particle selection should be representative of the defective units found during production



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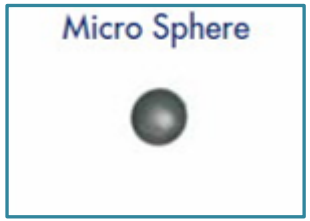
Spherical particles

Advantages:
- Can be bought in specific sizes (e.g. NIST)
- Lower risk of particles sticking to the container (closure)



Disadvantages:
- Behave differently from realistic particles found in production
- Operators learn to recognize patterns that are not realistic
- Might be confused with gas bubbles because of the spherical form
- To replicate a realistic particle you would need to mimic different physical properties in one sphere -> weight, feret max, volume…

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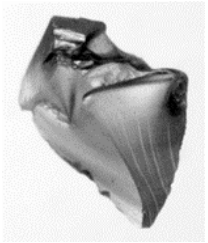
Realistic particles

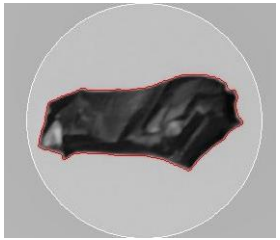
Advantages:

- Offer a behaviour that is representative of particles found in production
- Can be produced in all sizes and for nearly every material
- Give a realistic insight into PoD for different particles



Disadvantages:

- Sometimes a tendency to stick to different parts of the container



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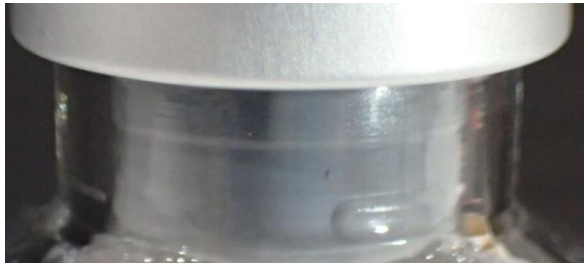
Adhering particles

- Particles adhering to any part of the container or the closure will be found during 100% inspection
- Especially on packaging material that has a surface area which has been treated with a silicon layer (e.g. PFSs, stoppers)
- Oftentimes in places that are difficult to inspect, e.g. between stopper and vial
- Static instead of moving



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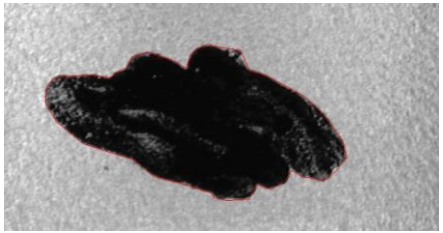
Additional defects

- Besides particle samples, oftentimes additional defects are added to a standard reference test kit
  - Container defects
  - Stopper defects
  - Product defects
  - Closing defects (e.g. cap or crimping defects)
  - Contaminations of the container



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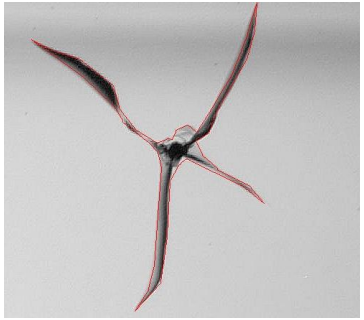
Container defects



- Container defects are found in the packaging itself
  - Most common: Scratches, Cracks, Chips…
  - Should be manufactured to mimic the same characteristics of container defects found during production
    - Example: width, length and depth of a scratch have a significant impact on the PoD of the defect
  - Container defects that are used to detect leakage in containers should not be included in a standard reference test kit but rather in a specific CCIT test kit

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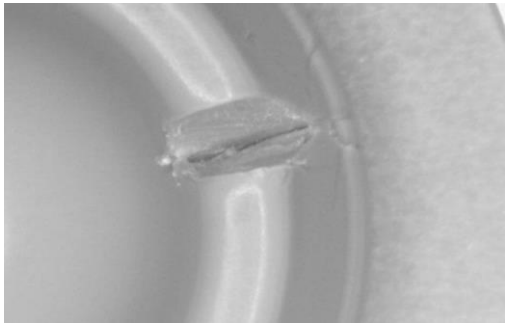
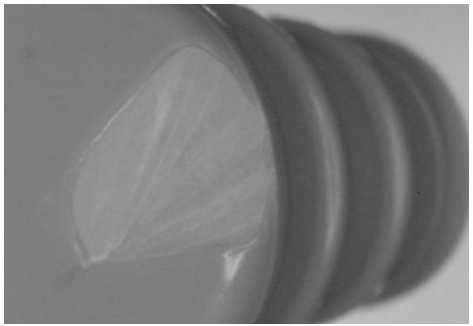
Stopper defects

- Stopper defects can be found in syringes and vials
- Most common: missing stopper, damaged stopper, deformed stopper, wrong stopper…
- Can have an impact on the sterility of the product in severe cases





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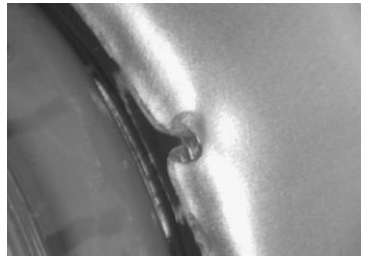
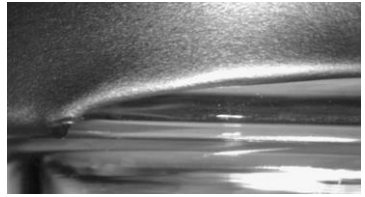
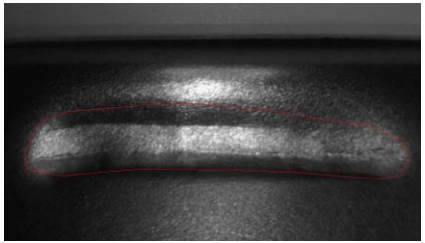
Cap defects and crimping defects

- Indicate a problem during the closing process of container
- Can be potentially impacting the sterility of the product
- Most common cap defects:
  - Uncrimped cap
  - Dents
  - Scratches
  - Missing flip-off







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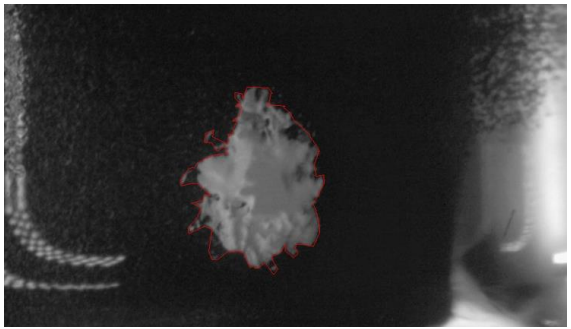
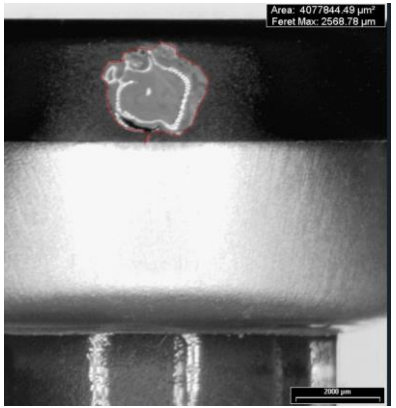
Contaminations

- Can be exterior or interior
- Can impact the sterility of the product if it is an interior contamination
- Difficult to ensure that contaminations remain static





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Solution defects

- Every defect that somehow changes the appearence of the product solution
- Critical defects, the sterility of the product is not warranted anymore
- Most common solution defects:
  - Turbidity
  - Discoloration
  - Filling discrepencies

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Size and composition of a test kit

- The amount of containers that need to be included in a test kit is highly individual and should be redetermined for each new container size and product family -> no standard composition possible

- Rule of thumb:
  - Usually around 200 - 300 samples including good samples in a qualification kit
  - Amount of defective samples should be around 10% of the test kit to avoid confirmation bias (for manual visual inspection)

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The defect library

- In the new revision of the EU GMP Annex 1 (August 2023)
  - 1. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge.
  - 2. Different defect types should be categorized, and batch performance analyzed
  - 3. A defect library should be generated and maintained which captures all known classes of defects
  - 4. The defect library should be used for the training of production and quality assurance personnel

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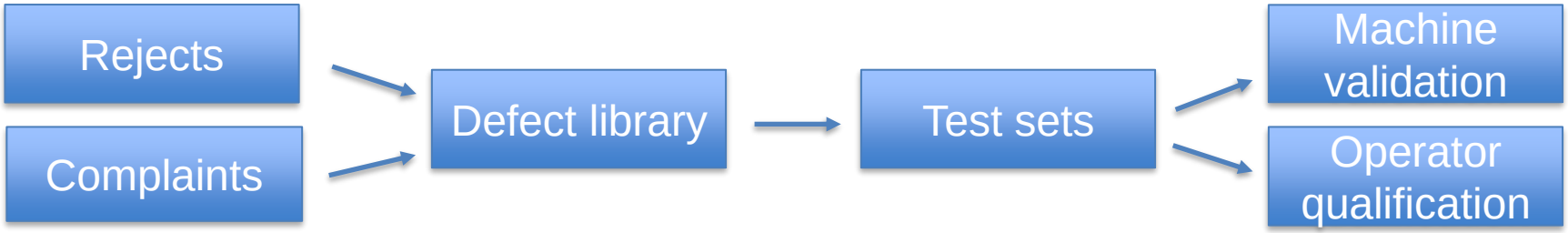
The defect library

- A defect library describes and categorizes the defective containers found during testing and should be the foundation on which the composition of a test kit should be build

- Usually consists of clear descriptions, example pictures and a categorization of the defect for all defects for one product



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The defect library – how to collect defects

- For already established facilities and product families:
  - Data collected from production rejects
  - Most frequently occuring defect types are selected

- For new product families/containers/facilities:
  - Use available information to evaluate the most common defect types
  - Select the defect types based on risk approach
  - Re-evaluate the defect standards after some time

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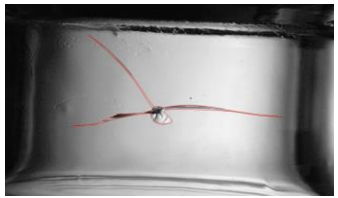
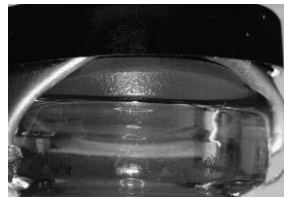
The defect library

- Defects are usually classified as Critical, Major or Minor defects
  - Critical:
    - Product could cause severe adverse reactions or death of the patient if the product is used.
    - Includes any nonconformity that compromises the integrity of the container and risks the sterility of the product
    - Inculdes also extrinsic particle sources like insect parts
  - Examples:
    - Cracks going through the container
    - Uncrimped cap





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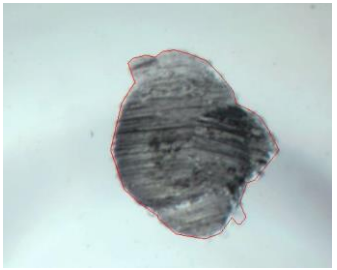
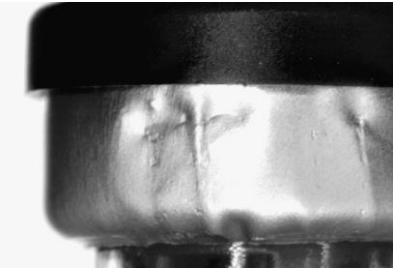
The defect library

- Defects are usually classified as Critical, Major or Minor defects
  - Major:
    - Carry the risk of temporary impairment or reversable medical reactions
    - Includes any defect that impairs or renders the product unusable
    - Includes visible intrinsic particle sources
  - Examples:
    - Outside contamination
    - Deformed container





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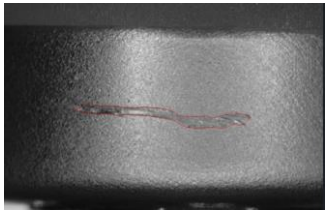
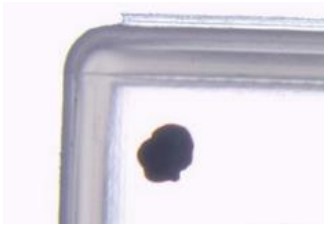
The defect library

- Defects are usually classified as Critical, Major or Minor defects
  - Minor:
    - Don‘t affect product usability or impact product performance
    - Consist of mostly cosmetic defects
  - Examples:
    - Superficial scratches
    - Airlines
    - Printing or stamping defects





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How to select defects for test kits?

- Visual-inspection particulate standards should include particles identified during product development, acquired from known production rejects, or created manually with well-characterized particulate material.

- The kind of defects that should be included should be based on a prior study of the particle/defect occurence during the real production

  – Multiple examples of each defect
  – Weighted towards critical defects

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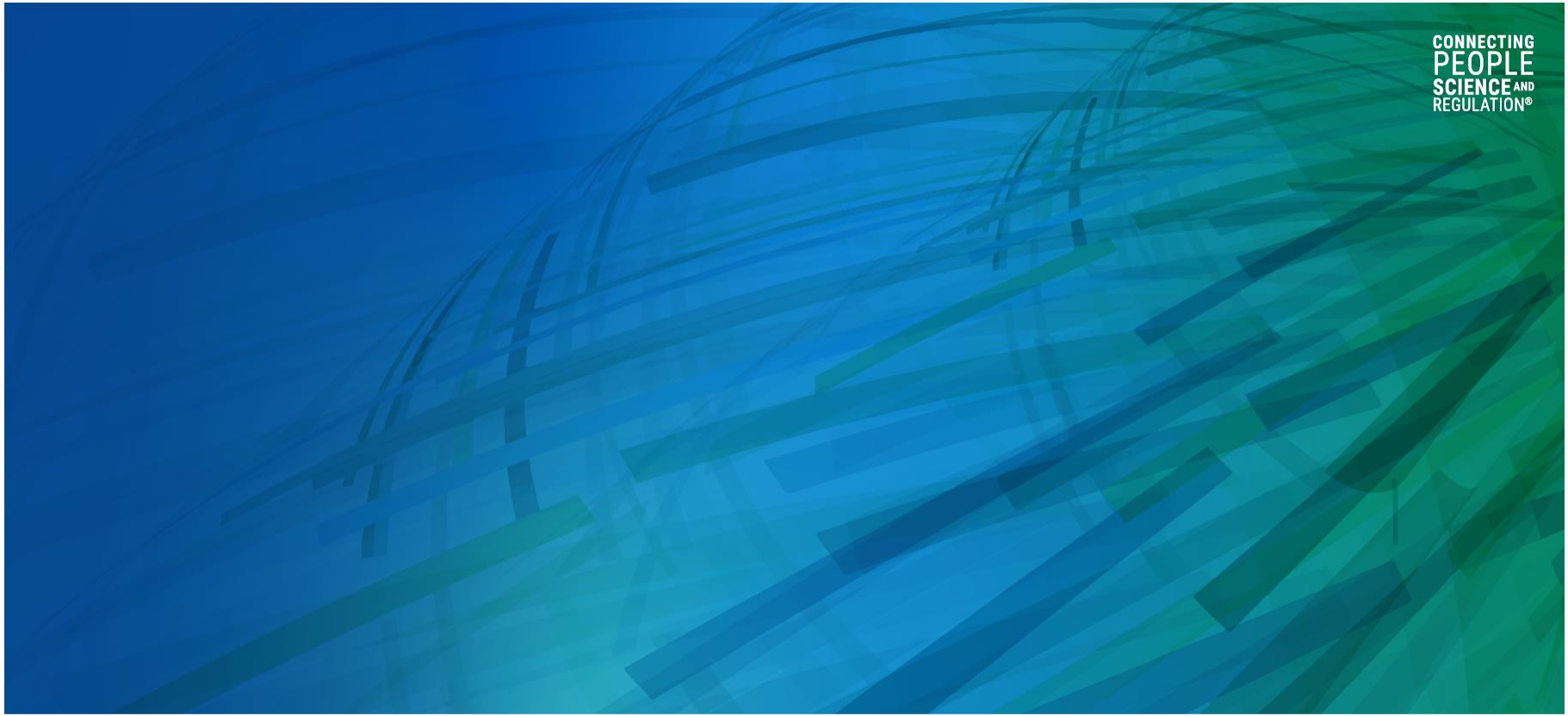

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