Agence nationale de sécurité du médicament et des produits de santé

Observation and Inspection Points for Sterile Products

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16th November 2019

A general view on the inspection within ANSM

2018 metrics

675 **inspections**

11% Unannounced inspections

6% International inspection

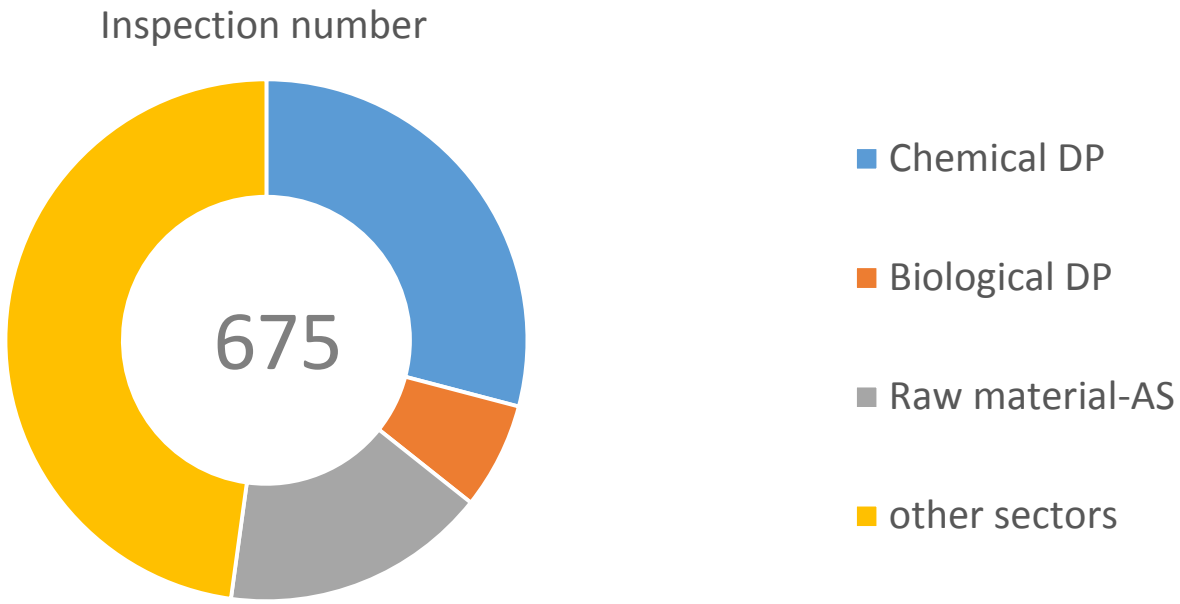
61 Injunctions 9%

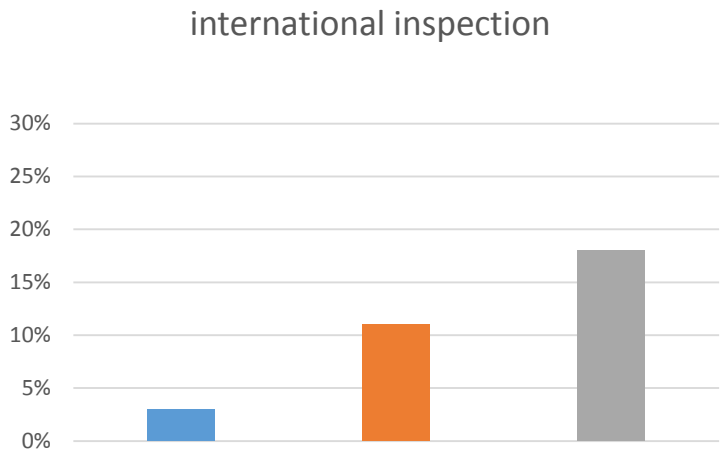
5 Regulatory actions

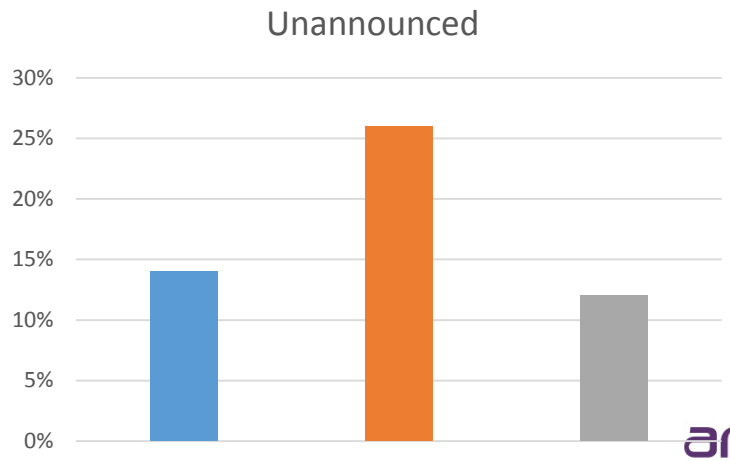
4 Financial fines

1 Penal citation

2018 metrics

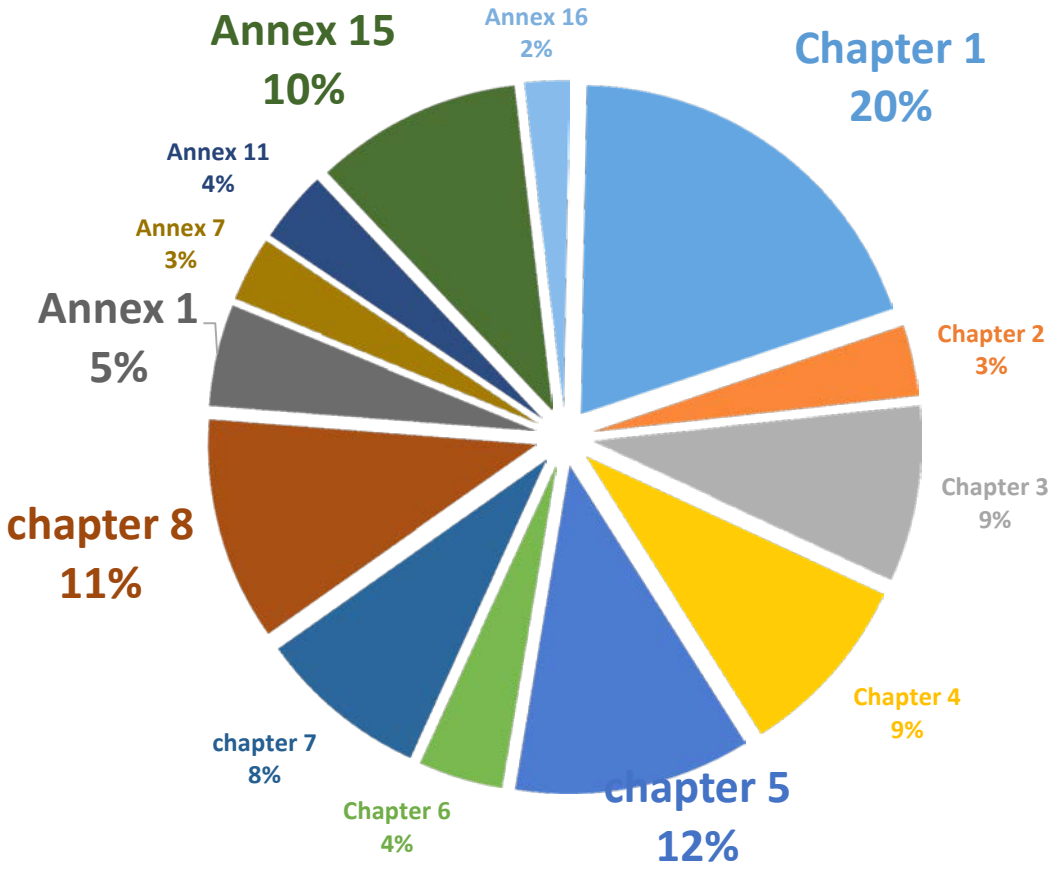




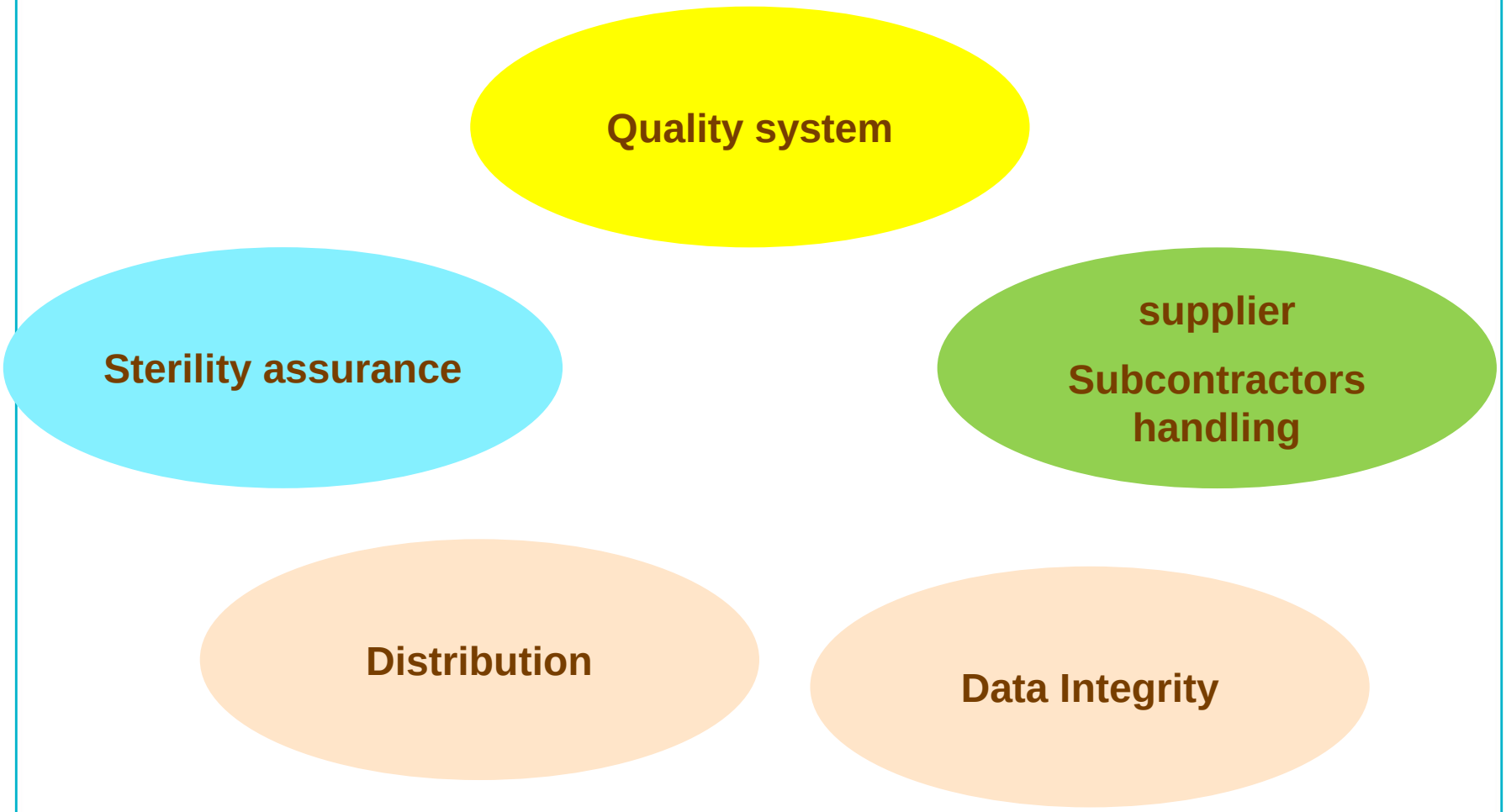


2018 metrics

- **850 major or critical observation**



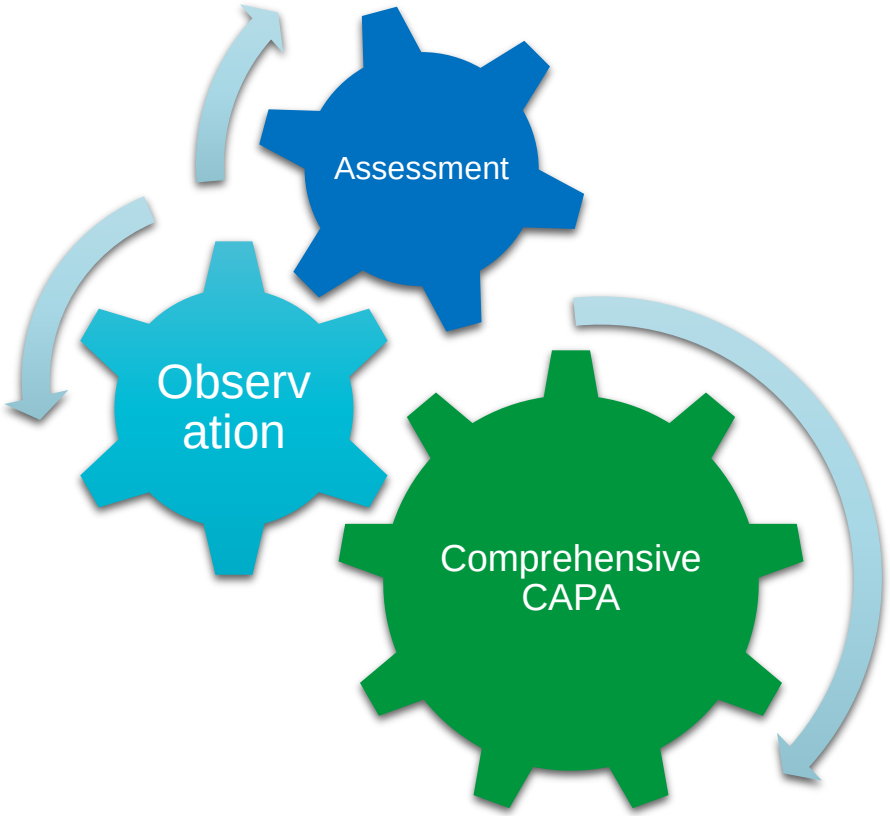
Points to consider



Inspection observation examples

Targeted approach

- Corporate audit
- Inspection
- External Audit
- Internal audit
- Complaint
- Deviation



Case study

- Manufacturer by either aseptic process or terminal sterilization of carpule, vials Complaint

- cartridge manufacture as CMO
  - bulk stage including visual inspection
  - Bulk undergoes a second visual inspection by the customer

- The CMO has other customers for cartridge (different products) but without further visual inspection

inspection 2016

- Complaint handling was deficient :
  - Investigation
  - CAPA
  - Timeliness
- Visual inspection was deficient:
  - Training and qualification kits
  - Qualification process (only 75% of critical defects have to be picked)
- Satisfactory CAPA submitted for each Deficiency

Customer feedback

Complaints

- Since December 2017 (11 batches a year) the second Visual inspection

  - Cracks
  - Particles including glass and silicon particles
  - Results of the second visual was however below the acceptance limit set by QTA (0,04 for critical)

Investigation 5M

- Visual inspection ruled out as operators don’t find the same defects (cracks)

- Packing process considered as a probable root cause

- Decision approved by the customer:
  - CAPA regarding packing process
  - No more investigation for same complaint while CAPA being implemented

Inspection 2019

- Complaint handling still deficient and categorization into critical, major and minor was inconsistent
  - minoring signals for cartridge (including signal from other customers)
- Vendor management for cartridge supply was deficient in that the quality agreement allowed critical defect (cracks) of empty cartridge to be part of the batch (AQL 1,5) while visual inspection of accepted cartridge allowed only 0,04
- Breakage handling was deficient (only removal of the broken cartridge)
- Complaint was reviewed by one unique Assistant Director with no cross-functional investigation

Outcome

- Failure for the site to manufacture products according to their specification
- Failure for the QMS to supervise the activities
- The Sterility assurance was impacted
- Strong action from the site to correct the situation through compliance management

Quality System

Supplier and sub-contractor handling

Gamma irradiation conditions

- Activity considered through
  - configuration & activity of the source
  - Distance between the source and the product,
  - Irradiation duration
  - Composition and density of the materials
- Importance of OQ & PQ
- Any cobalt replacement (typically 1/year) triggers requalification of the activity and configuration of the source

Stopper supply

A general quality agreement signed between the site and the supplier was reviewed including product specification. Neither the product specification nor the QTA gave information on:

- the manufacture condition of the stopper (room grade classification for instance)

- the audit condition of the gamma irradiating site (unknown address)

- the regular of OQ and its impact on PQ

Sterile Gowns supply

- The handling of sterile gowns was contracted out but no comprehensive assessment of the supply condition
- The quality agreement did not specify the irradiation process of the gown (irradiation dose for instance and the location of the sterilizing site). Only the delivery note mentioned the sterilizing site


Thank you
Any Question ?

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