WORKING TOGETHER TO IMPROVE HEALTH, WEALTH AND WELLBEING

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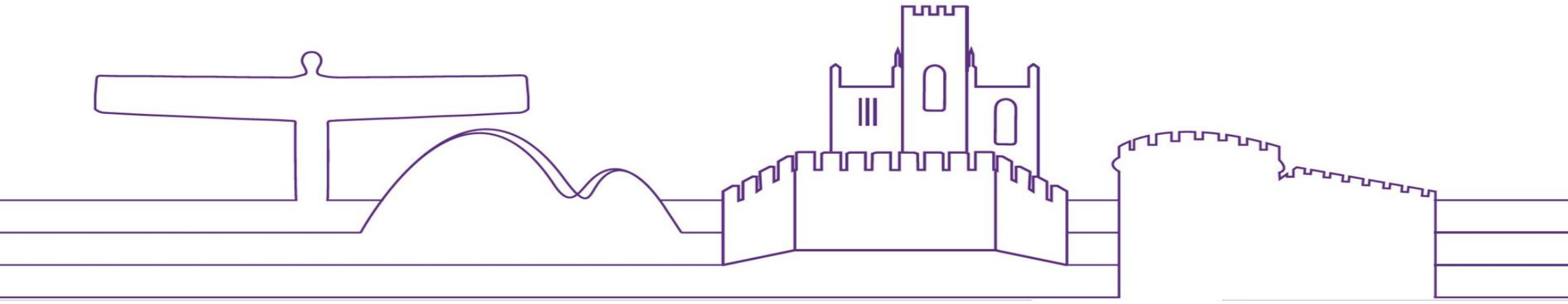
Practical Impacts of Annex 1 on Aseptic Facility Management



WORKING TOGETHER TO IMPROVE HEALTH, WEALTH AND WELLBEING

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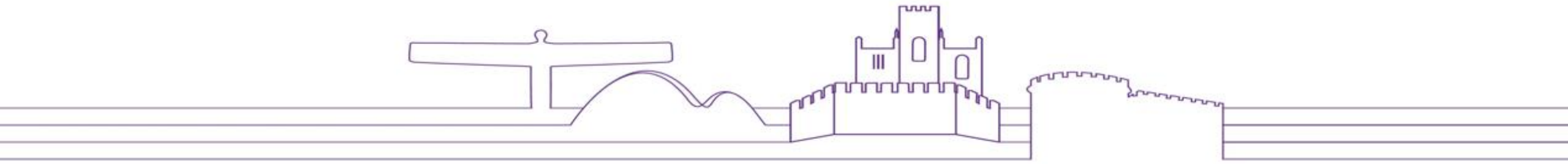
Practical Impacts of Annex 1 on Aseptic Facility Management:

- Monitoring
- Process Validation



Annex 1 - Update

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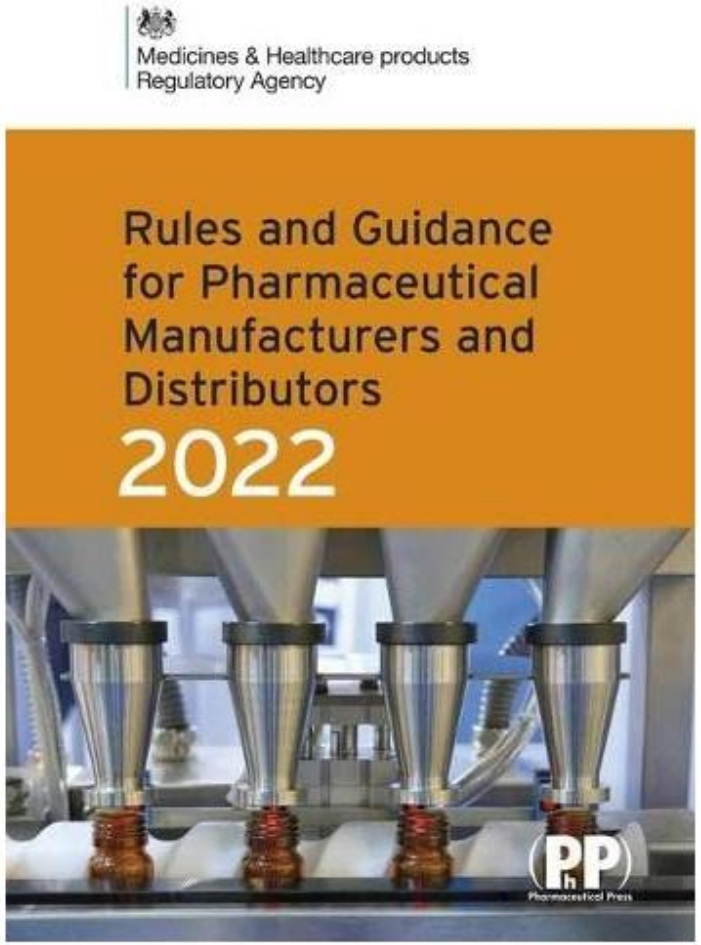
- What is Annex 1?
- What has changed?
- What's in it?
- What does it apply to?



Annex 1 - Update

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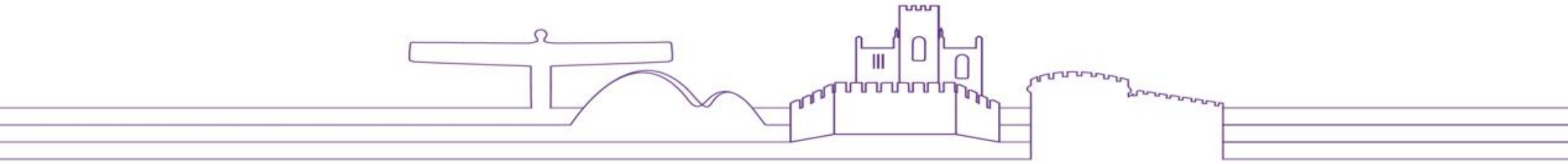
2008 Annex 1	2022 Annex 1
16 Pages	59 Pages
Sterile Manufacture Only	Consideration for non-sterile application
Risk mentioned 20 times	Risk mentioned 124 times
No requirement for overall strategy	Mandates introduction of CCS
Acceptance of open cabinets	Drive towards barrier technology



Annex 1 - Update

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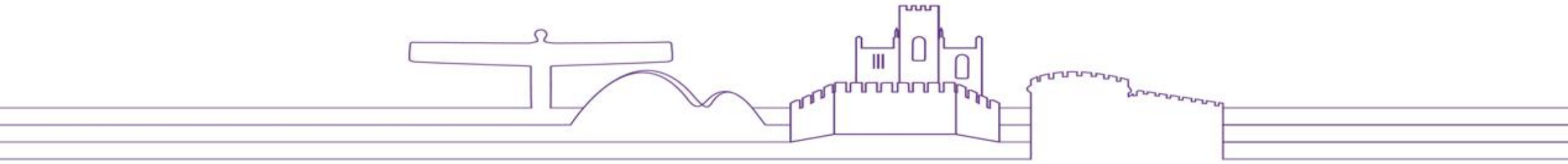
Intent of Annex is clear:

Prevention of microbial, particulate or endotoxin/pyrogen contamination by application of QRM principles.



Annex 1 - Update

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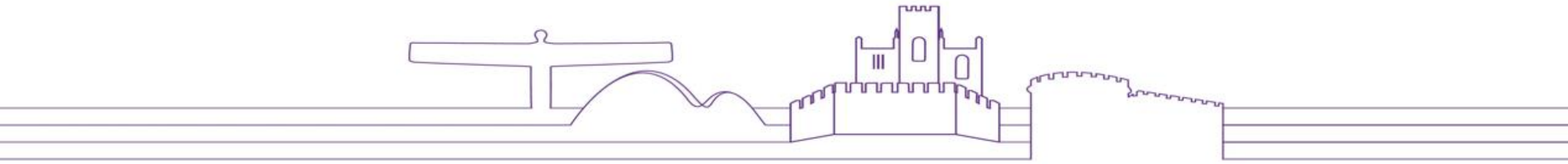
Structure generally follows a similar structure to the chapters of EudraLex Volume 4:

1. Scope
2. Principle
3. PQS
4. Premises
5. Equipment
6. Utilities
7. Personnel
8. Production Specific Technologies
9. Environmental and Process Monitoring
10. Quality Control
11. Glossary



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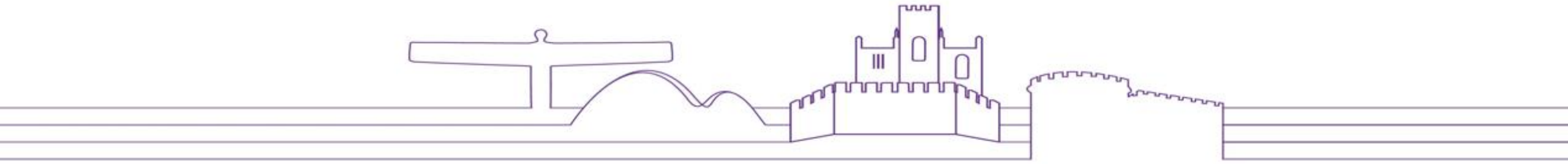

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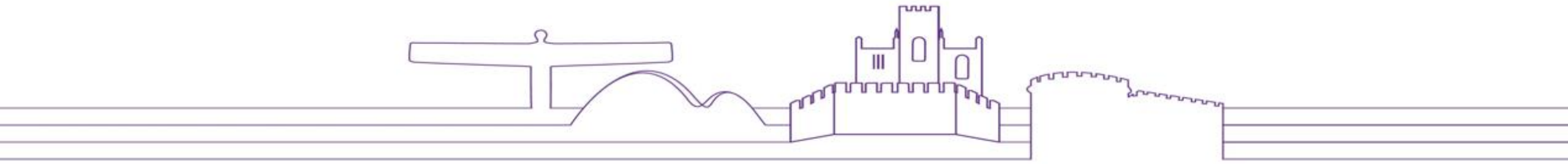

Monitoring

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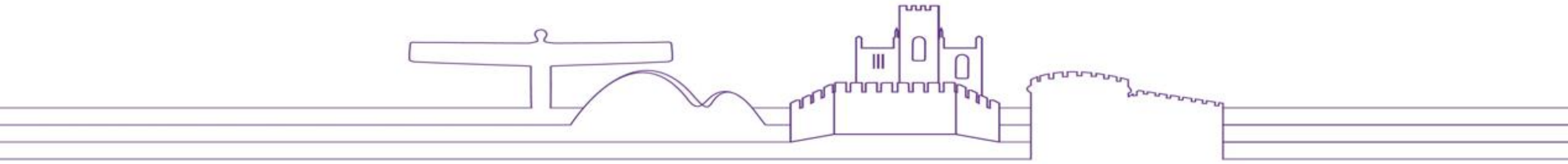
What do we mean?

Viable Environmental Monitoring
Non-viable Environmental Monitoring
Physical Monitoring

Qualification vs. Requalification
Periodic testing (annually, quarterly, monthly, and non-routine)



Routine Monitoring – Viable Environmental Monitoring

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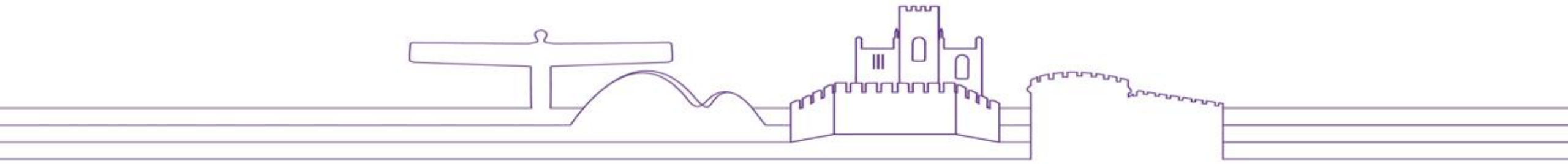
- EM programme design and rationale
  - Media
  - Incubation Regimen
  - Monitoring Methods
  - Monitoring Locations
  - Monitoring Frequency
  - Limits
- Additional Personnel Monitoring Requirements
- Risk Assessment



Routine Monitoring – Non-viable Environmental Monitoring

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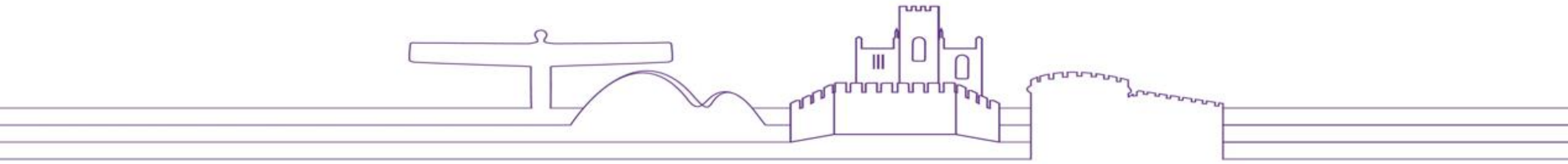
- EM programme design and rationale
  - Monitoring Methods
  - Monitoring Locations
  - Monitoring Frequency
  - Limits
- Risk Assessment



Routine Monitoring – Physical

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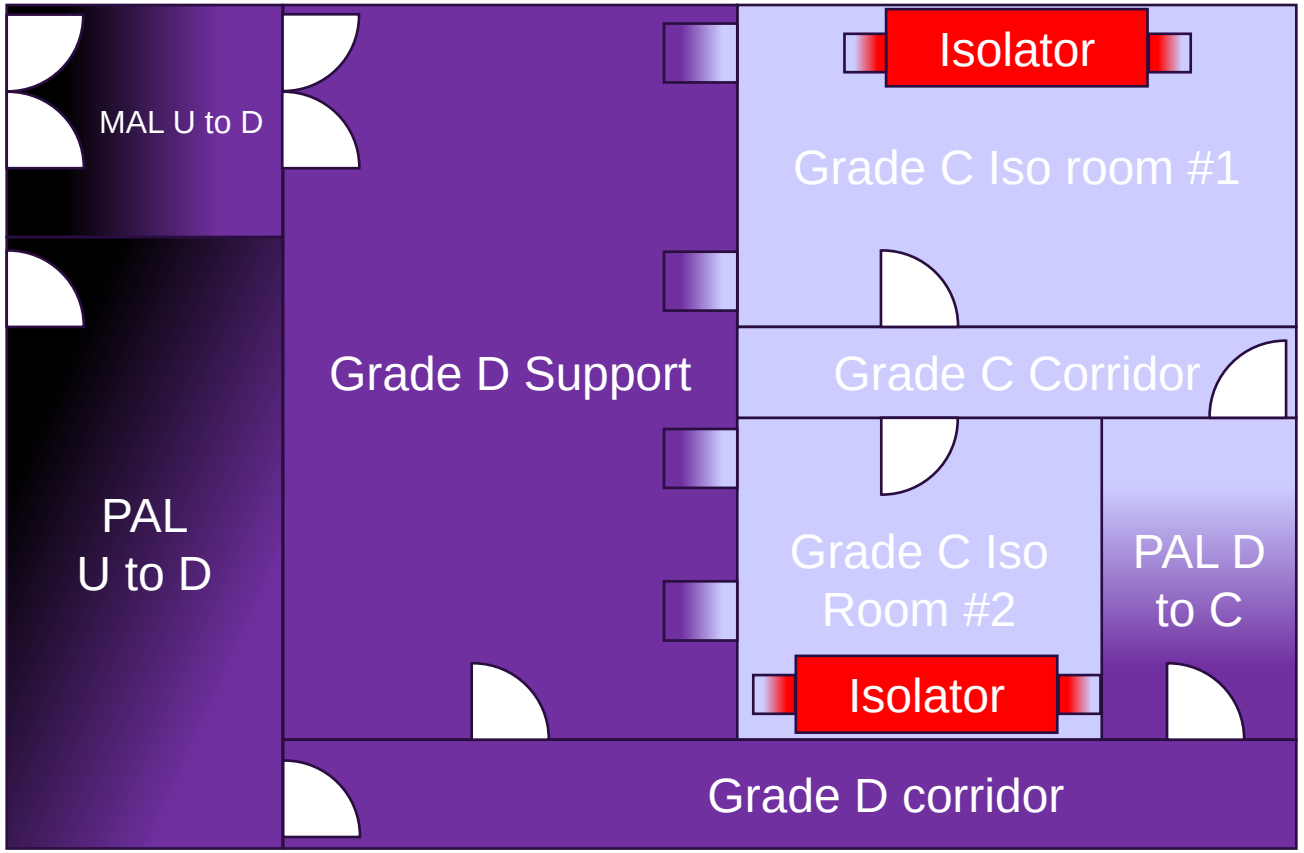
- Temperature
- Air change rates
- Humidity (?)
- Pressure Differentials
  - What's critical?
  - Limits



Classification and re-classification

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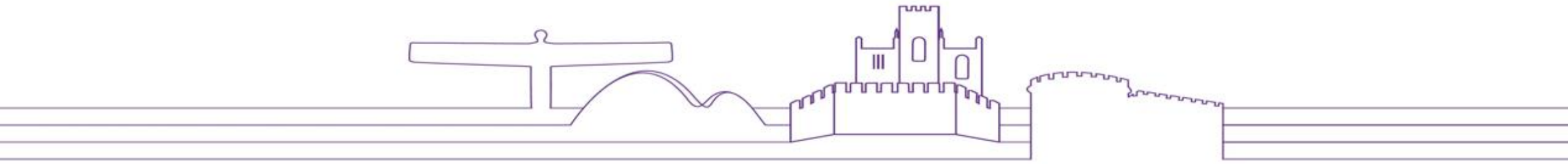
- Frequency
- At rest or operational?
- Differentiate qualification from routine EM
- Qualification Should include:
  - Filter integrity
  - Airflow volume & velocity
  - Pressure differentials
  - Airflow visualisation
  - Viable airborne and surface
  - Temperature
  - Humidity
  - Recovery
  - Containment Leak



Classification and re-classification

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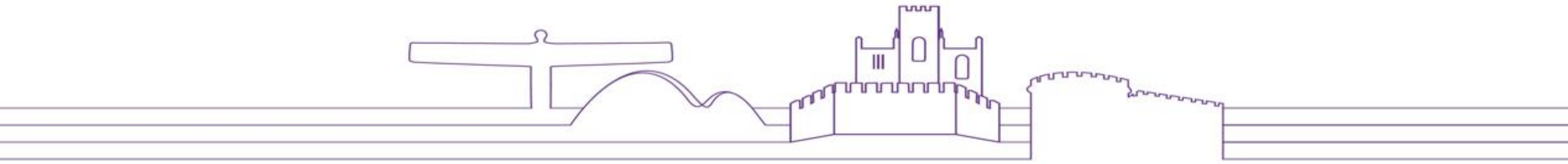
- How do you manage your facility requalification?
  - Who controls what tests are done?
  - Who controls the limits applied?
  - What do you check reports against?
  - If outsourced, do you have Technical Agreements in place?
  - Are external staff trained in local procedures?



Particle Counters

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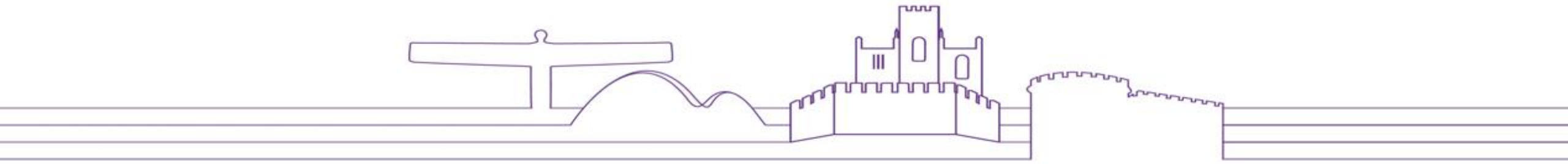
Annex 1; 5.9: “Particle counters, including sampling tubing, should be qualified. The manufacturer’s recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1m unless justified and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes….”

- ISO 14644 Part 21 specifically includes a section on sampling tube issues



Process Monitoring

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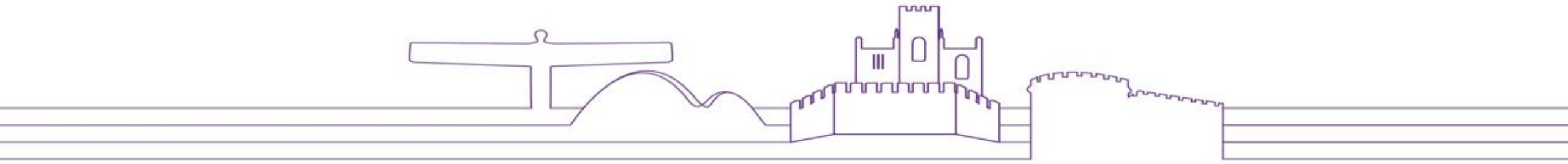
- ‘Normal’ Process Monitoring
  - Environmental Monitoring
  - IPC / Release Testing
    - Sterility Testing
    - Endotoxin / MAT
    - Sub-vis Particles
    - Visible Particles
    - Process Filter Integrity
- Section 10 Process Monitoring
  - EOS
  - Occasional Sterility
  - NOTHING at point of release
  - Reliance on Quality ASSURANCE vs Control



Process Validation

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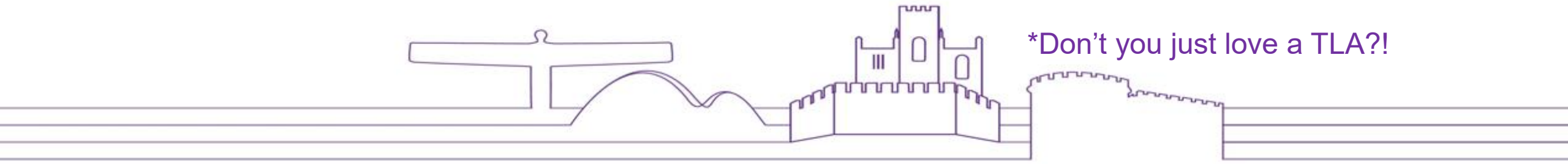
A route to validation

- PRA (QRM)*
- APS design
- APS execution
- Maintaining a validated state
- Operator Qualification



*Don’t you just love a TLA?!

Process Risk Management

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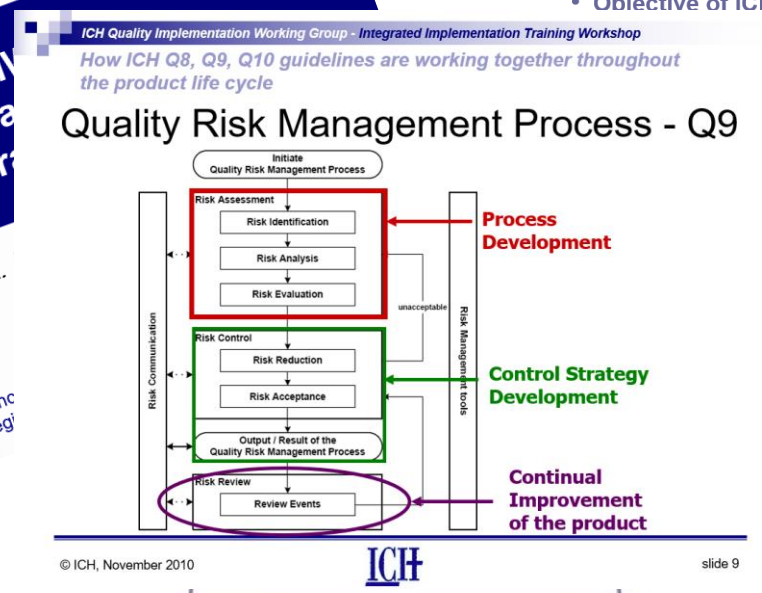
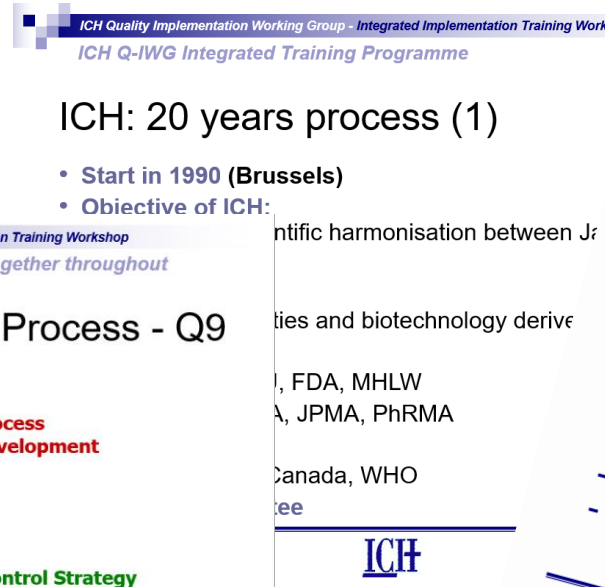
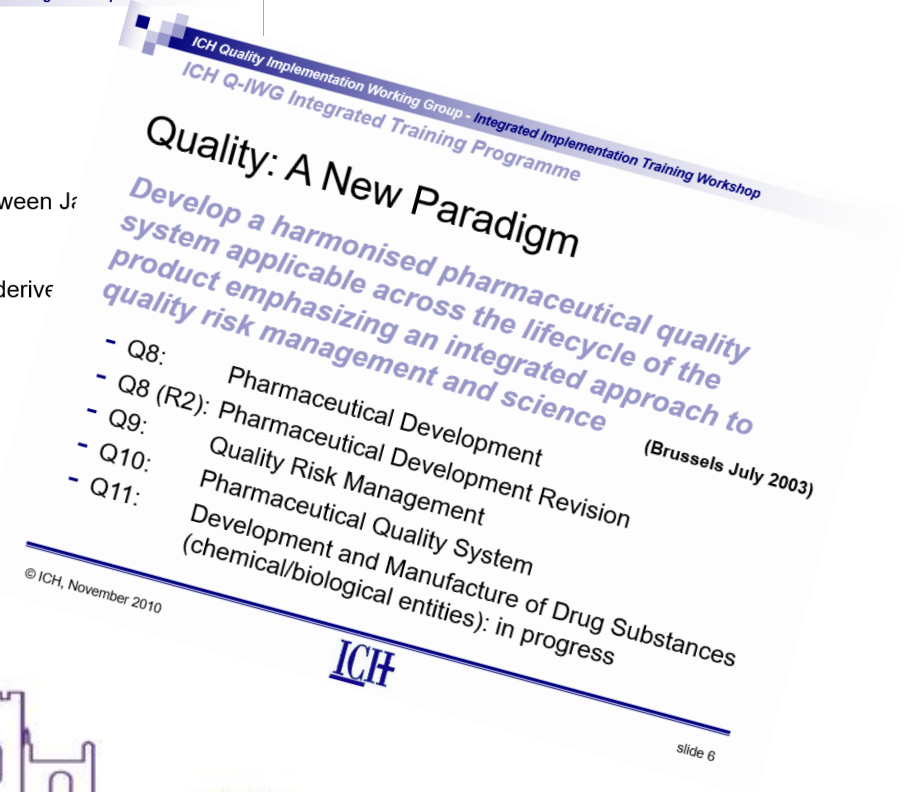
Annex 1 mandates QRM principles throughout







Process Risk Management

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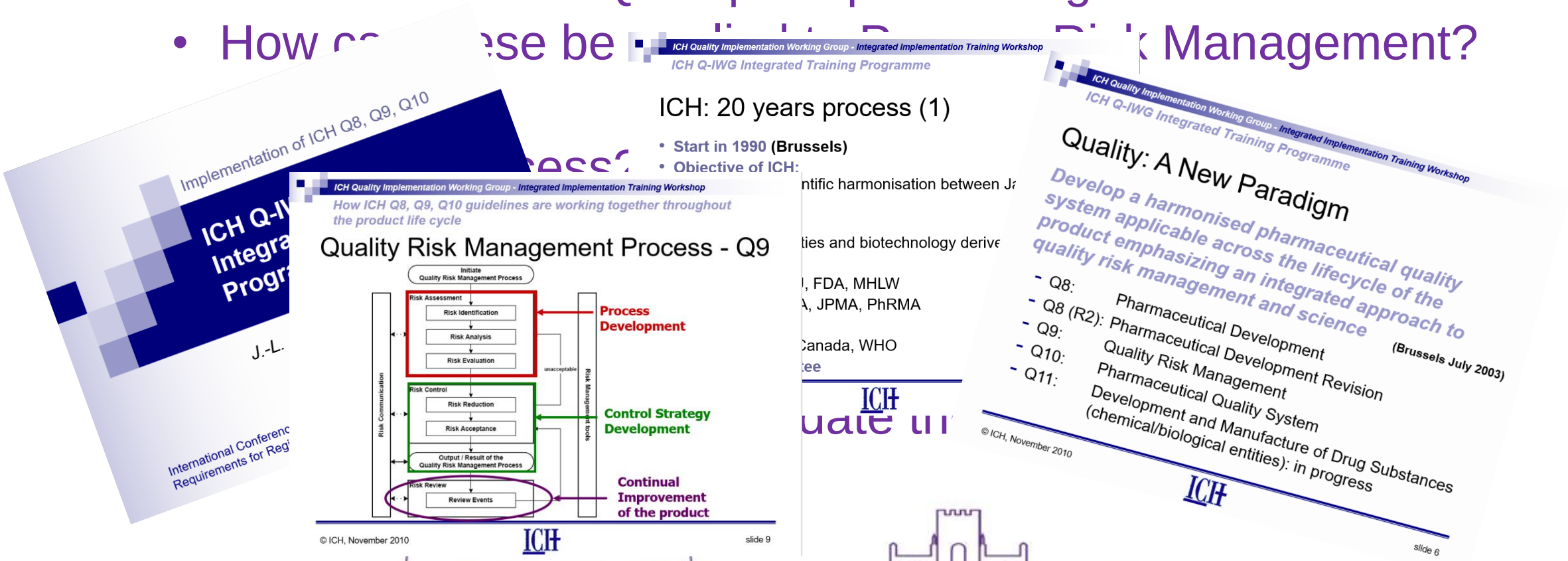
Annex 1 mandates QRM principles throughout

- How can these be [illegible] Risk Management?



Process Risk Assessment (PRA)

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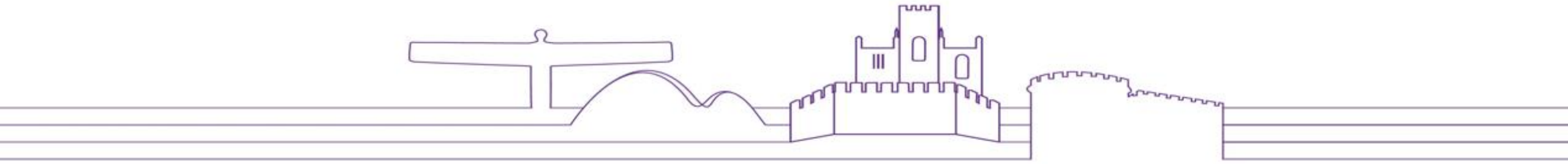
PRA applies QRM principles to a manufacturing process

- Process steps are evaluated in terms of their risks
- Focus is on viable, non-viable and endotoxin/pyrogen contamination
- FMECA is a good fit, other methods are available
- Output should be risks which are accepted and CAPA for those that aren’t
- Residual risks should be reviewed periodically



Aseptic Process Simulation (APS) design

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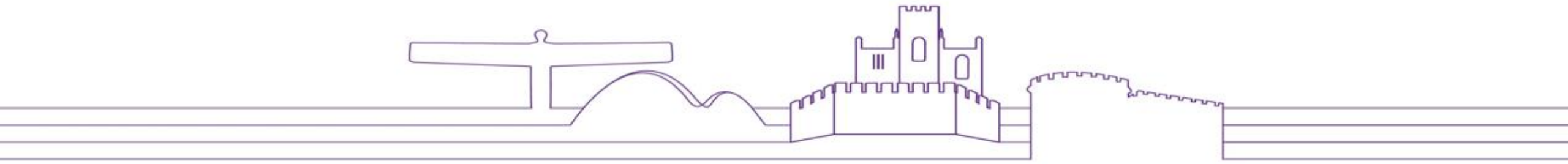
APS design

- One process will cover several products
- APS design must take into account anticipated interventions (identified in PRA)
- APS design should not attempt to validate bad practice (by ‘validation’ of high risks identified in PRA)
- Number of operators present should be defined



APS execution

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Maintaining a Validated State

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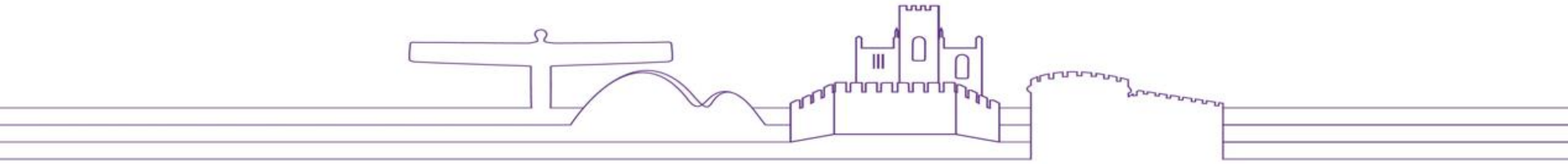
9.38: "…Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually…"

However:

9.39: "Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be… …revalidated with one APS approximately every 6 months for each operator…"



Operator Qualification

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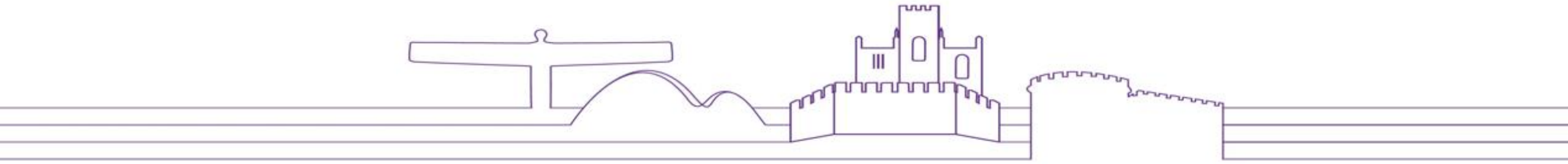
> “9.39: Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each operator. The APS batch size should mimic that used in the routine aseptic manufacturing process.”

- This is hard (for S.10 units)!
- This may lead to units reconsidering current process validation strategy where operator qualification is separate to process validation
- Operators and processes could be qualified simultaneously, all operators are required to participate in an APS every 6 months; process validation is therefore taken care of!
- Is the UOBV kit still suitable for the new Annex 1 world?



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Questions?