Manufacture of QCs

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QC Manufacture

Easy?

Difficult?

Many issues to consider
Hierarchy of QC samples

- Primary Standard
  - WHO International Standards
  - Approved by ECBS

- Secondary Standard
  - Calibrated to the IS
  - Can be used as QC

- Tertiary Standards
  - QC samples, calibrators
Regulations

- IS regulated by WHO ECBS
  - Highest order (no uncertainty attributed)

- Secondary Standards
  - Depends on “intended use” – most likely no regulation

- Tertiary Standards
  - Depends on “intended use” – most likely an IVD therefore jurisdictional IVD regulations
Regulations

US = FDA approval

Even longer process than EU for high risk devices (510k) and thorough supporting information required
Regulations

Australia = TGA MedDevRegs

- All devices listed on Australian Register of Therapeutic Goods
- Follows International Medical Device Regulators Forum (IMDRF)
- Goal - one global system of regulatory evidence
- Formerly GHTF
Regulations

Europe = IVD Regulation 746 (replaced IVD Directive 98/79/EC)

- Relationship with Notified Body required for Class C and D devices
- Registration allows application of CE marking
- Long process and thorough technical dossier required
Quality Control Materials

- Intended use – calibrator, control
  \[ = \text{IVD!!} \]
- Assay controls
- In-house manufactured QC samples
- Commercially manufactured QC samples
Assay Controls

- Ready to Use vs Preparation Required
- Validate the test run
- Independent of assay lot?
  - No if provided as a component of the assay
  - Yes if provided separately
- Constituents?
  - Similar to a real sample
  - Not similar (completely artificial)
In-house QC samples

- Usually diluted patient samples
- Unknown stability, quality
- No preparation of samples (fibrin, lipid, bacterial contamination)
- Unknown antibody profiles (different levels, maturity, epitopes, Ig classes)
In-house QC samples

- Poor lot-lot consistency
  - Due mainly to positives from different patients
- Limited stock longevity
- No peer group comparison
HIV western blot

- Different antibody responses in different individuals
- Assay response depends on conjugates, substrates and antigens used
- Individuals have different antibody profiles
Commercial QC samples

- Manufactured as IVD
- Comply with jurisdictional regulatory requirements
- Available to all = peer group
Commercial QC – Problems

- Consistent QC lot manufacture
  - Stock materials change
  - Manufacturing practices change
  - Validation techniques not always ‘sound’
- Evidence of QC lot variation
QConnect Blue

- Architect
- HBsAg II
- Production change required
QConnect Blue

Architect Anti-HCV

Same changes – consistent performance
Other manufacturer

- Bio-Rad
- Virotrol III
- HBcIgM results from three QC lots
Commercial QC – Problems

- Statistics for serological QC materials difficult to interpret
- Traditional methods not designed for qualitative data (including serology)
- Cannot implement newer methods such as Six Sigma or look at TEa
Conclusion

- In-house QC difficult to maintain
- In-house QC difficult to validate
- Using IS as a QC is inappropriate
- Selection of Commercial QC samples needs careful consideration
- Validate your statistical methods