Monitoring Assay Traceability through EQAS Surveillance

AACC Edutrack 3305, Orlando, 30 July 2002

Dr David G Bullock

Director, Wolfson EQA Laboratory
Organiser, UK NEQAS for Clinical Chemistry
International Relations Director, UK NEQAS Executive
EQA and traceability

- the role of EQA
- EQA and the IVD MDD
- Traceability and EQA
- Performance surveillance and vigilance
- EQA targets and calibration issues
- Laboratory medicine as a partnership
External quality assessment and proficiency testing

• For the purposes of this presentation

\[ \text{EQA} \equiv \text{PT} \]

In Europe:
• "PT" has licensing connotations
• EQA implies an educational approach
Role of external quality assessment

EQA provides assessment of:

- **individual laboratory performance**
- **the overall performance** (state of the art)
- **the influence of analytical procedures** (method, reagent, instrument, calibration)
- **the specimens distributed**

**EQA PROVIDES AN EDUCATIONAL STIMULUS TO IMPROVEMENT**
(providing information to a quality management system)
The *in vitro* medical diagnostic devices Directive (IVD MDD) - 1

- **Purpose**
  - a 'placing on the market' Directive - industry-driven
  - intended to eliminate (artificial) trade barriers
  - manufacturers set their own specifications

- **Effects**
  - 'stratification' of IVDs
    - general, self-test, Annex II list B
    - Annex II list A (blood safety)
  - *traceability requirements* - mostly profession-driven
  - common technical specifications for Annex II list A
The *in vitro* medical diagnostic devices Directive (IVD MDD) - 2

**Scope**

- all reagents, instruments, software, accessories
- all calibration and control materials
- EQA specimens and CRMs excluded

**Timescale**

- IVD MDD published December 1998
- Transition period 2000 - 2003; completion:
  - December 2003 - all products (existing and new) must then comply
  - December 2005 - supply of products manufactured before Dec 2003
Support for the IVD MDD

- **European Standards**
  - mandated from CEN by European Commission
  - prepared through CEN TC140
    - *(some in parallel with ISO TC212)*
- reference procedures and laboratories
  - EN 12286
  - prEN 15195
- traceability
  - prEN 17511
  - prEN 18153 (enzymes)
- EQA
  - prEN 14136
prEN 14136 - requirements on EQA

- For data to be used in procedure assessment:
  - for any procedure
  - **for an IVD** (or a combination of IVDs)

- Two elements:
  - basic recommendations of ISO/IEC Guide 43-1
  - additional requirements

*A Standard, but role equivalent to ISO/IEC Guide 43-3*
Additional requirements of prEN14136

- Independence of judgement
- Quality management
- Unequivocal identification of IVDs used
- Data analysis
- Surveillance procedures

*NB: compliance with prEN14136 is not mandatory
  - applies only if data are to be used for procedure (IVD) assessment
Additional requirements - 1

• Independence of judgement
  • from manufacturing or distribution interests
    • avoid "ensure own pass"/"engineer failure of others"
  • no mechanisms specified

• Quality management
  • accreditation advocated
  • EQAS design to ISO/IEC Guide 43-1 / ILAC G13
  • ISO 9000 quality management system
Additional requirements - 2

- IVD identification
  - must identify product(s) used
  - ensure adherence to manufacturer’s protocol
  - exclude from analysis if variant protocol used
  - *an EU database would have been helpful*

*establishing exactly what participants do is a problem for all EQASs!*
Variant protocols

- If believe manufacturer's protocol is wrong, it is unethical to follow it
  - done on basis of (sufficient) scientific evidence
  - can advance manufacturers' understanding

- In future, however, use of variant protocols
  - excluded from assessment with other users
  - requires full documentation

NB1: how can EQAS reliably identify & exclude these?
NB2: laboratories are responsible for results reported - "only following protocol" not an acceptable defence
How to assess IVD performance?

• Against manufacturer's claim?
  • manufacturers' preference
  • basis for assessment under IVD MDD
  • only basis for vigilance

• Against accepted performance criteria?
  • laboratories are assessed against these
  • the tools they use must be judged similarly

NB: laboratory medicine must support and enhance patient care
Is EQA data a reliable assessment tool?

• EQA reflects 'real life':
  • routine use
  • many lots (instruments)
  • many laboratories (operators)

• Confounding factors:
  • excessive pressure to pass
  • use of data for licensing
    • requirement to pass EQA to maintain viability
    • temptations to 'cheat'
  • *nature and behaviour of specimens*
Educational role of EQA

- Maintaining professional standards
  - EQA is only one aspect of performance
  - must be supported by effective QA and IQC

- EQA is an educational stimulus to improvement
  - by laboratories
  - by manufacturers
  - by EQA schemes
Laboratory performance surveillance in UK

- Performance or participation 'failure' stimulates:
  - intelligent scrutiny of data & history by scheme
  - informal contact from scheme
  - formal contact from scheme
  - referral to National QA Advisory Panel (NQAAP)
  - formal contact from NQAAP
    - must be advised to accreditation body (CPA)

- referral to Joint Working Group on Quality Assurance *
- notification of hospital's Medical Director *

* these stages never reached in 20 years
Apparent IVD-related problems in the UK

• Guidelines drawn up by EQA, BIVDA, MDA, NQAAP, and endorsed by JWG
  • *with/without communication to user laboratories*
  • talk to the manufacturer
    • ? "matrix effects", ie OK with clinical specimens
    • ? product changes - advance notification helps!
    • many issues are soluble at this level
  • inform NQAAP - routinely/urgently
  • inform Medical Devices Agency (Competent Authority for the UK) - ? as adverse incident report
  • document resolution
  • refer formally to MDA if not resolved
IVD-related actions - prEN14136

- Investigate apparent problems further
  - look at variability as well as median performance
  - try to exclude user effects (eg incorrect protocols)
  - compare with manufacturer's claims
    - *but is this good enough?*

- Talk to the manufacturer first

- May refer to Competent Authority
  - *but is it likely that vigilance issues will be identified first through EQA?*
Target values in EQA

- Reference method laboratory value
  - follow EN 12286, prEN 15195 & prEN 17511
  - assign uncertainty
  - expensive and impractical?

- Known composition

- Consensus
  - cheap and convenient
  - widely used, and will continue to be
  - NB: must not accept automatically - validate wherever possible
Reference method laboratory targets

• Are the materials good enough?
  • unreliable targets are a problem
  • excellent values on 'poor' material also bad news!
    • starting material matrix, quality
    • additives, preservatives
    • processing (eg lyophilisation)

• Can only apply reliably where there is confidence in the material's commutability & fidelity
UK NEQAS examples

- **Glycated haemoglobin**
  - fresh whole blood from authentic diabetic volunteers
  - reference laboratory network values
  - ? basis for traceability - 'DCCT-aligned' or IFCC standardised

- **Lipid assays**
  - fresh liquid serum without addition
  - reference laboratory network values
  - ? pool-related matrix effects still seen

- **EU (global) IMEP-17 study**
  - frozen liquid sera without preservative (DEKS)
  - reference method laboratory targets
  - final data awaited
EQA as Audit -
A Quality Improvement Cycle

1. Observe current practice
2. Set standards
3. Compare practice with standard
4. Implement change

EQA demonstrates need for education / new guidelines / new procedures / new calibration

EQA demonstrates improvement / reinforces best practice
European survey - Orosomucoid

Symbols = method principles
Letters = calibrants

PE = mean of results for specimen
CE = mean of results, recalculated using second specimen as calibrant
UK NEQAS for Specific Proteins
IgG, 1993 - 2001

MRVIS is an index of total error - low values represent good performance.

Average score for all participants is shown.
**UK NEQAS for Specific Proteins**

**Orosomucoid, 1994 - 2001**

**Introduction of CRM 470**

[prepared following European collaborative EQA study demonstrating calibrant discordance]
EQA view on calibration revision

• Global harmonisation is the aim
  • EQA continues to encourages harmonisation
  • to attain this, calibration changes are inevitable
  • movements should be towards the truth!

• Problems for EQA
  • geographical differences (eg CEA RMss)
  • shifts in bias & diversity of bias during changes
  • please tell EQA schemes first . . .
Conclusions

• Effective laboratory medicine is everyone's aim

• We must ensure an effective partnership:
  • clinical laboratories
  • industry
  • EQA schemes

• IVD MDD introduces more regulation, but:
  • to be constructive, such systems rely on co-operation
  • slavish adherence to protocols will not be effective
    • post-marketing surveillance is not vigilance
a. General


prEN ISO/DIS 15189 *Medical laboratories - Particular requirements for quality and competence.*

EN 12286 *In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - presentation of reference measurement procedures.*

prEN ISO/DIS 15195 *Clinical laboratory medicine - Requirements for reference measurement laboratories.*

prEN ISO/DIS 17511 *In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Metrological traceability of values assigned to calibrators and control materials.*

prEN ISO/DIS 18153 *In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Metrological traceability of assigned values for catalytic concentration of enzymes in calibrators and control materials.*

b. EQA schemes

prEN 14136 *Use of external quality assessment schemes in the assessment of the performance of in vitro diagnostic examination procedures.*


*EQA scheme accreditation handbook.* Sheffield, UK: Clinical Pathology Accreditation (UK) Ltd. [obtainable via www.cpa-uk.co.uk]

ILAC-G13:2000 *Guidelines for the requirements for the competence of providers of proficiency testing schemes.* [obtainable via www.ilac.org]

Joint Working Group on Quality Assurance conditions of participation in EQA schemes. [www.ukneqas.org.uk/Manage/JWG.htm]