The 1999 Stockholm Conference on Quality Specifications in Laboratory Medicine

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The Central Role of Analytical Performance Specifications

QUALITY IMPROVEMENT  →  QUALITY CONTROL

QUALITY SPECIFICATIONS = Analytical Performance Specifications

QUALITY ASSURANCE  ←  QUALITY ASSESSMENT
Needs for Analytical Performance Specifications

In introduction of an analytical system:
• detailing the analytical requirements and assessing available systems,
• preparing a specification/tender and creating a short list for evaluation, and
• objectively assessing the evaluation data generated.

For EQAS/PT organisers:
• to set criteria for satisfactory performance.

For manufacturers:
• in designing, assessing and marketing systems and reagents.

For laboratories and patients
• to undertake objective quality planning, select those methods that need improvement and ensure that APS are met so that patient care is facilitated.

Setting Analytical Performance Specifications

More than 50 years of effort:

• 1963 David Tonks
  \[
  ALE = 2CV = \frac{1}{4} \text{reference interval/mean} \times 100\% \quad \text{(biological)}
  \]

• 1968 Roy Barnett
  “Medically significant CV” – said to be “opinions of clinicians and laboratory specialists” (clinical)

• 1970 Cotlove, Harris and Williams
  Biological variation - tolerable analytic variability
  \[ CV < \frac{1}{2} \text{CVwithin-subject} \quad \text{(biological)} \]

• 1976 CAP Aspen Conference (1977) (biological)

Setting Analytical Performance Specifications

Then, intensive efforts:

- **1988** Odense Group
  Specifications for acceptable bias (biological)

- **1980s** Analysis of clinical situations [Nordic countries] (clinical)

- **1980s** Accumulation of data on biological variation (biological)

- **1997** Fraser, Hytoft Petersen, Libeer, Ricos
  Three levels of quality (biological)

- **1990s** EGE-Lab Working Group
  Biological variation and state of the art (biological and state of the art)

  European EQA Organisers Working Groups (biological)

  ISO TC 212/WG3  ISO 15196
  Analytical Performance Goals Based on Medical Needs

**Evidence-Based Medicine**
Editorial:
Fraser CG, Hyltoft Petersen P.
Analytical performance characteristics should be judged against objective quality specifications.

The 1999 Stockholm Consensus Conference

Dr Anders Kallner
World Health Organization
The 1999 Stockholm Consensus Conference

- sponsored by IFCC, IUPAC, and WHO
- 24-26 April, 1999
- more than 100 participants from 27 countries
- 22 formal presentations from the opinion leaders in the field
- Many discussions led by Dr Desmond Kenny, 1941-2006.

It was said, at his funeral, "Desmond Kenny was a good man and did good work". So he was, and so he did.

The Consensus Hierarchy

1. Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings

2. Evaluation of the effect of analytical performance on clinical decisions in general:
   a. Data based on components of biological variation
   b. Data based on analysis of clinicians' opinions

3. Published professional recommendations:
   a. From national and international expert bodies
   b. From expert local groups or individuals

4. Performance goals set by:
   a. Regulatory bodies
   b. Organizers of External Quality Assessment (EQA) schemes

5. Goals based on the current state of the art:
   a. As demonstrated by data from EQA or Proficiency Testing scheme
   b. As found in current publications on methodology.
The Consensus Hierarchy

• The above hierarchy includes currently available models; however, new useful concepts will undoubtedly evolve. Implementation of any of the models should use well-defined and described procedures.

• To facilitate the future debate on the setting of analytical quality specifications, there is a need for agreement on concepts, definitions and terms.

• There is a need for continuous improvement in the exchange of information on quality issues: between clinical laboratory professionals and the diagnostics industry, and between clinical laboratory professionals and the users of the laboratory service.

Success or Failure?

Consensus agreement

D Kenny, CG Fraser, PH Petersen… - … Journal of Clinical & ..., 1999 – informahealthcare.com

... The Stockholm Consensus Conference on Quality Specifications in Laboratory Medicine, 25-26 April 1999; Introduction: Strategies to set global quality specifications in laboratory medicine; ...

Cited by 130 (November 2104)
Success or Failure?

Some EQS organisers have adopted:

The Allowable Limits of Performance have been set using the Stockholm criteria hierarchy.


The TEa tolerance range... is determined according to the Stockholm Conference criteria, whereby biological variation data take the most important place......

What was not achieved in Stockholm?

There was no discussion about matrix-effects and consequently no specifications for allowable matrix

There was no discussion about measurements on ordinal scale

There was no conclusion about absolute and relative quality:
   Deviation from a ‘true’ value
   Deviation from the method mean

There was no agreement on which level of quality should be achieved

There was no agreement on consequences of poor quality

There was no agreement on the relation between clinical/biological specifications and specifications for EQAS and PT

Thanks to Per Hyltoft Petersen
Success?

Convocations of Experts on Laboratory Quality


Most experts used hierarchy and most used Level 2a

Level 2a – Biological Variation: Logical, Clinically-based and Simple

Imprecision
- $CV_A < 0.5 CV_I$

Bias
- $IBI < 0.25 \left[ CV_I^2 + CV_G^2 \right]^{1/2}$

Total analytical error
- $TEa < 1.65 \times 0.5 CV_I + 0.25 \left[ CV_I^2 + CV_G^2 \right]^{1/2}$
Database on Biological Variation

Updated for 2014! Desirable Specifications for imprecision, inaccuracy, and total allowable error, calculated from data on within-subject and between-subject biologic variation. This database is updated and compiled by Dr Carmen Ricos and colleagues. We are honored to be able to host this database.

http://www.westgard.com/biodatabase1.htm

BV and Test Result Variation

Ideal 0.10

<table>
<thead>
<tr>
<th>Ratio of analytical imprecision to within-subject biological variation</th>
<th>Percentage increase in result variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 Optimum</td>
<td>3%</td>
</tr>
<tr>
<td>0.50 Desirable</td>
<td>12%</td>
</tr>
<tr>
<td>0.75 Minimum</td>
<td>25%</td>
</tr>
<tr>
<td>1.0</td>
<td>50%</td>
</tr>
</tbody>
</table>
**BV and Effect on Reference Values**

![Graph showing the relationship between biological variation and analytical imprecision and bias](image)

**BUT - Further Developments**


Simple equations were derived from the relationship between biological variation and the analytical imprecision to calculate permissible imprecision and bias. Five quality classes are proposed for the various analytes reflecting the false-positive error rates (FPR). The new approach combines the theoretical base of biological variation with the technical state-of-the-art.

Further Developments


Six approaches:
(a) limits defined by regulations and external assessment programs,
(b) limits based on biologic variation,
(c) limits based on surveys of clinicians about their needs,
(d) limits based on effects on guideline driven medical decisions,
(e) limits based on analysis of patterns for ordering follow-up clinical tests, and
(f) limits based on formal medical decision models.

Whatever Happened to ISO 15196?

A “Technical Report – Type 2” was produced - 2001-06-18 - but not widely circulated. This did essentially reproduce the 1999 Stockholm consensus hierarchical approach ...... BUT

ISO/TC 212 N116 MEETING SUMMARY
Sydney, Australia, 19 and 21 May 2003

One project, ISO 15196 on performance goals, has been cancelled, with the expectation that WG3 will reconsider the need for the project and reaffirm its scope; if deemed appropriate by the TC, a new work item proposal will be circulated for vote.
Conclusions

*Much work has been done over the last 50 years on setting analytical performance specifications.*

Consensus was achieved at the 1999 Stockholm Conference on Strategies to Set Global Quality Specifications in Laboratory Medicine. The concept has been widely applied, particularly Level 2a, but there are caveats and deficiencies. New models have been developed but are not widely used.

*Laboratory medicine has changed marked over the last 15 years. The time is right to re-evaluate the 1999 concept – that is our current goal.*