The International Haemostasis *External Quality Control* Program
Intended use of Quality Control

Primary Purpose of the Clinical Laboratory

- To produce accurate results that will correctly diagnose and interpret patient issues.
- Two components to purpose:
  - Production of Accurate Results
  - Correct diagnosis and interpretation of patient issues

Intended use of Quality Control

Evaluation of the laboratory system performance

Quality Control

Internal Quality Control (IQC)

External Quality Assessment (EQA)
Internal Quality Control - Defined

Basically, it consists of “sampling” the analytical process periodically to test whether any significant changes have occurred.

The requested control materials involve plasmas with known values for a given parameter.

As per most regulatory requirements, labs are required to assay at least two different specimens, one low and one high concentration, for every test during every day of operation.

Purpose: to ensure precision and accuracy.
List of evaluation criteria (1)

**Accuracy (Recovery)**
- The ability to recover the correct amount of analyte present in the specimen.

**Linearity**
- Many definitions

**Precision**
- The ability to obtain the same result upon repeated measurement of a specimen.

**Reference Interval**
- The central 95% of results found in a “healthy” population. (normal range)

**Method Comparison**
- Comparing results obtained using different methods (multiple instruments / methods)
List of evaluation criteria (2)

- Analytical sensitivity (lowest reportable concentration)
- Specificity (interferences)
- Carryover (specimen to specimen)
- Reportable Range
  - Analytical Measurement Range
    - Maximum range of values for an instrument which can be assayed accurately without dilution
  - Clinical Reportable Range
    - Maximum range of values which can be reported
System performance evaluation

- Precise but inaccurate
  - Precision: acceptable
  - Accuracy: unacceptable
  - → Systematic error

- Accurate but not precise
  - Precision: unacceptable
  - Accuracy: acceptable
  - → Random error

- Precise and Accurate
  - Precision: acceptable
  - Accuracy: acceptable
Intended use of Quality Control

Evaluation of the laboratory system performance

Quality Control

- Internal Quality Control (IQC)
- External Quality Assessment (EQA)
External Quality Assessment - Defined

- Basically, it consists of evaluating the laboratory performance in relation to other laboratories.
- The requested control materials involve plasmas with unknown values.
- As per most regulatory requirements, labs are required to participate in an EQA scheme.
- Purpose: to identify degree of agreement within a group of peers.
Influencing factors

**External factors (Manufacturer)**

- Lot (variability):
  - reagents (variability)
  - calibrators
  - consumables

- Method:
  - analytical principle
  - equipment
  - reagents (manufacturer's choice)

- Calibration:
  - calibration traceability

**Internal factors (Laboratory)**

- Performance:
  - "in house" reagents
  - operator, maintenance, etc...
  - control with "trouble-shooting"

- Implementation:
  - choice of conditions
  - "in house" equipment
  - "in house" reagents
  - time, temperature, volume, etc

- Calibration:
  - calibration curve
Influencing factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Internal factors (laboratory)</td>
</tr>
<tr>
<td>Permanent</td>
<td>Internal factors (supplier)</td>
</tr>
</tbody>
</table>

**External factors (supplier)**
- **Lot (variability):**
  - reagents (variability)
  - calibrators
  - consumables

**Method:**
- analytical principle
- equipment
- reagents (manufacturer's choice)

**Calibration:**
- calibration traceability

**Internal factors (laboratory)**
- **Performance:**
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  - operator, maintenance, etc...
  - control with "trouble-shooting"

**Implementation:**
- choice of conditions
- "in house" equipment
- "in house" reagents
- time, temperature, volume, etc

**Calibration:**
- calibration curve

IQC

EQA

IQC

EQA
<table>
<thead>
<tr>
<th></th>
<th>IQC</th>
<th>EQA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope</strong></td>
<td>correct performance of test system within a laboratory setting</td>
<td>correct performance of test system in relation to other laboratories</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>each time a test is performed (1/day or every 8 hours)</td>
<td>periodically</td>
</tr>
<tr>
<td><strong>Sample value</strong></td>
<td>known</td>
<td>unknown</td>
</tr>
<tr>
<td><strong>Evaluation</strong></td>
<td>prospectively / simultaneously</td>
<td>retrospectively</td>
</tr>
</tbody>
</table>
1. Shipment of the kits (plasma) at various frequency => blind assay

2. Result submission

3. Reports => Collecting information for the purpose of *lab. accreditation* (Certification of quality)
Global Key Features

- **Internationalisation of the EQA**
  - Larger number of participants
  - Developed according to the requirements of the standard ISO 13528 «Statistical methods for use in proficiency testing by interlaboratory comparisons»

- **Enlargement of the range of parameters**
  - from routine to the most specialized tests

- **Cover all the measuring fields**
  - 4 different plasma levels
  - various clinical contexts

- **Global comparison of systems**
  - Peer groups

- **Flexible programs**
  - Suitable to each activity

- **Optimized ergonomics**
  - New dedicated website
Key features

Complete Stago EQA program:

1. Integrating all the reagents & instruments on the market (Stago & others)

2. Integrating all semi-automated systems (Stago & others)

3. Multiple program options
   * Diagnosis challenge plasma (clinical case) = a NEW "generation of programs"...
Global policy

**Qualiris QC Experience**
- 2 campaigns / year, 2 x 3 vials
- Standard: PT, APTT, Fib, TT
- Cat. #01046

**Qualiris QC Premium**
- 12 campaigns / year, 12 x 2 vials
- Standard: PT, APTT, Fib, TT
- Qualiris Diagnostic challenge
  - 3 campaigns / year, 6 vials
  - Cat. #85101

Optional parameters…

**Module 1: Factors + VWF**
- Cat. #85093

and / or

**Module 2: Thrombophilia**
- (AT, PC, PS) + AP, Plg
- Cat. #85094

Optional programs (kits)…

**Qualiris QC Heparin LMWH**
- 6 campaigns / year, 6 vials
- Cat. #01047

and / or

**Qualiris QC Heparin UFH**
- 6 campaigns / year, 6 vials
- Cat. #01048

and / or

**Qualiris QC Lupus Anticoagulant**
- 3 campaigns / year, 6 vials
- Cat. no #01063

**Qualiris QC D-Dimer**
- 6 campaigns / year, 6 vials
- Cat. #01049

**Qualiris Diagnostic challenge**
- 3 campaigns / year, 6 vials
- Cat. #01050

New in 2013

- Multiple combinations (flexibility)
- Answers all labs needs
Key Features (customer side)

Added value

Dedicated WEBSITE

- Easy data submission
- Specific access dedicated to distributors => global view of your customers
- Specific access dedicated to laboratory groups **NEW**
  - Remote management and follow up of laboratory group system performance

- Access to clear & customized reports
  - Real time reports **NEW**
  - Monthly, biannual and annual reports
  - Laboratory group reports **NEW**
  - National & International reports **NEW**

- Certificate of participation available on line for customers
- Traceability
  - Access to at least 5 year archived lab reports
Website

- Open account on line on the website
- Submission of customers’ technical information form NEW
  - type of instruments, parameters & programs used by the labs …
- Account management by the laboratory NEW
  - multiple user profile
Lab group access  \textit{NEW}

- Main account $\rightarrow$ Management of different user profiles (rights, access, reports)
Operating Process of the programs
Qualiris QC Premium

Level 1

Half year 1 (S1)

jan  |  feb  |  mar  |  apr  |  may  |  june

Level 2

Half year 2 (S2)

july | aug  |  sep  |  oct  |  nov  |  dec

Level 3

Level 4
<table>
<thead>
<tr>
<th>Month</th>
<th>S1 Vials</th>
<th>S2 Vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan</td>
<td>Orange</td>
<td>Orange</td>
</tr>
<tr>
<td>Feb</td>
<td>Blue</td>
<td>Blue</td>
</tr>
<tr>
<td>Mar</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Apr</td>
<td>Purple</td>
<td>Purple</td>
</tr>
<tr>
<td>May</td>
<td>Cyan</td>
<td>Cyan</td>
</tr>
<tr>
<td>June</td>
<td>Orange</td>
<td>Orange</td>
</tr>
<tr>
<td>Jul</td>
<td>Orange</td>
<td>Orange</td>
</tr>
<tr>
<td>Aug</td>
<td>Blue</td>
<td>Blue</td>
</tr>
<tr>
<td>Sep</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Oct</td>
<td>Purple</td>
<td>Purple</td>
</tr>
<tr>
<td>Nov</td>
<td>Cyan</td>
<td>Cyan</td>
</tr>
<tr>
<td>Dec</td>
<td>Orange</td>
<td>Orange</td>
</tr>
</tbody>
</table>

1 Kit S1 = 12 vials
1 Kit S2 = 12 vials
Qualiris QC Premium (Data analysis)

<table>
<thead>
<tr>
<th></th>
<th>12 Monthly Reports</th>
<th>2 Biannual Reports</th>
<th>1 Annual Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 vials (random &amp; blind sample) / month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ex: Half year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>jan</th>
<th>feb</th>
<th>mar</th>
<th>apr</th>
<th>may</th>
<th>june</th>
</tr>
</thead>
<tbody>
<tr>
<td>[image]</td>
<td>[image]</td>
<td>[image]</td>
<td>[image]</td>
<td>[image]</td>
<td>[image]</td>
</tr>
</tbody>
</table>

- **Half year analysis**
  - 3 vials per month
  - 3 months
  - Total: 9 vials

- **Annual analysis**
  - 3 vials per month
  - 6 months
  - Total: 18 vials
Qualiris QC D-Dimer

Level 1

Level 2

Level 3

1 kit / year
Qualiris QC D-Dimer

1 kit = 6 vials / year
Qualiris QC D-Dimer (Data analysis):

6 Periodic Reports
1 vial (random & blind sample) every 2 months

1 Annual Report
Annual analysis

X 2

X 2

X 2
Qualiris QC Heparin (UFH & LMWH)

Level 1
Level 2
Level 3

1 kit UFH / year
1 kit LMWH / year
Qualiris QC Heparin (UFH & LMWH)

1 kit = 6 vials / year
Qualiris QC Heparin UFH & LMWH (Data analysis):

- **6 Periodic Reports**
  - 1 vial (random & blind sample) every 2 months

- **1 Annual Report**
  - Annual analysis
  - Orange vials: x2
  - Pink vials: x2
  - Blue vials: x2
Qualiris QC LA

- Negative level
- Low positive level
- High positive level

1 kit / year
Qualiris QC LA

1 kit = 6 vials / year

White Caps
Qualiris QC LA (Data analysis):

3 Reports
2 vials every 4 months

1 Annual Report
Annual analysis

Global analysis
Qualiris Diagnostic Challenge

Level 1
1 kit / year
3 Periodic Reports
1 vial (random & blind sample) / campaign

Level 2

Level 3
1 vial (random & blind sample) / campaign

NB: 2 vials per level = to supply enough volume for additional tests (eg: specialized tests)
Key Features

Diagnostic Challenge Unique on the market

- Pathological plasma associated to clinical case
- Depending on the clinical case, various tests are performed
- Multiple Choice Questionnaire (on line)
- Clinical diagnosis is made

→ Global lab performance self assessment in order to improve the patient safety
Diagnostic Challenge Report (focus on 2 parts)

Individual Report

Clinical Analysis & Discussion

Diagnostic Challenge 1 - 2010

Discussion by Dr F. Depasse, Clinical Pathologist, ISTH member

- Lupus anticoagulants in pediatrics
  
  Lupus anticoagulants are often detected in young children in particular at the end of an ENT infection.

  The presence of this type of anticoagulants is often transient, but may persist following a series of infections.

  In children, detection of a lupus anticoagulant is generally not correlated to a hemorrhagic or thrombotic risk and allows a surgery if any other coagulation disease, particularly of hemorrhagic type, is excluded. It is recommended to perform a Factor VIII and a Factor IX assay to confirm the absence of moderate hemophilia which may have been unknown until then.

  In that specific clinical context, the aim of the tests is to rule out an hemorrhagic risk; the use of specialty tests as the Diluted Russell Viper Venom Time (DR/VT) (screen and confirm) is highly recommended for the diagnosis. On the opposite, during a specific investigation of Lupus Anticoagulant for the diagnosis of the antiphospholipid syndrome, it is highly recommended to perform a Diluted
Examples of the three 2012 clinical cases

**DC1: Willebrand disease**
We report the case of a three-year old Julien referred to laboratory for screening for a bleeding disorder. His parents came to visit the general practitioner because of frequent and prolonged nosebleeds and bruising. Complete Blood Count with platelets count and automated differential are normal.

**DC2: Acquired Haemophilia A**
We report the case of a 34 year-old man, presenting with acute abdominal pain. The Complete Blood Count results are consistent with appendicitis. According to the clinical outcome the physician diagnoses peritonitis.
As there is no medical or surgical history or mention of antiplatelet drug intake in the previous week, and according to the life-threatening situation, it has been decided to operate immediately without preoperative workup.
A short time after the surgery, it is noted that the haemoglobin level drops, suggestive of unexpected and severe bleeding. Moreover, the Platelet count is normal.

**DC3: HIT**
We report on the case of Mrs. G., 91 years old, hospitalized for pulmonary embolism.
She has no severe renal insufficiency.
She receives curative treatment by tinzaparin 175 IU/kg OD.
VKA treatment has been started 24 hours after tinzaparin treatment initiation.
The physician prescribes a haemostasis work-up for monitoring treatment.
You receive this sample, drawn 4 to 6 hours after tinzaparin injection, on the third day of tinzaparin treatment.
Reports & statistical exploitation
The statistical indicators

**Universal = accessible by all**

- Total number of results (n): total number of all the results released by the subscribed laboratories
  - The minimum "n" number for statistics to be processed
  - is 12 for one exploitation

- "Robust" Mean and "robust" Standard Deviation (M & SD):  
  => The robust mean (M) is regarded as the target value

  - CV (%) = (SD / M) * 100
  - express the reproducibility of the method
The statistical indicators

**Bias (%)** = \[
\frac{\text{lab result} - M}{M} \times 100
\]

- allows to appreciate the measurement accuracy of the result returned by the laboratory.

**Z Score** = \[
\frac{\text{lab result} - M}{SD}
\]

- allows to appreciate the measurement accuracy of the result returned by the laboratory, by taking into account the technical performances (dispersion of the results).

- The Z* Score can be interpreted as follows:
  - A: Set in the ±2 interval: your result is satisfying
  - B: Included between [+/- 2; +/-3]: supervision is necessary
  - C: > [+/- 3]: corrective action is essential
<table>
<thead>
<tr>
<th>Global</th>
<th>All kind of Cephalins : (Stago + Others)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodology</td>
<td>Segmentation / activators : (aPTT example)</td>
</tr>
<tr>
<td></td>
<td>- CK Prest (Kaolin)</td>
</tr>
<tr>
<td></td>
<td>- aPTT (Silica)</td>
</tr>
<tr>
<td></td>
<td>- Cephascreen (Polyphenols)</td>
</tr>
<tr>
<td>Technical</td>
<td>Segmentation / reagents :</td>
</tr>
<tr>
<td></td>
<td>- pool of all results carried out with CK Prest,</td>
</tr>
<tr>
<td></td>
<td>- pool of all results carried out with aPTT,</td>
</tr>
<tr>
<td></td>
<td>- pool of all results carried out with Cephascreen.</td>
</tr>
<tr>
<td>Peer Group</td>
<td>Combination : analysers / reagents</td>
</tr>
<tr>
<td></td>
<td>(Stago or Others)</td>
</tr>
<tr>
<td></td>
<td>=&gt; the sharpest degree of comparison</td>
</tr>
</tbody>
</table>
Review a monthly report
### Table: APTT (Silica)

<table>
<thead>
<tr>
<th>Overall participants</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT</td>
<td>1023</td>
<td>52,0</td>
<td>3,42</td>
<td>6,58</td>
</tr>
<tr>
<td>Silica</td>
<td>380</td>
<td>51,6</td>
<td>2,05</td>
<td>3,97</td>
</tr>
<tr>
<td>STA® PTT-A</td>
<td>380</td>
<td>51,6</td>
<td>2,05</td>
<td>3,97</td>
</tr>
<tr>
<td>STA® PTT-A - STA-R®</td>
<td>106</td>
<td>53,2</td>
<td>2,16</td>
<td>4,06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Your result</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT</td>
<td>51,0</td>
<td>-1,89%</td>
<td>-0,29</td>
<td>A</td>
</tr>
<tr>
<td>Silica</td>
<td>-1,16%</td>
<td>0,29</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>STA® PTT-A</td>
<td>-1,16%</td>
<td>0,29</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>STA® PTT-A - STA-R®</td>
<td>-4,07%</td>
<td>-1,00</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

### Graphs:
- **Histogram of Monthly Report**
- **Comparison levels**
- **Assessment of the method accuracy**
- **Assessment of the precision**
- **Colored guidelines**
- **Histogram of the result's dispersion**
- **Laboratory result**
Youden Plot Graph

Vial 3

Vial 4

Laboratory result

+/- 1 DS

+/- 2 DS
1. Qualiris is open to every system (reagents + analyzers); even from the competition (Siemens, IL...).
   - Qualiris is not only dedicated to Stago customers. This makes Qualiris independent as every laboratory can be enrolled in Qualiris programs.
   - Every peer group comparison might be represented if a minimum of 12 values is reached. There is no difference with others competitors or organizations.

2. International recognized algorithm
   - Statistical indicators developed in accordance with the requirements of ISO 13528 Standard are used for Qualiris statistical calculation.
     >> Guarantee of integrity

3. Independent calculation
   - Robust mean is calculated with the participants' values. Qualiris plasma are not assayed by Stago.
     >> No bias coming from the EQA organizer (Objective calculation)
   - Robust algorithm do not exclude aberrant values
     >> No interference / influence by EQA organizer
   - Peer group comparison. In market where one supplier is well established, the huge number of local supplier participants influences the global mean, adding a bias in results' interpretation. The peer group comparison allows each participant the most objective assessment of its performance.
     >> No impact of the participants' breakdown
Thank you for your attention

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