What Matrix, Which Matrix!

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on behalf of the EBF TT-45

Open Symposium
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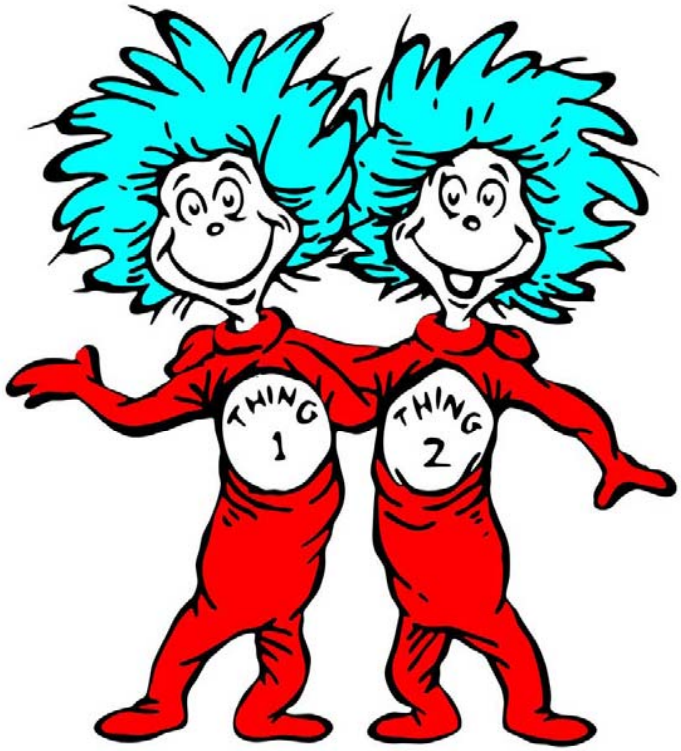
Outline

- Scope
- Starting Point
- Survey
- Survey Part II
- Proposed Best Practice
- Risk Assessment
- Further work

Scope

- A rat is a rat,
- Please say it's so?
- Sprague Dawley,
- Hans Wistar,
- Zucker so sweet,
- Treat them the same
- Without any blame.



Starting Point

- A team was required.
- So that's what we did.
- Steering from Peter,
- Till Magnus took over,
- The team was appointed,
- Nathalie, Bernhard,
- Stuart and Kluas,
- Brigitte, Petra,
- Stephanie and Me!

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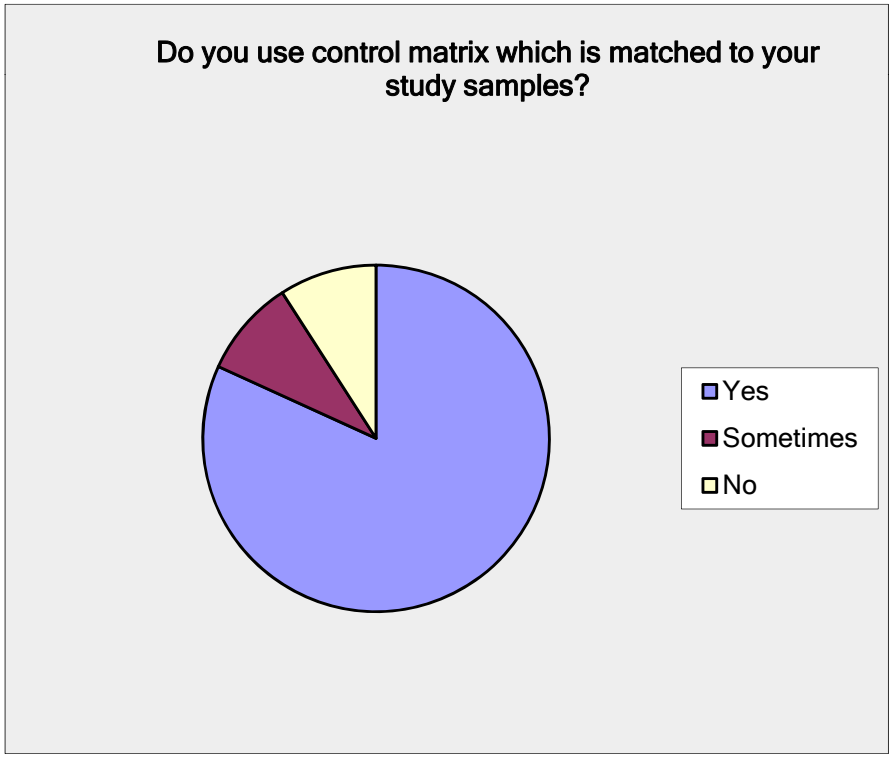
Survey

- A survey we needed,
- It's the EBF way!
- The Monkey was used,
- But the topic too big.
- We focused our efforts,
- Clinical LC-MS, hooray.

Survey Part II

- We asked all the people,
- We asked and we asked,
- They answered the survey.
- So here since you asked
- A graph, yes a graph!



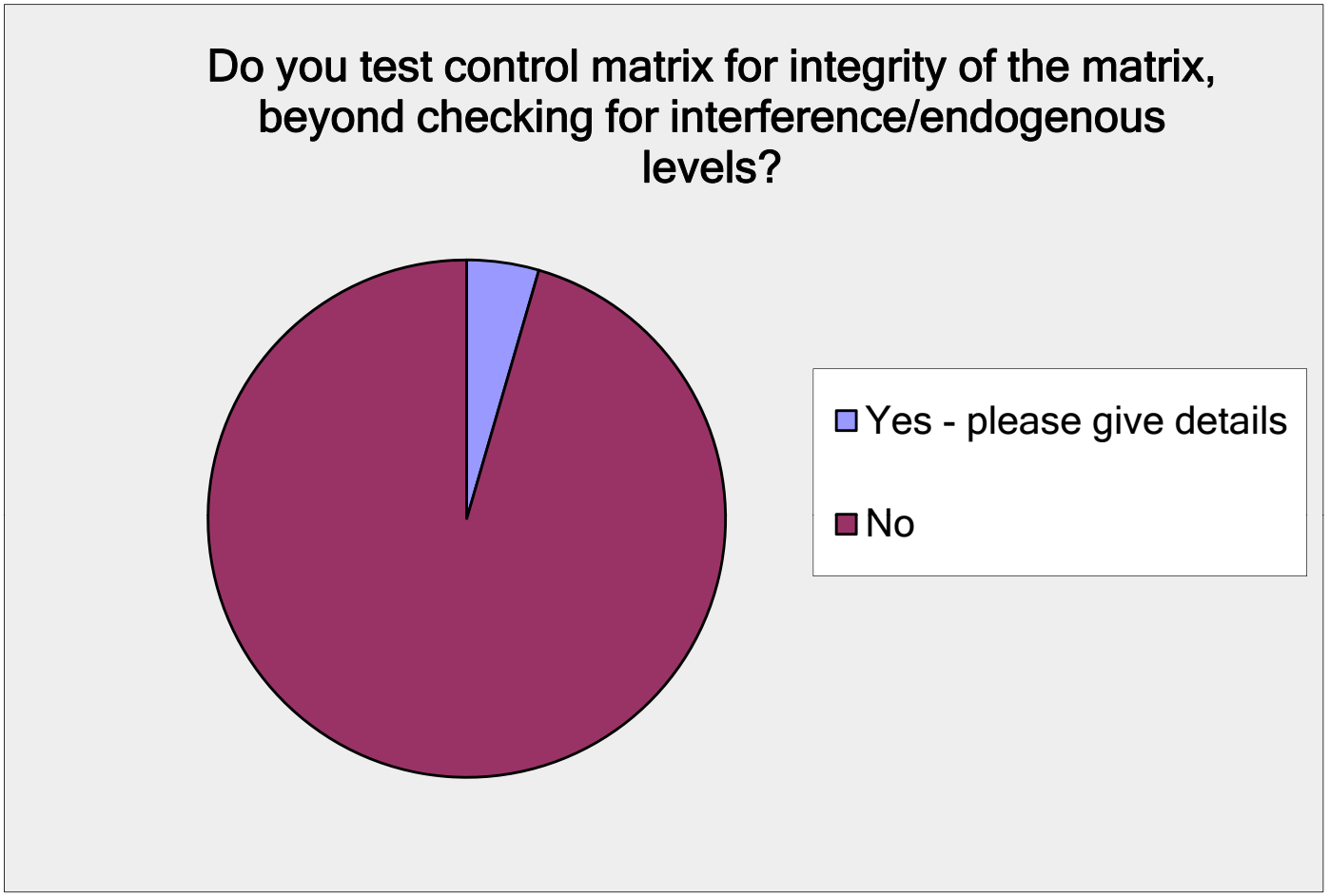
Survey Part II

- Graphs I can show you,
- Yes more than a few,
- But that would be boring,
- So here's what I'll do.
- Lets go exploring,
- And see what it shows!
- But lets do it non-Seus way.

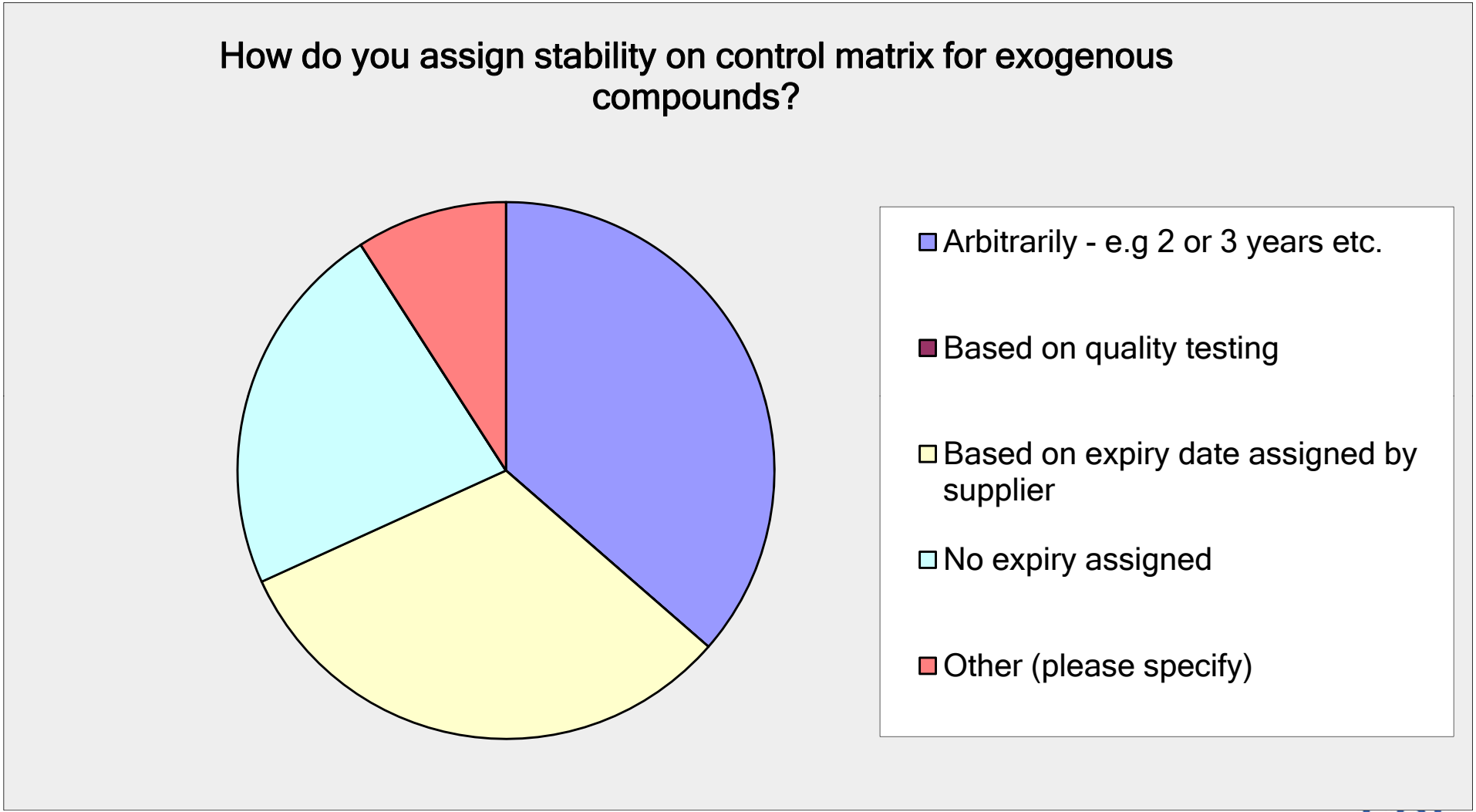
Proposed Best Practices

- Based on the results of the survey and experience and discussion and debate within the Topic Team the following suggestions are being put forward as our best practice for Clinical analysis of small exogenous molecules.

Control Matrix



Control Matrix



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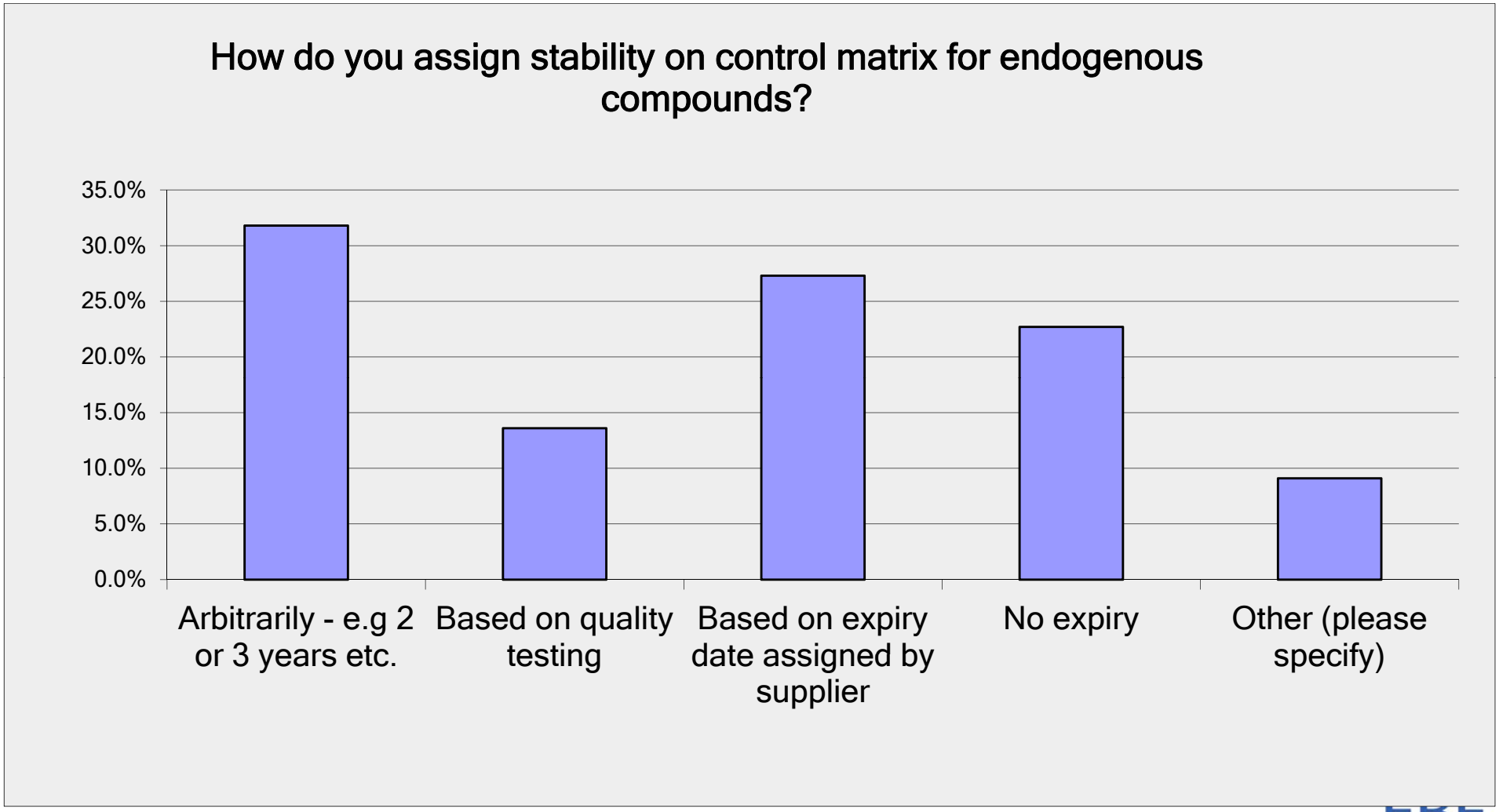

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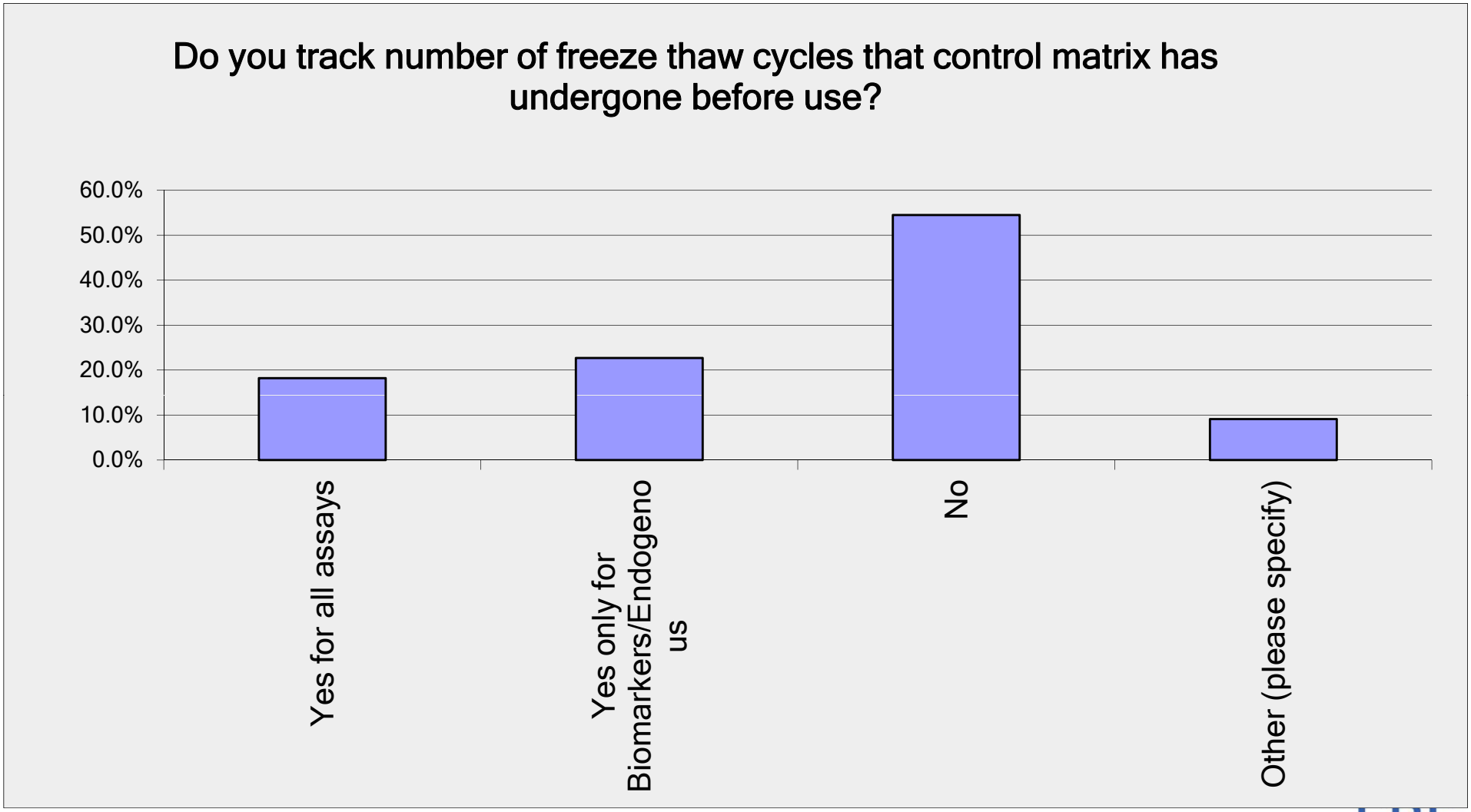


Control Matrix

- Best practice for Control Matrix
  - Pressure on suppliers to minimise freeze/thaw cycles – and record and supply history.
  - Know the history of the matrix.
  - Sub aliquot all control matrix into smaller containers on 1st defrost/collection or order small aliquots for single use.

Clinical Control Matrix

- Quality Controls (QC's)
  - The QC's to be used to analyse clinical samples should be prepared from a pool.
  - The matrix used should be matched to the subject population to be analysed. Minimum – Anticoagulant, sex and disease state (if appropriate).
  - The pool of matrix used should have the lots and volume of matrix used recorded.

Control Matrix Stability

- While currently this is not standard practice we suggest that if you do want to assign stability to your control matrix for your assay then the approach should be –
  - Stability in control matrix should be made by analysing spiked QC's against Calibration standards or QC's in fresh matrix.

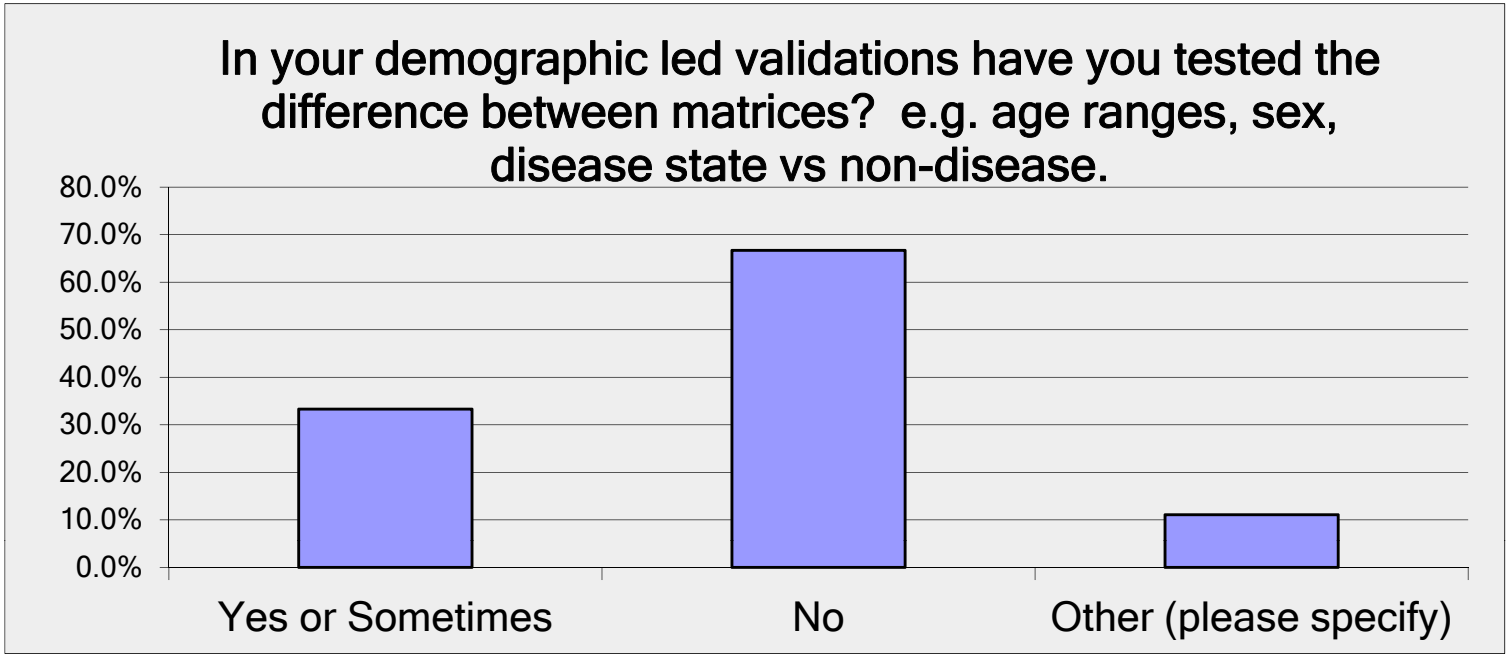
Calibration Standards (Cals)

- The pool used for the calibration standards (Cals), need not be the same as the pools used for the QC's but good scientific practice (and our proposal) would be to use a separate pool or individual for the Cals.

Assay Validation

- The QC's used to validate the assay should meet the requirements on the slides earlier for QC's.
- Disease state matrix could be limiting so during the validation suggest this is investigated as part of the validation process to allow comparison against healthy matrix.
  - Minimum of MF to be assessed in at least n=3 disease state matrix. If possible then n=6 should be done.
  - Practically the inclusion of a test within the validation would allow the use of 'standard' control matrix within the analysis e.g. Male vs Female

Risks Assessment



The number of people who tested for demographic issues reported that there were very few instances of differences.

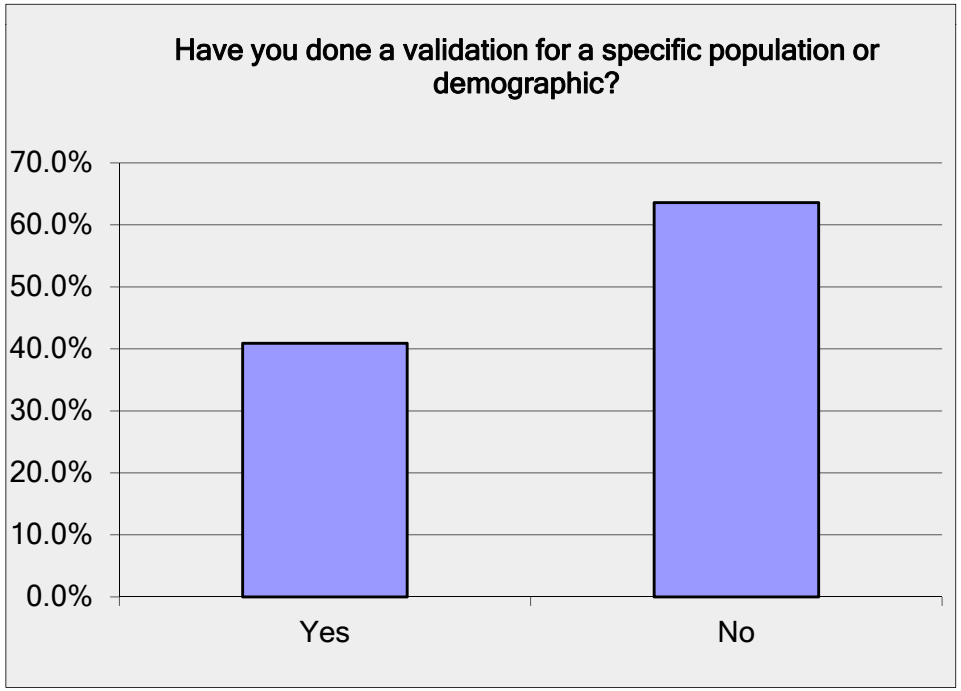
1 respondent had done 2 and found differences in both

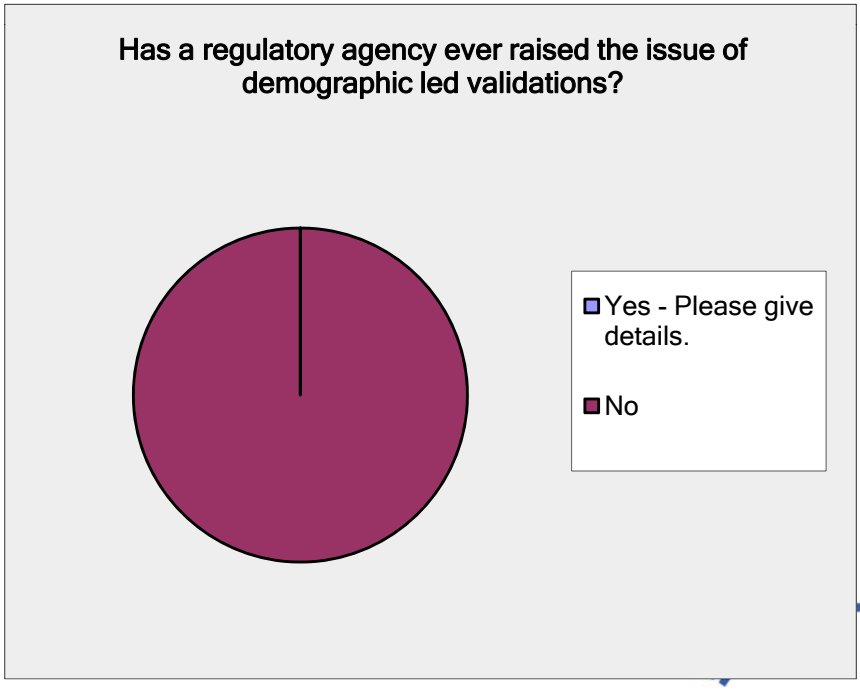
Some reported approx. 20% of those tested demonstrated issues

A demographic led validation is done so rarely there is a limited data set to work with.

Regulatory Focus

- While many respondents had completed validations that were demographically led, there was no reported regulatory questions for a demographic led validation.





Risk Assessment

- Use a stable labelled Internal Standard where ever possible!
  - This will reduce the potential risks
  - It will also give you indicator of potential issues

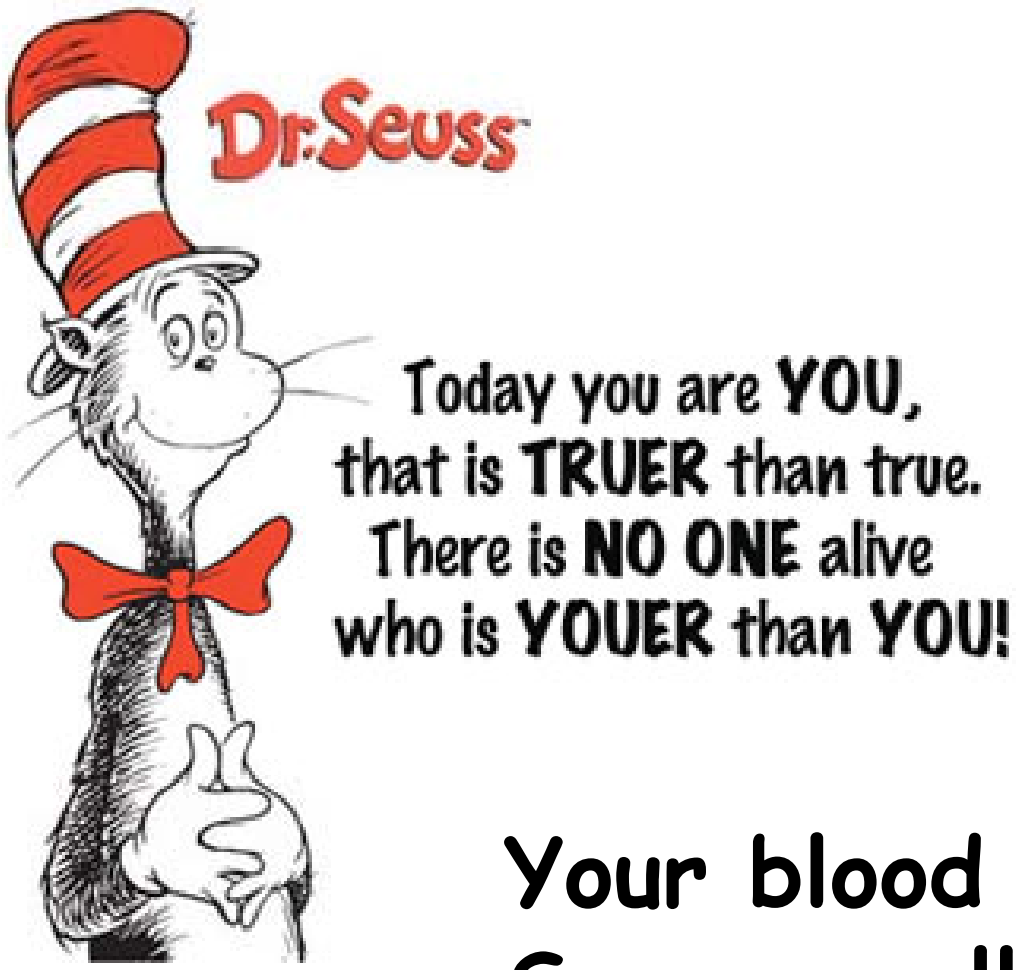
Risk Assessment

- Consider the Bioanalytical data in context to the program and study.
- Consider the impact of quality and risk on the data that is required.

Further Work

- The team still have to look at the following -
  - Chromatographic Pre-clinical exogenous
  - LBA Clinical exogenous
  - LBA Pre-clinical exogenous
  - Endogenous – LBA and Chromatographic

- Aim to produce a best practices document.



Your blood is like mine,
So we really can't whine,
And it's analytically fine,
To treat yours as if mine.

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