EBF European Bioanalysis Forum

# Incurred Sample Reanalysis : EBF's Perspective and Experience


EBF steering committee :

Philip Timmerman (Johnson & Johnson), presenter

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Richard Abbott (Shire Pharmaceuticals)




EBF

# EBF History - 1

Oct 12th 2006 – **B**russels

- In a “EU-DVDMDG type meeting”, over 10 EU companies, together with some CROs, joined to discuss mostly ISR in an open and stimulating atmosphere.
- At the end of the meeting a number of companies, formally launched the idea of a broader European BA Organization

# EBF History - 2

## Nov 10th 2006 - **B**erlin

- 1st EBF meeting at Schering (currently Bayer Schering Pharma)
- 12 companies signed up to join EBF
  1. Merck KGaA
  2. Boehringer-Ingelheim
  3. Novartis Pharma AG
  4. F. Hoffmann-La-Roche
  5. NV Organon
  6. Shire Pharmaceuticals
  7. Bayer Schering Pharma AG
  8. Sanofi-Aventis Deutschland GmbH
  9. Astellas
  10. AstraZeneca
  11. UCB
  12. Johnson & Johnson
- groundrules of EBF were discussed and agreed

# EBF – how are we organized ?

Ground rules :

- only pharma companies can become member.
- EBF only represents EBF and not individual member companies.
- each company assigns 1 representative (and a deputy) to the EBF.
  - the representative is single point, represents all EU-BA areas of the member company.
  - the deputy replaces the representative when he/she cannot attend.
  - Meeting attendance is mandatory for representative or deputy after 2 missed meetings.
- we don't :
  - exchange portfolio or IP information
  - allow advertisements of members or invites
- Steering committee :
  - 4 member companies assigned for 2 years
  - communicate on behalf of the EBF on EBF matters
- Internal discussions within EBF aim to recommend or influence opinions/procedures towards our members, business partners, regulatory bodies,….

# EBF members – Feb. 2008

1. Abbott
2. Astellas
3. AstraZeneca
4. Bayer Schering Pharma AG
5. Boehringer-Ingelheim
6. Ferring Pharmaceuticals A/S
7. Grünenthal GmbH
8. GSK
9. F. Hoffmann-La Roche
10. Johnson & Johnson
11. H. Lundbeck A/S
12. Merck&Co
13. Merck KGaA
14. Novartis Pharma AG
15. Organon
16. Orion Corp. Orion Pharma
17. Pfizer
18. Sanofi-Aventis
19. Servier
20. Shire Pharmaceuticals
21. Solvay Pharmaceuticals
22. UCB

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# EBF : Scope - 1

- Our focus is bioanalysis within pharmaceutical R&D

- Bioanalysis is defined as :
  - ✓ quantification of small and large MW drug and metabolites in body fluids and tissues
  - ✓ quantification of PD and safety biomarkers amenable to conventional bioanalytical techniques (binding assays, chromatographic assays)
  - ✓ bioanalytical characterization of biologicals

# EBF : Scope - 2

## Identified areas for discussion are :

- Science
- Procedures
- Business tools and Technology
- Regulations

## A few examples are :

- New or emerging guidelines on
  - method development and validation
  - reporting and archiving
- Biomarkers
- LIMS, ELN, CSV
- Metabolite quantification
- Technological developments in industry (chromatography, MS, automation)

# EBF – how are we organized ?

## Steering committee meetings

- Steering committee members only
- Frequency and venue :
  - Approx. 1 month prior to open or closed meetings in **B**erlin

## Closed meetings :

- For member companies only
- Frequency and venue :
  - twice per year (January and June - 1.5 day) in **B**asel area

## Open meetings :

- Including CRO, regulatory bodies, academia, vendors, others
- Frequency and venue :
  - Yearly, October or December in **B**arcelona are

## Participation to other meetings/organisations on BA topics

- Non profit related
- Examples are : AAPS – BSAT – FABIAN – GMPfrance - RPS

# Incurred Sample Reanalysis (ISR)

## The white paper

# ISR : Statements in “BMV White Paper” - 1

Reproducibility and accuracy in incurred samples may be altered by:

- metabolites converting to the parent drug
- protein binding differences in patient samples
- recovery
- sample inhomogeneity
- MS ionization due to matrix effects

Intention for the investigation of incurred samples:

- to assure that the effects which may influence the analytical result are under control when the method is applied to study samples: scientific issue!!

In general

- it is accepted that the chance of incurred sample variability is greater in humans than in animals

# ISR : Statements in “BMV White Paper” - 1

preclinical studies:

- needs to be performed on all species used for GLP toxicology experiments
- No additional ISR investigations needed once the initial assessment is performed

clinical studies:

- extent and nature of incurred sample testing is left to analytical investigator
- Study sample results :
  - may be reported in respective study report and/or as addendum to the MVR.
  - may be used for comparison purposes and do not necessarily have to be used in calculating reported sample concentrations
- selection of samples:
  - concentration, patient population, special populations, concomitant medication
- selection of studies:
  - first in human, PoC in patients, special population and bioequivalence studies

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# Incurred Sample Reanalysis (ISR)

## What we discussed within EBF

# ISR : EBF's discussions

- Desire to share thoughts and align if possible
- open items and unclarities :
  - For which study do we reanalyse incurred samples?
  - How many samples to reanalyze?
  - Use of individual samples or pooled samples?
  - When to perform reanalysis?
  - Which acceptance criteria?
  - Where to report data?
  - Which value will be reported in the study?
  - Etc...

# EBF's position after Internal Discussions until May 2007

- agreement that there is a scientific rationale to investigate ISR, albeit less in preclinical species
- intend to investigate/document the incurred sample reproducibility :
  - once per species/matrix in preclinical methods (all or main tox species?)
  - at a few occasions for clinical studies (at least volunteers and patients, maybe also special populations,.. ….or ….every time scientific reasons recommend re-evaluating the incurred sample reproducibility)
- number of samples to be reanalyzed at BA-scientist discretion
- use simple statistics as acceptance criteria.

# EBF : ISR Questionnaire, version 1 August 2007

- Aim : to get better clarification and understanding on how EBF's initial agreements and commitments on ISR where implemented
- 35 questions
  - 6 general questions
  - 12 questions related to clinical samples only
  - 13 questions related to preclinical samples only
  - 4 questions related to ligand binding assays only
  - Answers grouped into 15 key areas (13+2 for LBAs)
  - 19 out of 20 companies responded (8 gave input in LBA questions)
- Details discussed at Autumn 2007 EBF meeting (e.o. August) and results presented at BAST meeting in September (**B**oston)

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# EBF : ISR Questionnaire

Some side remarks :

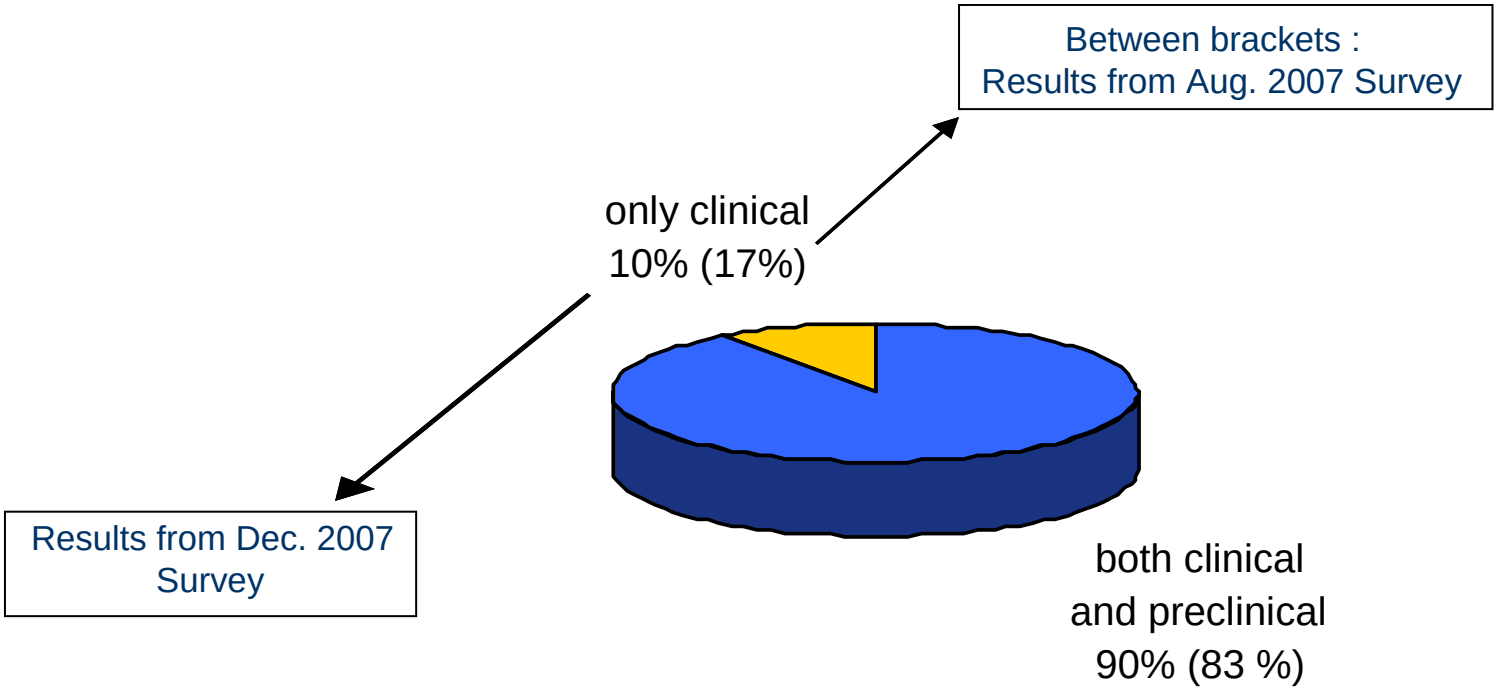
- Since experience was still low, answers of EBF members reflected a mix of “experience” and “commitment” or “intent”

- Questionnaire repeated in Dec. 2007 to monitor evolution :
  - Identical to version 1
  - 5 questions where added on EBF impact
  - 21 (all members in Dec responded (10 gave input in LBA questions))
  - Details presented today

Summary presented in next slides……..

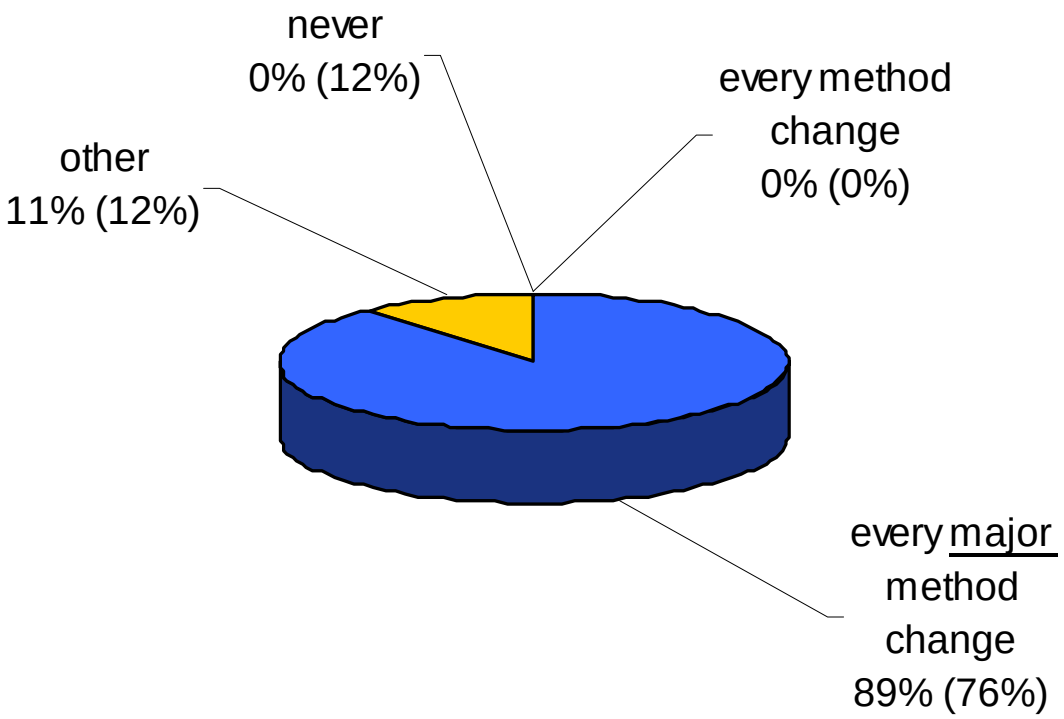
# General questions

1. Do you perform ISR for both clinical and preclinical samples?



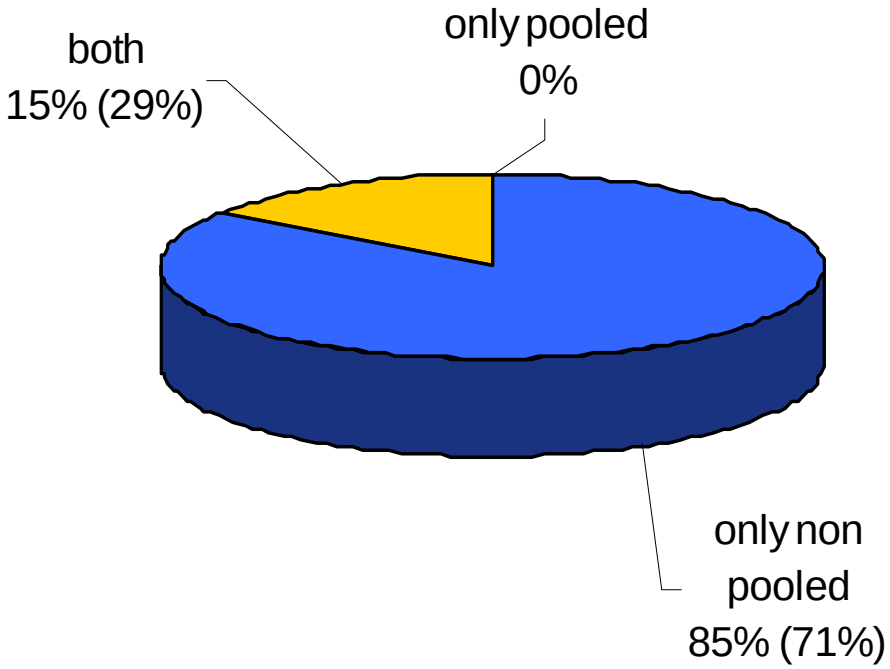
# General questions

## 2. How often do you re-evaluate ISR for a method ?



# Questions on both pre-clinical and clinical samples

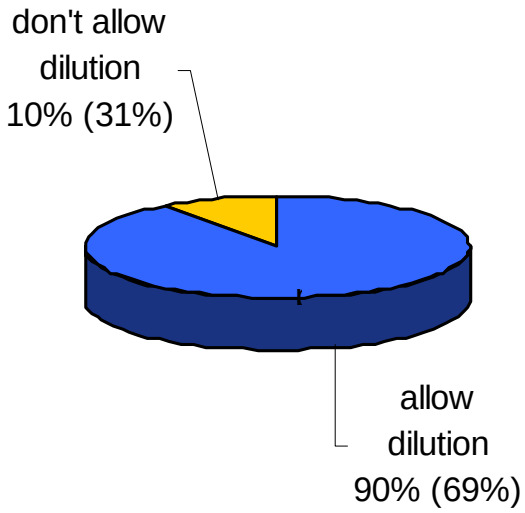
3. Do you use pooled or non pooled samples to investigate ISR ?



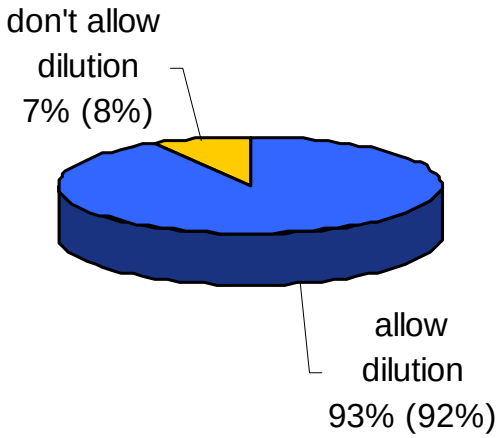
# Questions on both pre-clinical and clinical samples

## 4. Do you allow the use of diluted samples ?

### Clinical samples

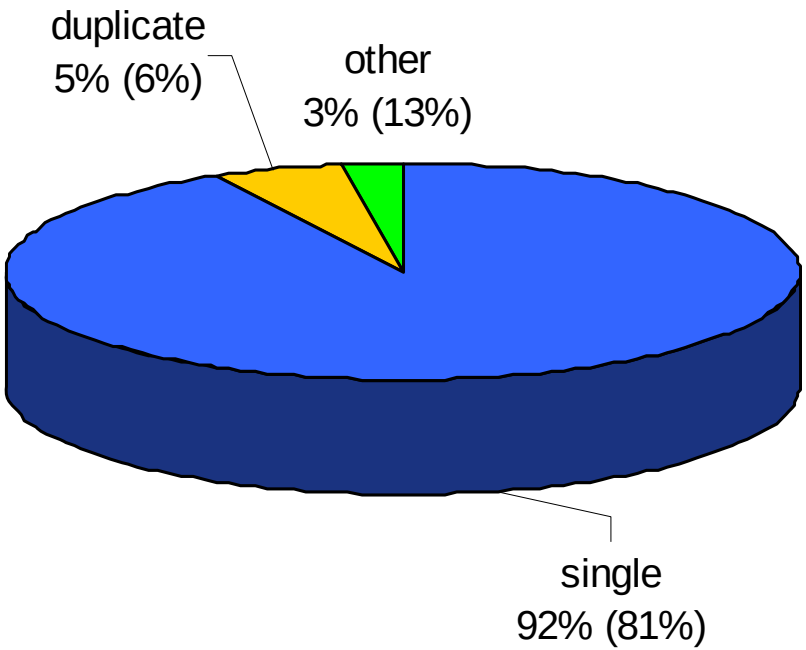



### Pre-clinical samples

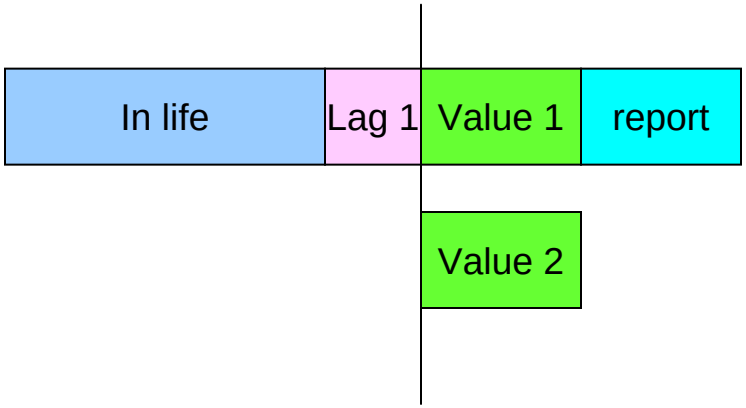


# Questions on both pre-clinical and clinical samples

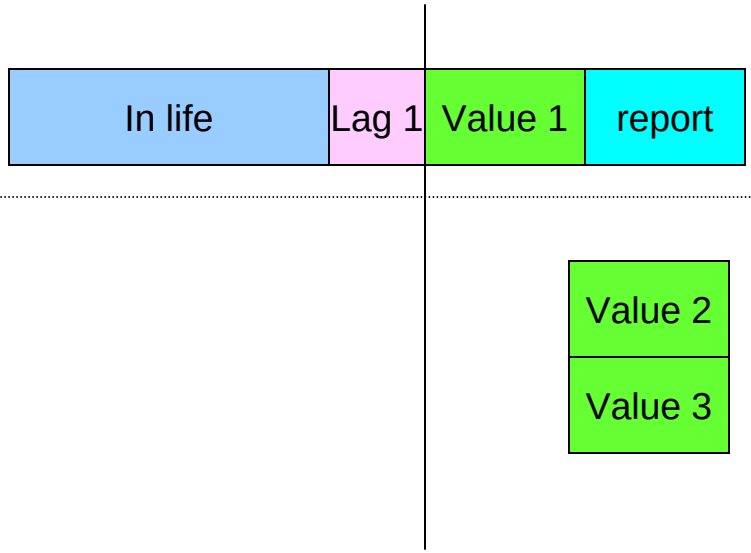
5. For ISR assessment, are samples reanalysed in single/duplicate/other?



Scenario 1




Scenario 2

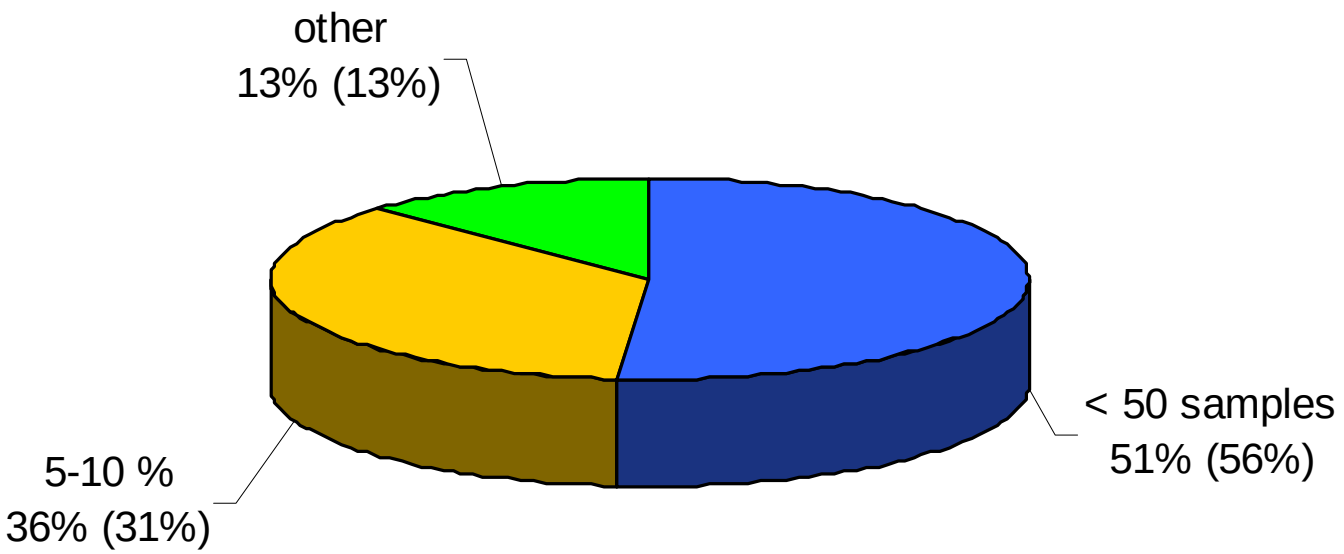



study

MVR

# Questions on both pre-clinical and clinical samples

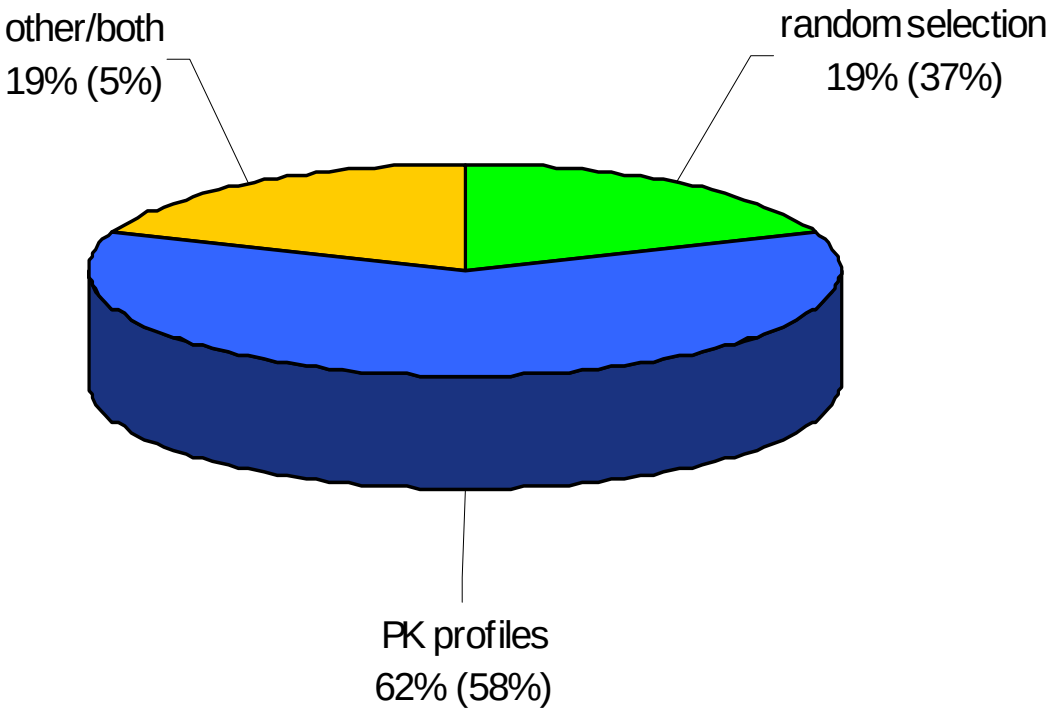
## 6. how many samples are reanalysed to document ISR?




EBF discussed "Confirmatory Re-Analysis of Incurred Samples - An Industry Perspective" from M. Rocci given at AAPS National Biotechnology Conference in San Diego (2007), but preferred more simple sample selection criteria

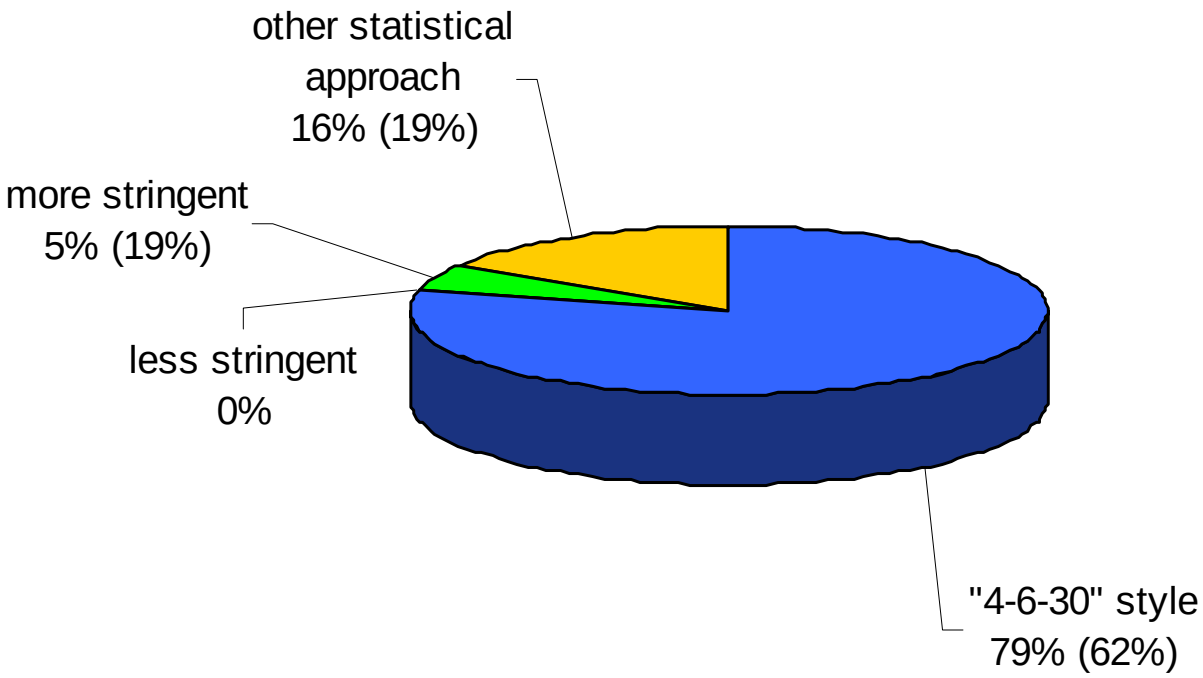
# Questions on both pre-clinical and clinical samples

## 7. For ISR assessment, how are samples selected ?



# Questions on both pre-clinical and clinical samples

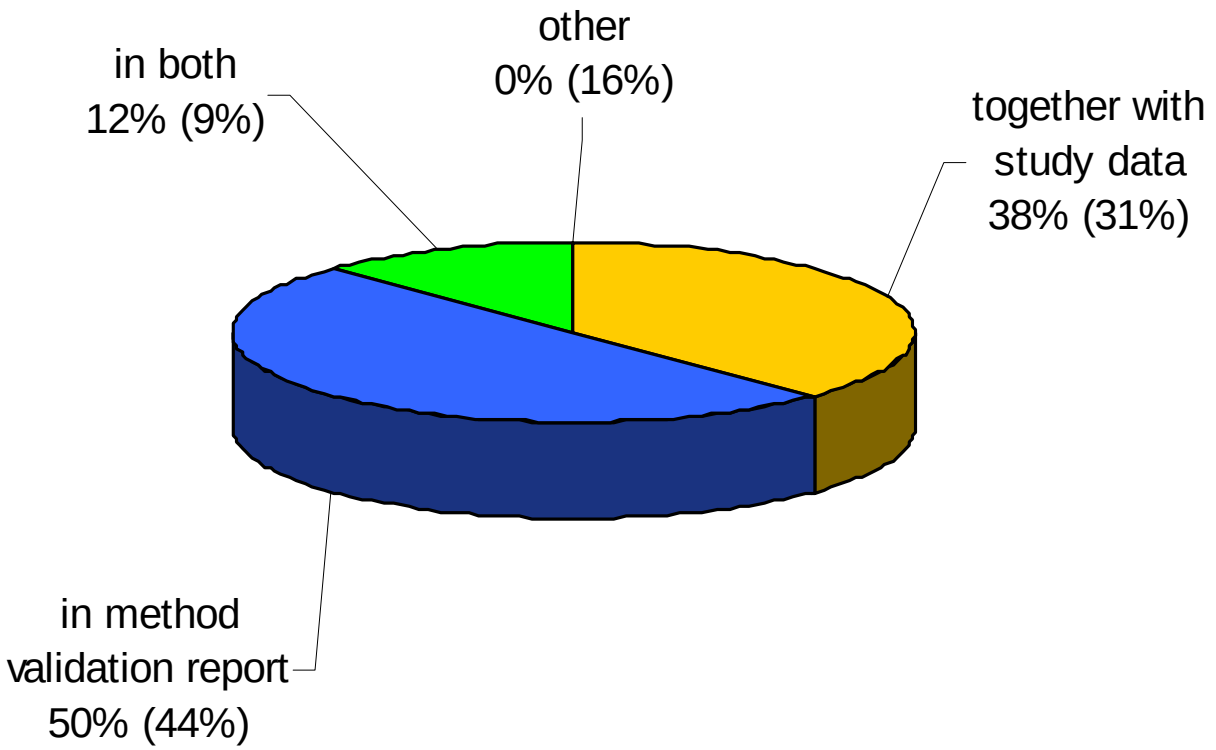
## 8. What are the acceptance or rejection criteria ?




During August 2007 EBF meeting all member companies agreed to share experience and jointly revisit acceptance criteria after approx. 1 year, based on more data.

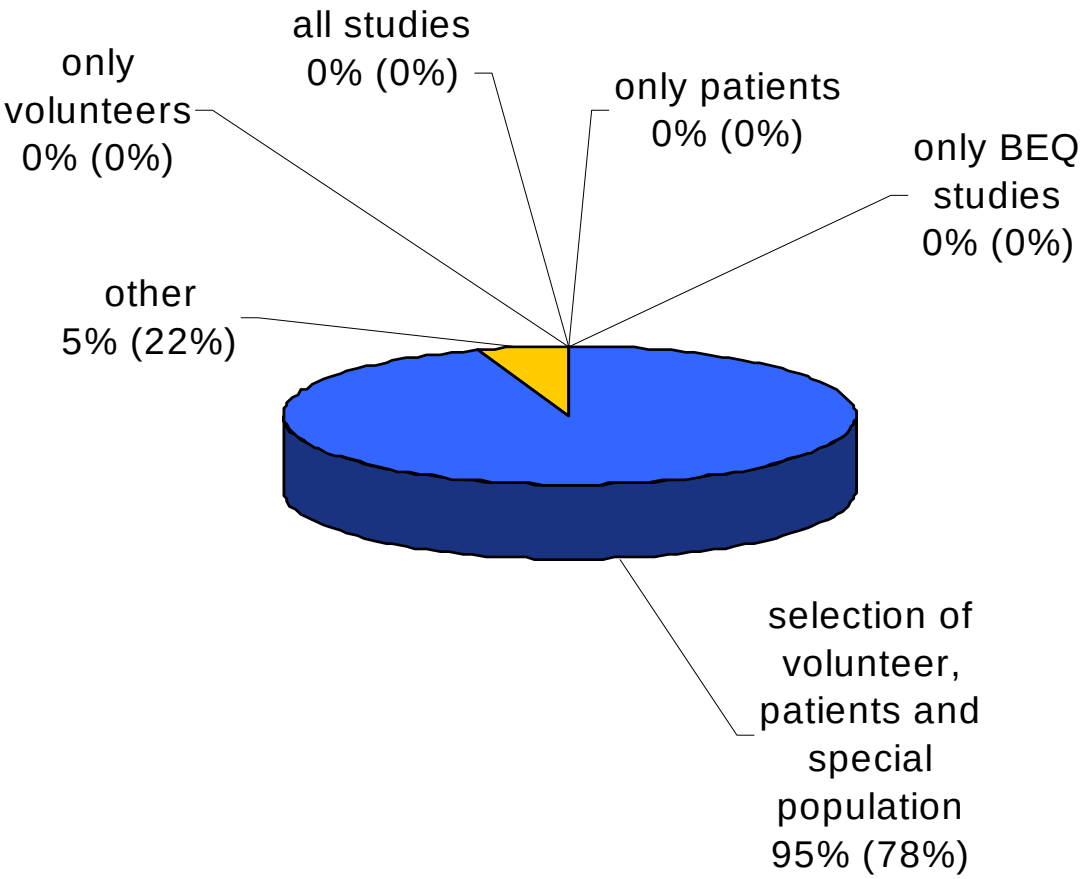
# Questions on both pre-clinical and clinical samples

## 9. Where do you document the results of ISR ?



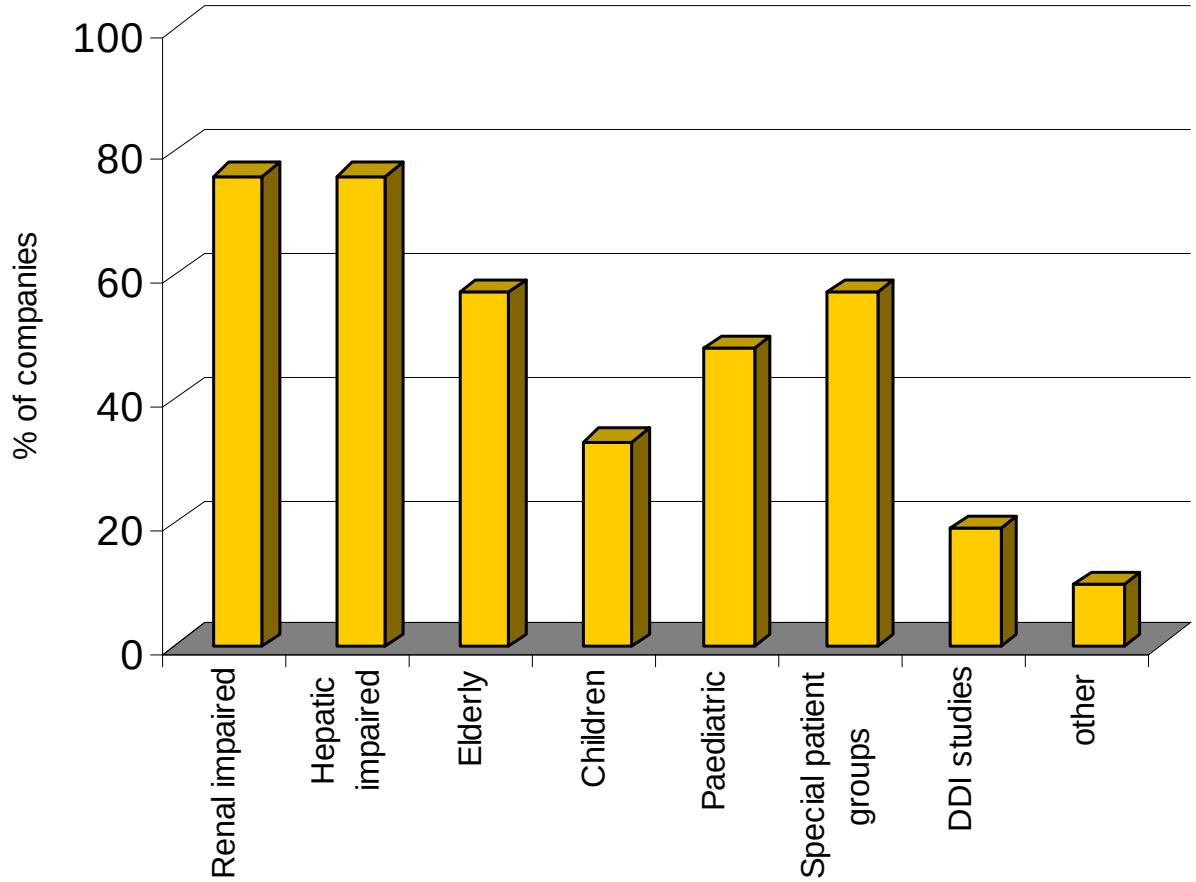
# Questions related to clinical samples :

10. Which clinical studies do you select for evaluation of incurred sample reproducibility ?



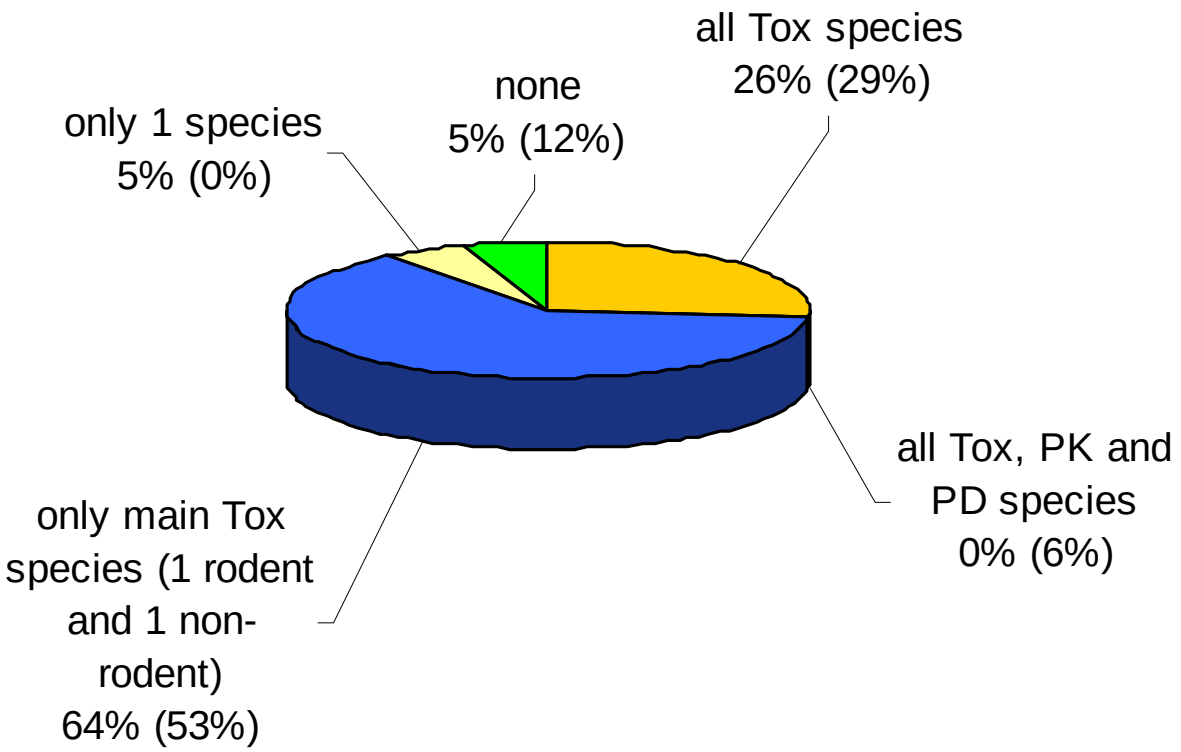
# Questions related to clinical samples :

## 11. What do you consider “special population” when assessing ISR ?



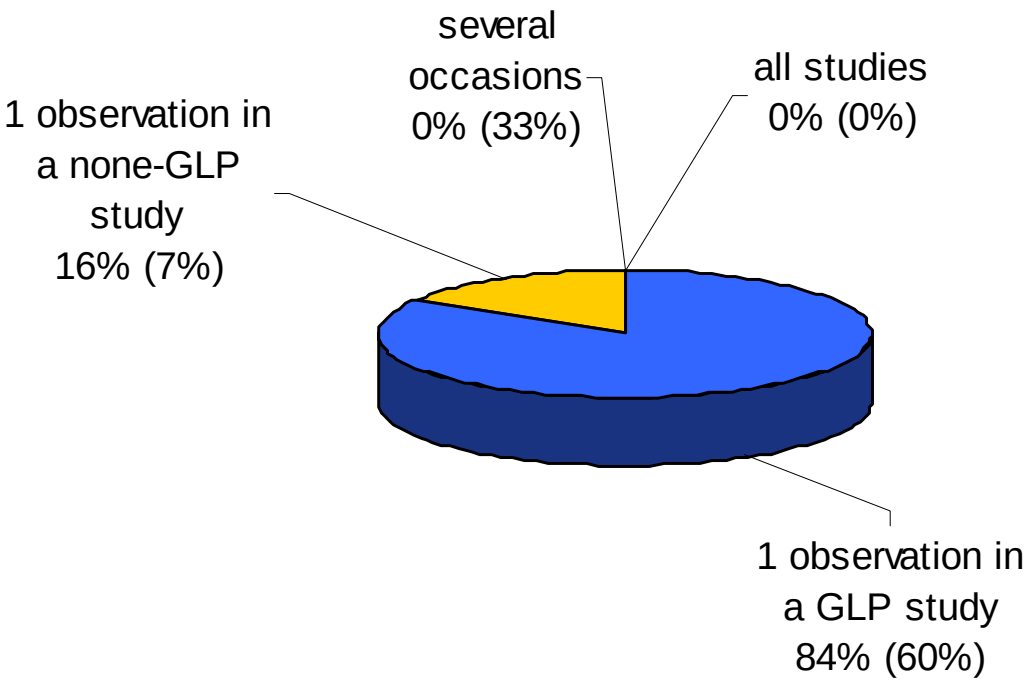
# Questions related to pre-clinical samples :

## 12. Which preclinical species do you select for incurred sample reproducibility ?



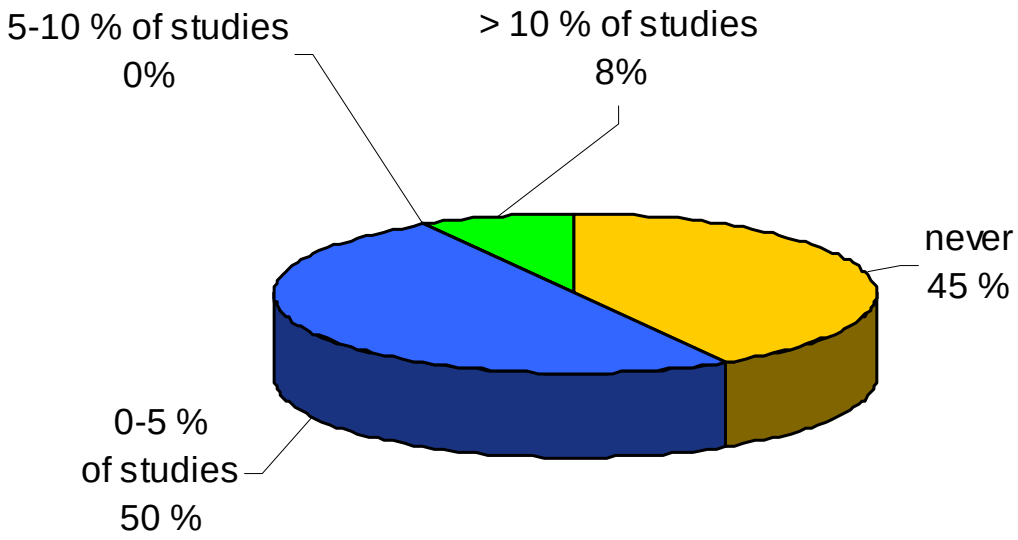
# Questions related to pre-clinical samples :

## 13. Which studies do you select to assess ISR in pre-clinical species ?



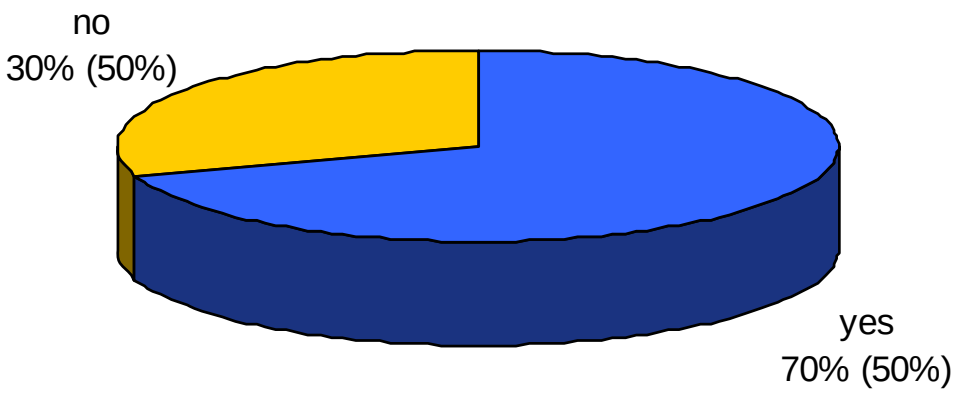
# Experience ……

=> How often do you observe imprecision that requires further investigation?



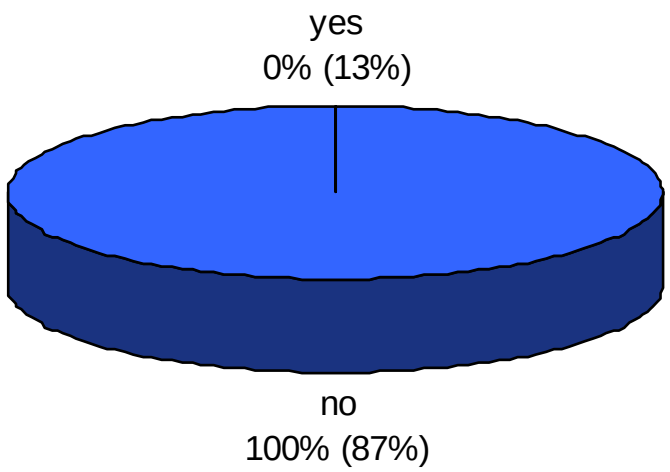
# Questions related to LBA assays :

## 14. Do you have other acceptance criteria for ISR for LBAs?



# Questions related to LBA assays :

15. Do you have a different approach for LBAs with respect to study or sample selection, pooling, diluting or reporting ?



# ISR – EBF summary

## Small molecules

- 35 survey questions grouped in 13 key areas
- alignment of processes within EBF member companies is growing :
  - 69 % in Aug. 07 survey → 81 % in Dec. 07 survey (average of 13 key areas)
  - For 10 key areas > 75 % alignment (only 5 in August 07)
  - For 3 key areas in < 75 % alignment (still 8 in August 07)
    - Number of samples selected
      - 5-10% (36%) *versus* < 50 samples (51%) (in practice, the result is often the same…..)
    - ISR for which preclinical species :
      - Only 2 main tox species (64 %) *versus* all tox species (29%)
    - How/where are data reported : 62 %
      - At least in MVR (62% or 50%+12%*) *versus* in at least clin/preclin study (50 % or 38%+12%*)

        * 12% in both

## Large molecules

- still little experience

# EBF – plans for near future

## Internal

- Monitor ISR performance
- surveys, benchmark exercises, sharing of procedures, alignment or presentations/publications on e.g. :
  - Method validation procedures
  - Immunogenicity assays and regulatory requirements
  - Sample management issues
  - Reporting - method validation & study reports
  - Metabolite quantification
  - LIMS – ELN
  - CSV
  - incurred sample stability
  - Discovery BA

## External

- collaborate with scientific and interprofessional groups on BA related topics
  - Open EBF meetings in EU together with business partners (academia, vendors, CROs) or regulatory bodies
  - Presentations at other meetings
  - collaborations with other BA oriented organisations

# Acknowledgements

All EBF members