The Regulatory Space

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on behalf of the EBF

EBF – ADC Training Day
Bringing ADC into practice
20 June 2017, Lisbon

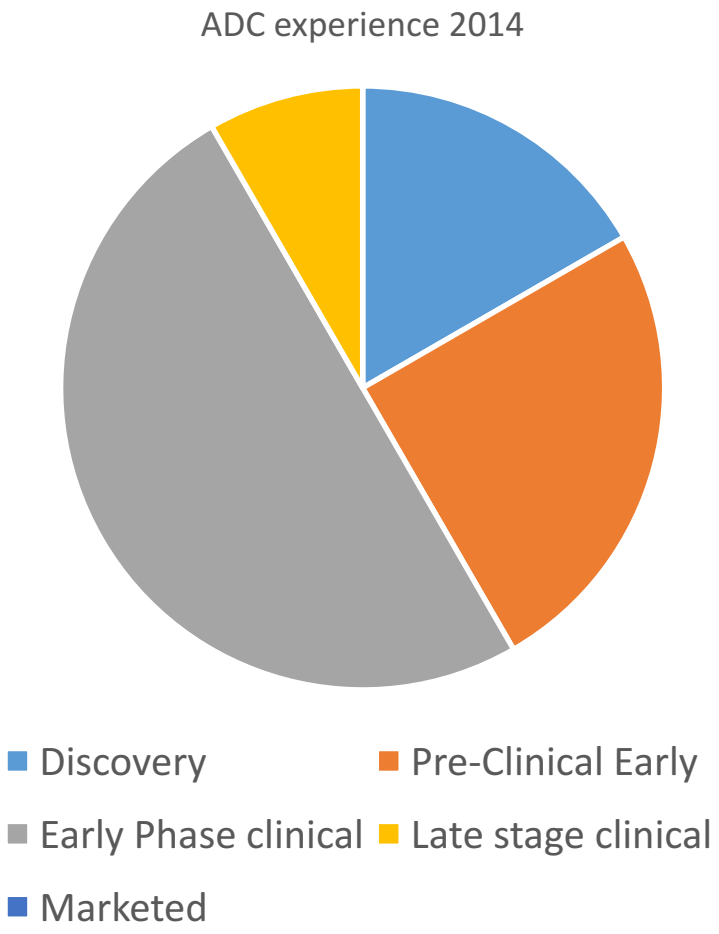
Regulatory Landscape

Three marketed compounds to date

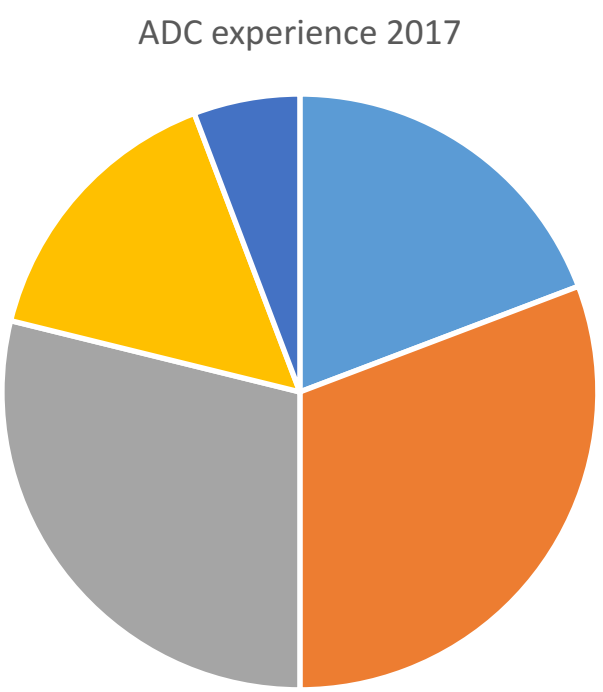
- All oncology medicines, so often granted accelerated regulatory approval
- Industry starting to use this technology to deliver other medicine types

ADC Bioanalytical Experience Across The EBF

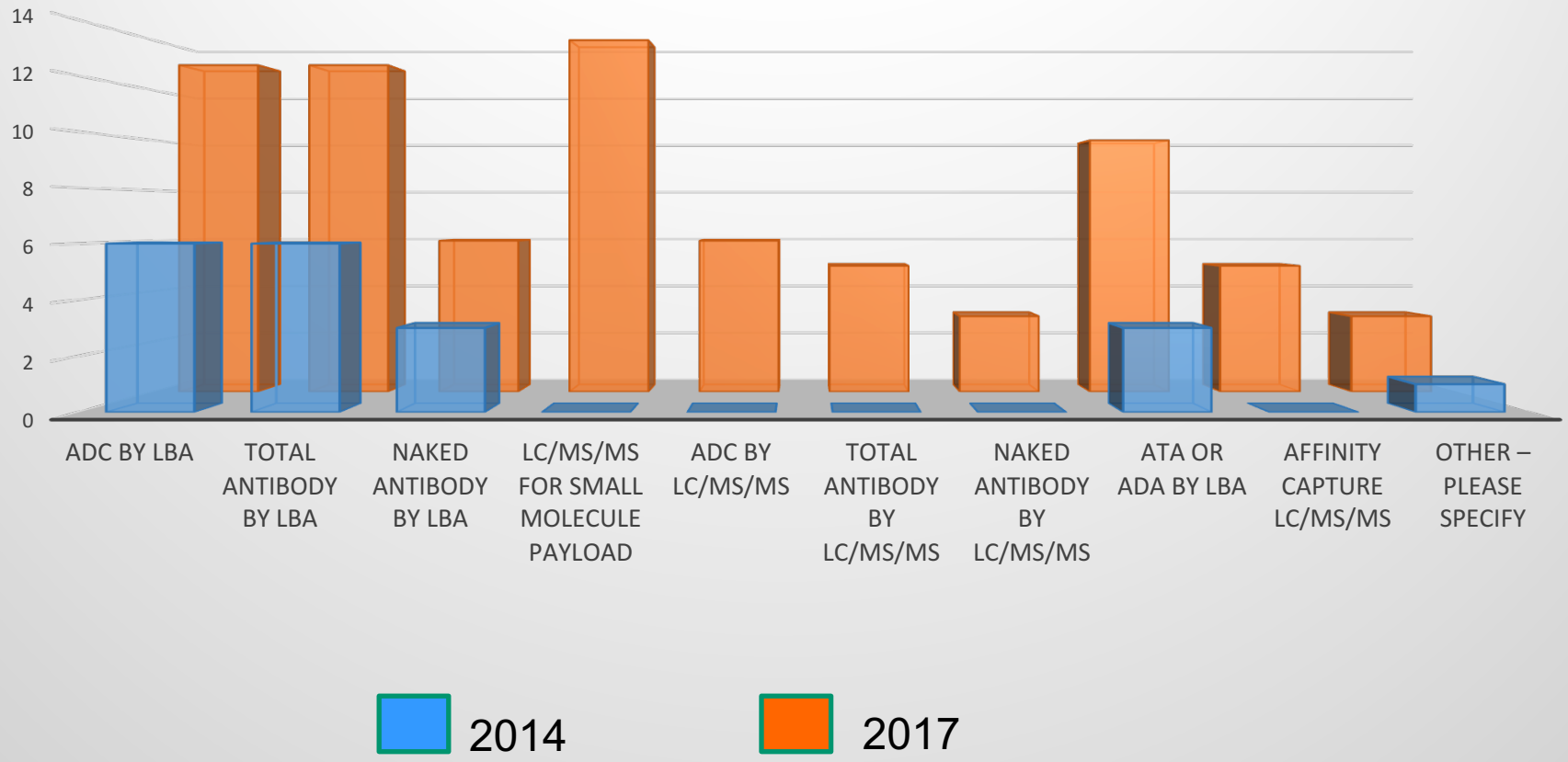
Approx. 6 Companies



18 Companies (44 replies)



ADC assays across EBF



Bioanalytical development for ADC

- Broken down into 4 categories
  - Discovery
  - Preclinical GLP
  - Early clinical (FTIH/repeat dose)
  - Late stage clinical (phase 2B to filing)

Discovery - recommendations

- 3 assays required
  - Total mAb (LBA)
  - ADC assay (LBA)
  - Payload (small toxic molecule, LC/MSMS)
- Species
  - Rodent / Non rodent species used for safety
  - Pharmacology species used for efficacy
- Matrix:
  - EDTA Plasma
  - Tumour Tissue
- Options
  - Drug/Antibody Ratio (DAR, LC-MS) for candidate selection with optimal linker stability
  - LC/MS/MS for antibody assays (lead optimization)

Discovery - recommendations

Assay qualification

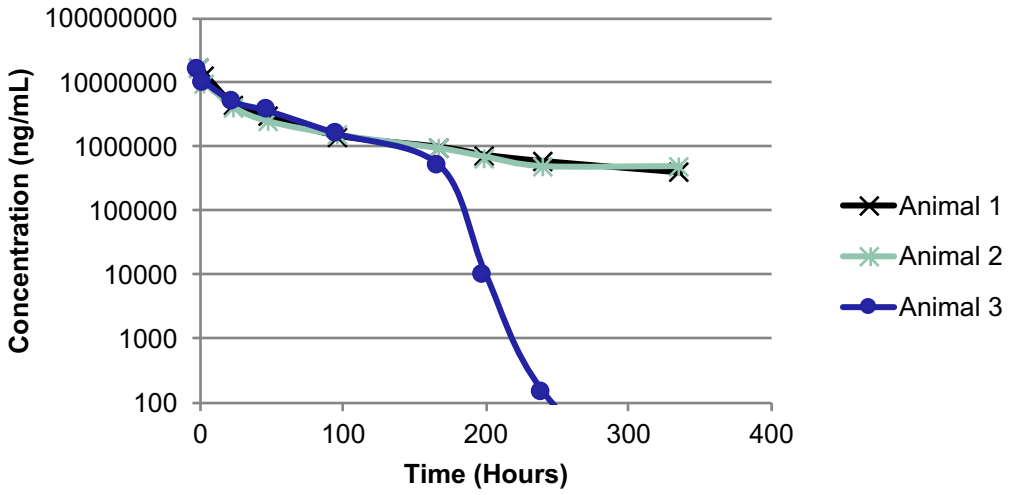
- Fit for purpose: Tiered approach
- 1 run precision & accuracy
- Assay sets acceptance criteria
- Selectivity (testing of individual's blanks)
- Specificity (testing of reference ADC's)

➢ Matrix stability

- Exploratory RT or 37°C plasma stability

Discovery – recommendations (cont)

- Assays used to support PK, TK, PK/PD studies
- ADA assay is developed if PK or toxicology indicates possible ADA



- Possibility of generic assays at this stage to save time (anti human IgG assay)

Preclinical GLP - recommendations

- Same 3 Assays validated to GLP following EMA/FDA guidelines
  - Scientific validation (if not labelling studies)
  - GLP material for validations
  - Stable label internal standard for LC/MS/MS

- ADA assay developed
  - Option of only deploying if PK shows ADA

Preclinical GLP – recommendations (cont)

- ADC Stability – FDA request
  - *In vitro* experiment: 96hour stability of preclinical and human matrix at 37^{o}C
  - Monitor for appearance of free payload
  - Expect <5% appearance

Early Clinical- recommendations

- Validate 3 assays in human matrix
- ADA assay developed and deployed

Late phase Clinical- recommendations

- If assays understood remove total mAb assay
- Assays for Mass Balance and Drug metabolism support including DAR
- Continue ADA analysis

Unanswered questions

- What is the impact when a different batch gives a different DAR value?
- Late phase experience – We have the experts here now

Nice to haves – or are they?

- Change in time of DAR
- Impact of DAR

Need to understand

Further thoughts around best practice

- Very comprehensive publications now available
  - No single package fits all (diverse molecules: MAb, linkers and payloads)
- Need a bespoke approach designed to answer specific questions
- Broad array of assays in the analytical toolbox