A Method Development Case Study – Successes and Learnings from a CRO-Pharma Alliance

European Bioanalysis Forum Open Symposium

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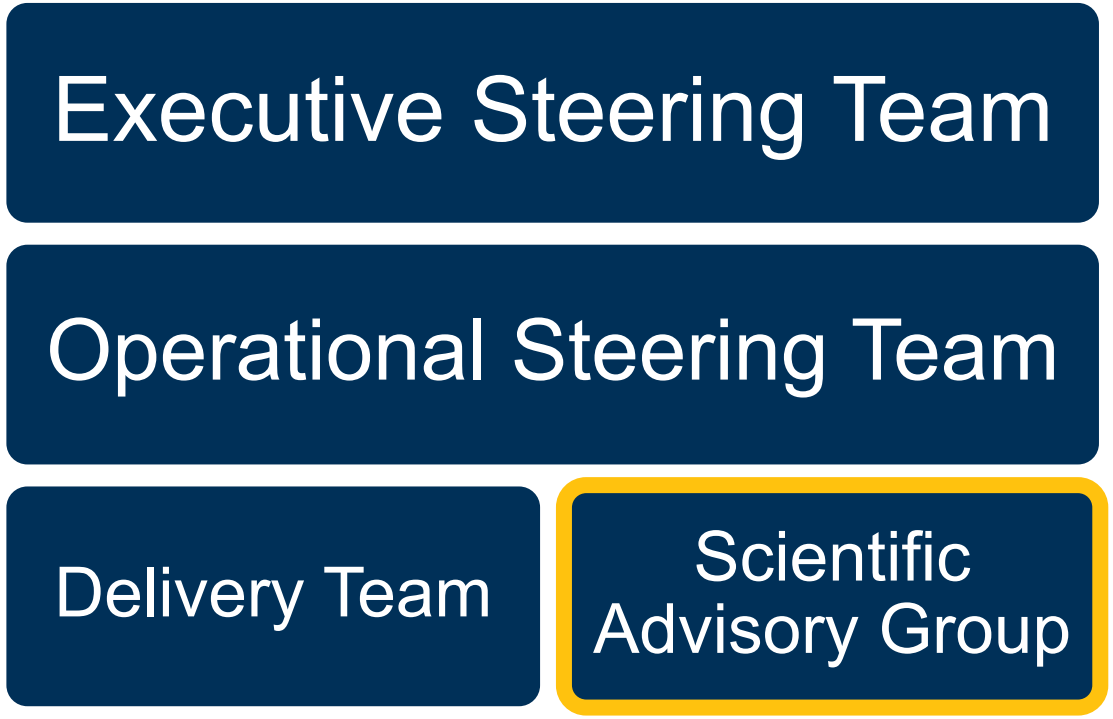
AstraZeneca – Covance Partnership

Scientist-to-Scientist Communication



- Established in 2011
- Joint teams and governance
- Dedicated Scientific Advisory Group
  - Encourage direct scientist to scientist communication
  - Support joint publications and presentations
  - Proactively evaluate portfolio technology needs and changing regulatory landscape
  - Provide scientific guidance and awareness to operational teams

Arfvidsson C, et al., AstraZeneca and Covance Laboratories Clinical Bioanalysis Alliance: an evolutionary outsourcing model. Bioanalysis. 2017 Aug;9(15):1181-1194

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Method Development Process

Planning and Preparation

Scientific Advisory Group

- Proactive portfolio review
- Early engagement
- Elevate and educate scientific workforce
- Issue guidance for operational teams

Joint Bioanalytical Leads

- Requirements intake
- Timing
- Intended use of the data
- Regulatory considerations
- Bioanalytical plan

Project Execution

- Leverage previous knowledge
- Direct scientist-scientist communication
- Issue escalation

Spotlight on Antisense Oligonucleotides

Bioanalytical Plan

Overview

- Antisense Oligonucleotide (ASO)
  - Short, Single stranded nucleic acids
  - Target a single genetic pathway
  - Bind RNA by Watson-Crick base pairing
  - Highly polar

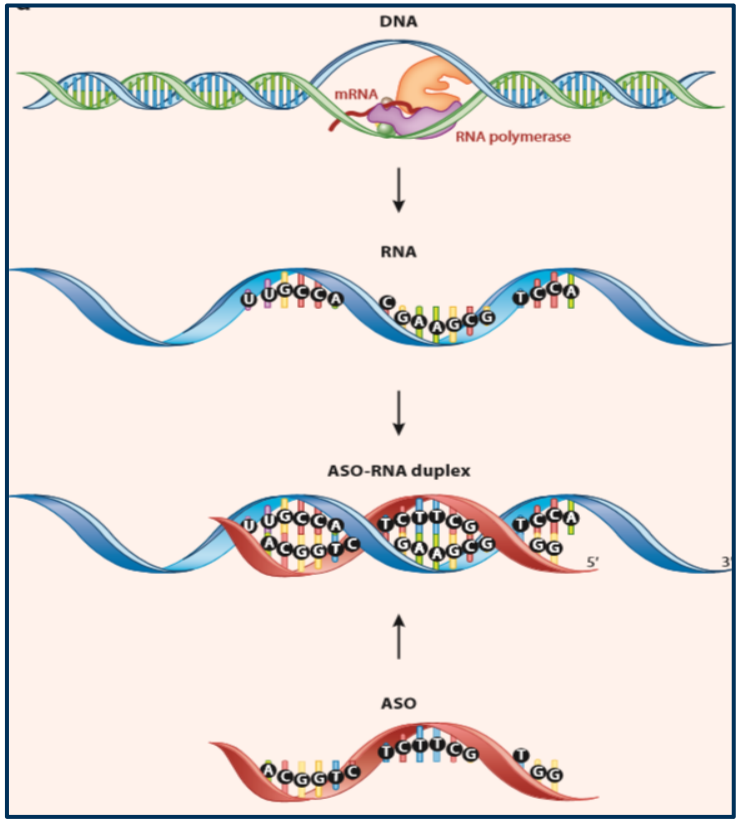

Figure 1. ASO binding to the targeted RNA*

*C. Frank Bennett, Therapeutic Antisense Oligonucleotides Are Coming of Age. Annual Review of Medicine (2019)0:307-21

Spotlight on Antisense Oligonucleotides

Bioanalytical Plan

Platform Considerations

- Common Technical Challenges
  - Stability
  - Cross-reactivity
  - Non-specific binding
  - Sensitivity
  - Chromatography

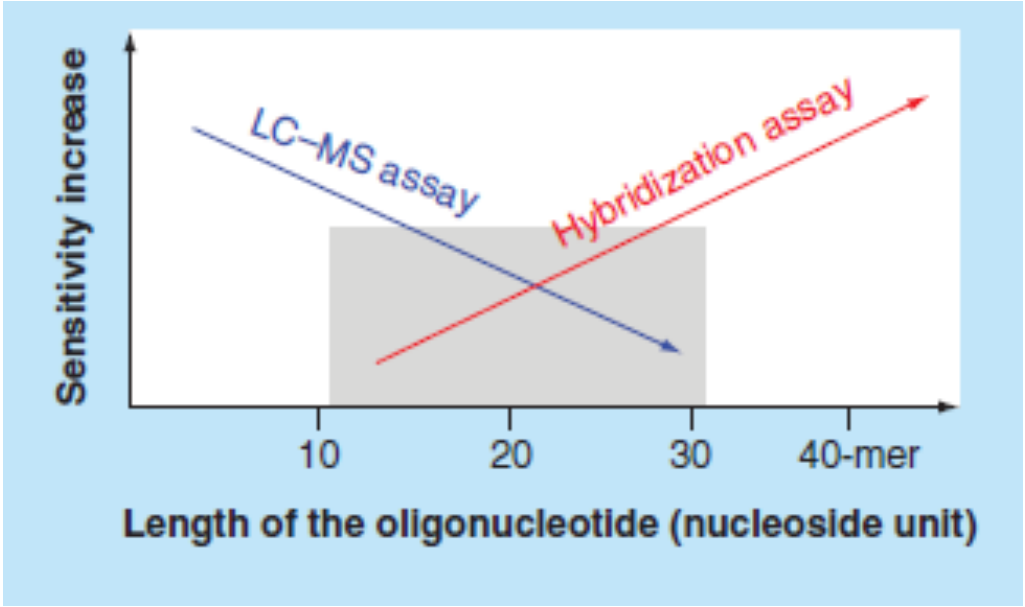

Figure 8. Dependence of assay sensitivity on the length/size of analyte oligonucleotide*

*Laixin Wang & Chengjie Ji, Advances in quantitative bioanalysis of oligonucleotide biomarkers and therapeutics. Bioanalysis (2016) 8(2), 143-155

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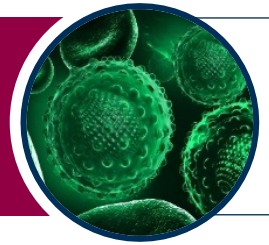
Knowledge Transfer

CASE STUDY 1



CHALLENGE

Transfer of complex method details

SITUATION

- Upcoming project:
  - Human plasma PK analysis
  - Antisense oligonucleotide
  - Low LLOQ required
- Team held knowledge transfer meeting months in advance of lab work

KEY TAKEAWAY

- Restructure timing of communication to better align with project activities
  - Initial discussion: align materials, understand expertise needed, general schedule
  - Kick-off meeting: Techniques and Details

Optimize Knowledge Transfer Processes

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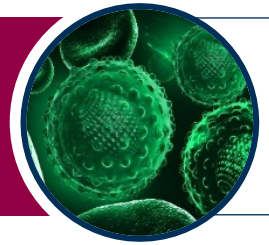
Complex Troubleshooting

CASE STUDY 2



CHALLENGE

Scientific issues during method development/method transfer

SITUATION

- Human plasma PK assay
- Method issues when the assay changed hands – determined to be due to assay performance issues with freshly prepared, never frozen standards
- High pressure, high visibility
- Multiple stakeholders involved

KEY TAKEAWAY

- Operations team drove troubleshooting
- Work as team focused on the solution
- Balance communication
  - Provide clear summary of plans and results
  - Seek feedback
  - Don’t delay to await approval

Earn Trust and Empower Teams

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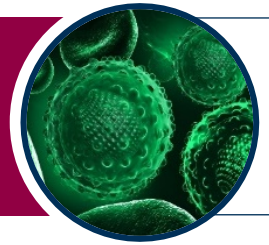
Flexibility

CASE STUDY 3



CHALLENGE

Unsurmountable obstacle, requires pivot

SITUATION

- Human plasma and urine assays
- Initial bioanalytical plan called for hybridization based assay
- Scientific issues were escalated to the joint bioanalytical leads
- Team decided to commence LC-MS/MS method development in parallel

KEY TAKEAWAY

- Methods were successfully developed and validated
- Scientists came together to assess
- When faced with unsurmountable obstacle, team quickly pivoted to alternative solution to deliver results

Operate with Transparency and Flexibility

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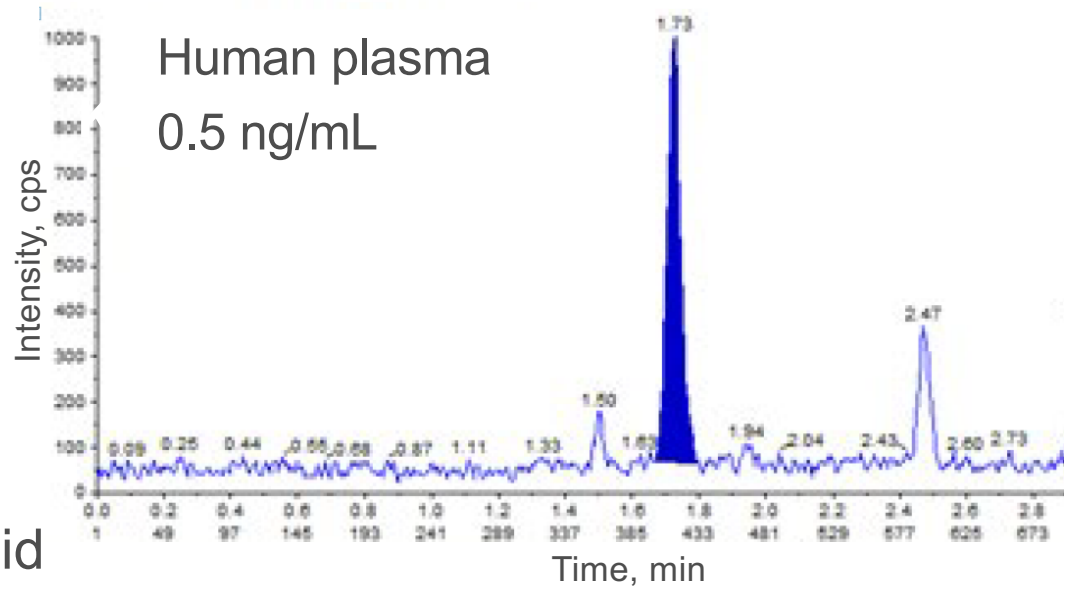
Flexibility

CASE STUDY 3

Clinical Method Development

Human Plasma LC-MS/MS Method

- Leveraged lessons learned from previous experience
- Stable isotope labelled internal standard
- 0.500 ng/mL LLOQ
- RP-IPC utilizing TEA and HFIP
- Confirmed selectivity against 5 metabolites
- BSA included in intermediate solutions to avoid non-specific binding
- MD and VAL progressed quickly and smoothly



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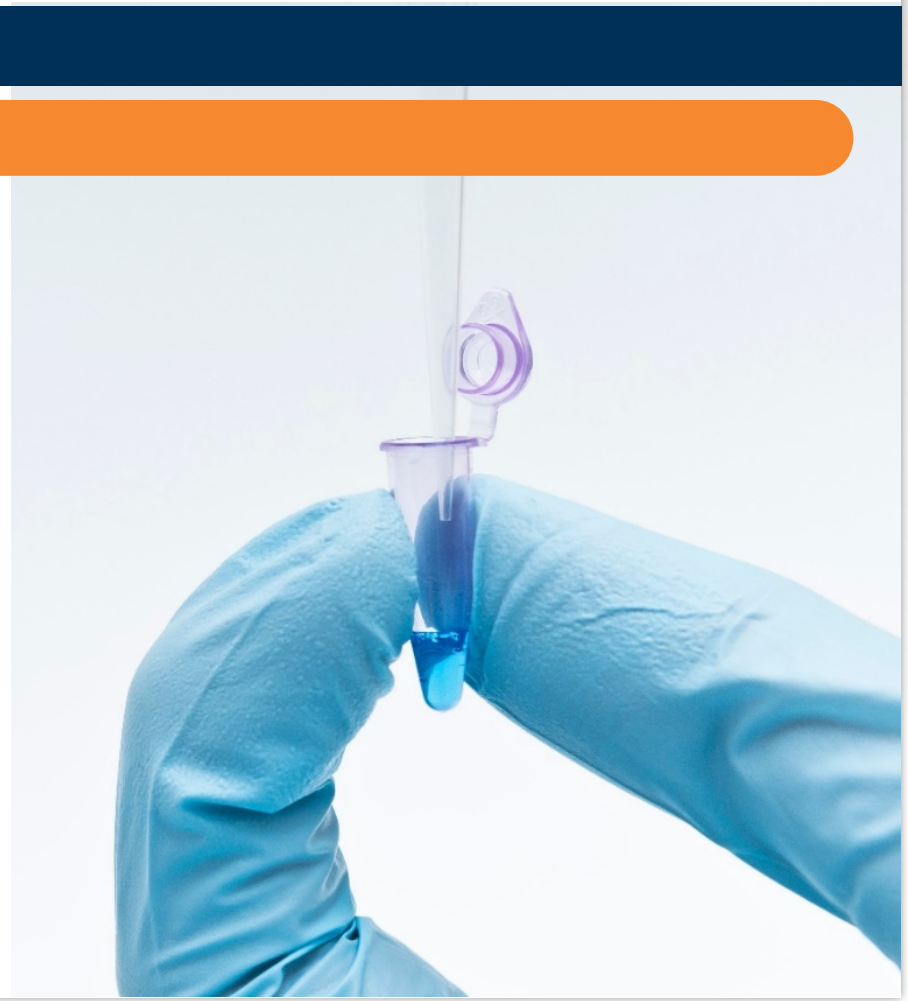
Flexibility

CASE STUDY 3

Clinical Method Development

Human Urine LC-MS/MS Method

- Leveraged previous experience
- Stable isotope labelled internal standard
- 1 ng/mL LLOQ
- Non-specific binding to tubes
  - 53% loss after 5 transfers
  - Added Tween to address
- Further testing discovered non-specific binding to urine precipitate as well
  - Recovery with CHAPS



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Flexibility

CASE STUDY 3

Clinical Method Development

Conclusions

- Suite of methods validated
  - Human Plasma via LC-MS/MS and ECL
  - Human Urine via LC-MS/MS
  - Anti-drug antibody
- Issues were escalated with transparency leading to decision to commence parallel method development on alternate platform to commence
- Enables head-to-head comparison of platforms to better inform strategy
- Approach evolved from hELISA/ECL to LC-MS/MS as primary technology

Collaborative Evolution of Strategy

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Method Development Process

Overview & Highlights

Optimize processes for efficient knowledge transfer

Learn and progress

Scientific Advisory Group

- Proactive portfolio review
- Early Engagement
- Sharing previous methods & lessons learned
- Issue guidance for operational teams

Joint Bioanalytical Leads

- Requirements intake
- Timing
- Intended use of the data
- Regulatory considerations
- Bioanalytical plan

Project Execution

- Leverage previous knowledge
- Direct scientist-scientist communication
- Issue escalation

Communicate openly and honestly

Leverage each contributor's unique expertise

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