your bioassay is in good hands: transfer from a CRO perspective

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Outline

- When, Where & Why
- Team with a CRO?
- Documentation
- Communication
- Training
- Equipment
- Critical Reagent Care
  - Cells
- Timing case studies
- Verification
- Lessons learned

Preparation

Implementation

Review
The Bioassay

Bioassay Development

Technical Transfer

Bioassay Qualification (Characterization)

Investigation

Reduce Variability

Specifications Defined & More Regulatory Guidances

Bioassay Validation

Implementation

Accuracy

Precision

Range

Linearity

Specificity

Criteria Failed

All Criteria Met

Technical Transfer
Bioassays: Transfer When?

Preclinical

Basic Research
- Development

Clinical: Phases I, II, III
- Evaluation
- Qualification
- Validation

Post-Filing
- Commercial Release

Development, Qualification, Validation, and Lot Release/stability assessment

After failed Qualifications or Validations
- for supplemental development
Bioassays: Transfer
Where?

- Across the hall
- Across the street
- In the next state/country
- On another continent

- Internal: PD or QC
- External partner
- Contract Research or Manufacturing Organization (CRO/CMO)
Bioassays: Transfer

Why?

• Manage resources

• Staff
  — Is R&D available for new bioassay development
  — Are bioassays effectively going to QC?
  — Is QC sufficiently staffed to complete assays on time?

• Space for people and equipment
  — Is there a waiting line at the plate reader?

• Equipment
  — Calibrated, mapped, certified?
  — Is the certification applicable to your assay?

• Increase capacity – outsource to CRO/CMO
Business Agreement

- Formal written legal document
  - Takes time to negotiate Terms & Conditions
- Who pays for what
- Clear timelines
- Contingency plans
- Communication – defined esp. budgetary
- Protocols – transfer and/or training
- Separate the legal and get started on the science
  - Options: Letter of Intent, Consulting Agreement, Purchase Order
Documentation

Is there a method from the R&D lab?

Does an SOP exist?

Start method development with laboratory notebooks...write everything down...and establish an SOP as you gain confidence in the method.

Once you have a draft SOP...start filling in the details:

- Very inclusive list of reference SOPs
- Specifics at every time point... ‘±30 min’
- Specifics for every liquid handling step
  – 0.025 ml transfer with a 0.1 ml pipette and a 0.1 ml tip
  – 1.0 ml transfer with a 1.0 ml pipette and a 1.0 ml tip
  • Vs. a 1.0 ml pipet or 5 ml pipet, or 10 ml piptet
• **Time for a Kickoff Meeting**
• Invite all the VIPs
  – Upper Management
  – Scientists and analysts from both sides
  – Quality Assurance from both sides
  – Project Management
    • Shipping/Receiving
    – Consultant(s)
• Clear goals
• Contingency plans
• Write down all agreed upon aspects of transfer with timelines and associated names

Start actively managing the project!
Documentation

**Write a Training Protocol**

- No guidance on specific number of bioassays
- Include transfer acceptance criteria...be prepared to move the assay
- Specify raw materials and consumables
- Define methods used
- List equipment required
- Timing – difficult task vs. meeting manufacturing timeline
Team with a CRO?
Questions to ask

Take a look at the website and schedule a phone call.

- Can I visit the site?
- Do you have a Quality Agreement?
- Do you have suitable equipment? (be specific)
- How many trained scientists
  - If cell based bioassay ask about relevant cell type experience
- Where will you conduct training for my bioassay?
- What is your communication plan? PM support?
- Will you provide references?
Questions to answer

- **How many analysts have performed your bioassay?**
- Execution of SOP has undocumented steps
  - ‘Tribal Knowledge’?
- System Suitability Criteria not set
- **Is your assay designed to follow regulatory expectations?**
- How much work will be needed to get there if transferring an R&D assay to GMP environment?
- **Can WE satisfy the clinical timelines?**
Your bioassay is in good hands and...

- The CRO may well have experience-based advice to offer
- Final decisions are always yours, but take advantage of the CRO’s scientist’s experience.
- Remember……. “That’s how it’s always been done” is not a good enough reason, alone, to keep doing it that way
- cGMP CRO must also stay in line with their SOP’s, not just yours
- The CRO must and will defend methods and data every bit as much as the client
Common Pitfalls

- Heroic efforts usually don’t make up for **inadequate planning**

- **Setting assay criteria** based upon data gathered during a short time frame (less variable), rather than real-time

- **Settling** for a variable or failure prone assay

- Moving directly from **development to validation**
If the dragon wins

Perform a Root Cause Analysis

- Materials
- Methods
- Machines

- Measurements
- Environment
- People

Problem

time
Bioassays: Transfer Components for success

- Training
- Equipment
- Critical reagent care

All sources of variation
Analyst Training

- **Minimum of two analysts trained**
- Bioassay SOP
- Data analysis understanding
  - Review good, bad and ugly data examples

- **Cross-training at originating vs. recipient lab; two schools of thought...**
- Stable platform at originating lab
  - Critical reagents, equipment and data analysis computer systems
- Comfort level for new analystes at recipient lab
Analyst Training

- **Use a Training SOP to document number of bioassay runs and results expectations.**
- Start with simple assays using the Reference Standard or Training Samples.
- Training Samples can be made from previously tested lots.
  - Label as Training Samples with newly coded identification numbers.
- Train up to a standard/routine bioassay run.
- What is the expectation regarding the size of a standard/routine bioassay run?
  - Three plates with Reference Standard, Controls and six samples?
  - Train as you will perform with fully burdened bioassay runs that include the Reference Standard and previously tested “controls”.
- Does the training data fall within the range described in the Training SOP?
 Analyst Training

- **Required interactions**
  - Face-to-face cross-training – combination of scientists with analyst-to-analyst interactions
  - Follow-up using your trended data to monitor method performance by different analysts

- **Additional considerations for cell-based bioassays**
  - Specific cell culture SOP training
  - Culture examples/ pictures, know/ understand pitfalls
  - What do good and bad cultures look like?
  - Master the cell culture methods prior to performing the bioassay
  - Practice seeding cells in plates with multichannel pipets and/or conduct specific training on liquid handling machines

- **CRO/CMO should communicate personnel changes**
Analyst Training

Maintenance Assays

• How are the potentially long periods between lot release, stability sample assays addressed?

• Does each analyst perform periodic (monthly) ‘Maintenance Assay’ with RS and one sample from a Proficiency Panel?

• Not just the 100% sample or RS; dig out those Training Samples.

• Analysts may alternate months.

• Maximum sample numbers periodically.
Certified, qualified, or mapped?

- Equipment is *Certified* using “standard setting” equipment which has a known valid relationship to a recognized national or international standard.
- Certification is used as an alternative concept to “calibration” in ISO standards.
- Certification is usually performed by the equipment manufacturer.
- Examples of certified equipment:
  - pipettes, pH meters, thermometers, centrifuges, biosafety cabinets.
Equipment

• **Installation/Operational/Performance Qualifications (IOPQ)**
  • Plate readers/spectrophotometers, cell counters
  • Flow cytometer, surface plasmon resonance system, aggregometer

• Data analysis software

• **Temperature mapped equipment**
  • Incubators; including the room temperature ones
  • Freezers
  • Refrigerators
  • Vapor phase liquid nitrogen storage
Equipment

- **Do you have enough equipment?**
- **Are analysts waiting in line at the plate reader?**

- **Recommend a facility wide environmental monitoring system**

- **Additional considerations for cell-based assays**

- **Incubators**
  - Air flow, HEPA filtered?
  - Humidity level (>90%), supplemental humidification
  - CO$_2$ control: infrared or thermal conductivity backed up with Fyrite® (classic/absorbing fluid) or portable/electronic
  - Space to separate ‘cultures’ from bioassays
Critical Reagent Care

- **Reference Standard (RS)**
  - Make sure there is enough (originating Dept/Lab retains)
  - May or may not be well characterized, can be non-GMP
  - May evolve along with product development
  - May not be the same formulation as the drug product
  - Ship from originating lab to recipient lab in batches
  - Monitor stability – freeze/thaw → bioassay + 2nd method?
  - Document stability as part of a protocol
  - Monitor results with Statistical Process Control (SPC) chart
  - Qualify new/next RS lot with a protocol
    - Characterize with all methods (bioassay + analytical)
    - How many bioassay runs constitute an assignable value?
Critical Reagent Care

- **Precision Control**
  - A drug lot different than the RS tested from time-to-time in accordance with the bioassay SOP to assess precision

- **Proficiency Sample**
  - A sample or panel of samples used for monitoring analyst training proficiency

- **Storage**
  - Use multiple locations/chambers

- **Shipping**
  - Utilize temperature tracking
Critical Reagent Care - Cells

Know your cells
• Primaries $\rightarrow$ lines $\rightarrow$ primaries (thaw and assay)

Invest in cell culture specific training
• Cell culture and general observation
• Cell culture specific data analysis
• Communication – description of cell characterization

Quarantine cells

Use R&D cell banks to save time

Passages $\neq$ population doublings

Well mixed cells lead to bioassay success
Case Studies
Three months is average for transfer of a cell-based bioassay
Four to Five months...if some optimization is required before Qualification

- Critical Reagents Received
- Analysts 1&2 Comparable Data
- Plate mapping leads to optimization
- Proficiency assays by both Analysts
- Real Time Data Analysis
- cGMP Documents and Parts Ready
- Qualification Protocol
- Bioassay Qualification
- Qualification Report Accepted
- SOP and Acceptance Criteria Amended

Preparation ➔ Implementation ➔ Review
Transfer - How Long?

Six months...if the unexpected happens such as a supply issue for a rare reagent

- Lose time with business documents
- Substitute in a LOI or P.O. and start testing!
- Must incorporate cell testing time
- Contingencies for the unexpected!
- Address the unexpected quickly and directly
Transfer Verification

• “to establish the truth, accuracy or reality of”
• You’ll find the tribal knowledge only after you run someone else’s assay.

• Confirmation that the assay performed as expected?
• Expectations met?
  – SOP details included
  – Transfer Protocol complete
  – Business agreement confirmed
Lessons Learned

- Communicate, communicate, communicate
- Plan your bioassay transfer
- Choose your CRO carefully
- Verify the Basics
  - Document everything
  - Analyst training
  - Equipment
  - Critical reagent care
- Know your cells
- Consult a biostatistician
  - Assay design & data analysis
- Communicate, communicate, communicate
Questions & Discussion
thank you!