Outsourcing, Technology Transfer & CMO-Client Relationships

Analytical Methods Technology Transfer

Contract Manufacturing / Outsourcing
Munich, 23-24 November 2017

Jon M. Crate
Advantage Analytical

Presentation Outline

Technology Transfer and Maintenance of Analytical Services Relationships

Importance

Key Concepts and Strategies

Specific Tools to Attain Control

Conclusions

Quick Discussion

Exercises

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Importance of Analyticals

- Regulatory Agencies Require Complete Analytical Characterization
- Analytical Testing Results are the Bulk of Typical Submissions
- Every Pharmaceutical Decision is Based on Analytical Results
- The Cost of Erroneous Results can be Huge
- Risk Assessment Needed at Each Step Guides Focus
- Effective Technology Transfer is Essential to Success
- What to Keep In House and What to Outsource Depends on Relative Capabilities and Practical Considerations

Outsourcing per FDA

Quality Systems Approach to Pharmaceutical CGMP Regulations

- "Hiring a second party under a contract to perform the operational processes that are part of a manufacturer's inherent responsibilities"

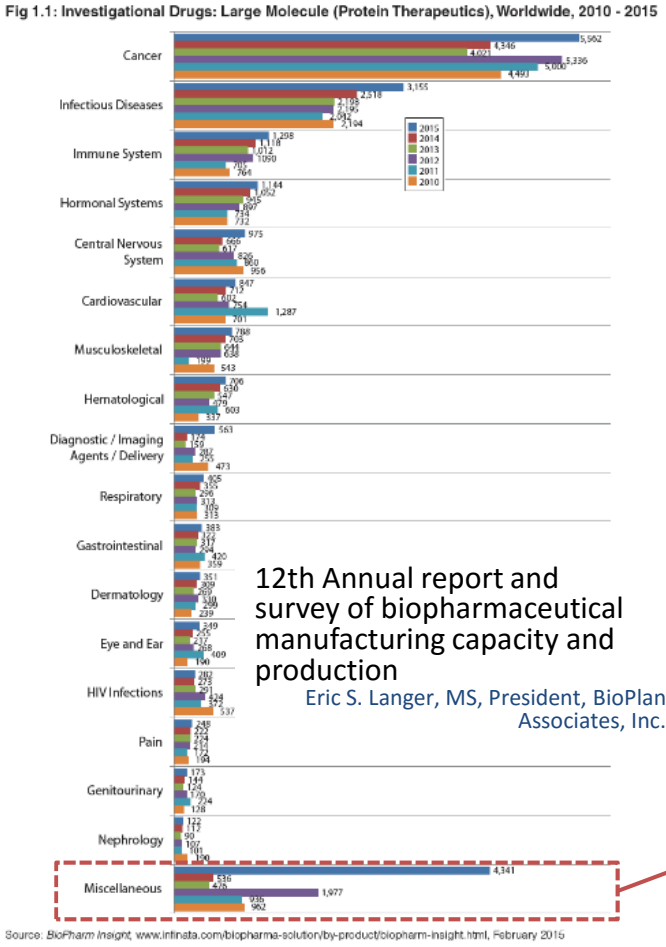
Cooperative Man *gics*

- For biological
- manufacturing
- arrangements
- Regardless of
- outsourcing of a manufacturing process must be in compliance with FDA regulations"

What about outsourcing of analytical testing?

Not directly addressed!

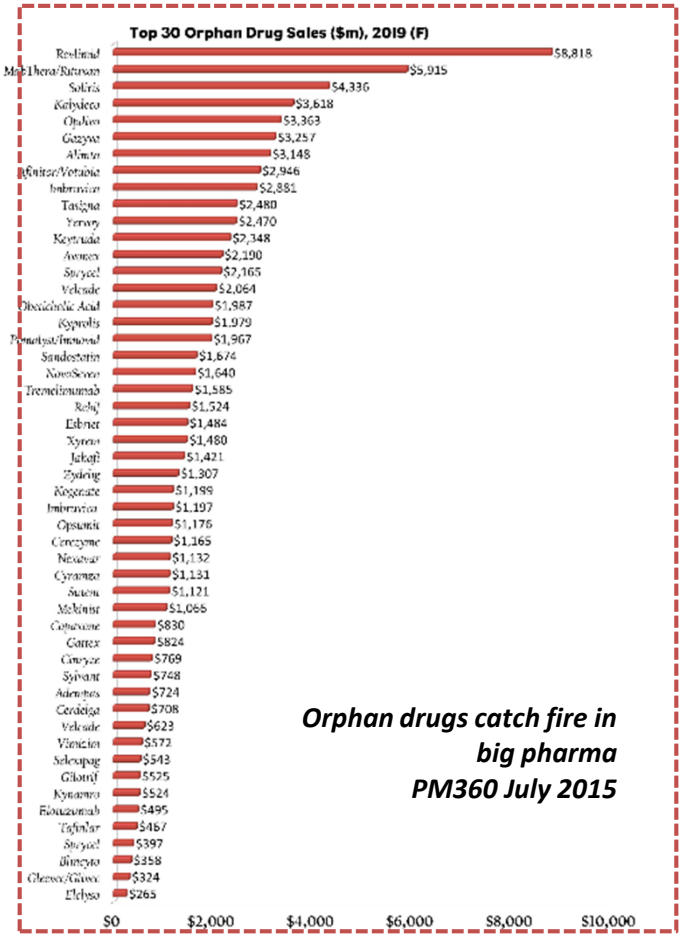
The New BioPharma Reality



12th Annual report and survey of biopharmaceutical manufacturing capacity and production

Eric S. Langer, MS, President, BioPlan Associates, Inc.

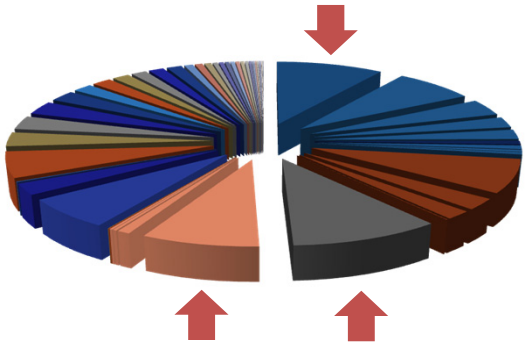
Biopharma Extreme Product Diversity



Orphan drugs catch fire in big pharma
PM360 July 2015

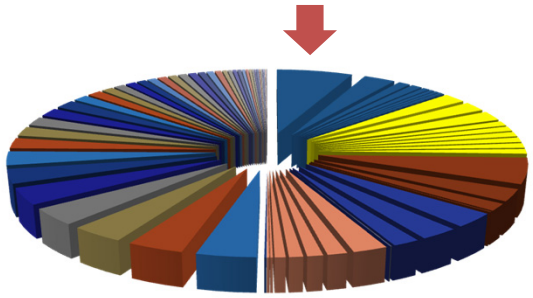
The New BioPharma Reality

Last century product distribution



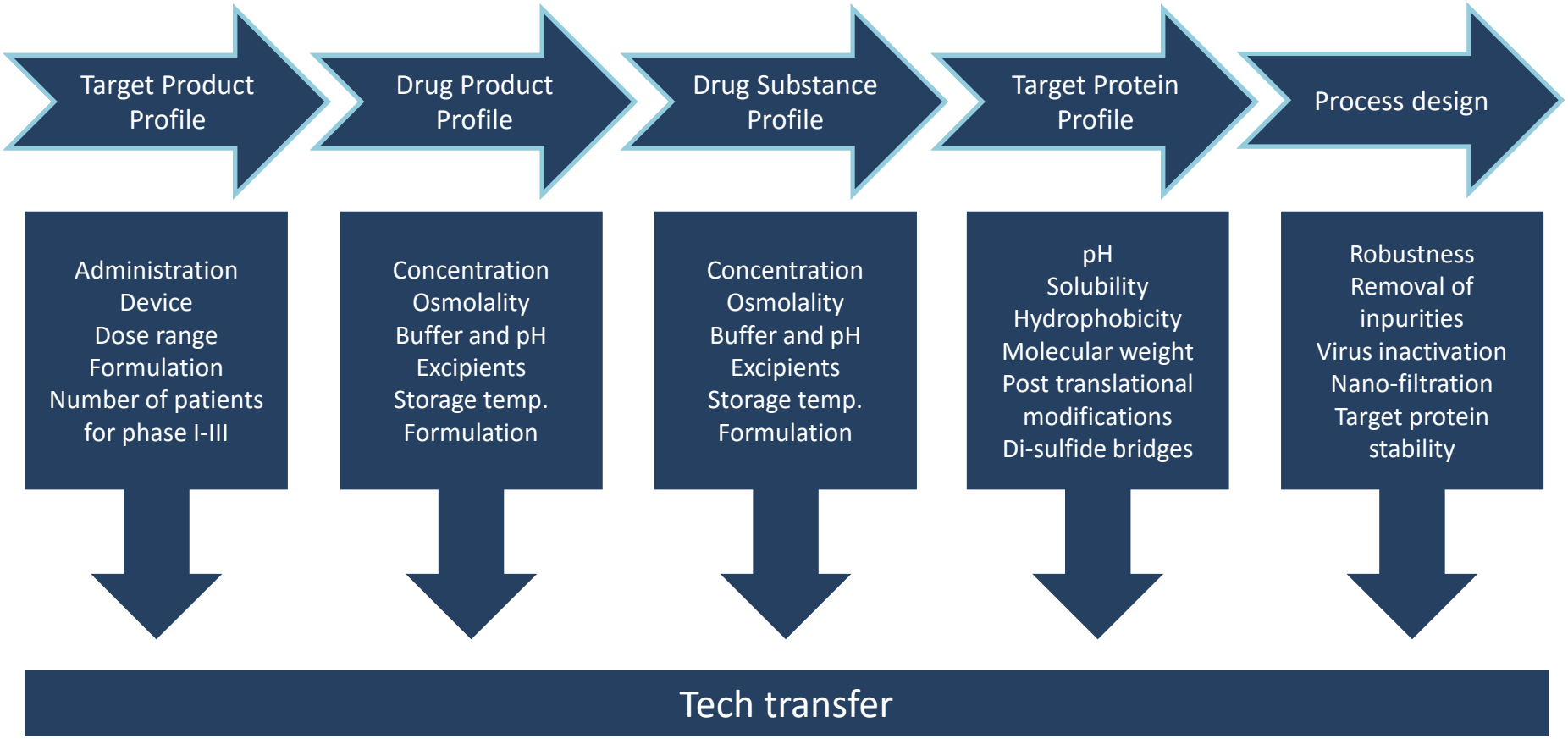
Focus on manufacturing Speed

Today's product distribution

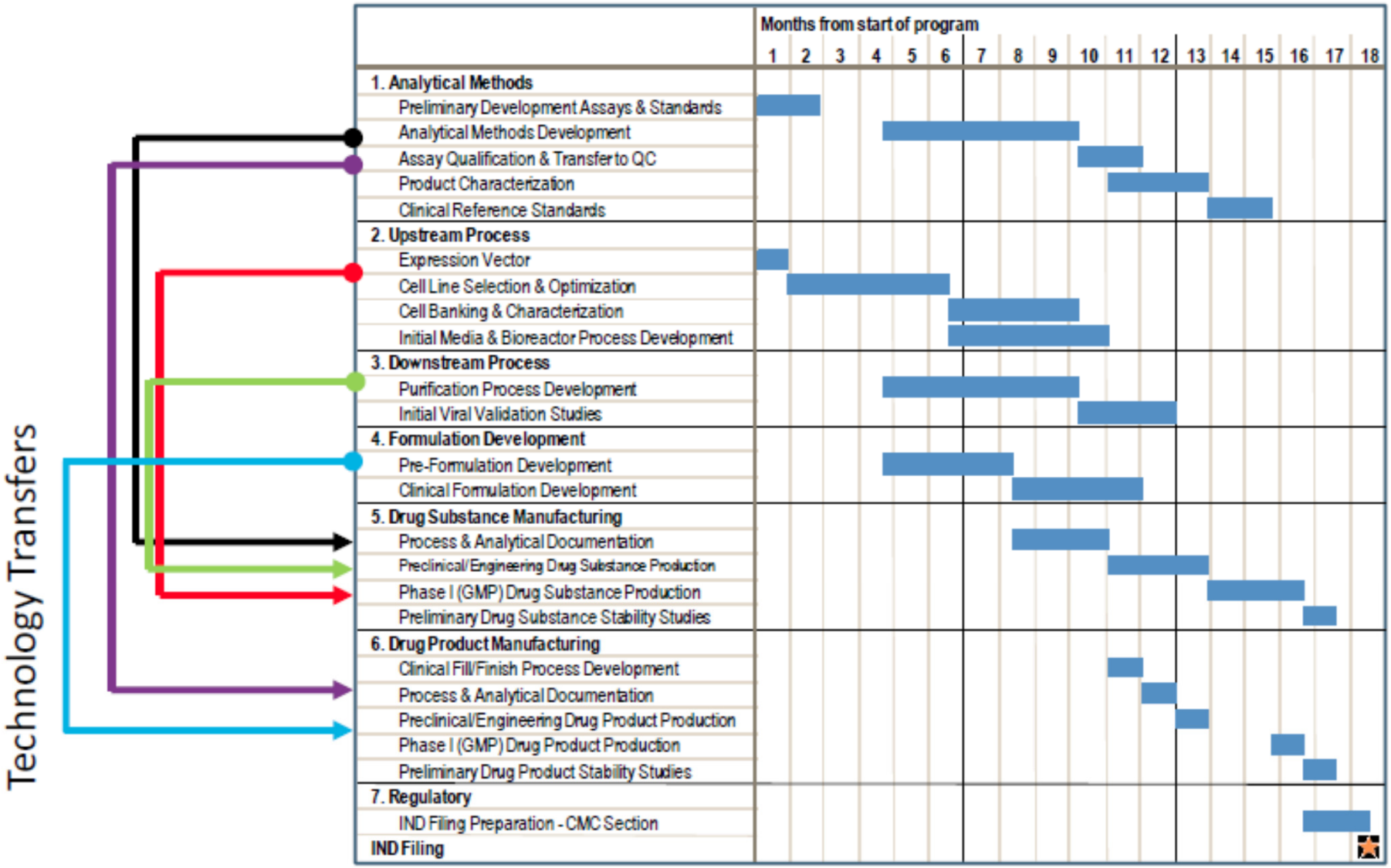


Focus on change-over speed

Importance of Analytical Testing



Timeline: mAb Development



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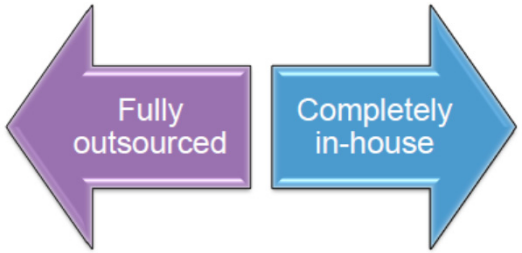
Contract Testing for Biologics Different!

- Large number of GMP tests required for biologics
- Additional characterization methods, plus extractable / leachable studies
- Technology platforms for biologics still evolving
  - Charge profile methods, HPLC vs. UPLC
- How to effectively manage the balance between internal work and outsourcing, and how to most effectively manage the outsourcing that you do?



To Outsource, or not…

Analytical Testing	Basic Compendial, Routine, In Process Testing Stability Testing, Release Testing,	Advanced Product Specific Method Development, Advanced Molecular Characterization Niche Testing (NMR, UHR-Q-TOF)
Large Pharma Large CMO or CDMO	CMO	In-House, CMO, CDMO, or CRO
Large Pharma Smaller CMO	CMO	In House or CRO
Smaller Pharma Large CMO or CDMO	CMO	CMO, CDMO or CRO
Smaller Pharma Smaller CMO	CMO	CRO

Analytical Methods: Method Validation

Method Validation – Definitions

FDA:

Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

EU:

Action of proving, in accordance with GMP-principles that any procedure, process, equipment, material, activity or system actually leads to the expected results.

ICH:

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use.

(ICH Topic Q2B, March 1995)

Definitions of Terminology

- *Test Method*: A written procedure which details the process designed to assess a quality or safety attribute of an intermediate, drug substance or drug product.
- *Platform Method*: A method which is intended to be applicable to multiple products (e.g. monoclonal antibodies, HPAPIs, excipients).
- *Method Development*: The process by which a test method is created or modified. It is implied in this process that the parameters chosen for the final test method have scientific basis. DOE techniques should be employed to understand the robustness and the range of effectiveness of each parameter as well as their interactions.
- *Method Qualification*: The process by which the performance of a test method is evaluated and documented. The experiments conducted are a subset of the ICH requirements (subset of ICH validation).
- *Platform Method Assessment*: The process by which a platform method is deemed suitable for platform method verification with a new investigational material.
- *Platform Method Verification*: The process by which a qualified platform method is demonstrated to be suitable for a new investigational material.
- *Method Validation*: An increased level of study of individual quality attributes of a method executed by a pre-defined protocol that outlines the experimental design and acceptance criterion for a method to be determined suitable for intended use.

FDA Guideline for Industry
Text on Validation of Analytical Procedures (1995)

TABLE OF CONTENTS

ICH Harmonised Tripartite Guideline

Q2(R1) - Validation of Analytical Procedures: Text and Methodology

Q6B - Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

FDA

Guidance for Industry - Analytical Procedures and Methods Validation (Draft)

Pharmacopoeias

USP, European and Japanese Pharmacopoeia

Other

Adaptation and Justification for Adaptation

- Identify sources of potential errors
- Demonstrate that the method is acceptable for intended use
- Establish proof that a method can be used for decision making
- Satisfy Regulatory (FDA, EU, JP) requirements
- To lay a foundation to enable different labs and analysts to show they can obtain the same results as others
- Ensure that the test results used to release clinical and commercial supplies are accurate and reliable

- Product-specific methods are fully validated and are suitable to support commercial.
- The latest this should occur is prior to the start of Process Validation runs.
  - All release and stability methods must be validated prior to initiation of testing for PV.
  - In-process methods intended to be implemented for routine use, that will be used to make process decisions, should also be validated.
  - In-process methods specific for the purpose of supporting PV only or FIO, should be validated to be suitable for use prior to initiation of PV.
  - Gaps in methods used for ICH batch testing verses PV batches should be clearly identified for potential bridging or corrective actions.

Early Stage Tech Transfers

- Identify the Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) that define the process and need to be controlled
  - CQAs unlikely to be established yet
  - CPPs likely to affect quality attributes not well defined yet
  - Early stage transfers difficult since there is not a robust data set to refer to for trouble shooting
- Target Product Profile (TPP) serves as a guide to capture product attributes as they emerge

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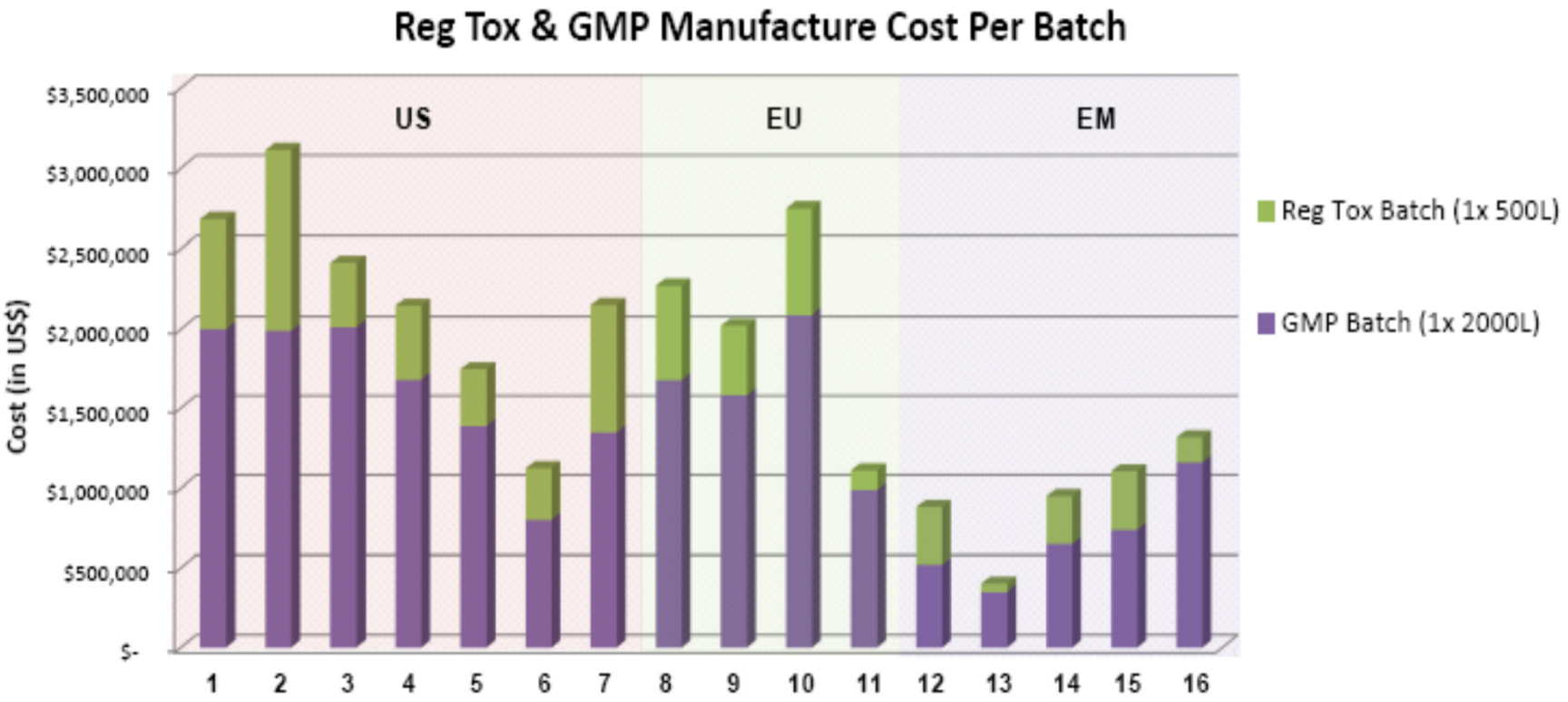
Cost of Erroneous Results

Importance of Risk Assessment

Cost of Erroneous Results

When Things Go Wrong, It Can Be Spectacular

Cost of Erroneous Results



Reg/Tox Batch - $200k to $1.1M
2000L GMP Batch - $500k to $2M

Cost of Erroneous Results

- When Things Can Go Wrong

PDA Outsourcing 2017 Munich FMEA ITEM	SEVERITY	LIKELIHOOD	non-DETECTION	RPN	MITIGATION
Out of Specification Batch Not Detected	3	1	3	9	Replicate
In Specification Batch Reported as Out of Spec	3	1	3	9	Testing

- High Consequence Low Probability Event
  - p(Error) = 1/10,000 = 10^{-4}
  - p(Error)Lab1 + p(Error)Lab2 = 2/10,000 = $2x10^{-4}$
  - p(Error)Lab1 x p(Error)Lab2 = $1/10,000^2$=1/100,000,000 = 10^{-8}

Cost of Erroneous Results

- When Things Could Have Gone Wrong

PDA Outsourcing 2017 Munich FMEA ITEM	SEVERITY	LIKELIHOOD	non-DETECTION	RPN	MITIGATION
Out of Specification Batch Not Detected	3	1	~~3~~ 1	~~9~~ 3	Replicate
In Specification Batch Reported as Out of Spec	3	1	~~3~~ 1	~~9~~ 3	Testing

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CMO Selection

CMO Selection Scorecard	Diamond Biotechnologies	Garnet Biotherapeutics	Emerald Biologics	Opal Technologies	Ruby BioPharma	Jade Biologicals
Geographic Location	San Francisco CA, USA	Cambridge MA, USA	Dublin, Ireland & San Diego CA, USA	Dusseldorf, Germany	Bangalore, India	Wuhan, China
# of Employees	150	5000	10000	1000	4000	5000
Years in CMO Business	5	15	20	10	15	10
FINANCIAL STABILITY (5%)						
Comments						
QUALITY (20%)						
Comments						
CAPABILITIES/EXPERIENCE (15%)						
Comments						
UPSTREAM PROCESSING (10%)						
Comments						
DOWNSTREAM PROCESSING (10%)						
Comments						
RELATED SERVICES (15%)						
Comments						
REGULATORY EXPERIENCE (10%)						
Comments						
ESTIMATED DURATION (WKS) (15%)						
Comments						
COST COMPETITIVENESS ($)						
Technology Transfer						
Reg/Tox DS Batch						
Number of Reg/Tox Batches						
GMP DS Batch						
Number of GMP Batches						
Total $	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Comments						
TOTAL SCORE	0	0	0	0	0	0

1- Lowest Rating
2- Middle Rating
3- Highest Rating

CRO/CTO Selection

CMO Selection Scorecard	Diamond Biotechnologies	Garnet Biotherapeutics	Emerald Biologics	Opal Technologies	Ruby BioPharma	Jade Biologicals
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Comments						
TOTAL SCORE	0	0	0	0	0	0

1- Lowest Rating
2- Middle Rating
3- Highest Rating

CRO/CTO Selection – Performance - Pilot Study

- Request for Quotation – Invitation to Bid
  - Maximum Number of Laboratories For Screening, Send Digital "Request for Information"
  - Choose Top 10, Send "Request for Quotation" RFQ Contains Listing of Testing Services, Number of Samples, Number of Replicates, Timeline for Deliverables
  - Choose Top 4 to 6 Labs Send "Pilot Study" Use well characterized materials as "Unknowns"
  - Use Fully Validated Methods

CRO/CTO Selection – Performance - Pilot Study

- Perform Tech Transfer of Validated Methods
- Use Well Characterized Materials (2 to 4 Different)
  - Must be Uniform
  - Must have Adequate Supply
- Identify as to Class (Mab, Peptide, etc.)
- Use Blind Replicate Samples (2 to 4)
- Require Statistical Sample Replicates (4 to 6)
- Perform Statistical Analysis of Results
  - One Sided t-Test (comparing to grand average)
  - Two Sided t-Test (comparing blind replicates)

Winning Laboratories Are Now Fully Qualified

Building Collaborative Relationships

CRO Responsibilities

- Meeting commitments with respect to technical, quality, and timing agreements
- Communication of difficulties
- Support of regulatory requests

Sponsor Responsibilities

- Clear expectations, defined upfront
- Timely response
- Technical expertise
- Prioritization, when needed
- Respect and appreciation

Analytical outsourcing is a joint project
Goal: *Our* data, *Our* methods

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Conclusions

- Multiple Models for Analytical Outsourcing
- Most successful when well managed
  - Risk Assessments guide Focus of Attention
  - Prequalify Analytical Vendors in advance
  - Start Analytical Tech Transfer early as possible
- Technical challenges higher than in-house
  - Diversity of products and required testing
  - Made more difficult by distance
  - More difficult due to dual QA Systems
- Excellent results require Partnership
  - Copious Focused Communication is needed
  - Trust Built by Qualification, Verification and Track Record of Consistent Performance

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Basic Exercise

1. Quality: After having carried out the quality control of the produced drug substance, it appears that the SE-HPLC target of more than 95% main peak was not reached. The content of di-and polymeric mAb was 5.5%, resulting in a purity of 94.5%.

   What actions will you take, and will you regard the batch as failed and ask the CMO to produce a new batch at the CMO's expense?

Basic Exercise

Specification	Analytical result	Pass/not pass
>95	95,4	
>95	96	
>95,0	95,0	
>95,0	95,1	
≥95	94,6	
≥95	95	
≥95,0	94,9	
≥95,0	94,95	

Basic Exercise

Specification	Analytical result	Pass/not pass
>95	95,4	-
>95	96	+
>95,0	95,0	-
>95,0	95,1	+
≥95	94,6	+
≥95	95	+
≥95,0	94,9	-
≥95,0	94,95	+

Success Defined, Attained