QbD Technologies:
Risks Management **Lecture 2** 2023

Incorporating Risk Management for Technology Transfer

Developing a Control Strategy

R&D Spending Related to NCE's?

PHARMA & HEALTHCARE 8/11/2013 @ 11:10AM | 143,565 views

The Cost Of Creating A New Drug Now $5 Billion, Pushing Big Pharma To Change

One common mistake is allowing projects to linger on when the odds of success have become low, says Roger Perlmutter, who ran Amgen's R&D and is now doing the same thing at Merck. Another problem, he argues, is CEOs believing they can order up another drug like their last big hit, instead of following the science.

Who's to blame – Discovery or Development?

Where's all the money going?

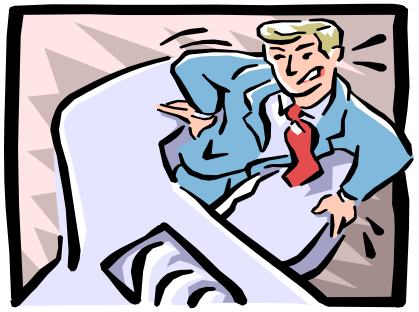
- On average, drug companies spend about 37% of their overall R&D budgets on clinical affairs[1]
  - Patient Recruitment - Patient recruitment costs more and consumes more time than any other aspect of clinical trials.
  - Budgeting and Performance Assessments - Timely results from patient recruitment campaigns should inform mid-trial decision-making and resource allocation.
  - Clinical Operations Structure and Workflow
- Thus Discovery and Development account for over 60% of the spending!
- We all must do our share to spend wisely☺

[1] http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=109&STORY=/www/story/06-23-2004/0002198373

[2] http://www.cuttingedgeinfo.com/acceleratingclinicaltrials/

The Challenges of Development

- Scientific Demands
  - Development becomes a "material science" problem
    - Stability, solid state form and formulations
  - Discovery has established a biological lead
- Business Realities
  - Increased compound throughput
  - Decreased timelines
  - Static or decreased staffing resources
- Regulatory Compliance & Expectations
  - Good laboratory and manufacturing processes (GxP)



Thus…Collect data in an organized and efficient manner!

Role of Automation

- Important to the entire process of drug discovery and development
  - Can help reduce costs while maintaining safety and quality
- Hardware components play a large role
  - Many components required to automate laboratory tasks can be purchased and "augmented" to fit your needs
- Future of Automation is going to be in software developments
  - Data visualization, integration, reporting, analysis
  - Helps pull data together for scientists from a variety of areas
    - Discovery – why they picked that molecule
    - Development – how they formulated the molecule
    - Clinical – how did the molecule and formulation effect the clinical outcome

Summary – Important Balance

Quality

- Drives development Standards (ICH)
- Leverage international standards to guide lean development

Speed

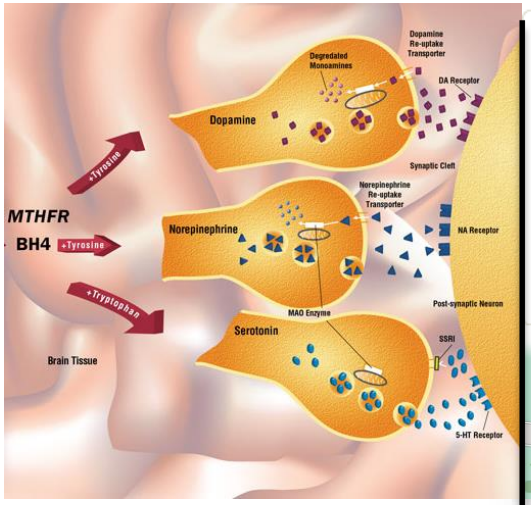
- Analytical Automation and Informatics Strategies
- Helps provide efficient reporting and advanced multivariate analysis

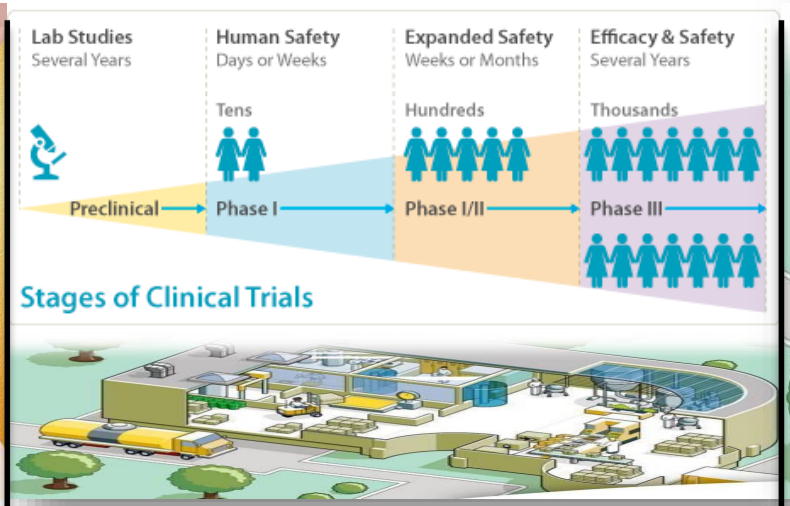
Costs

- If you obtain Quality and Speed, you'll drop costs for the patients and the company

Our Challenge: Lab to Patient – STEAM

- Worlds most complex bioreactor: Homo sapiens
  - Small variations can have catastrophic effects





Discovery/L&A | *Development* | *Commercial*

Lifecycle Risk Management

Clinical Trial Phases - Overview

Phase I	Phase II	Phase III	Phase IV
20-80 participants	**100-300 participants**	**1,000-3,000 participants**	**Thousands of participants**
Up to several months	Up to (2) years	One (1) - Four (4) years	One (1) year +
Studies the safety of medication/treatment	Studies the efficacy	Studies the safety, efficacy and dosing	Studies the long-term effectiveness; cost effectiveness
70% success rate	33% success rate	25-30% success rate	70-90% success rate

https://cern-foundation.org/?page_id=292

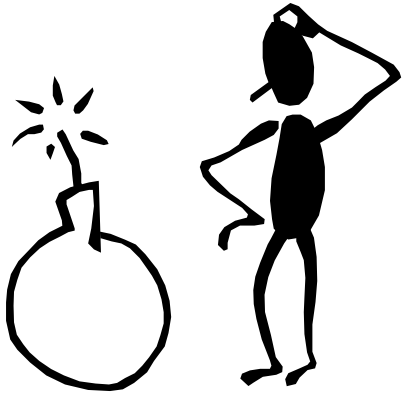
ICH Quality Risk Management Guideline

- "Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries."
- "It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm"
- The purpose of this document is to offer a systematic approach to quality risk management
- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

Risk Management in Laymen Terms

1. Tell me the manufacturing process to make the product
2. Tell me how great the process is
3. TELL ME HOW THE PROCESS MAY FAIL
4. TELL ME HOW I CAN PULL THE PROCESS BACK INTO CONTROL AFTER "FAILURE" OBSERVED

Dog and Pony Show



How to Fix it?

Risk Management Approach

- Failure Mode and Effects Analysis (FMEA)
  - Developed by the US military back in the 1940's
- Some Basic Steps
  - Break down the product and process into its components or steps
  - Identification and assessment of the following for every item listed: function(s), potential failure mode(s), failure mode effect(s), failure mode cause(s), and controls for detecting or preventing the failure mode(s);
  - Evaluation of the risks associated with the failures modes and prioritizing them according to importance;
  - Implementation of corrective actions to minimize the occurrence of the more significant failure modes;

Risk Management is a methodology to derive a process and product independent measure of performance related to the clinic

Risk Evaluation– Risk Priority Numbers

- Risk Priority Numbers (RPN) provide 3 key inputs
  - Sensitivity ranks the strength and type of relationship between the process parameter/material attribute and the CQA of the product
  - Probability of occurrence causing process parameter/material attribute significant variation
  - Detection: capability to detect and monitor MA, CQAs and Process Controls variation
- RPN = Severity X Probability X Detection
  - Scale 1 to 1000
- Risk Priority Numbers (RPN) calculated for each
  - Process Parameter, Material Attributes

Risk Management Approach

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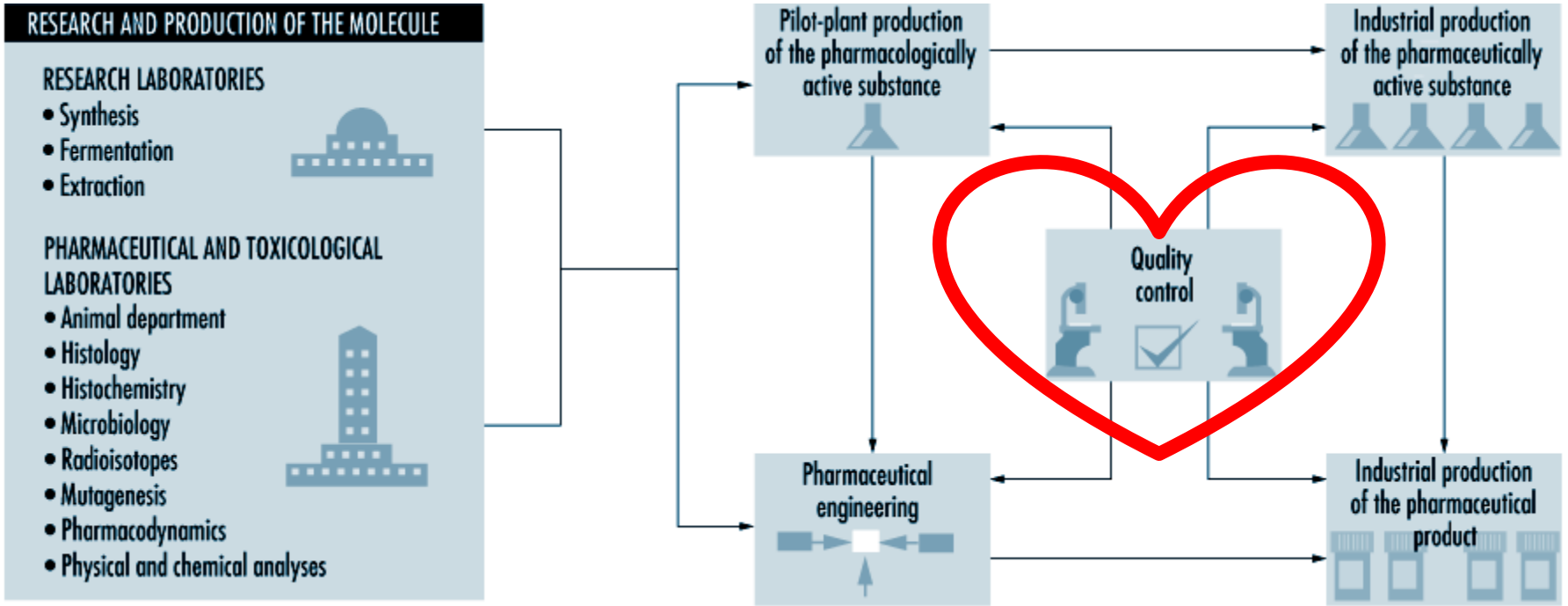
Pharmaceutical Processes



Discovery/L&A *Development* *Commercial*

Lifecycle Risk Management

Ref: http://www.ilocis.org/documents/chpt79e.htm

Sample Manufacturing Processes

- Drug Product Formulation
  - Solids manufacturing
- Active Pharmaceutical Ingredient
  - Small molecule
  - Large Molecule

Solids Manufacturing – High Level Overview

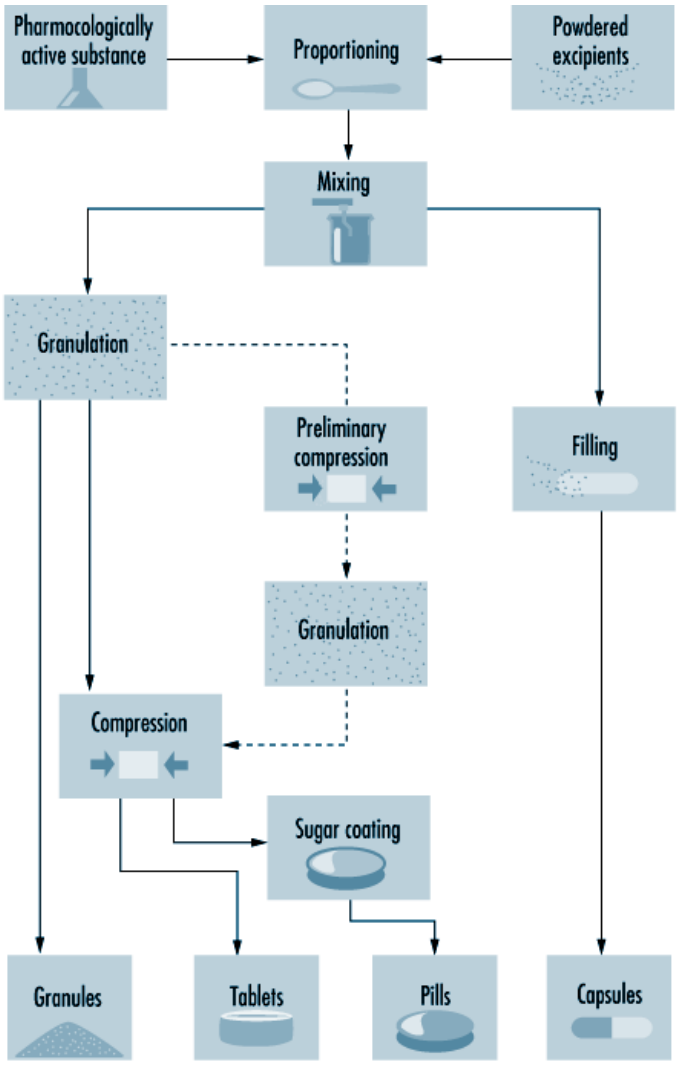
Raw materials
- Standard set of excipients
- Filler, Lubricant, Disintigrants

Blending
- Dry blending of materials

Granulation
- Mixing and gluing materials together

Compression
- Prepare a premeasured amount of material for human consumption

Coating
- Coloring, printing, extended release



Remember our Specs (Lecture 1)?

- Identity (2)
  - HPLC, TLC, UV, IR, optical rotation
- Assay (HPLC, NIR, UV/VIS)
- HPLC impurities
- Chiral HPLC (or CE)
- Dissolution or Drug Release
- Water Content
- Hardness, Friability, Disintegration
- Content uniformity
  - Consistency of a dosage form (90-110%)

What steps effect what quality attribute?

	Raw Materials	Blending	Granulation	Compression	Coating
Identity					
Assay					
Impurities					
Dissolution					
Water Content					
Hardness					
Friability					
Content Uniformity					
Other?					

Create a table that matrix out the quality attributes versus the unit operations

What steps effect what quality attribute?

	Raw Materials	Blending	Granulation	Compression	Coating
Identity					
Assay					
Impurities					
Dissolution					
Water Content					
Hardness					
Friability					
Content Uniformity					
Other?					

What Unit Operations will affect the "Identity" of the drug product at the end?

What steps effect what quality attribute?

	Raw Materials	Blending	Granulation	Compression	Coating
Identity	X				
Assay					
Impurities					
Dissolution					
Water Content					
Hardness					
Friability					
Content Uniformity					
Other?					

Basically the first step is the most critical
(mess it up in the beginning – no way to fix)

What steps effect what quality attribute?

	Raw Materials	Blending	Granulation	Compression	Coating
Identity	X				
Assay	X				
Impurities					
Dissolution					
Water Content					
Hardness					
Friability					
Content Uniformity					
Other?					

Assay

Presumably driven by purity of API coming into the process

What steps effect what quality attribute?

	Raw Materials	Blending	Granulation	Compression	Coating
Identity	X				
Assay	X				
Impurities					
Dissolution	X	X	X	X	X
Water Content					
Hardness					
Friability					
Content Uniformity					
Other?					

Dissolution

Can be impacted by any of the unit operations

ultimately a higher risk quality attribute

What steps effect what quality attribute?

	Raw Materials	Blending	Granulation	Compression	Coating
Identity	X				
Assay	X				
Impurities	X		X		
Dissolution	X	X	X	X	X
Water Content	X		X		X
Hardness	X			X	
Friability	X			X	
Content Uniformity		X	X	X	
Other?					

Dig one layer deeper

- What in the unit operation may impact that particular quality attribute?
  - Granulation – Temperature effect on Dissolution

Process Step	Parameter	Severity	Probability	Detection	RPN
Mix – Pre-Heat	Temperature	3 – Small	1	10	30
Spray	Temperature	10 - High	6	10	600
Drying	Temperature	7 - Medium	4	10	280
Cooling	Temperature	1 - Low	1	10	10

Dig one layer deeper

- What in the unit operation may impact that particular quality attribute?
  - Granulation – Temperature effect on Dissolution

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- Easy to communicate highest risk parameter in the unit operation with respect to dissolution
  - Absolutely still a judgment – but converts data to action

Standardize Sampling Strategy for Solids

PD Workflow

Characterization Work

QC Lab Workflows

API

Filler

Disint

Binder

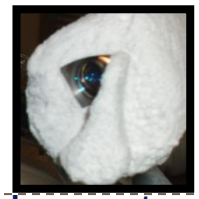
Lube

NIR

Disso

LC

TPW



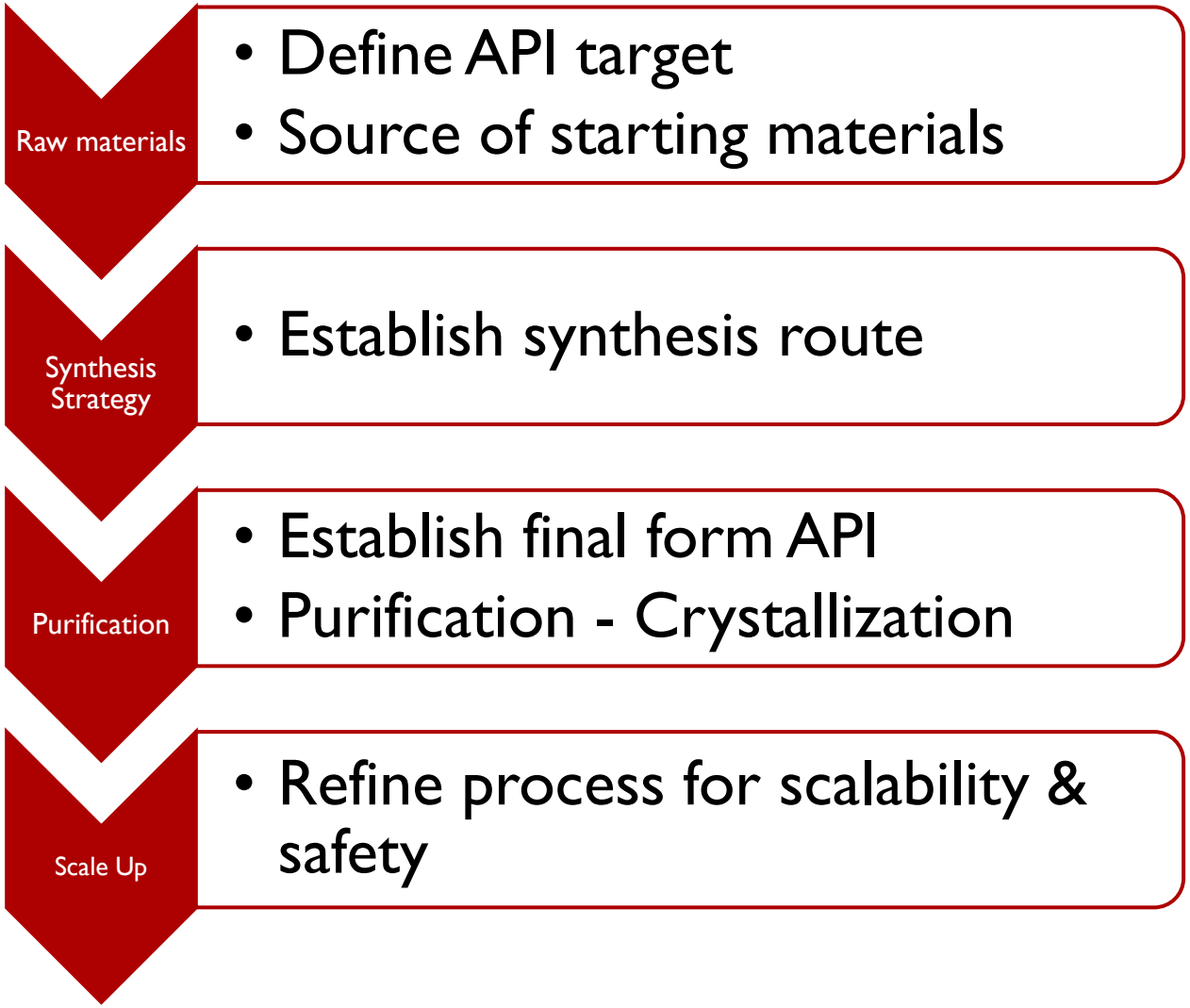
Lasentec

NDC

BREAK TIME

10min

Small Molecule API – High Level Overview

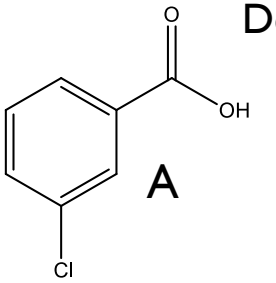


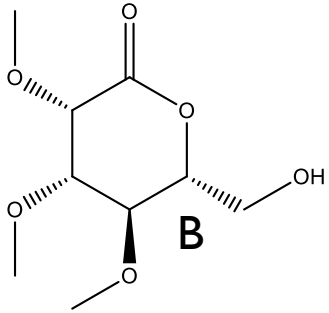
Small Molecule – API – High Level Overview

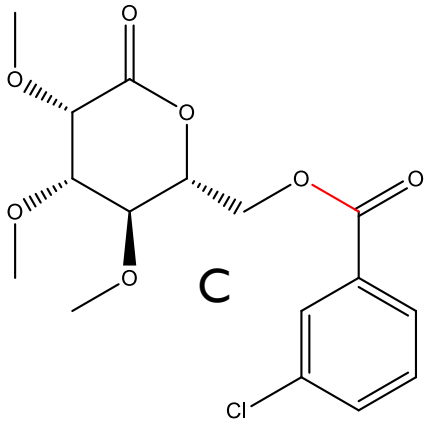
Starting Materials
- Petroleum Industry
- Natural Products

Starting Materials
A & B
- GMP
- Characterize
- Acceptance
- Specs

DPIC
Decision Point Increased Control







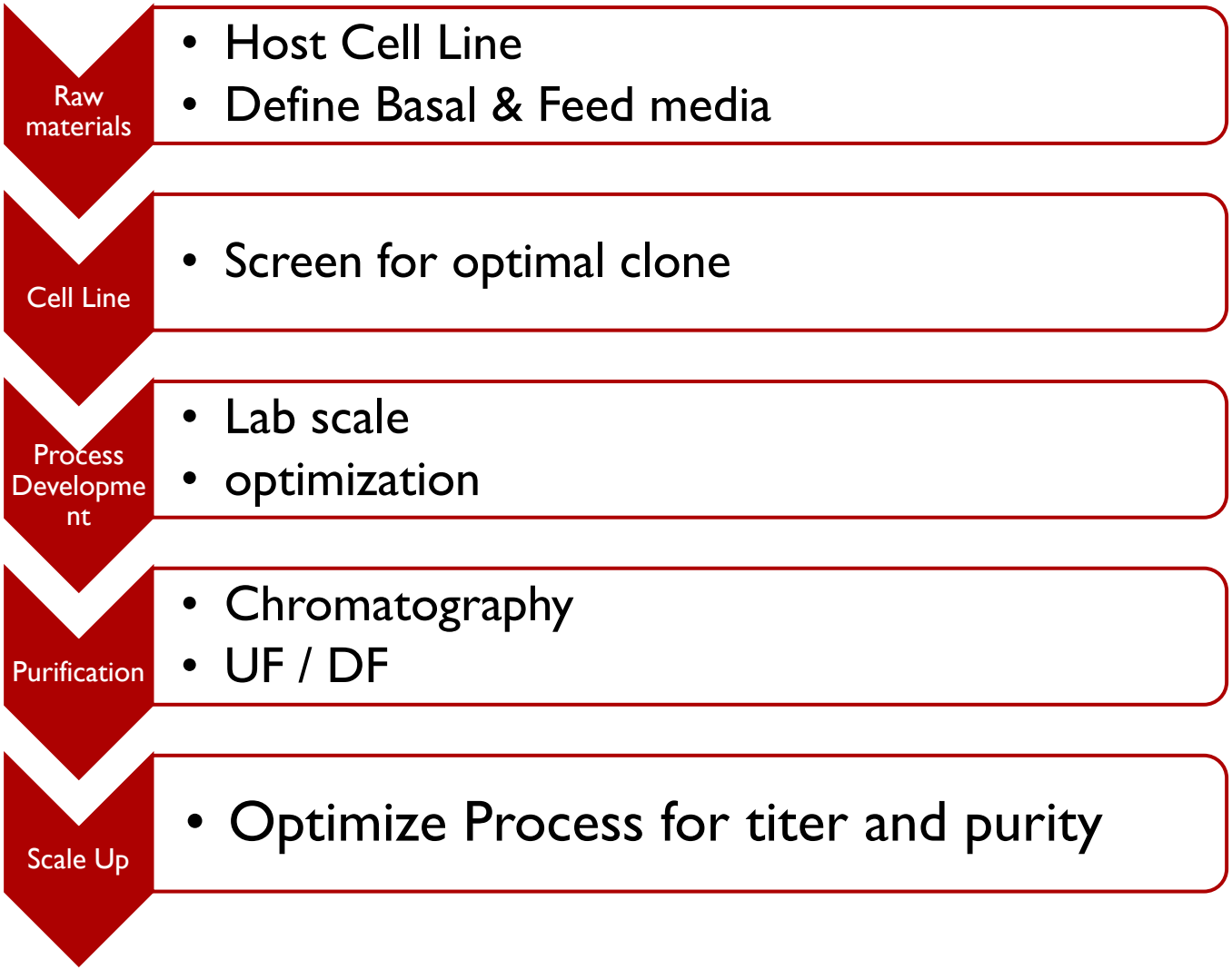
Specification for API

- Identity (2)
  - Want to ensure you have the right compound!
  - 2 methods like 2 engines on an airplane … yes you only "need" one
- Assay (HPLC/NIR/UV-VIS)
  - Measures the purity of the API – typically >98%
- HPLC Impurities
  - <1% unspecified, 1-3% specified, >3% generally unacceptable
  - Again, these will change as a function of development time
- Specific rotation
- Chiral Purity (HPLC or CE)
- Water content (Karl Fischer or loss on drying (LOD))
- Residual solvents
- Heavy Metals
- Residue on Ignition (ROI)

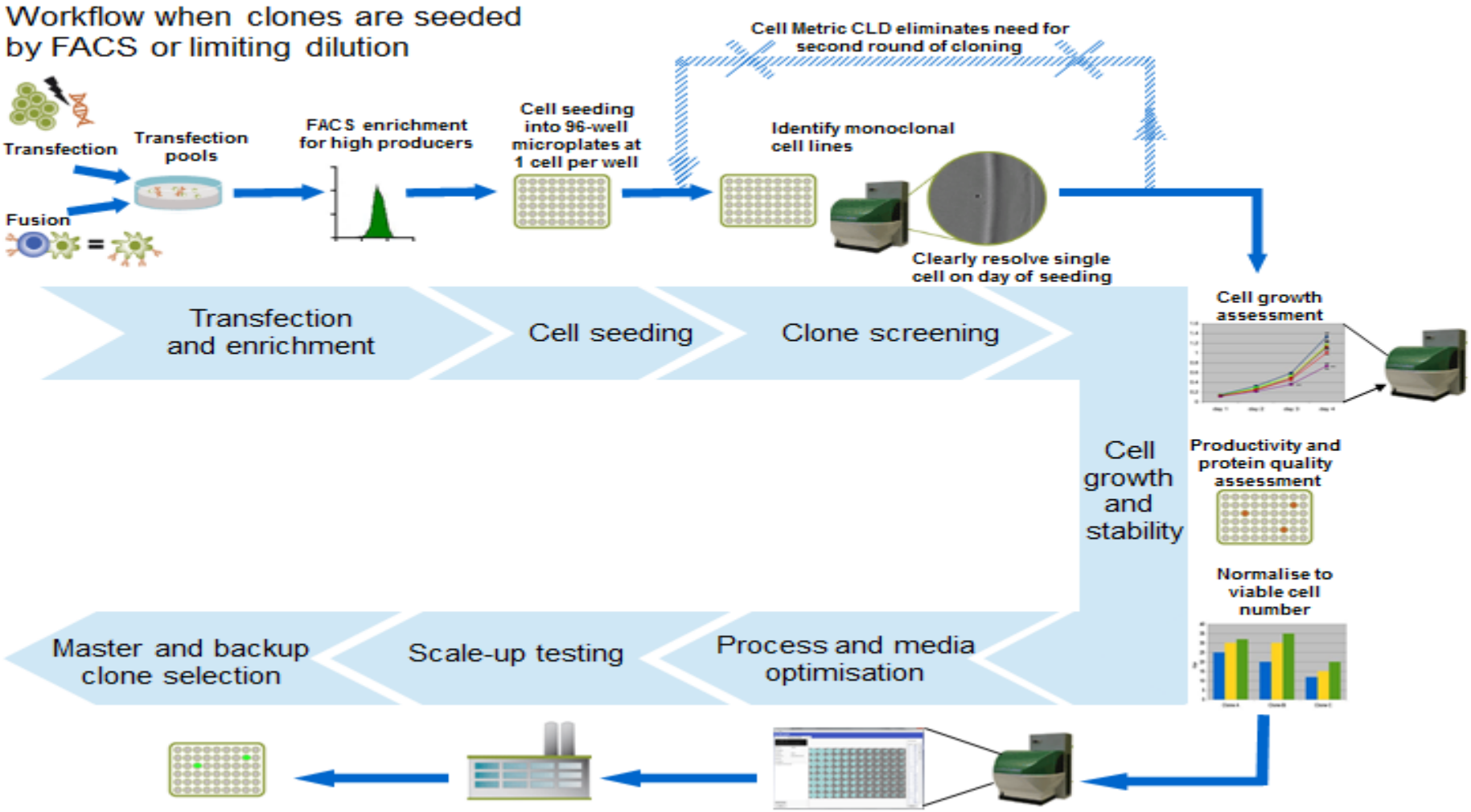
Specification for API - SM

- Identity (2)
  - Want to ensure you have the right compound!
  - 2 methods like 2 engines on an airplane … yes you only "need" one
- Assay (HPLC/NIR/UV-VIS)
  - Measures the purity of the API – typically >98%
- HPLC Impurities
  - <1% unspecified, 1-3% specified, >3% generally unacceptable
  - Again, these will change as a function of development time
- Specific rotation
- Chiral Purity (HPLC or CE)
- Water content (Karl Fischer or loss on drying (LOD))
- Residual solvents
- Heavy Metals
- Residue on Ignition (ROI)

Large Molecule API – High Level Overview

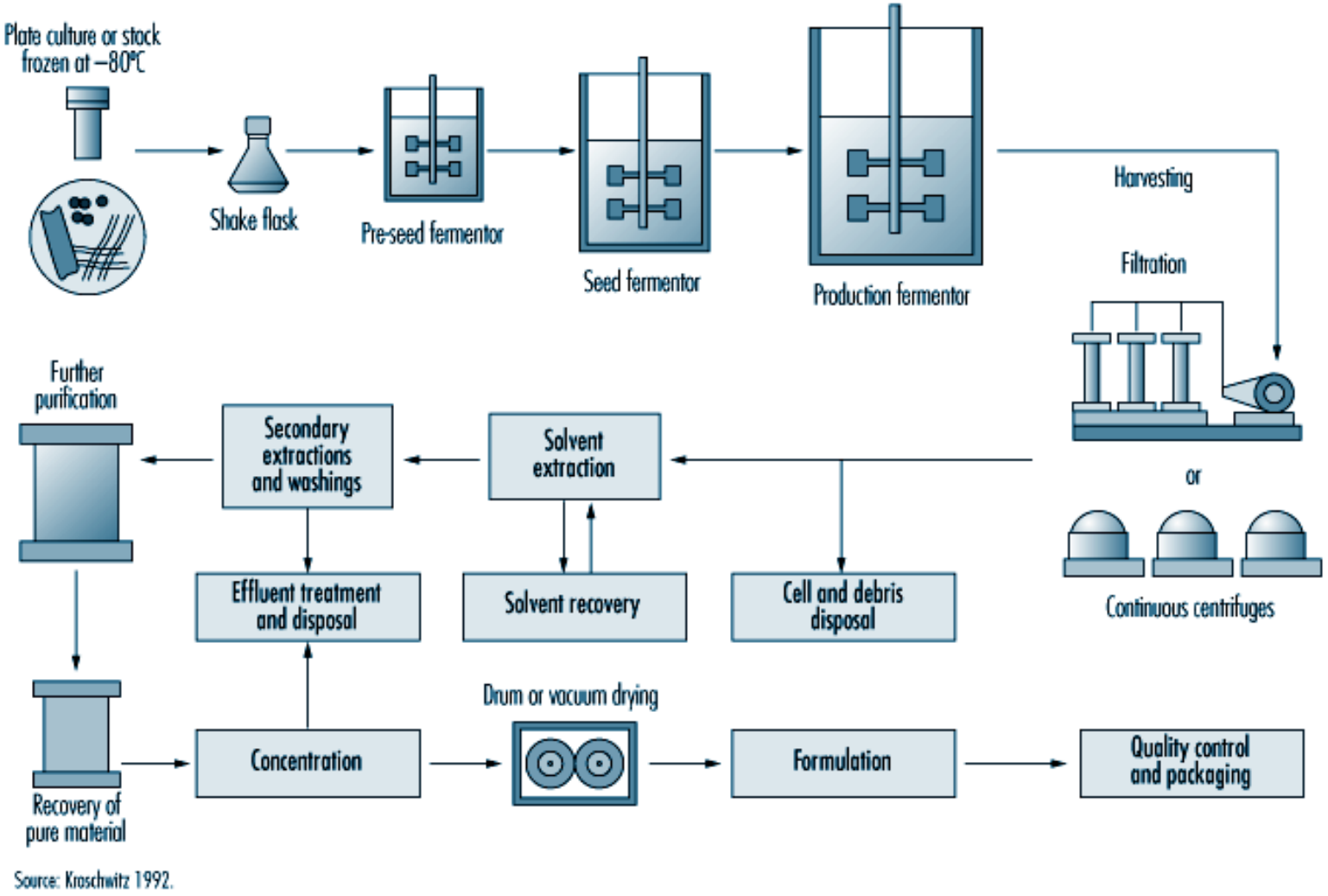


Large Molecule – Cell Line Development



http://www.solentim.com/workflow/cell-line-development/

Large Molecule – High Level Overview



Specification for API - LM

- Identity (2)
  - Want to ensure you have the right Product
  - 2 methods like 2 engines on an airplane … yes you only "need" one
- Assay (HPLC / Mass Spec (MS))
  - Measures the purity of the API
  - Glycosylation
  - Oxidation
  - Aggregate
- HPLC - MS Impurities
  - <1% unspecified, 1-3% specified, >3% generally unacceptable
  - Again, these will change as a function of development time
- Protein Content (A280)
- HCP (Host Cell Protein)
- Heavy Metals

FMEA Knowledge Management

- Defining the rationale behind the decisions as a function of current knowledge enables risk management to steer the appropriate direction
- Transparent communication helps decision making
- Introduce Template & Fill out example in class

API (CMA's)	Severity	Rationale	Probability	Rationale	Intrinsic Criticality	Current Control	Detection/ Process Control	Risk evaluation (RPN)
API Particle Size	8	BCS Class II/IV would lead to the rationale that dissolution could be rate limiting in the absorption. However, the dog studies carried out in Concept screening did not support this assessment	8	Particle size can play a role in the final drug product manufacturability and the CQA's and ultimately the bio performance. The high loading perspectives leave this to be evaluated in future development work	64	tested by supplier and sometimes by the receiving site	3	192
API Polymorphic form	8	Polymorphs known to cause drastic solubility changes which can effect bioavailability	5	Knowledge around polymorphism still under investigation, to date, only 2 forms known, but during chemical development scale up, the potential is still possible	40	Monitoring only by both DPD and CD	5	200
API purity	8	based on no weight adjustment applied, weight adjustment as a function of assay/purity would mitigate the risk	3	variation limited by CoA	24	tested by supplier and by the receiving site, methods still under development	3	72
API residual solvents	8	Residual solvents are important to track, but need to be evaluated as a function of time to ensure they stay within defined limits	2	variation limited by CoA	16	tested by supplier and by the receiving site	1	16
API rheological properties	5	Wet granulation process minimizes effects	3	Wet granulation process will ensure the risk of these parameters are not cascaded downstream	15	Not routinely tested	5	75
API Surface Area	8	BCS Class II/IV would lead to the rationale that dissolution could be rate limiting in the absorption. However, the dog studies carried out in Concept screening did not support this assessment	8	Particle Surfce area can play a role in the final drug product manufacturability and the CQA's and ultimately the bio performance. More development work is needed in this area	64	tested by supplier and sometimes by the receiving site	3	192

FMEA Example

- Review FMEA Template
  - What is it
  - Where to find it
  - How to navigate it
- Fill out example in class
  - How to use template
  - Score interactively
  - Upload example to Canvas