Outsourcing, Technology Transfer & CMO-Client Relationships

CMC Tech Transfer

PDA Europe
Outsourcing & Contract Manufacturing
Munich, Germany, 23-24 Nov. 2017

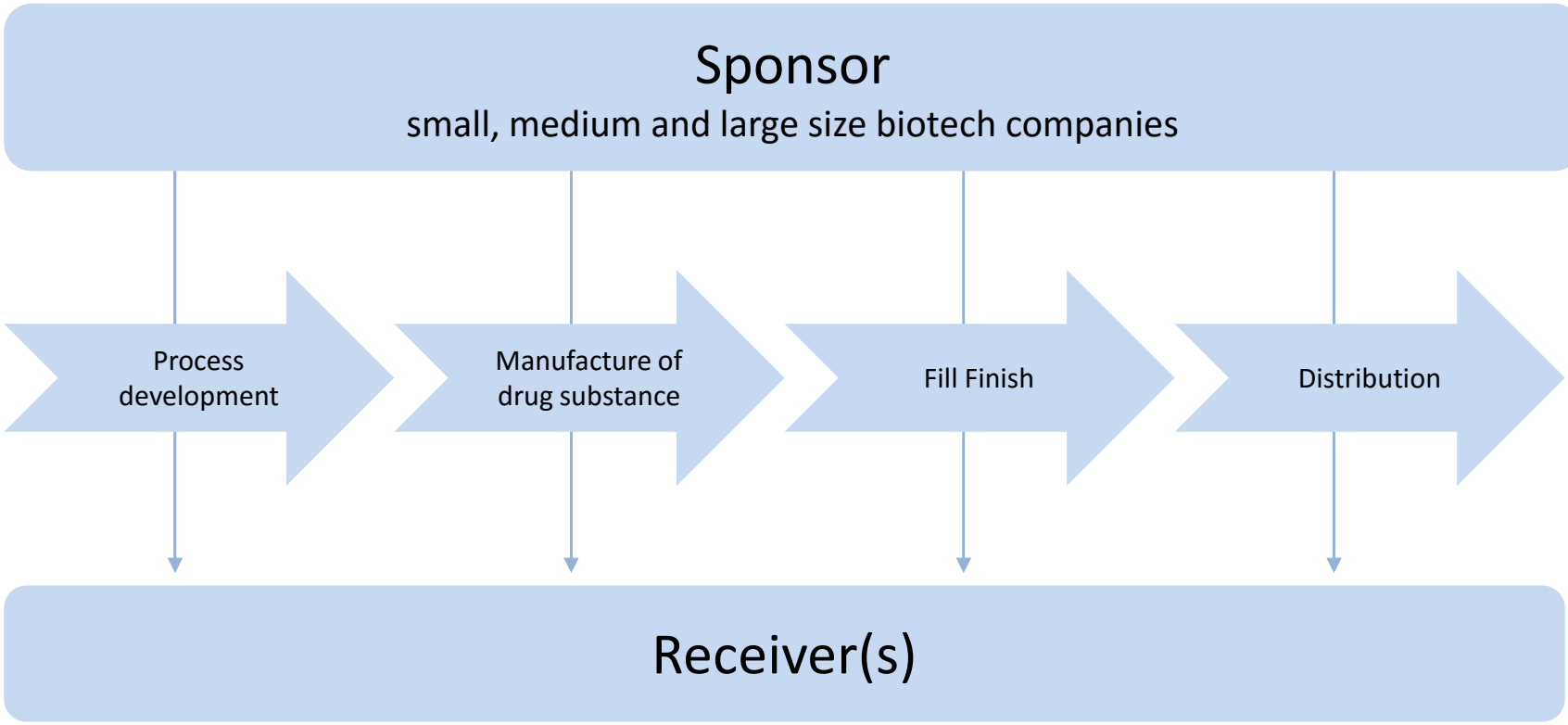
Kim Hejnaes
Hejnaes Consult

Presentation Overview

1. Introduction
2. Tech transfer
3. Transfer management
4. Risk assessment
5. Pitfalls
6. Group work

This presentation relates to outsourcing activities in development and manufacture of phase I-II clinical trial materials.

Responsibility / oversight / decisions / culture / QA systems / shipments / deviations / delays / cost / resources



WHAT IS TRANSFERRED?

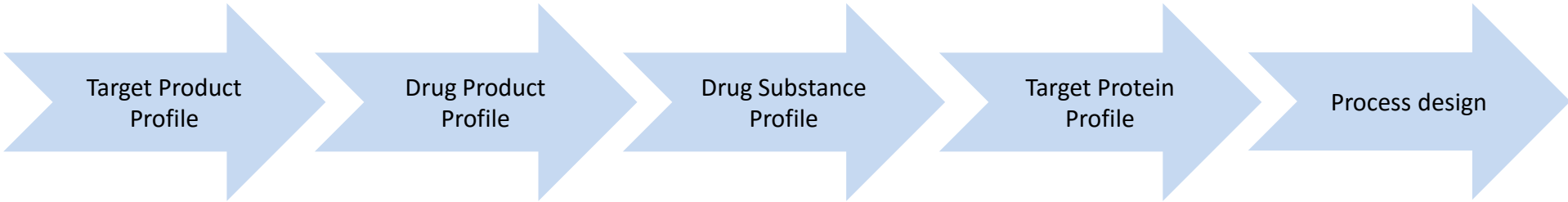
1. Knowhow
2. Documentation
3. Certificates
4. Specifications
5. Specific analytical methods
6. Reference materials
7. Cell banks
8. Drug substances
9. Drug products

Internal versus external transfer

SPONSOR INPUT – EXAMPLES

1. Target product profile
2. Drug substance concentration
3. Drug substance storage temperature
4. Drug product formulation
5. Device
6. Shipping temperatures
7. Specifications
8. Expected timelines
9. Stability study temperatures, time points and test program

SPONSOR PREPARATION

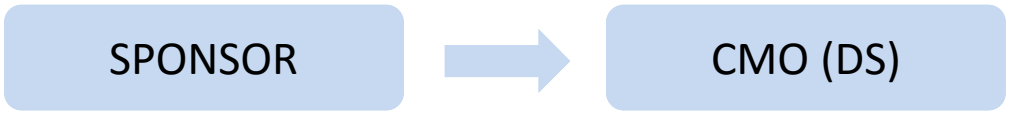


A Target Product Profile (TPP) is a planning tool for therapeutic candidates based on FDA Guidance for Industry

A drug product profile is a description of the drug product formulation

A drug substance profile is a description of the drug substance composition

A target protein profile is a description of the active ingredients chemical and physical properties



1. RCB, MCB or WCB
2. Analytical procedures
3. Reference material
4. R&D documentation
5. Profiles
6. Timelines
7. Drug substance specifications
8. Drug substance formulation
9. Amount of drug substance required
10. Strategy (development, technical and GMP batches)

SPONSOR AND CMO → FILL-FINISH (DP)

1. Analytical procedures
2. Reference material
3. Drug substance (intake procedures)
4. R&D documentation
5. Profiles
6. Timelines
7. Drug product specifications
8. Drug product formulation
9. Amount of drug product required
10. Strategy (development, technical and GMP batches)
11. Placebo vials
12. Shipment procedures

SPONSOR + FILL-FINISH PARTNER → DISTRIBUTION PARTNER

1. Shipment procedures
2. Intake procedures
3. Labeling
4. QP-release

SHIPMENTS – EXAMPLE

1. Define shipment address and shipment date
2. Should shipment be divided into two shipments (dummy shipment)
3. Sample description
4. Insurance
5. Incoterm 2010
6. Select courier
7. Decide on container, shipment temperature, logger and OOS ranges
    1. Example with cracked vials
8. Packing
9. Customs (what happens if…….)
10. Intake procedure
11. Storage temperature upon arrival
12. Distribute temperature curve to partners and acknowledge receipt of shipment

ANALYTICAL METHODS

What do you want to transfer – the sample or the analytical method?

Three types of analytical methods:

1. Compendial (e.g. Appearance, pH and osmolality)
2. Generic (e.g. Residual HCP ELISA, LAL, SDS-PAGE)
3. Specific (e.g. RP-HPLC, SE-HPLC, Potency assay)

Transfer of specific analytical methods is complicated and CXOs are not always accepting the transferred method as is.

1. Verified (non GMP)
2. Qualified (Phase I+II)
3. Validated (Phase III)

All parties to use the same reference material

Process specific samples

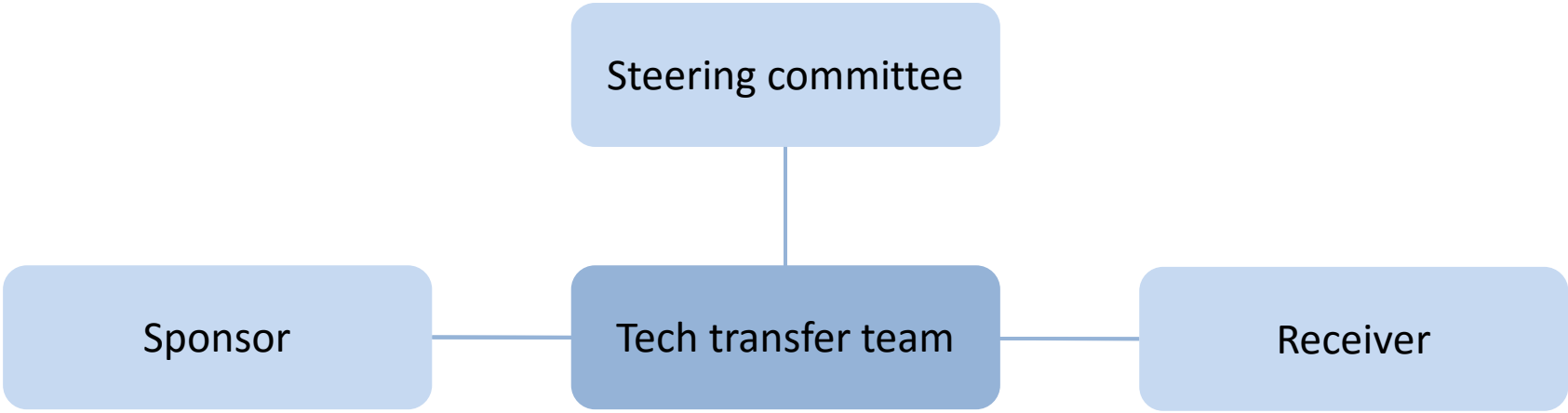
Stability study samples

Fill-Finish specific samples

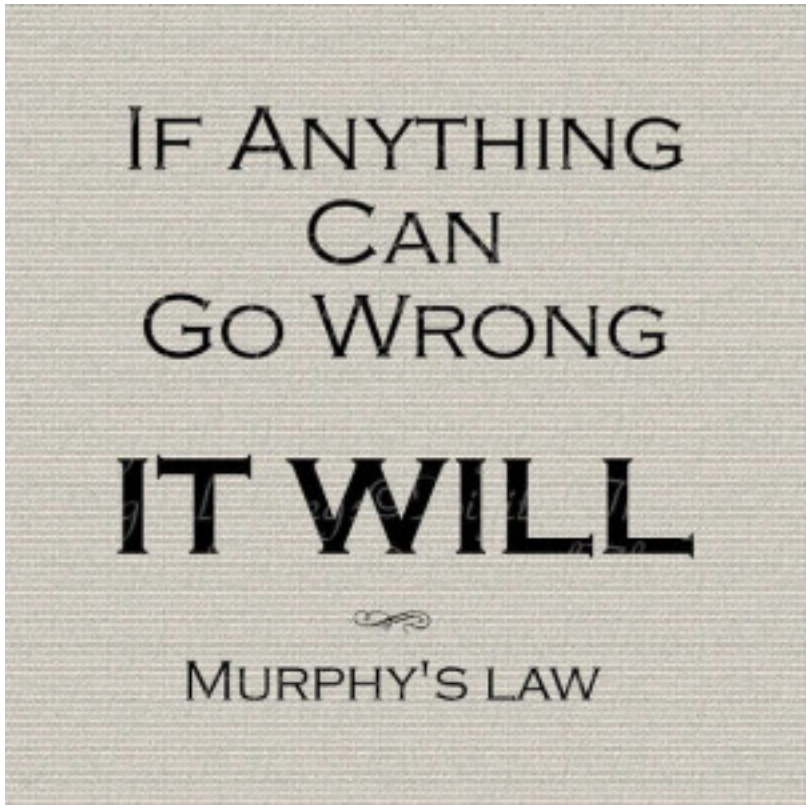
High class analytical CRO
Qualified generic and specific methods
Quality by Design

CMO and Fill-Finish make use of compendial and verified methods

ORGANIZATION



Murphy‘s law



RISK ASSESSMENT

It is commonly understood that risk is defined as the combination of the **probability** of occurrence of harm and the **severity** of that harm. However, achieving a shared understanding of the application of risk management among diverse stakeholders is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm.

ICH guideline Q9 Quality Risk management

COMMON RISKS

- Objective which is not clear (or clearly defined)
- Objective that is not properly communicated and/or shared
- Objective that cannot be operationally translated
- Lack of change control

PDA Technical Report no. 65

FMEA is a qualitative and systematic tool, usually created within a spreadsheet, to help practitioners anticipate what might go wrong with a product or process. In addition to identifying how a product or process might fail and the effects of that failure, FMEA also helps find the possible causes of failures and the likelihood of failures being detected before occurrence.

Step 1: Finding the participants

Step 2: Brainstorming (identify items that could potentially go wrong)

Step 3: Address Severity, Occurrence and Detection

Step 4: Calculate the RPN number

Step 5: Prioritize

Step 6: Mitigation

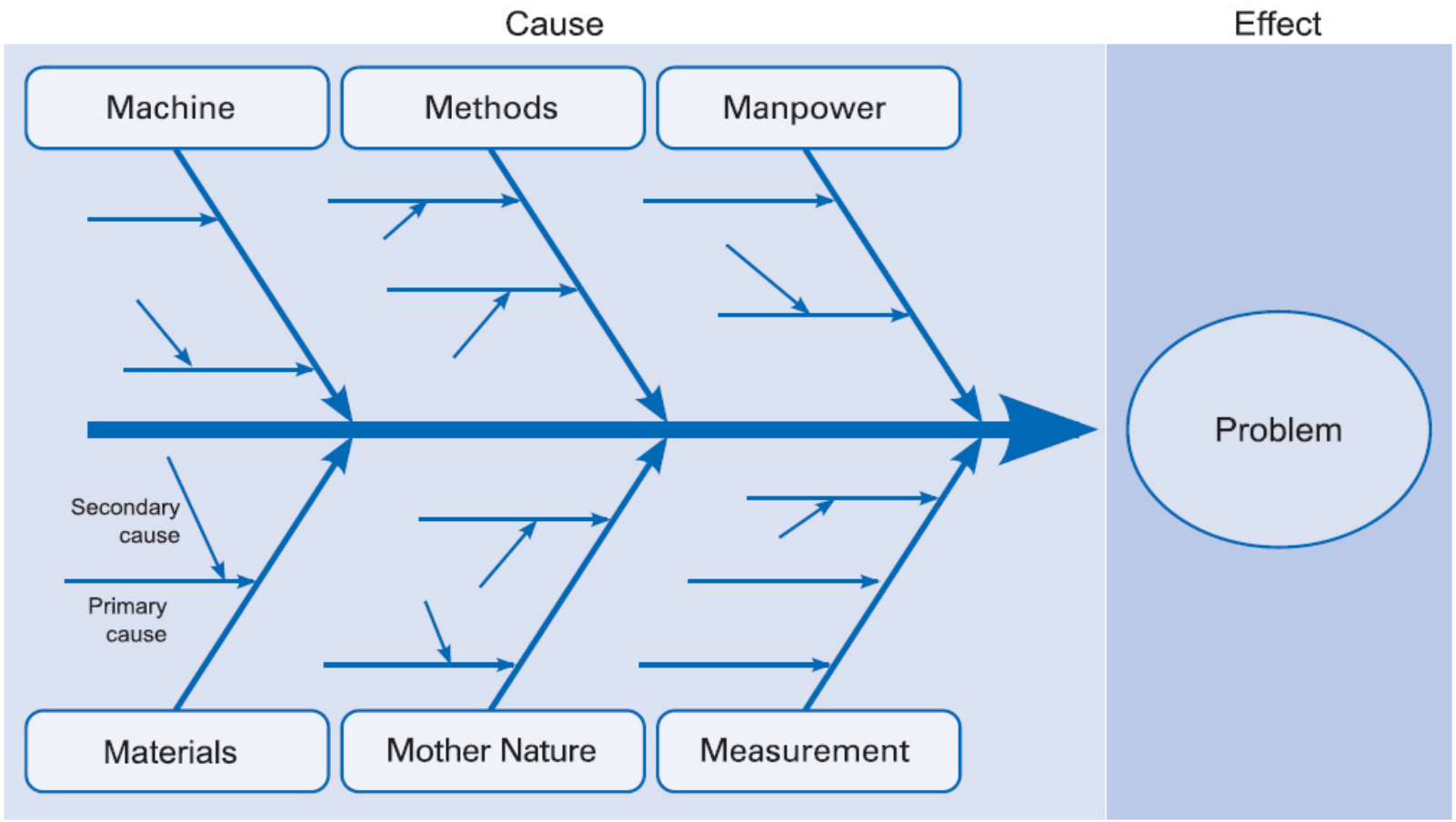


Figure 4.1.3-1 Example of Ishikawa (Fishbone) Diagram

Failure Mode and Effects Analysis

SEVERITY	RISK	VALUE
No impact on products quality attributes	Low	1
Moderate impact on products quality attributes	Medium	2
Severe impact on products quality attributes	High	3

OCCURRENCE	RISK	VALUE
Highly improbable that the negative event will occur	Low	1
Some possibility that the negative event will occur	Medium	2
Highly probable that the negative event will occur	High	3

DETECTION	RISK	VALUE
Highly probable that the negative event will be detected	Low	1
Some possibility that the negative event will be detected	Medium	2
Highly improbable that the negative event will be detected	High	3

RPN = SEVERITY ○ OCCURRENCE ○ DETECTION

SEVERITY	OCCURRENCE	DETECTION	RPN
1	3	3	9
3	1	3	9
3	3	1	9

The Risk Priority Number (RPN) is not a measure of risk, but of risk priority. Some numbers cannot be a RPN, for example 17.

EXAMPLE

DESCRIPTION	SEVERITY	OCCURRENCE	DETECTION	MITIGATION
Incorrect sealing of the vials can result in non-closure of the vials	3	3	3	Validation of the sealing step will be done. Dye intrusion test. Vials will be analyzed by UV-visible light spectroscopy after immersion in a solution of methylene blue.

SOURCE: PDA technical report 65

RISK CONTROL

1. Establish the context
2. Identify the risk
3. Analyze the risk
4. Evaluate and prioritize the risk
5. Mitigation

PITFALLS IN TECH TRANSFER

1. Incomplete planning
2. Lack of communication
3. Lack of risk management
4. Lack of oversight
5. Responsibilities are not defined
6. Hiding information
7. Intake procedures not fully understood
8. Underestimating analytical method transfer problems
9. Delays in delivery

It is common practice to execute a thorough risk assessment of the manufacturing process and fill finish operations as part of tech transfer.

We have selected ten items (see excel sheet in the work shop folder/binder). You are asked to address Severity, Occurrence and Detection and hereafter calculate the risk priority number (RPN) and suggest mitigating actions.

Group work

Analysis				Risk Priority Number Evaluation				Mitigation Plan
Item	Variable	QA Impacted	Potential criticality/cause of lack of quality attribute description	Severity	Occurrence	Detection	RPN	Consideration / Action
Process	Grade C and grade A filtration	Particle matter	Release from the filter membrane may impact the particle matter profile of the solution.	3	2	3	18	Regarding the release from the filters used in grade C, the solution is sterile filtered before filling. A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected.
		Sterility	A filter with an integrity issue can compromise the sterility of the solution	3	1	1	3	The filter arrives in the RU with the integrity certification of the supplier. According to the RU's procedure, each 0.22/0.2 um filter is tested after and before use. Leachable/extractable documentation and certifications will be provided by the supplier. If needed, specific analyses can be done by the supplier to identify possible leachables and extractables. Adsorption and compatibility studies will be performed as a part of the filter validation.
			A filter can become clogged.	3	1	1	3	Clogging of the filter with potential impact on the sterility of the overall process is evaluated in a preliminary phase of the transfer, including supplier trial for scale up of their size. Analysis of the exact filtration system and critical process parameters that will be used during drug manufacturing are necessary. Both velocity max or pressure max trials are reliable and can anticipate potential failures. Media fill challenge of the filter change procedure is a valid practice to downgrade the associated risk and estimate the impact on sterility as a result of the filter change.
		pH	Adsorption on the membrane filter can impact density, osmolality, and pH of the solution.	3	3	3	27	Adsorption studies will be done as a part of the filter validation. High impact has to be considered in the case of biological compounds due to the potential impact of changes in preservative concentrations.
		Density	Incompatibility between filter and solution can modify the system's chemical profile.	3	3	3	27	Compatibility studies will be done as a part of the filter validation.
		Sterility	Clogging issue can have an impact on the microbiological growth attributes and chemical characteristics of the solution.	3	3	2	18	The appropriate size of the filter will be defined in the RU with a specific laboratory trial with the filter supplier. The solution will be filtered through the filter until clogging occurs. Volume filtered, time of filtration, surface area, and flow rate will be analyzed and correlated. The RU's minimum filter size will be defined. A dedicated protocol and report will be issued with the results of the trial.
	Grade C and grade A filtration	Sterility	Holding time before filtration can increase the bioburden of the compounded solution.	3	2	2	12	During the validation activities, the holding times will be challenged according to a dedicated protocol. The chemical characteristics and microbiological growth attributes of the solution will be analyzed.
	Filling	Volume in container	Incorrect filling weight can result in out-of-range container volume.	3	1	1	3	No further actions are needed because the RU's procedures are already in place to periodically check the weight of the solution dosed into the vials during filling activities.

THANK YOU