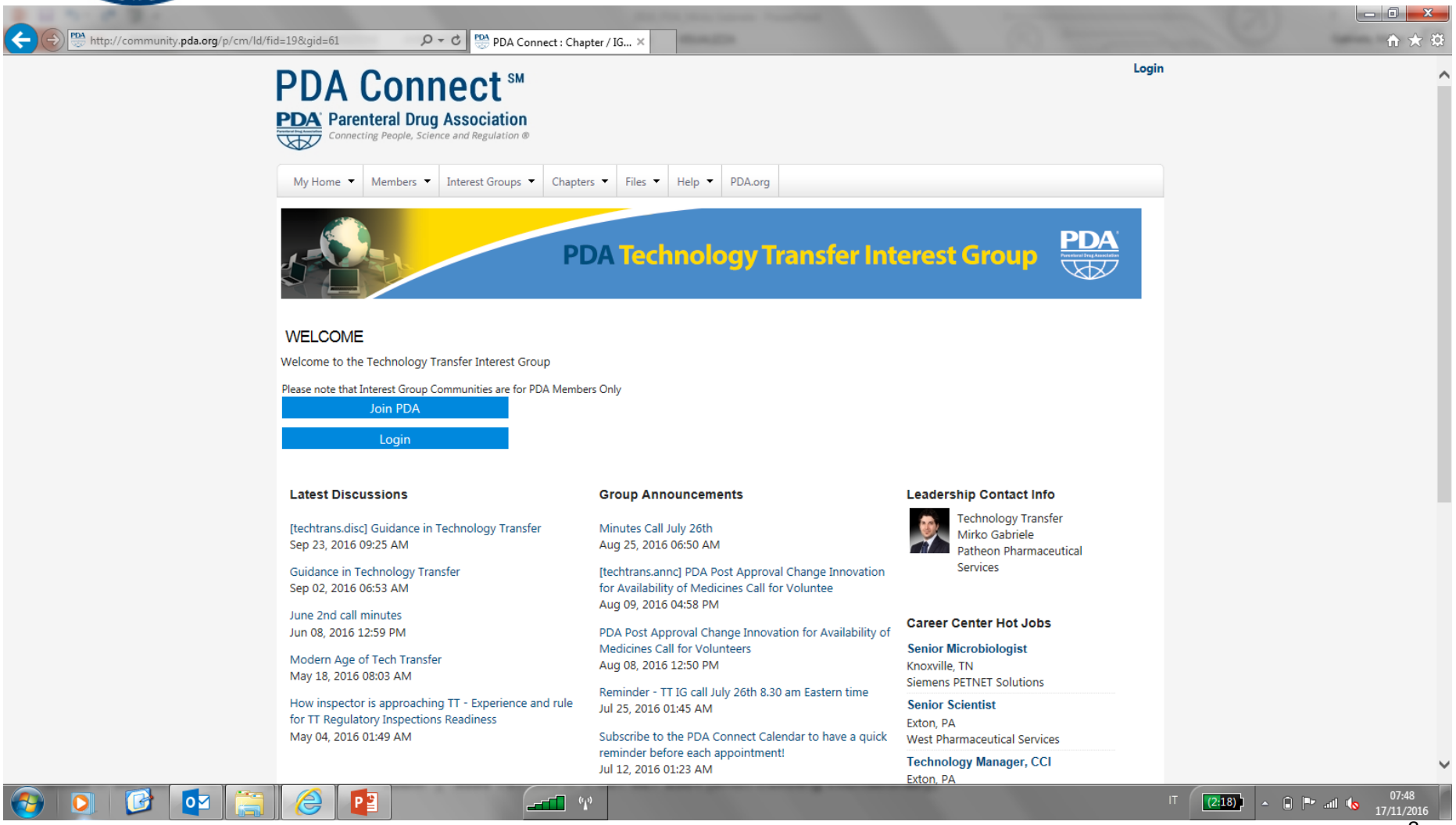
Technology Transfer

Risk Management in TT – Siviglia Nov 2018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Leadership Contact Info
Technology Transfer
Mirko Gabriele
Patheon Pharmaceutical Services
Career Center Hot Jobs
Senior Microbiologist
Knoxville, TN
Siemens PETNET Solutions
Senior Scientist
Exton, PA
West Pharmaceutical Services
Technology Manager, CCI
Exton, PA
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07:48
17/11/2016

Why Join this training

$1T

Global Rx sales by 2020

$160B

Global pharma and biotech R&D spend by 2020

60 to 10

Shrink in number of Pharma players due to M&A in the last 20 years

TT IS AND WILL BECOME A MORE CRITICAL BUSINESS NEED, A "BEST TO BEST DEAL" WITH CUSTOMERS, TOP PLAYERS LOOKING FOR CDMO TOP PLAYERS

Why Join this training

- Incredible **increase** of number of **Technology Transfer projects** (TTP) in the pharmaceutical environment, both internal & external and consequent increase of attention on Technology Transfer (TT) handling by Authorities;
- Project **complexity** is growing day by day;
- **Risks of failure** is always high;
- **Quality Risk Management (QRM) & Project Management (PM)** skills and knowledge are fundamental for success!

My expectations for the two days…

- Meet new people
- Networking
- Share experience on TT
- Benchmarking on TT organization, Approaches
- Understand opportunity for improvements

What about you?

What is your expectation?

Day 1

Thursday, 23 November 2017	9:00 – 17:30
9:00	**Welcome & Attendees Introduction**
9:00	**Technology Transfer – Definition and Main Principles** • Opportunities along product lifecycle • Regulatory guidance on technology transfer • Planning and Social Intelligence • Tool for planning
10:00	**Technology Transfer – Definition and Main Principles (continued)** • Tool for Social Intelligence • Role and responsibility • General org chart in technology transfer
11:00	**Coffee Break**
11:30	**Technology Transfer Project Management Tools** • Timelines • Leadership • Communication
12:30	**Lunch Break**
13:30	**Technology Transfer Documentation** • Technology Transfer Plan • Technology Transfer Report • Feasibility batches Protocol and Report
14:30	**Technology Transfer Procedures**
15:30	**Coffee Break**
16:30	**Analytical Transfer** • General approach (transfer vs validation) • Analytical Master Plan
17:00	**Recap of the Day**
17:30	**End of Day 1**

Day 2

Friday, 24 November 2017	9:00 - 16:30
9:00	**Recap of the Main Concepts of Day 1**
9:30	**Introduction into Technical Report TR 65** • Project staging • Risks in technology transfer • Risk Management in technology transfer
10:30	**Introduction into Technical Report TR 65 (continued)** • Severity/Occurrence/Detection in technology transfer • FMEA
11:00	**Coffee Break**
11:30	**TR 65 - Case Study 1 'Analytical Method Transfer (AMT)'** • Design of Comparative AMT Test Studies • Selecting AMT Performance Characteristics • AMT Documents
12:30	**Lunch Break**
13:30	**TR 65 - Case Study 2 'Manufacturing Process Transfer'** • Overvew of Manufacturing Process Transfer • Development to Commercialization Technology Transfer Process • Intracompany Technology Transfer Process
16:30	**End of Course**

Technology Transfer – definition and main principles

Terminology

Receiving Unit (RU)

The involved disciplines at an organization where a designated product, process or method is expected to be transferred.

Risk Management (RM)

Risk is combination of severity of harm and probability of occurrence (ICH Q9).

Applicable to Technology Transfer Projects – harm is event that could delay/stop a project

Comparability

The demonstration that the quality attributes are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product (ICH Q5E).

Technology Transfer (TT)

The transfer of product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization (ICH Q10).

Technology Transfer Project (TTP) is a set of planned and controlled actions based on well-defined acceptance criteria needed to transfer a technology from a sending unit (SU) to a receiving unit (RU).

Sending Unit (SU)

The involved disciplines at an organization from where a designated product, process or method is expected to be transferred.

Technology Transfer main concepts

A process for conceiving and implementing a new/novel application for an existing technology *(Reisman, 1989)*

The technology transfer consists of actions taken ….to realize the quality as designed during the manufacture (*NIHS, 2005*)

A logical procedure that controls the transfer of an established process together with its documentation and professional expertise to a site capable of reproducing the process and its support functions to a predetermined level of performance
(WHO Guideline on transfer technology, 2008)

Technology Transfer main concepts

The Technology Transfer Project (TTP) is defined as a set of planned and controlled actions, based on well-defined acceptance criteria needed to transfer a technology from a sending unit (SU) to a receiving unit (RU).

The Technology Transfer implies four main topics:

- Technical knowledge
- Documentation management
- Project management
- Personnel training and skills

PDA – PMCO Program – Technical Report N.65

Technology Transfer main concepts

The Technology Transfer Project (TTP) is defined as a set of planned and controlled actions, based on well-defined acceptance criteria needed to transfer a technology from a sending unit (SU) to a receiving unit (RU).

Technology = Drug

Technology Transfer Projects must have product quality, product safety and process performance as primary objectives.

Good Transfer Practice → Good, Reproducible, Safe and Effective Manufacturing Practice → **Good & Safe Product delivered to the Patient**

Technology Transfer main concepts

The Technology Transfer Project (TTP) is defined as a set of planned and controlled actions, based on well-defined acceptance criteria needed to transfer a technology from a sending unit (SU) to a receiving unit (RU).

Scope of the project must be clearly stated and agreed upon within the team and a structured plan needs to be developed.

Project is a sum of non-repetitive activities which are:

- addressed to a particular goal
- have to be performed in a defined time range
- employ defined resources
- and are managed by a team.

Technology Transfer main concepts

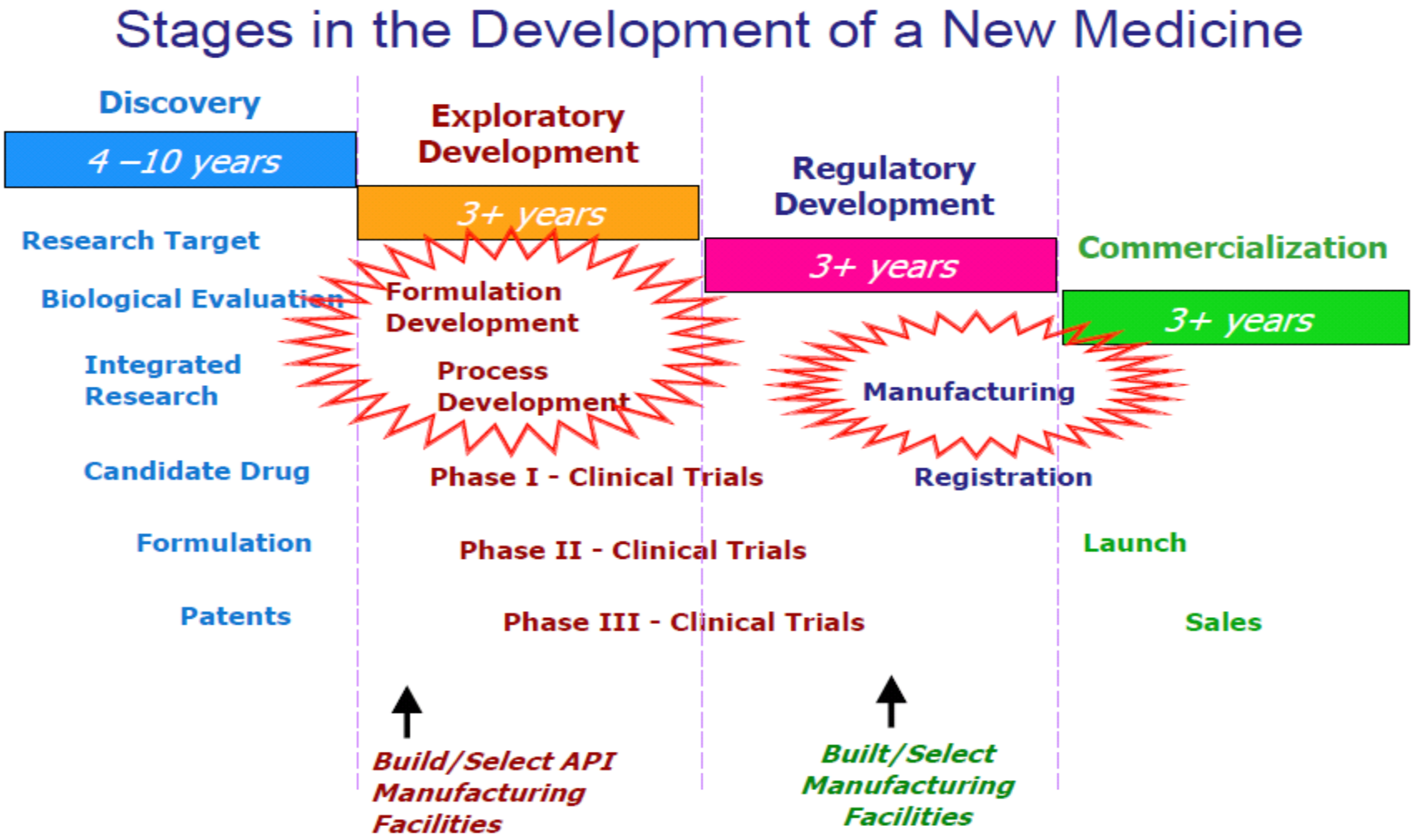
The Technology Transfer Project (TTP) is defined as a set of planned and controlled actions, based on well-defined acceptance criteria needed to transfer a technology from a sending unit (SU) to a receiving unit (RU).

Two main Risk Categories in Technology Transfer:

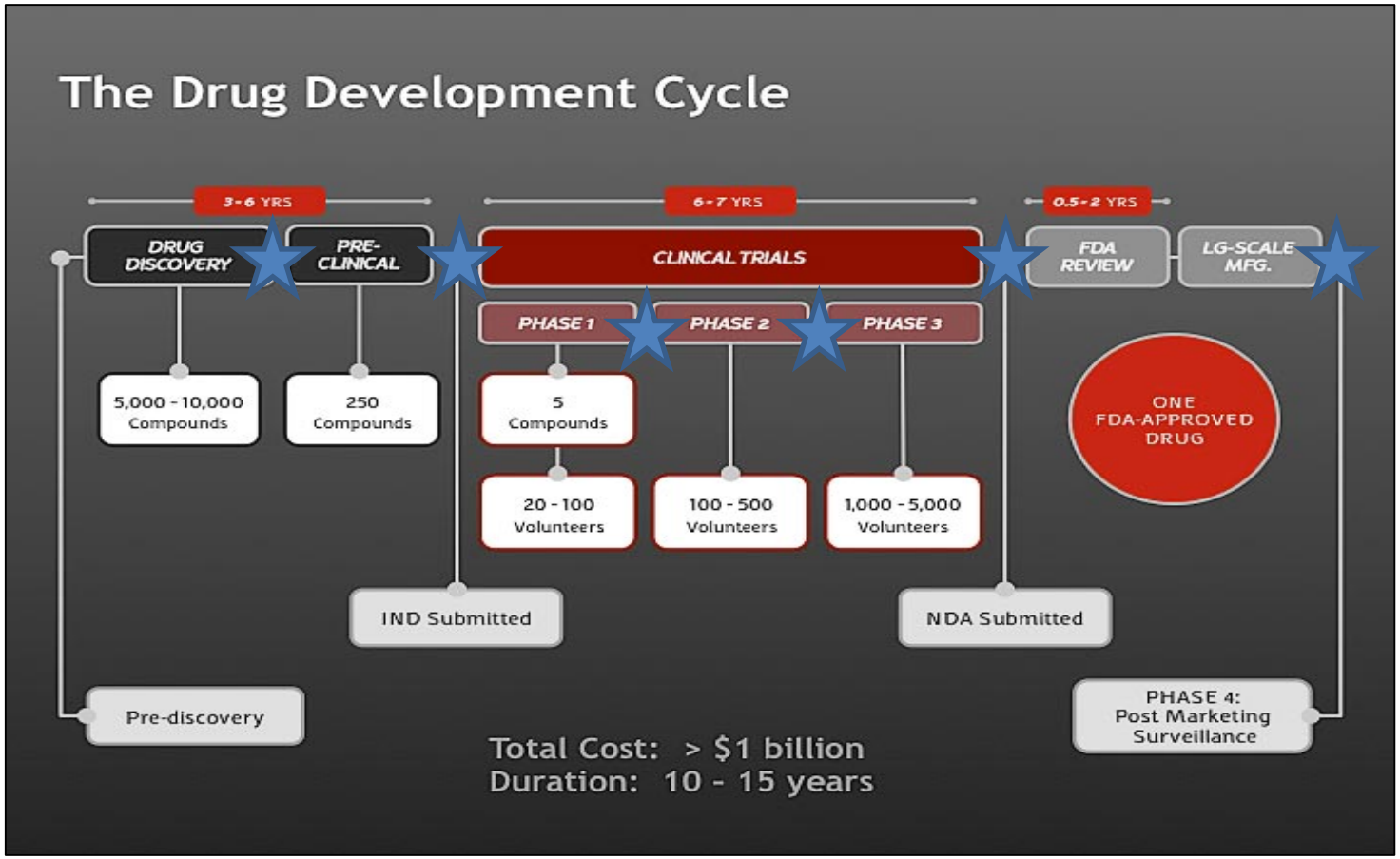
- *Project Risks*, associated with project management and people handling
- *Process Risks*, associated with technical issue during process execution

Technology Transfer – When ?

Technology Transfer – When?



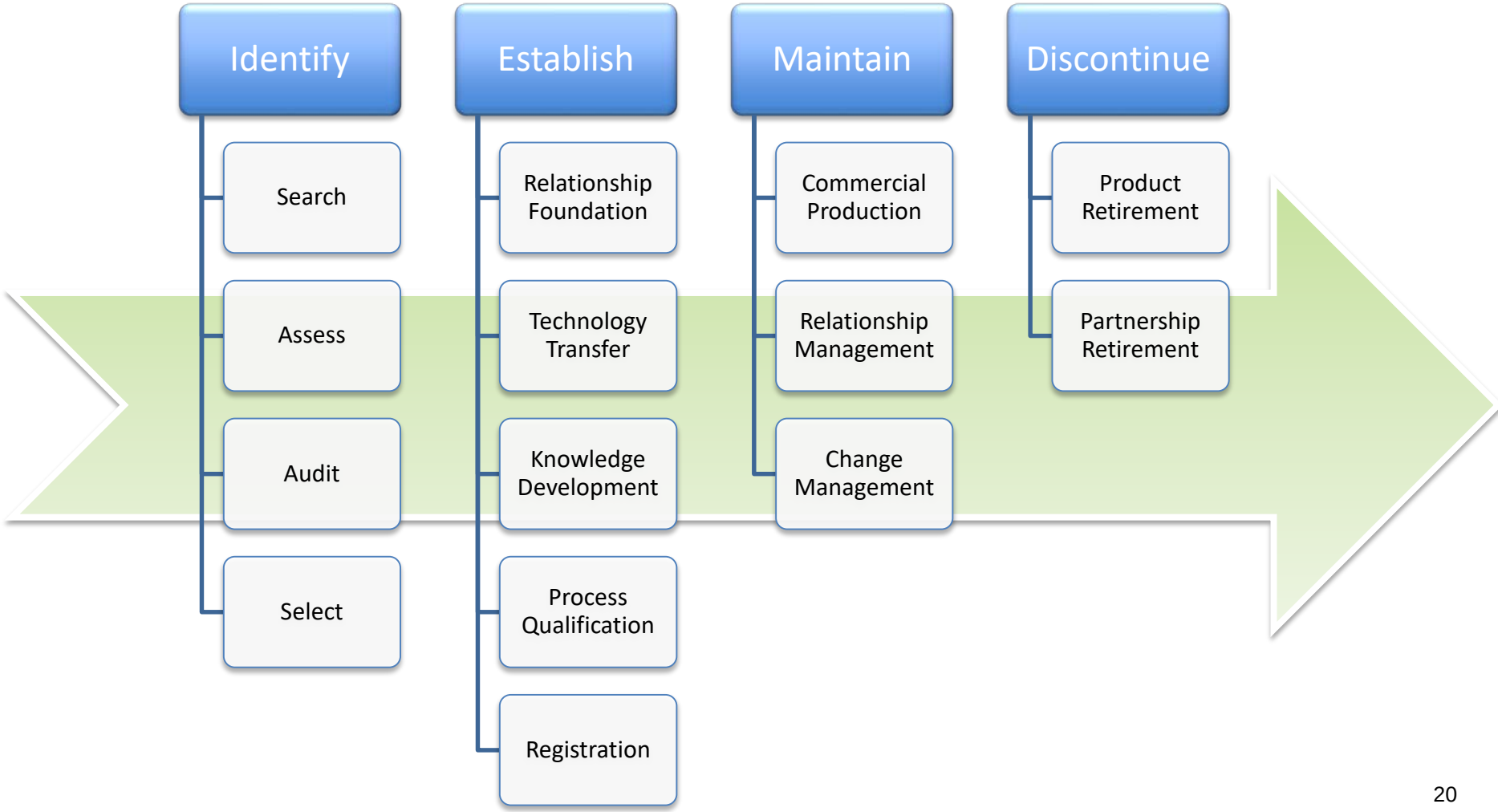
Technology Transfer – When?



Technology Transfer main concepts

Risk of Selection Partner!

Technology Transfer – When?



Technology Transfer – When?

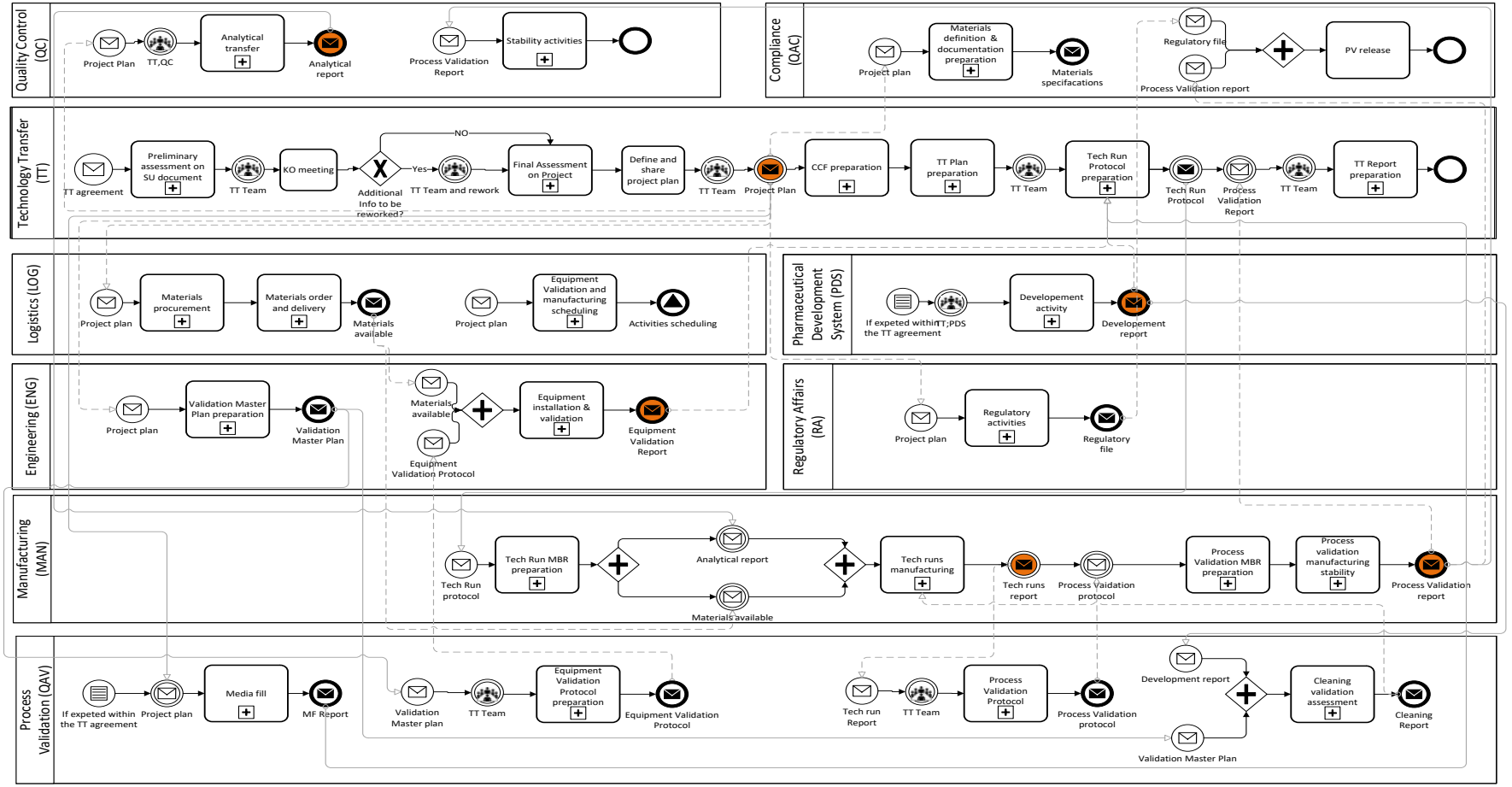
Different pharmaceutical Technology Transfer Project contexts can be managed; each with specific peculiarities; assuming the technology to be transferred is the drug manufacturing process, several possibilities arise:

- *Development to clinical phase TTP*
- *Clinical Phase to Commercialization TTP*
- *Commercial TTP*

- *Intra-company site to site TTP*
- *Inter-company site to site TTP*

Technology Transfer – Standard Project description

Technology Transfer main concepts



Technology Transfer main concepts

5 main steps!

1. Planning

a. Definition of Project Scope and Rationale and the overall project plan

b. Technology and Knowledge clearly stated

c. Delvierables defined

d. Control philosophy agreed

e. Risks evaluated and mitigation plan defined

Technology Transfer main concepts

5 main steps!

2. Process Readiness

a. Control and Achieve the readiness set for the poject

b. Each TT phase and milestones has its own readiness

c. Stage/Gate step along the project exeution

d. Process changes tracking and handling

e. Training and expertise challenge

Technology Transfer main concepts

5 main steps!

3. Implementation and Qualification

a. Facility modification

b. Equipment installation and modification

c. Analytical transfer

d. Cleaning and environmental monitoring

e. TT batches

f. Process Validation

Technology Transfer main concepts

5 main steps!

4. Licensing & Manufacturing

a. Regulatory submission

b. Monitoring of the manufacturing batches

Technology Transfer main concepts

5 main steps!

5. Project Closure

a. Continuous improvement

b. Lesson learned

Technology Transfer main concepts

3.4.2 Multidisciplinary Technology Transfer Project Team

Each pharmaceutical TTP requires the involvement of a well-trained, multidisciplinary team at both the SU and RU. The team needs such soft skills as leadership, effective communication, and pharmaceutical market access principles. The team also needs the following technical proficiencies to drive the team toward a positive outcome:

- Quality assurance
- Quality control
- Manufacturing
- Engineering
- Finance
- Maintenance
- Environment, health, and safety
- Research and development
- Regulatory affairs
- Legal issues
- Project management

Technology Transfer main concepts

The technology transfer protocol must establish the context for the TTP, including internal and external contextual factors and which risk-management tools to use. The external context might include competitive, financial, regulatory, legal, environmental, and cultural aspects. The internal context can involve company policies and procedures, systems, operational objectives, personnel training and knowledge, available resources, and culture.

All personnel with management roles in the transfer, including the two team leaders, should agree to and sign the project plan. A gate review by senior leadership (or sponsor) is used to make visible the plans and risks and provides approval to move to the next stage. In same cases project committee, which has a mainly consultant role, could be useful for the success of the project.

Take Away

- *Multidisciplinary Context*
- *Be always focus on Patient as this is our final «Client»*
- *Dynamic and challenging environemnt*
- *Two main Risks categories to be considered*

Technology Transfer – Project Risk ans Social Intelligence

Technology Transfer main concepts

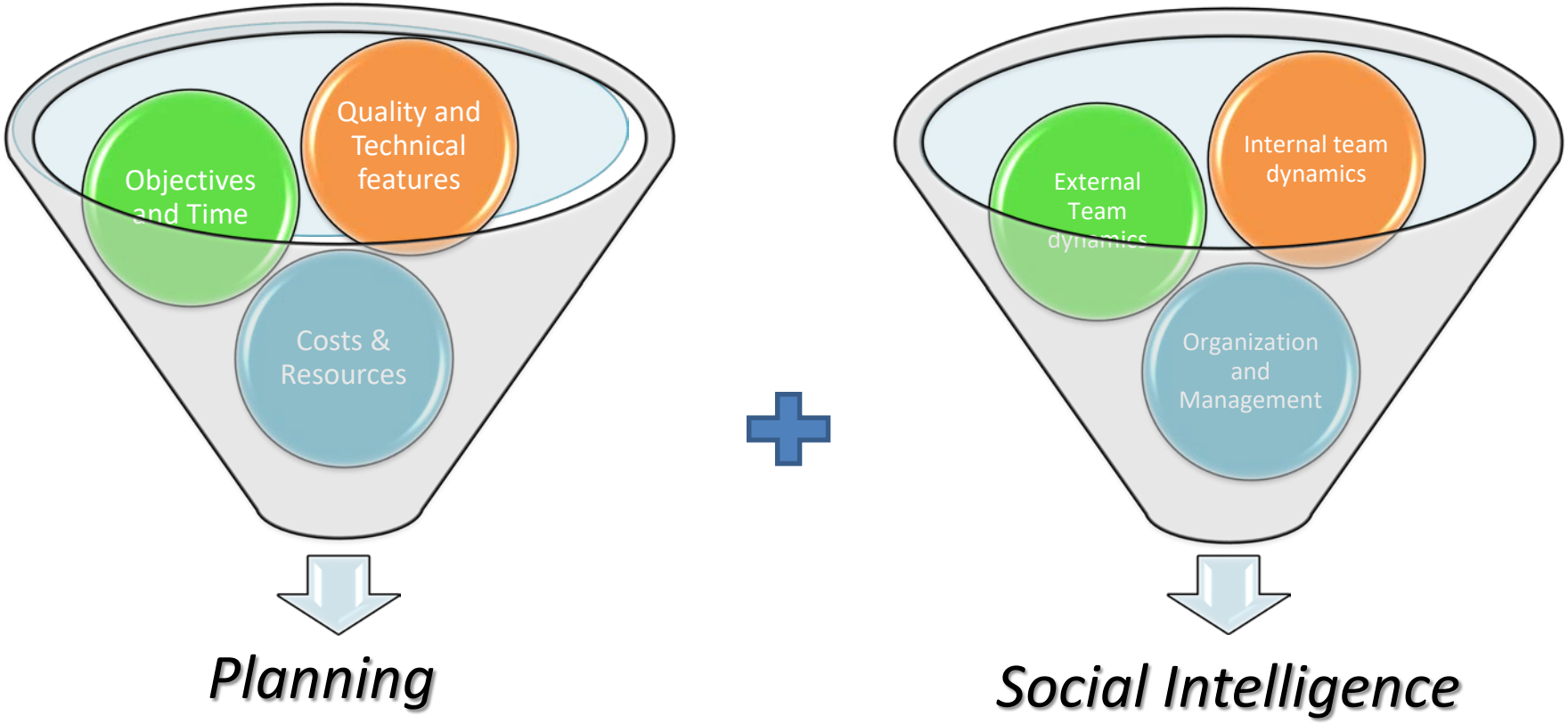
The Technology Transfer Project (TTP) is defined as a set of planned and controlled actions, based on well-defined acceptance criteria needed to transfer a technology from a sending unit (SU) to a receiving unit (RU).

Technology Transfer main concepts

Which are the main Project risks?

1. *Project Scope missed or misunderstood*
2. *Underestimating of new site/process impact on product attribute*
3. *Lack of product/ process understanding*
4. *Lack of communication*
5. *Lack of escalation process*
6. *Wrong extimation of time/resources/costs*
7. *Lack of engagement of Team members*
8. *Lack of performance monitoring during execution*

Technology Transfer main concepts

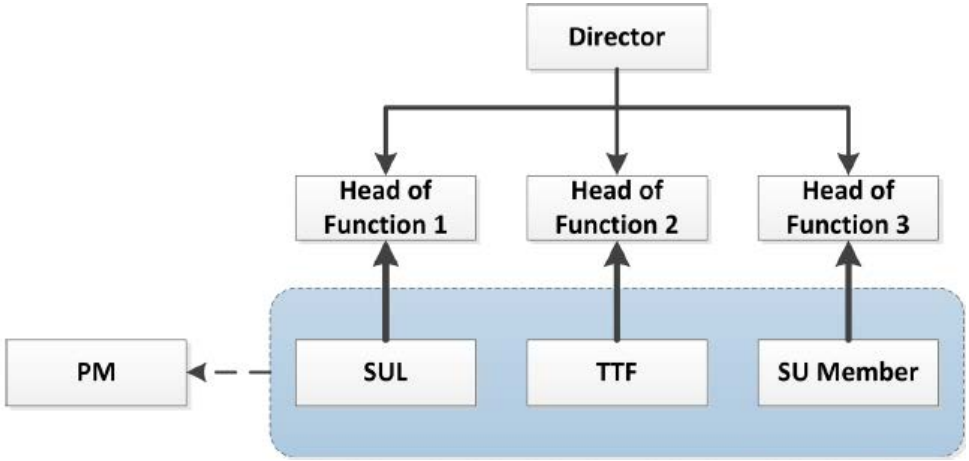


Technology Transfer main concepts

An organizational model that identifies the *people or groups responsible for each task* must be developed and identify which matters are subject to risk-based decisions.

Two main organizational model are seen in the pharma environemnt: *light matrix* and *hard functional*

Often a light matrix approach is preferred. The hierarchical relationship between a project figure (such as an SU leader, technology transfer department, or SU staff member) is maintained in a priority way (bold arrow). This organizational model minimizes the impact of the transfer activities on the routine activities of the units involved in the transfer



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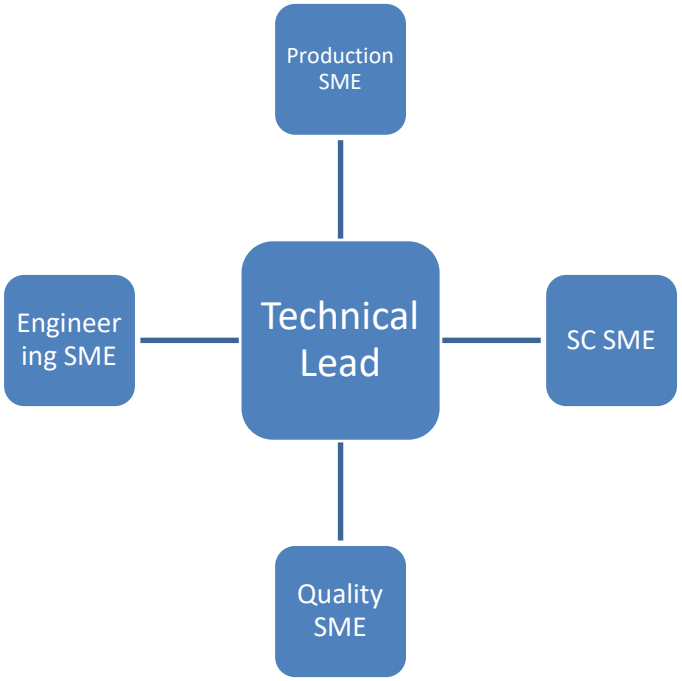
Technology Transfer main concepts

In a hard functional approach, a «Business Unit» is created around the technology transfer needs. Main SMEs report directly to the Technical Lead with a «silos» approach.

Typical of small companies with few TTs per year, it seems to be the best way to provide hard control of well defined and specific activities in a routine and standardized environment.



Technology Transfer main concepts

Each team in the RU and SU should be coordinated by a team leader who is the “owner” of the technology project and is responsible for implementing the technology at the RU or SU (e.g., manufacturing in the case of transfer of an industrial process).

The SU and RU technology team leaders should regularly update the project manager on the progress of the activities, budget use, potential technical or economic issues, and proposed corrective actions.

Technology Transfer main concepts

How to reduce Project Risk…

Technology Transfer main concepts

The success of a Technology Transfer is largely related to the **communication** skills and relationship of the Technology Transfer **team** members.

- Open communication between team members
- Effective and timely communication
- Direct communication between subject matter experts

The Technology Transfer leader facilitates meetings and communication between teams

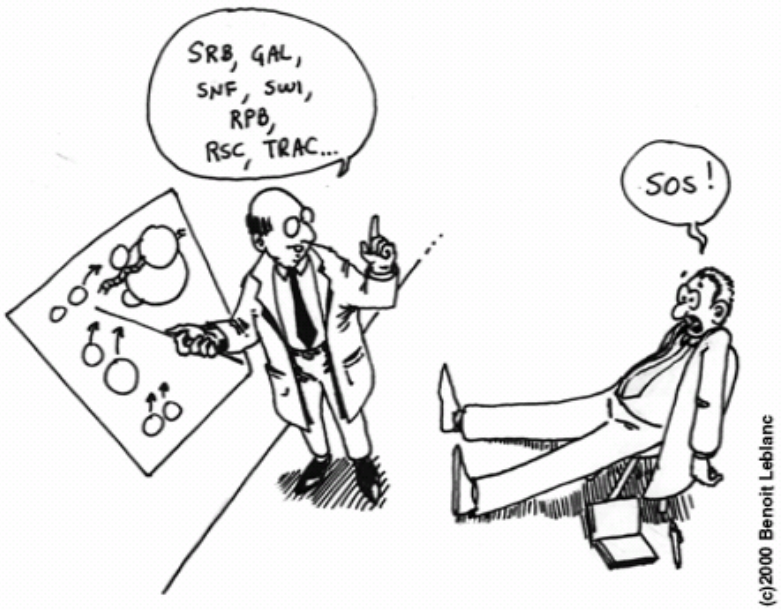
Technology Transfer main concepts

1) Weekly Technical Call

2) Weekly Project Management Call

3) Monthly Stirring Committee

4) Business Review meetings



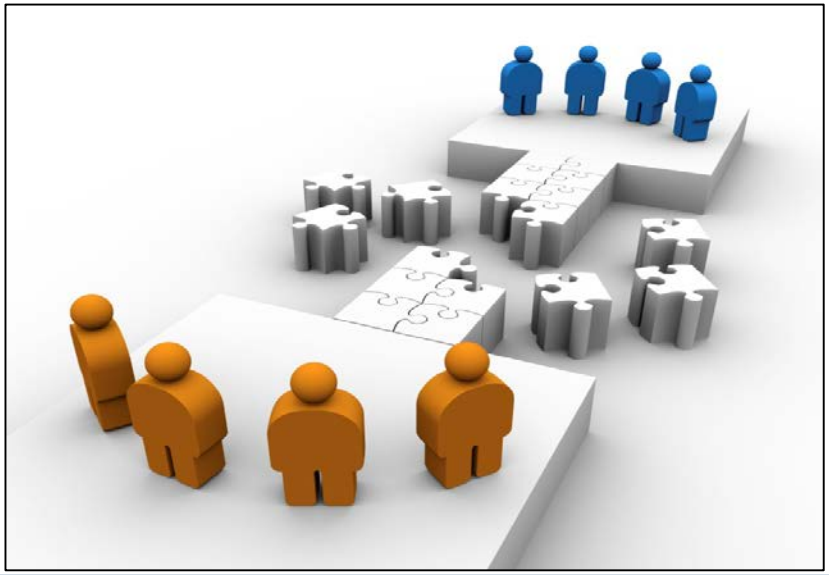
Cultural / organizational differences to be considered and assessed!

Technology Transfer main concepts

#	Meeting	Attendees	Frequency	Tentative Duration (min)	Purpose	Tool	Deliverables
1	Intra Company alignment	SU Leader RU Leader	Weekly/Biweekly based on project step	30	Alignment between Receiving Units and Sending Units in terms of evaluation/plans/actions	Project Dashboard	Meeting Minutes
2	Project Meeting	RU Leaders SU PM (or equivalent role)	Weekly	30	Discussion between PMs on Project status and execution, performance and communication between teams, main risks to be mitigated to avoid delay or stops	Project Dashboard Project Plan Risk Register	Meeting Minutes
3	Technical Meeting	RU Leader SU PM (or equivalent role) SMEs from parties based on agenda	Weekly	60	Detailed technical discussion on project tasks or issues	Technical Documents Project Plan Risk Register Project Dashboard	Meeting Minutes Risk Register updated Project Dashboard updated
4	Internal Sponsor meetings	SU Leader RU Leader RUSponsor	Biweekly	30	Update the project sponsor on Project status , SU relationship, RUteam performance and needs, risks and mitigation plan, issues and related action on going for resolution	Project Dashboard Risk Register	N/A
5	Project Sponsors Meetings	RUSponsor SU Sponsor RU Leader SU PM (or equivalent role)	Monthly	30	Update the SU/RUSponsors on the Project status, Relationship, Team performances, risks and needs	Project Dashboard Risk Register	Minutes

Technology Transfer main concepts

- Technical Skills
- Planning
- Multitasking and Organization
- Flexibility
- Troubleshooting
- Negotiation
- Goal oriented



Technology Transfer main concepts

- **TTPMs are the "*General Manager of the project*" for our clients**

- Take ownership of project/product opportunities and drive them **from early quotation stages to <u>manufacturing and routine supply</u>:**
  - Relationship management – **Key window for the sending unit into the receiving unit**
  - Relationship management – **Key and entrusted** by all the members of the TT team
  - Project / Opportunity **Cost Evaluation and Budget management**
  - Contract Negotiation and ongoing MSA maintenance
  - **Project Management – leading all company functions, Operations, Quality, Finance, Quotation group, Business development and Account executives.**
  - Financial Reporting – revenue forecasting

The TTPMs have a strong site technical knowledge linked with business acumen

Technology Transfer main concepts

Roles and Responsibilities….Clear Definition in the team, avoiding conflicts and putting in place a clear efficient way of executing the TT

Project Stage	SU	RU
Planning	Identify relevant documents	Implement SU-provided documents
Process Readiness	Transfer documents to RU	Organize validation and implementation plans
	Review document implementation at RU	Validate and implement the technology being transferred
	Train RU personnel	Train personnel
Implementation and Qualification	Support RU during validation, start up, and follow-up	Execute start up, evaluate results
	Support RU in failure and gaps evaluation after startup phase	Solve any failure or deviations occurred during startup phase
	Support RU during improvements identification and implementation	Identify potential improvements after start up data evaluation
Closure	Support and sponsor RU in the continuous verification phase after start up	Continuous verification and improvement plan set up

Technology Transfer main concepts

Role / Project Deliverable (or Activity)	Project Leadership									
	Technology Transfer (TT)	Business Managment (BM)	Quality Control (QC)	Quality Compliance (QAC)	Logistics (LOG)	Engineering & Equipment Validation (ENG)	Manufacturing (MAN)	Process & Cleaning Validation (QAV)	Regulatory Affairs (RA)	Pharmaceutical Development System (PDS)
Preliminary assessment	A/R	A/R	C	C	I	C	C	C	C	I/C
Meet the customer and verify information	A/R	A/R	I	I	I	C/I	I	I	C	I/C
Define and share the project plan	A/R	I/C	I	I	I	C/I	I	I	I	I
Change Control Form preparation	A/R	I/C	C	R/C	C	I	C	C	C	C
Technology Transfer Plan preparation	A/R	I/C	C	C	I	I	C/I	C/I	C	I
Tech run protocol preparation	A/R	I/C	C	I/C	I	I	C/I	C/R	I	I
Technology Transfer Report preparation	A/R	I/C	I	I	I	I	I	I	I	I
Analytical transfer	I/C	I	A/R	I/C	I	I	I	I	I	I
Stability Activities	I/C	I	A/R	I/C	I	I	I	I	I/C	I
Materials definition & documentation preparation	I/C	I/C	I	A/R	I	I/C	I/C	I/C	I	I
PV release	I/C	I/C	I	A/R	R	I/C	R	I/C	I/C	I
Materials Procurement	I/C	I/C	I	I	A	I/C	I	I		I
Materials Order and delivery	I/C	I/C	I	I	A	I/C	I	I		I
Equipment validation and manufacturing sheduling	I/C	I/C	I	I	R	A/R	I	I		I
Validation Master Plan	I/C	I	I	I	I	A	I/C	I	I	I
Equipment Installation and Validation	I/C	I	I	I	I/C	A	I/C	I	I/C	I
Tech run MBR preparation	I/C	I/C	I/C	I/C	I	I	A	I/C	I	I
Tech run manufacturing	I/C	I/C	I/C	I	R/C	I	A	I/C	I	I
Process Validation MBR preparation	I/C	I/C	I/C	I/C	I	I	A	C	I	I
Process Validation manufacturing stability	I/C	I/C	I/C	I	R/C	I	A	I	I	I
Regulatory activities	I/C	I	I	I	I	I	I	I	A	I
Development activities	I/C	I/C	I	I	I	I	I	I	I/C	A/R
Media Fill	I/C	I/C	C/R	I	R	I	R	A	I	I
Equipment Validation Protocol Preparation	I/C	I/C	I	I	I	A	I	I/C	I	I
Process Validation Protocol	I/C	I/C	C	I	I	I/C	C	A	I	I
Cleaning Validation assessment	I/C	I/C	C/R	I	I	I	C	A	I	I

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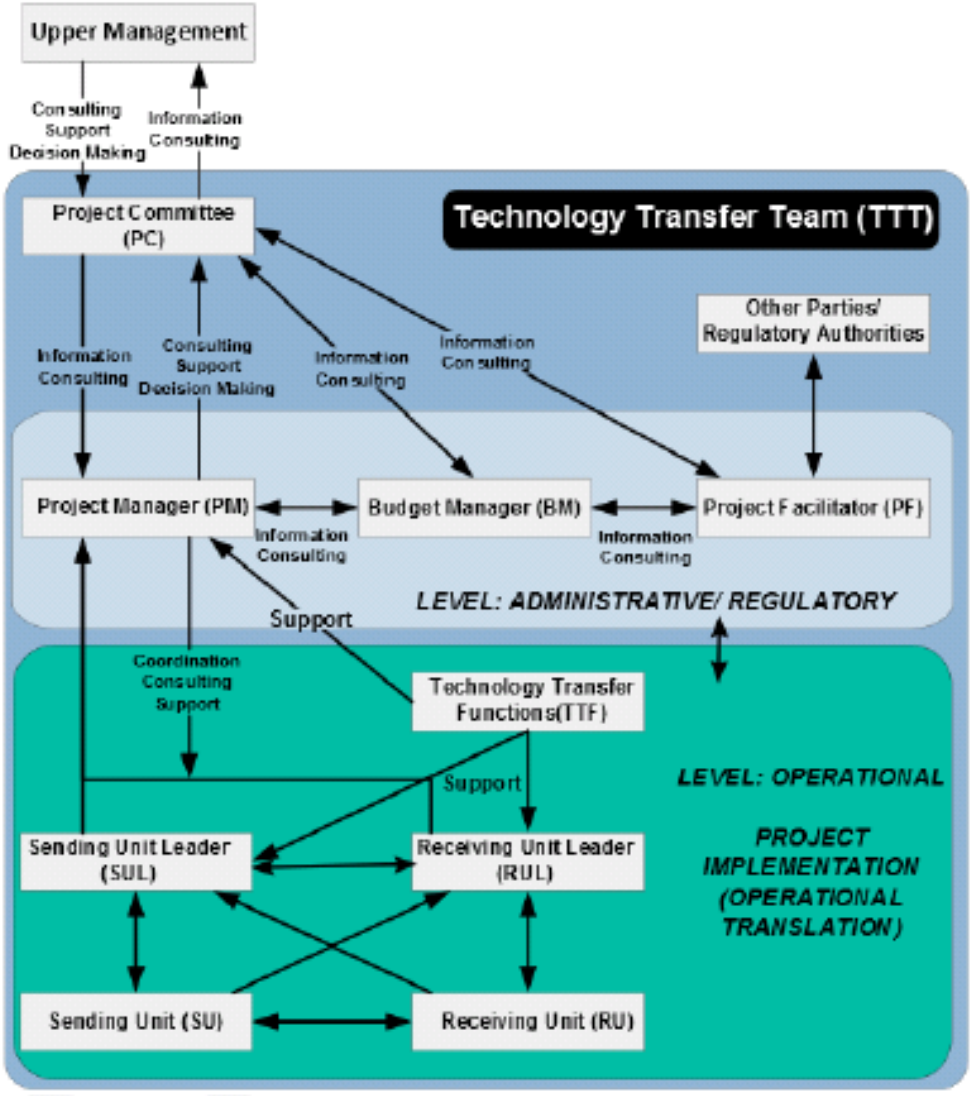
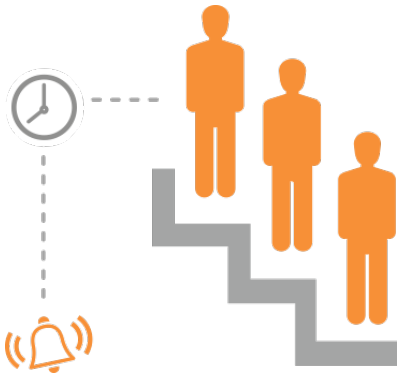
Technology Transfer main concepts



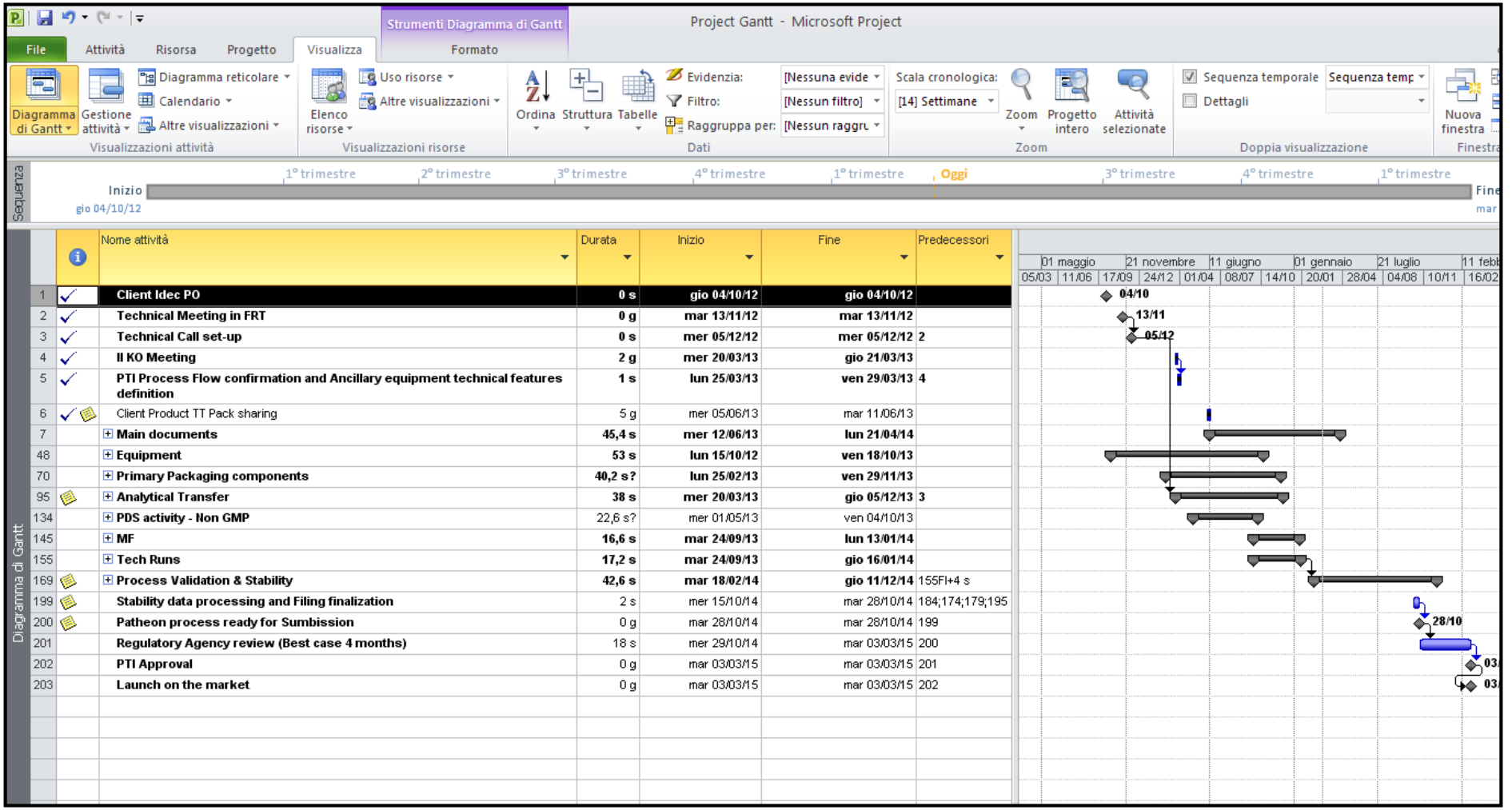


Technology Transfer main concepts

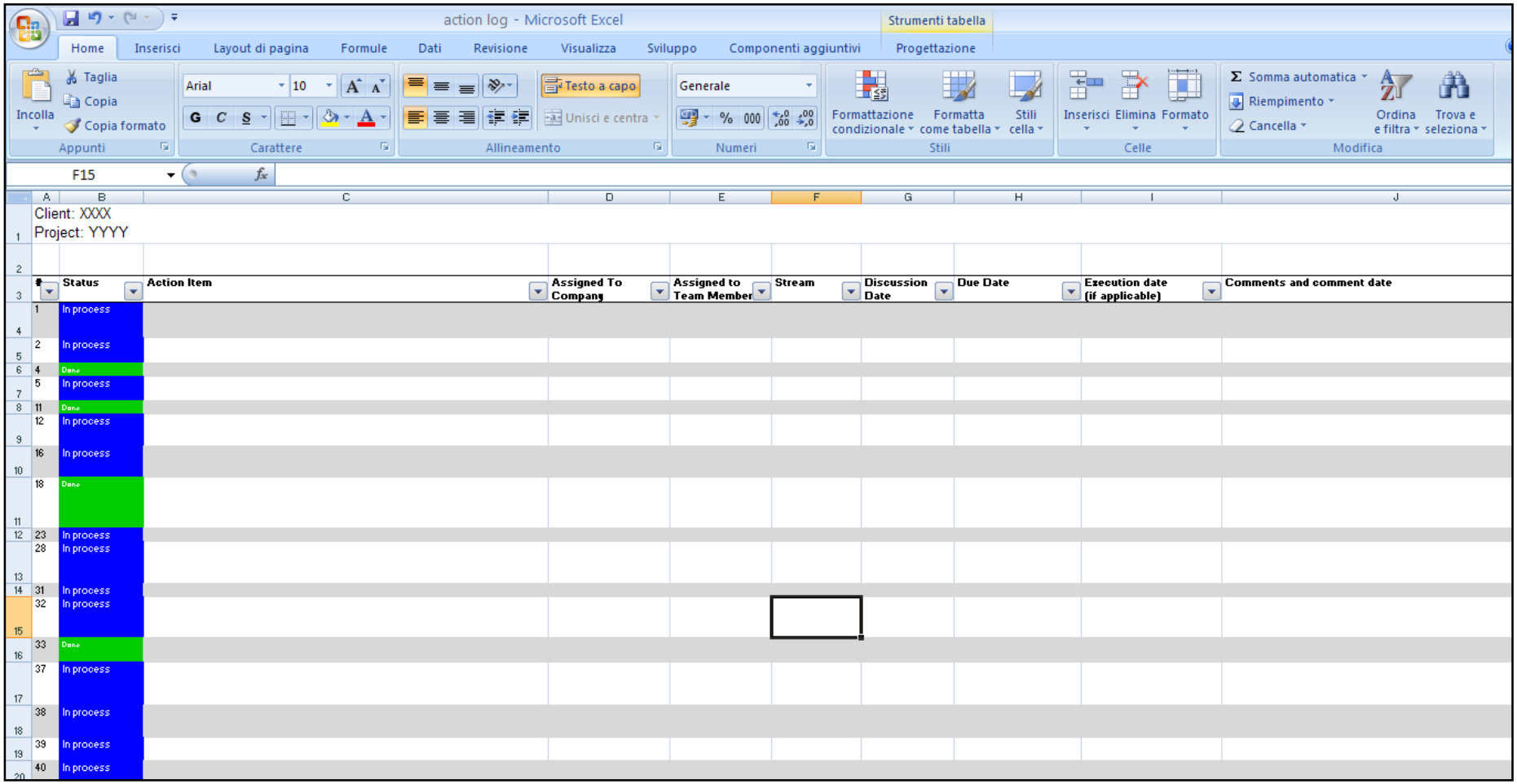
- Project Gantt
- Action List
- Decision List
- Risk Register
- Activities completion tracking

Define scope, plan, execute and track

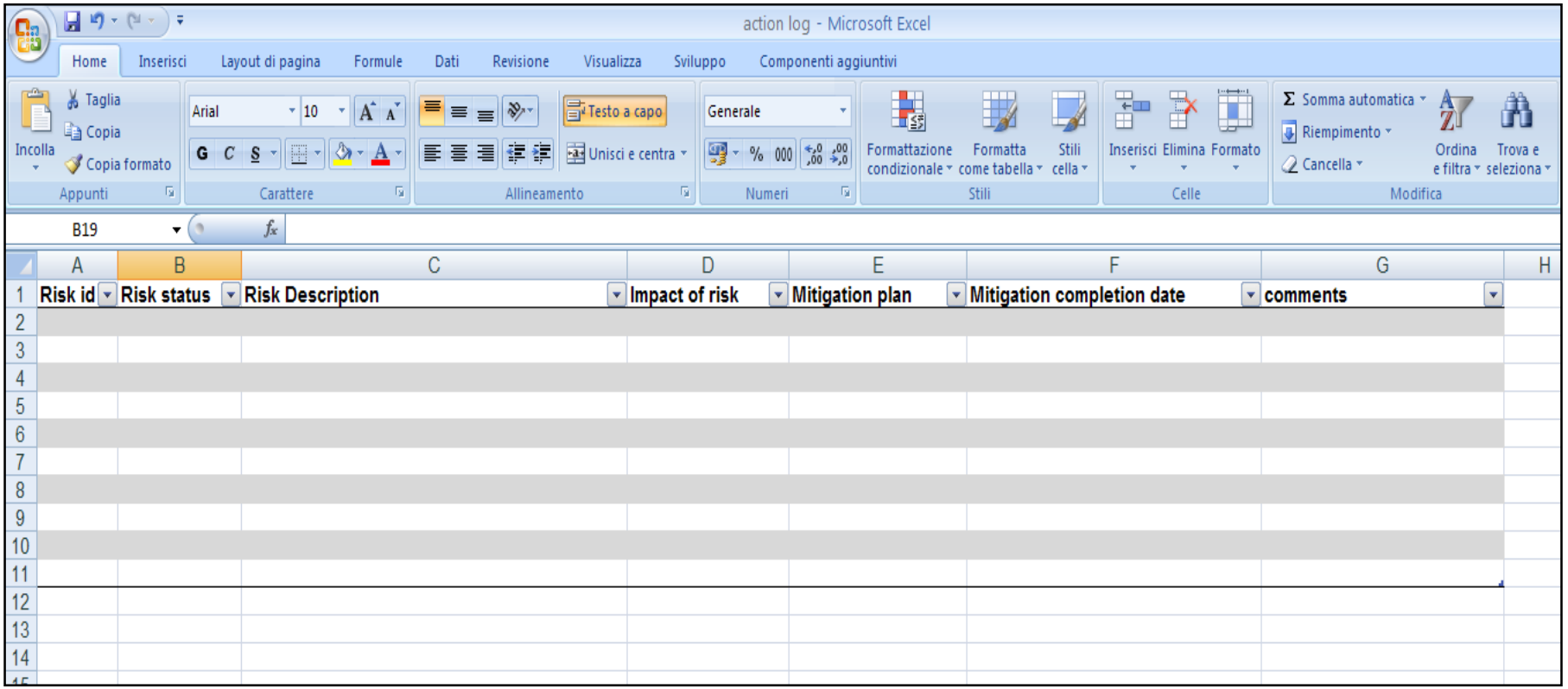
Technology Transfer main concepts



Technology Transfer main concepts



Technology Transfer main concepts



Risk id	Risk status	Risk Description	Impact of risk	Mitigation plan	Mitigation completion date	comments

Technology Transfer main concepts

Docs/Info/Topic	YES	NO	N/A	Is there any disalignment/issue to be solved? (Y/N)	Action List (in case of gaps in column F)
1.0 Environmental Health & Safety					
1.1 Complete EHS Questionnare					
1.2 MSDS for Drug Substance					
1.3 MSDS for Excipients					
1.4 Toxicity Data					
1.5 API exclusivity data (If Available)					
2.0 Materials					
2.1 Drug Substance					
2.1.1 Vendor Specification / CofA					
2.1.2 Sample of CofA, (Supplier/Client) including Bulk / Tap density and PSD data					
2.1.3 BSE/TSE Statement					
2.1.4 Residual Solvent Statement					
2.1.5 Letter Stating GMP status of manufacturer (if non-compendial)					
2.1.6 Import Routing Guide					
2.1.7 Memo to outline Micro Validation requirements or waiver					
2.1.8 Allergen letter (if applicable)					
2.1.9 API registration referential : CEP, DMF, scientific data)					
2.1.10 API Letter Stating Stability Data, including the requirement of templates during shipment.					
2.1.11 API supplier Audit report					
2.1.12 API supplier inspection					
2.1.13 API shipping container					
2.1.14 API packaging container (pictures)					
2.1.15 API critical handling information (e.i. light, moisture, oxygen, and/or heat sensitive, use of solvents)					
2.1.16 API shelf life					
2.1.17 API holding time, retest period					
2.2 Excipients					
2.2.1 Vendor Specification / CofA					
2.2.2 Sample of CofA (including bulk, tap density and PSD data)					
2.2.3 BSE/TSE Statement					
2.2.4 Residual Solvent Statement					
2.2.5 Letter Stating GMP status of manu					
2.1.6 Validated Test Methods (if non-co					
2.1.7 Memo to outline Micro Validation re					
2.1.8 Allergen letter (if applicable)					
2.3 Packaging Components					
2.3.1 Vendor Specification					

RACI Matrix

Project Deliverable (or Activity) \ Role	Project Leadership – Sending Unit	Project Leadership – Receiving Unit	Project Leadership – Sponsor
. Project Assessment			
Preparation of the Tech Pack	R *(and A within the SU)*	A	
Analysis of the Tech Pack and confirmation of its appropriateness	I	R/A	
Sharing previous Project Gantt	R	A	
Previous lesson learnt sharing (process product management / Client management)	R	A	
Set up and handle an appropriate communication plan with SU	I	R/A	I
Set up and handle an appropriate communication plan with Client	I	R/A	C
Set up appropriate escalation process	I	R/A	C
Project Team and project governance definition	I	R/A	I
Client/Contract and CoS management		R/A	I
Set up an appropriate reporting process to upper management		R/A	C
. Project Planning			
Overall Technical Assessment preparation		R/A	
		A	
		R/A	
		A	
		R/A	I
		R/A	I
		A	
		R/A	
		A	

#	Meeting	Attendees	Frequency	Tentative Duration (min)	Purpose	Tool	Deliverables
1	Intra Company alignment	SU Leader RU Leader	Weekly/Biweekly based on project step	30	Alignment between Receiving Units and Sending Units in terms of evaluation/plans/actions	Project Dashboard	Meeting Minutes
2	Project Meeting	RU Leaders Client PM (or equivalent role)	Weekly	30	Discussion between PMs on Project status and execution, performance and communication between teams, main risks to be mitigated to avoid delay or stops	Project Dashboard Project Plan Risk Register	Meeting Minutes
3	Technical Meeting	RU Leader Client PM (or equivalent role) SMEs from parties based on agenda	Weekly	60	Detailed technical discussion on project tasks or issues	Technical Documents Project Plan Risk Register Project Dashboard	Meeting Minutes Risk Register updated Project Dashboard updated
4	Internal Sponsor meetings	SU Leader RU Leader Patheon Sponsor	Biweekly	30	Update the project sponsor on Project status , Client relationship, Patheon team performance and needs, risks and mitigation plan, issues and related action on going for resolution	Project Dashboard Risk Register	N/A
5	Project Sponsors Meetings	Patheon Sponsor Client Sponsor RU Leader Client PM (or equivalent role)	Monthly	30	Update the Client/Patheon Sponsors on the Project status, Relationship, Team performances, risks and needs	Project Dashboard Risk Register	Minutes

Technology Transfer main concepts

Company Name

Projects KPI - Schedule Adherence

KPI in percentage %

Client	Product	Stage	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL	Launch Date
		TT	N/A	100	N/A	0	25	0	N/A	N/A	N/A				25	March-17
		Registration	0	100	N/A	N/A	N/A	100	N/A	33	N/A				50	January-18
		TT	100	0	0	N/A	0	0	N/A	N/A	N/A				14	TBD
		TT	N/A	100	100	0	40	0	N/A	0	0				33	November-17
		Development	100	N/A	100	0	50	50	0	N/A	N/A				40	July-18
		TT	N/A	N/A	N/A	N/A	50	100	100	N/A	50				67	September-19
		TT	N/A	N/A	100	N/A	67	100	100	100	67				83	August-18
		Development	N/A	100	100	100	100	100	100	N/A	N/A				100	December-19
		TT	100	100	100	100	100	100	0	67	100				75	September-16
		TT	N/A	100	N/A	N/A	14	0	0	N/A	100				20	November-17
		TT	N/A	N/A	N/A	N/A	N/A	0	0	N/A	N/A				0	December-17
		TT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				0	January-18
		TT	N/A	N/A	100	N/A	20	N/A	N/A	N/A	25				30	March-18
		Com - New API	N/A	100	100	N/A	N/A	N/A	N/A	100	100				100	Commercial
	Site Total		75	90	91	38	40	52	17	56	56				50	

Measurement	Color Code	Range
Red		Less Than 90%
Yellow		90% - 94%
Green		Over 95%

Technology Transfer main concepts

Company Name

Projects KPI - Right the First Time (RFT)

KPI in percentage %

Client	Product	Stage	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL
		TT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		Com - New API	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		Registration	N/A	N/A	N/A	N/A	N/A	92	N/A	N/A	N/A				92
		TT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		TT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		Development	100	N/A	N/A	N/A	N/A	100	N/A	N/A	N/A				100
		TT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		TT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		Development	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		TT	N/A	N/A	N/A	N/A	N/A	0	N/A	N/A	100				0
		TT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		TT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A				N/A
		Com - New API	N/A	N/A	100	N/A	N/A	N/A	N/A	N/A	N/A				100
	Site Total		100	N/A	100	N/A	N/A	88	N/A	N/A	100				90

Measurement	Color Code	Range
Red		Less Than 90%
Yellow		90% - 94%
Green		Over 95%

Technology Transfer – Risk Assessment

Technology Transfer – Risk Management

Risk

- combination of the probability of occurrence of harm and the severity of that harm

Quality Risk Management

- Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.

Risk reduction

- processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level.

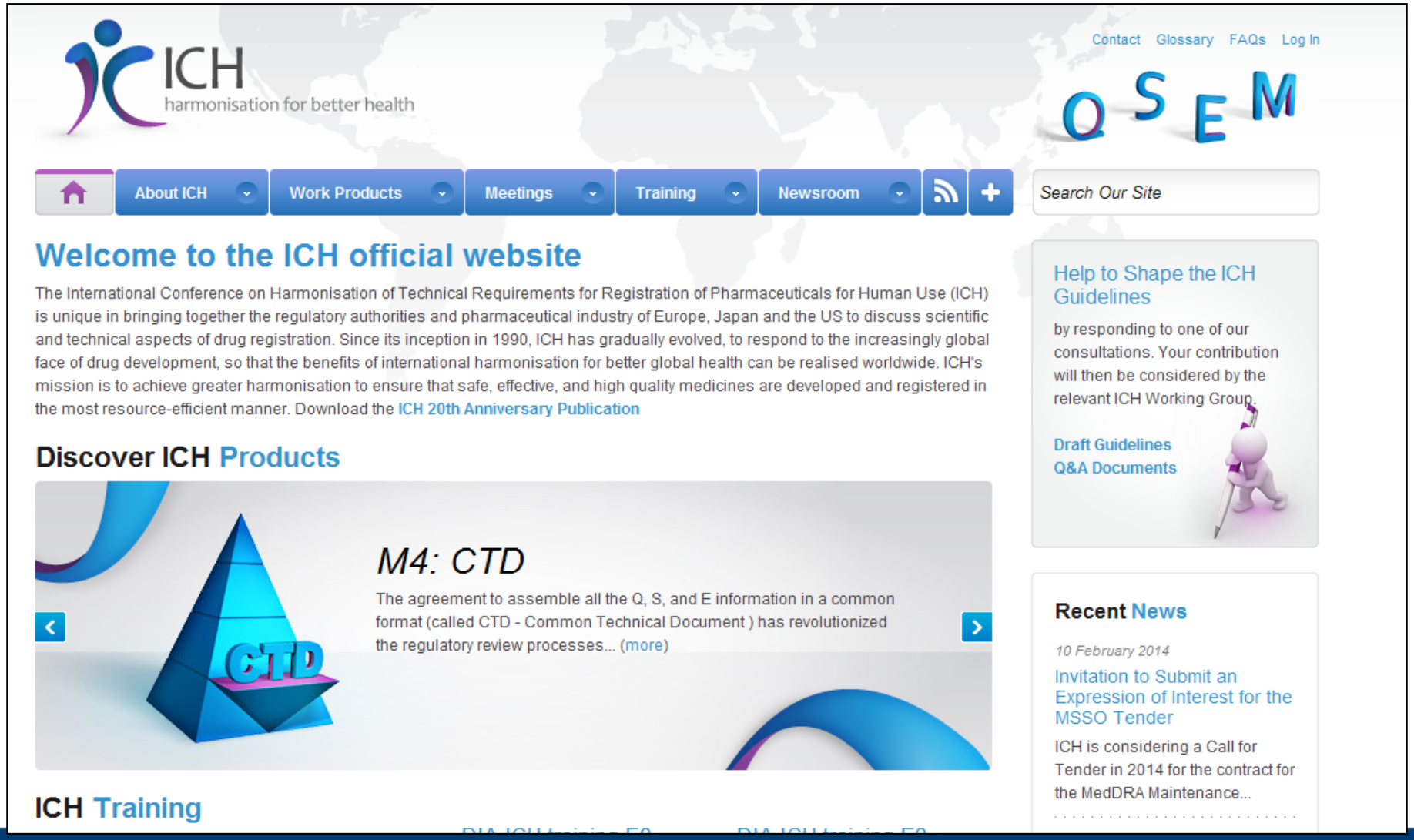
Risk acceptance

- formal decision to accept the residual risk or a passive decision in which residual risks are not specified

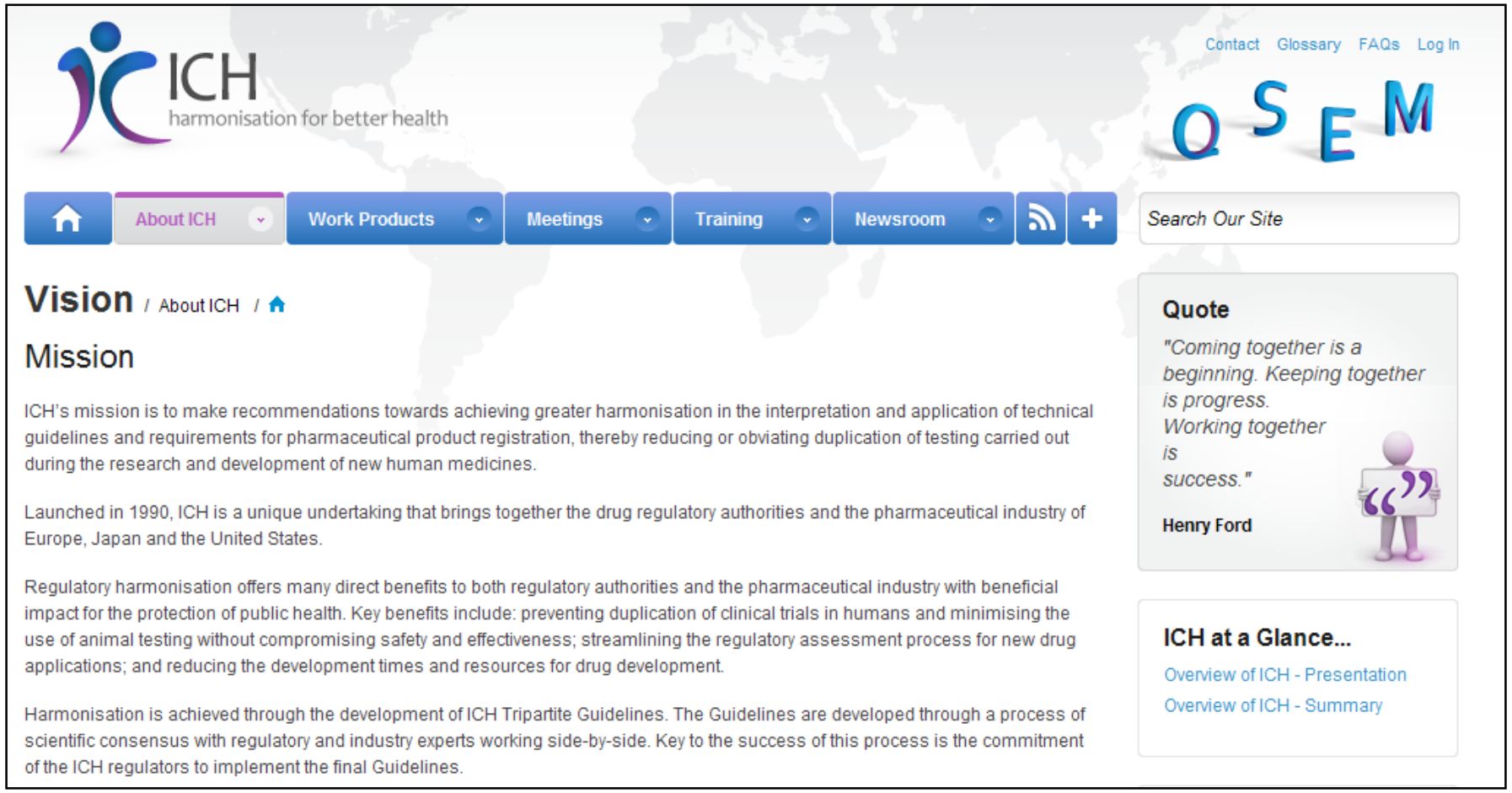
Risk communication

- sharing of information about risk and risk management between the decision makers and others

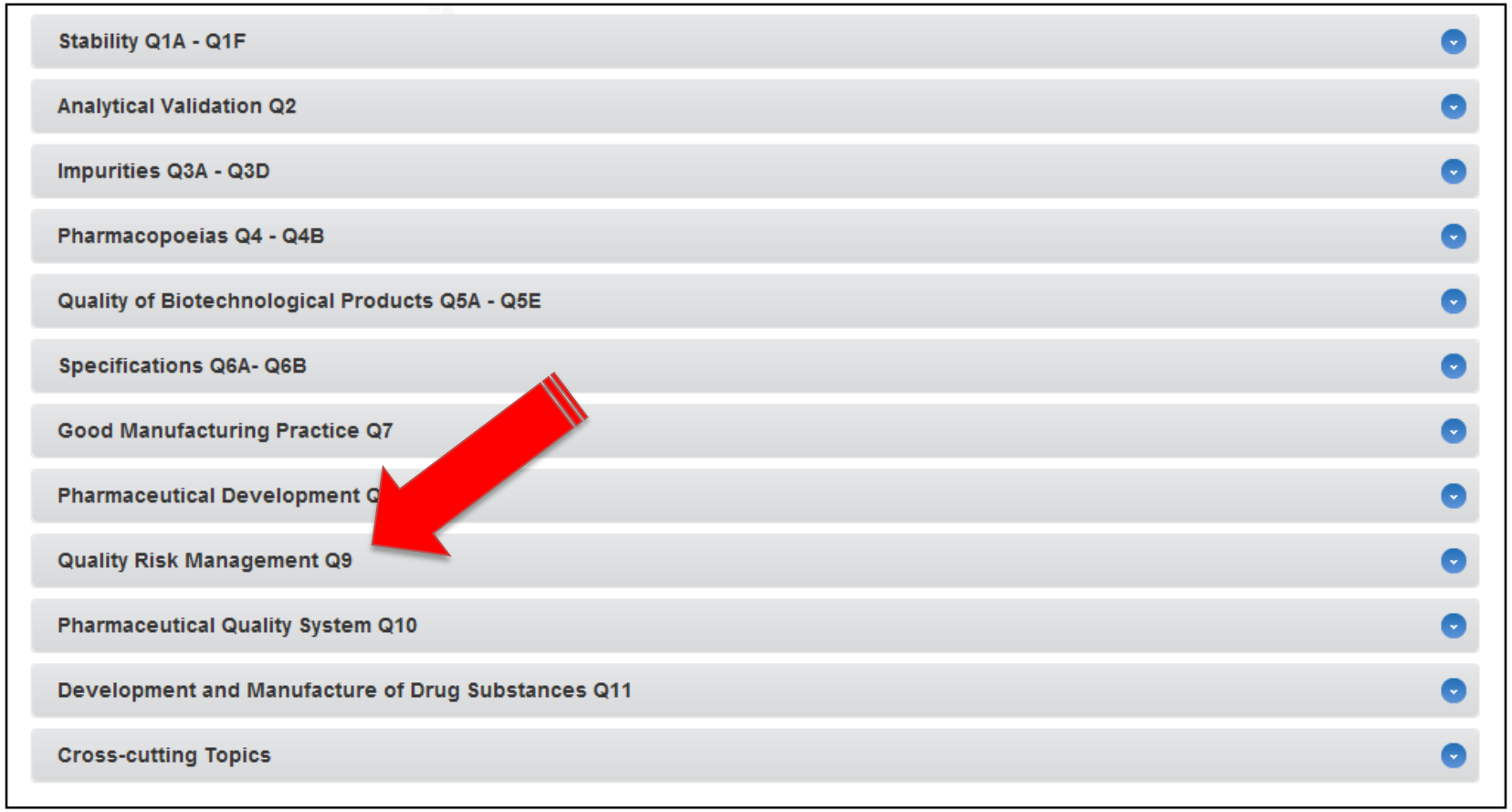
ICH & Risk - http://www.ich.org/



ICH & Risk - http://www.ich.org/



ICH & Risk - http://www.ich.org/



ICH & Risk - http://www.ich.org/

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.

In relation to pharmaceuticals, although there are a variety of stakeholders, including medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies.

ICH & Risk - http://www.ich.org/

Two primary principles of quality risk management are:

• The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient;

• The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

ICH & Risk - http://www.ich.org/

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics, and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

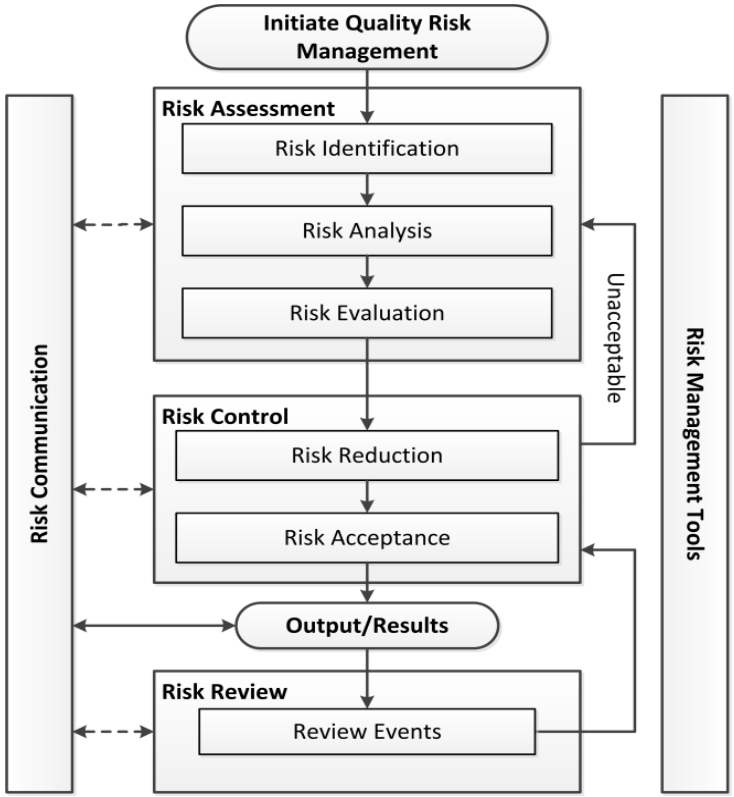
Decision makers should

• take responsibility for coordinating quality risk management across various functions and departments of their organization and

• ensure that a quality risk management

ICH & Risk - http://www.ich.org/

The quality risk management (QRM) is “a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.”



Technology Transfer – Risk Management

Risks of Technology Transfer

- Often, poor attention to its objectives (e.g., too tight or too broad process specifications) destines a TTP for failure. Technology transfer can affect drugs and patients. Consequently, in all technology transfer activities that a project team designs and executes, the team needs to keep in mind the scope of the technology being managed and the potential impact of technology transfer failure.

- Some common risks are:
  - Lack of information
  - Objective that is not clear (or clearly defined) or not properly communicated and/or shared
  - Poor preliminary assessment with lack of changes identification
  - No or poor assessment of the effects of changes to the objective
  - Lack of project management

Technology Transfer – Risk Management

❑The selection of a risk management approach should be done at the beginning and applied along the TTP. This approach will facilitate decision-making at different points throughout the TTP while ensuring that all activities are performed in a manner that protects patient safety.

❑To realize the utmost benefit from QRM, companies must adapt their culture, systems, and procedures. They must shift from a risk-averse to a risk-aware culture by creating procedures and tools that enable individuals to apply benefits from QRM to the TTP

Technology Transfer – Risk Management

Stage Gate	Strategy	Analytical and Quality Control Testing	Regulatory	Process	Facilities/ Engineering	Risk Management and Components
1 Planning	Perform preliminary risk assessment prior to beginning late-phase development using risk ranking and/or preliminary hazards analysis approach.					
2 Process Readiness	Update preliminary risk assessment (transition to PHA)	Update risk assessment (transition to PHA) for SU and RU readiness for AMT	Risk mitigation through SLA and quality agreement between SU and RU	Update risk assessment (transition to PHA) for manufacturability of late-phase development process	Update risk assessment (transition to HAZOP) for operating process at manufacturing site	Update risk assessment (transition to PHA) for RMs/ components, including assessment of the impact of any changes in the suppliers or manufacturing sites of the RMs
3 TTP implementation and Qualification	Review and update risk assessment/PHA from stage gate 2 if necessary. Mitigate identified high risks.					
4 Licensure & Manufacturing	Convert PHA risk assessment from stage gate 3 to FMEA/FMECA risk assessment, including re-evaluation of risk ranking after risk mitigation plan implementation					
	Update risk assessment from stage gate 4 for commercial process	Complete risk assessment for SU and RU readiness for AMT	Risk mitigation through SLA and quality agreement between SU and RU	Update risk assessment for manufacturability of commercial process	Update risk assessment (HAZOP) for operating process at commercial site	Update risk assessment for RMs/components, including assessment of the impact of any changes in the suppliers or manufacturing sites of the RMs

Technology Transfer – Risk Management

As applied to Technology Transfer (TT), this activity, done at the beginning of the project, can detect the most likely potential causes of technical failures and allow planning for mitigating those risks.

Following ICH Q9, the risk can be estimated based a combination of three main factors:

- Severity (S)
- Occurrence (O)
- Detection (D)

Technology Transfer – Risk Management

Severity considers the potential impact on the quality attributes of the product and hence on patient health.

It can be rate based on the table below

Severity	Risk Classification	Value
No impact on the product's quality attributes or on patient health	Negligible	1
Moderate impact on product's quality attributes and on patient health	Moderate	2
Severe impact on product's quality attributes and on patient health	Critical	3

Technology Transfer – Risk Management

The occurrence factor is defined as the frequency of occurrence of the event. In a TTP phase, occurrence is based on the combination of the SU knowledge of the product and the RU experience on process.

It can be rate based on the table below

Occurence	Risk Classification	Value
Highly improbable or impossible that the negative event occur	Remote	1
Some possibility that the negative event will occur	Medium	2
Highly probable or certain that the negative event will occur	High	3

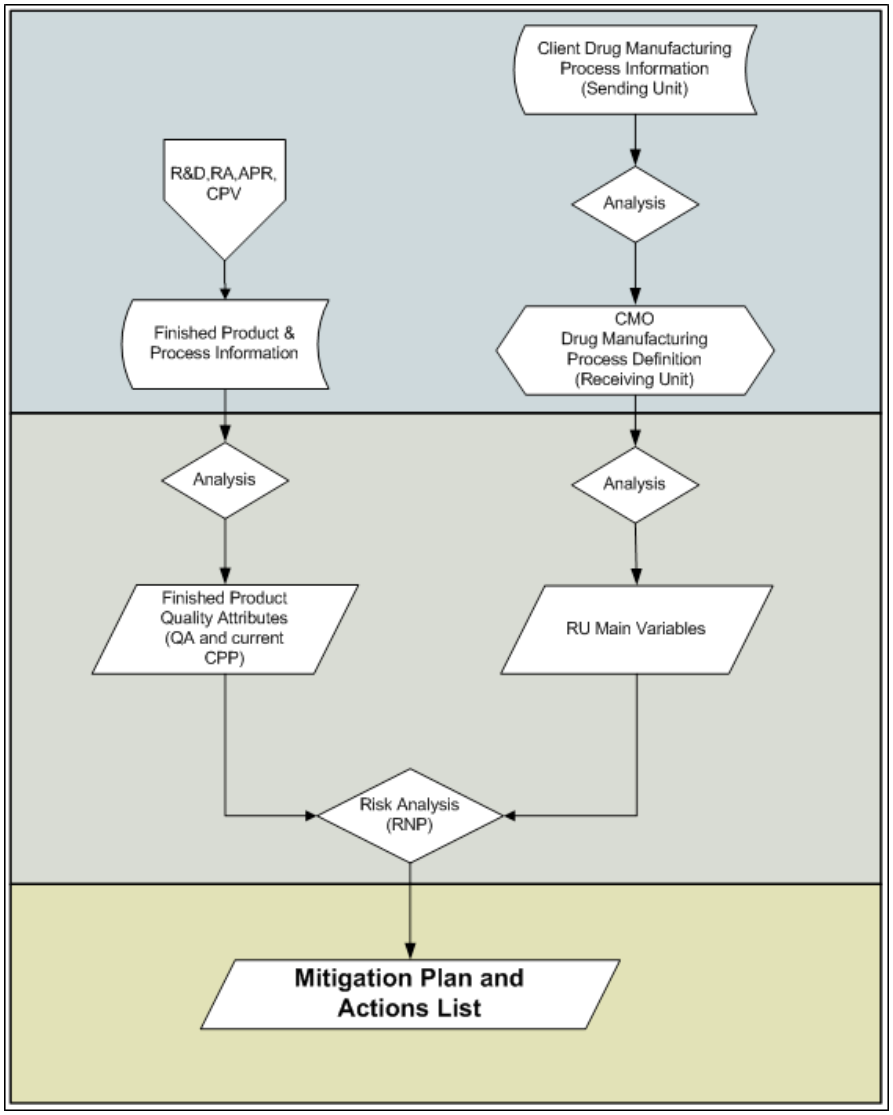
Technology Transfer – Risk Management

The detection factor is defined as the probability of detecting the events if they occur, based on the control system in place.

It can be rate based on the table below

Probability	Risk Classification	Value
Highly probable or certain that the negative event will be detected by the control system in place	Remote	1
Some possibility that the negative event will be not detected by the control system in place	Medium	2
Highly improbable or impossible that the negative event will be detected by the control system in place	High	3

Technology Transfer RA Approach



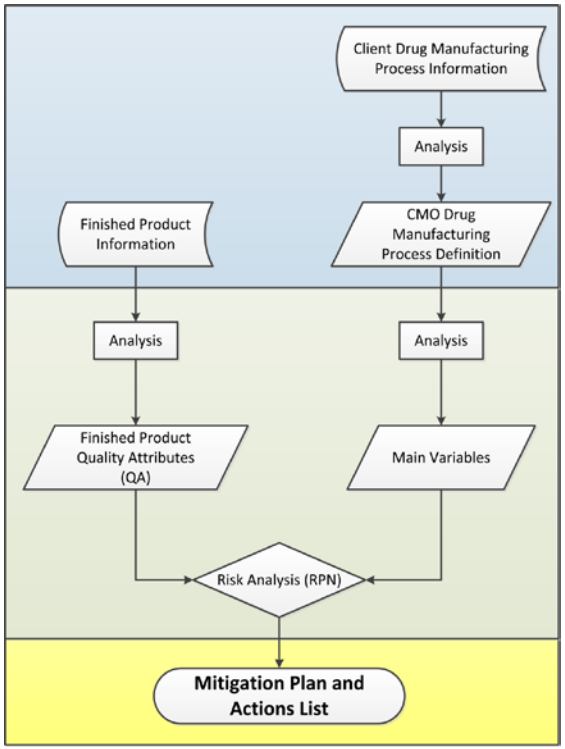
Data collection

Data evaluation

Data use

Technology Transfer RA Approach

Our Risk Assessment and Mitigation approach is based on several Source of information, linked to create a TT Starting Story



Source 1 – Definition of the Main Process Variables of the product (SU -> RU) *(examples below)*

List of main items considered for the evaluation	Relative Variables		
Process	Mixing Holding Compounding Grade C filtration Grade A filtration	Filling Stoppering Crimping Solution transfer Steam terminal sterilization	Identification Wrapping Visual inspection Secondary packaging Line cleaning
Primary packaging and GMP materials	Stoppers Vials Seals	Filters Disposable tubes Disposable bag	Fixed tube Gasket
API and excipient attributes	API pH API appearance	API density API osmolality	Excipient attributes

Source 2 – Definition of the Quality Attributes (RU) *(examples below)*

Quality Attribute		
Appearance	pH	Volume in container
Identity	Density 20°C	Cosmetic appearance
Assay	Osmolality	Sterility
Impurity	Particle matter	Endotoxins

Technology Transfer RA Approach

Risk Assessment and Mitigation Approach:

- is part of part of Company DNA, therefore application is a must for all our TTs and during the whole project lifecycle;
- Has to be in line with the current regulatory guidance, GMP and based on scientific sound
- Has to be managed by appropriate flexible, robust and efficient tools
- Is a multifactorial exercise that takes in considerations internal and external variables of the project/process/product/lines
- Provides a clear path forward starting with QbD and development (where necessary) and ending with a reproducible, efficient and in quality market supply

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
Primary Packaging & GMP materials	Stoppers	Impurity	An impurity from the stopper can modify the solution chemical profile	3	2	3	18	The stopper components have been chosen by the SU during the development studies. The same stoppers will be used to guarantee no anomalous interaction with stopper coating and rubber. Stability data were collected by the SU; no interaction issues were reported to RU.
			The coating material can modify the chemical solution profile	3	2	3	18	
		Appearance	Substances released from the stopper or from the coating can induce flocculation or coagulation events in the solution	3	2	1	6	
			Substances released from the stopper or from the coating can modify the appearance of the solution	3	2	1	6	
		Sterility	The bioburden of the stopper can impact the effectiveness of currently used and validated sterility cycles	3	1	3	9	A risk assessment will be done to compare the several stoppers currently used in RU with the SU stoppers, to evaluate the possibility to use a sterilization cycle already validated. In the case in which no comparable stoppers are found, a new stopper sterilization cycle will be validated.
		Particle Matter	Release from the stopper may impact the particle matter profile of the solution	3	2	3	18	A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected.
	Vials	Impurity	Impurities released from the glass can impact the solution profile	3	2	3	18	Type I glass, USP/EP grade will be used. The validation batches produced will be analyzed via stability study. All release tests will be repeated regularly during the stability program to confirm no anomalous changes to the system profile.
			Leachables and extractables from the glass can modify the chemical profile of the solution	3	2	3	18	
		Appearance	Leachables, extractables, and ions can induce flocculation or coagulation of the system	3	2	1	6	
		Cosmetic Appearance	Vials of finished product can be rejected for cosmetic defects	2	2	1	4	*No further actions are needed.* Incoming statistical checks will be done on each lot of vials prior to use. An agreement with the supplier is in place that defines appropriate AQLs for each defect. These AQLs are in line with the cosmetic requirements received by the SU.

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	Mixing, Compounding	pH	Dissolution time insufficient for complete dissolution and an homogenous system	3	3	1	9	During the Performance Qualification, the mixing device of the tank used in the RU will be challenged. Mixing studies will be agreed with the SU and performed during the engineering batch. The User Requirements of the RU tank have properly defined the mixing needs based on the characteristics of the colloidal system. The initial evaluation and information sharing between SU, RU and the disposable technology Supplier have identified the appropriate mixing device. The PQ challenge of the mixing system will include appropriate tests suggested by the supplier/owner of the technology
		Osmolality	Dissolution speed insufficient for complete dissolution and an homogenous system	3	3	1	9	
		Appearance	Mixing system not appropriate to guarantee uniform batch mixing	3	3	3	27	
		Density	Temperature of the system out of range specified by the SU	2	1	1	2	*No further action needed.* The colloidal system is not sensitive to temperature. The RU WFI loop cooling and temperature control system will guarantee a 15-25°C range.
			Sampling mode device impact on the analysis results	3	2	2	12	The sampling system will be made of pharmaceutical grade glass. The SU have collected data on compatibility and the solution is declared compatible with glass devices
		Sterility	Preparation time impact on bioburden level of the final compounded solution	3	2	2	12	Validation activities will include hold time challenges according to a dedicated protocol. Chemical characteristics and microbiological attributes of the solution will be analyzed.
		Particulate matter	Particle release from disposable hoses may impact the particulate matter profile	3	2	3	18	Use Silicon, Pt-cured, disposable hose certified for pharmaceutical use for solution transfer. To address particle release from the hoses used in Grade C, filter the solution 2 times before filling (0.45 um + 0.22/0.2 um in grade C area and 0.22/0.2 um in grade A area). Regarding the particle release from the hoses used on the filling machine, a final 100% visual inspection will be done. Vials with a particle matter defect will be rejected.

Technology Transfer RA Approach

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	Mixing and compounding	pH	Dissolution speed is insufficient for complete dissolution and a homogenous system.	3	3	1	9	During the performance qualification, the mixing device of the tank used in the RU will be challenged. Mixing studies will be agreed on by the SU and performed during the engineering batch.
		Osmolality	Dissolution speed is insufficient for complete dissolution and a homogenous system.	3	3	1	9	
		Appearance	Mixing system is not appropriate to guarantee uniform batch mixing	3	3	3	27	The user requirements of the RU tank have properly defined the mixing needs based on the characteristics of the colloidal system. The initial evaluation and information sharing between SU, RU, and the disposable technology Supplier have identified the appropriate mixing device. The PQ challenge of the mixing system will include appropriate tests suggested by the supplier/ owner of the technology
		Density	Temperature of the system is outside the range specified by the SU	2	1	1	2	No further action needed. The colloidal system is not sensitive to temperature. The RU WFI loop cooling and temperature control system will guarantee a 15-25°C range.
			Sampling mode device can affect the analysis	3	2	2	12	The sampling system will be made of pharmaceutical-grade glass. The SU has collected data on compatibility, and the solution is declared compatible with glass devices.
		Sterility	Preparation time can affect the bioburden level of the final compounded solution	3	2	2	12	Validation activities will include hold time challenges according to a dedicated protocol. Chemical characteristics and microbiological attributes of the solution will be analyzed.
		Particulate matter	Particles release from disposable hoses may impact the particulate matter profile	3	2	3	18	Use Silicon, platinum-cured, disposable hose certified for pharmaceutical use for solution transfer. To address particle release from the hoses used in grade C, filter the solution three times before filling (0.45 um + 0.22/0.2 um in grade C area and 0.22/0.2 um in grade A area). Regarding the particle release from the hoses used on the filling machine, a final 100% visual inspection will be done. Vials with a particle matter defect will be rejected.
			Mixing system shedding may impact the particulate matter profile	3	2	3	18	Supplier has provided leachable/ extractable documentation and certifications. Compatibility studies to be conducted with specified analytical methods with the supplier.

Technology Transfer RA Approach…in GMP

Technology Transfer involves:

- ❑ Procedure in place to handle documentation exchange, review and evaluation within unit and between S & R units
- ❑ Reviewers list and approvers list
- ❑ QA/RA overall super-visioning of the document and its contents

…under GMP!

Technology Transfer RA Approach

Knowledge management and transfer are key requirements of the TTP for preserving product quality and process performance after technology transfer.

Because of the large amount of multidisciplinary information collected, evaluated, and elaborated during the TTP, a systematic approach to acquiring, analyzing, storing, and disseminating information related to the technology should be considered and customized on the basis of the team and the project.

Appropriate level of training in place

...under GMP!

Technology Transfer RA Approach

- Batch records & Bill of materials
- Item specifications and justifications
- Summary of stability
- Lists of potential impurities and degradants and typical levels
- Starting materials and material safety data sheets
- Assay-related documents
- Drug master file for active pharmaceutical ingredients (APIs) and excipients
- Qualification of bioburden tests
- Solubility profiles
- Process flow diagram that provides a rationale for the synthesis, route, and form selection; technology selection; equipment;, clinical tests; and product composition
- Vendor qualification (for transfers to contract manufacturing organizations [CMOs])
- Training protocols
- Process validation report and master plan & Cleaning validation protocols and reports
- Project implementation plan & Risk assessments performed for the process or testing.

Technology Transfer RA Approach

Technology Transfer Protocol

A roadmap must be designed from the very beginning of the project to ensure comprehensive project management. The SU and RU should jointly develop a TTP plan that will govern the entire project. Critical inputs to the technology transfer plan include a regulatory strategy and a gap analysis

Outputs of this stage include a finalized project plan describing activities, resources, schedule, and project risk assessment.

Technology Transfer RA Approach

The Technology Transfer Protocol document should drive the overall process and define the strategic approach by describing at least:

- The manufacturing process being transferred
- Sampling and testing steps
- Roles and responsibilities of the SU and the RU
- RU's equipment and facilities
- A brief description of both sites (SU and RU) that includes gaps and/or differences
- Documentation requirements
- Project schedule, including roles and responsibilities of personnel (a Gantt chart is helpful here)
- Technology transfer tools, including templates
- Risk list and mitigation plan
- Correlations to previous and subsequent tasks

Technology Transfer RA Approach

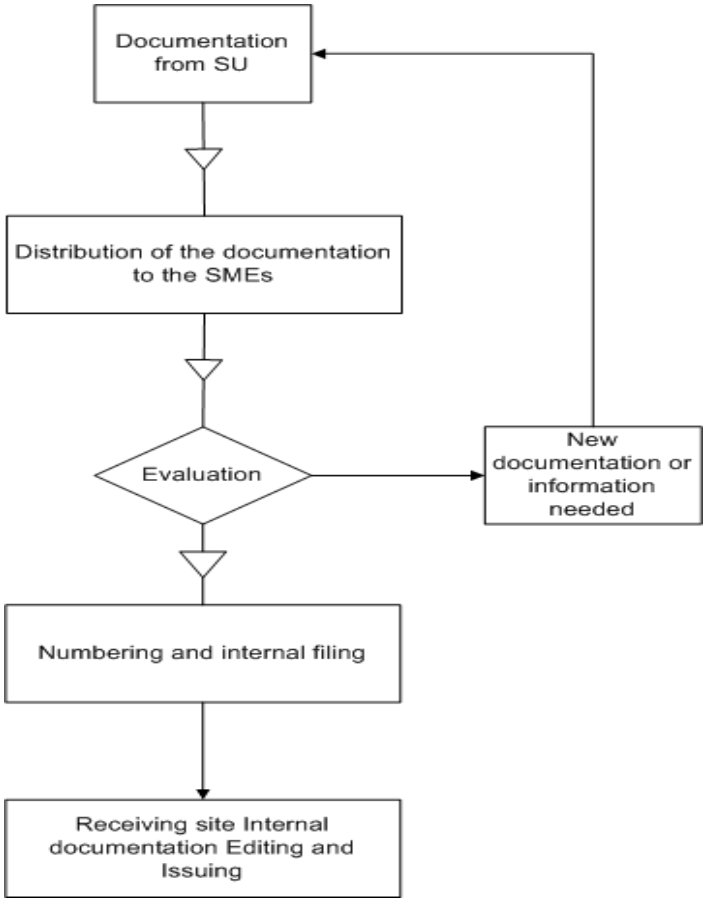
SOP for TT Protocol/report handling

- ❑ Chapter 1. *Application area:* Which kind of documents are needed
- ❑ Chapter 2. *Responsibilities:* Who is responsibile for what
- ❑ Chapter 3. *Documentation flow:*
  - ➢ How the documentation is received from the SU
  - ➢ How it's distributed among the team
  - ➢ How it's stored and numbered
- ❑ Chapter 4. *Project identification:* procedure (codes, numbering)
- ❑ Chapter 5. *Project planning tools*
- ❑ Chapter 6. *Project monitoring tools*
- ❑ *Chapter 7. Project closure tools*
- ❑ *Chapter 8. Document History*
- ❑ *Appendix. Template and signature page*

- ❑ Chapter 4. Project Story
- ❑ *Chapter 5.* Project Results
- ❑ *Chapter 6.* Lesson Learnt and CPV
- ❑ Chapter 7. Document Closure
- ❑ Chapter 8 . Document History

Technology Transfer RA Approach

Visual Management support



Technology Transfer take away from day 1

- TT is a multidisciplinary envirnoment
- Process Mapping and R&R matrix are key for site/company TT performance
- Two main areas of working: planning & social intelligence with appropriate tools and rules
- Communication and Teamworking are key for the success of the TT
- Two main kinds of risks have to be considered during TT planning & execution:
  - ✓ Project and Process risks
- Risk Assessment and Risk Management exercises have to be initiated as soon as possibile at the beginning of the projects and mantained along the project lyfecycle

Technology Transfer – Analytical Transfer

Technology Transfer Analytical transfer Pillars*

- An analytical procedure is developed to test a *defined characteristic of the drug substance* or drug product against established acceptance criteria for that characteristic;

- Each *NDA and ANDA must include the analytical procedures* necessary to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product.8 Each BLA must include a full description of the manufacturing process, including analytical procedures

- Data must be available to establish that the *analytical procedures used in testing meet proper standards* of accuracy, sensitivity, specificity, and reproducibility and are suitable for their intended purpose

* Analytical Procedures and Methods Validation for Drugs and Biologics – guidance for industry – FDA;
VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY – ICH Q2

Technology Transfer Analytical transfer Pillars

- Early in the development of a new analytical procedure, the choice of analytical instrumentation and methodology should be selected based on the intended purpose and scope of the analytical method and robustness of the methodology should be challenged

- Parameters that may be evaluated during method development are specificity, linearity, limits of detection (LOD) and limits of quantitation (LOQ), range, accuracy, and precision.

- Typical validation characteristics which should be considered are listed below:

  - ✓ Accuracy
  - ✓ Precision
  - ✓ Repeatability
  - ✓ Intermediate Precision
  - ✓ Specificity
  - ✓ Detection Limit
  - ✓ Quantitation Limit
  - ✓ Linearity
  - ✓ Range

Technology Transfer Analytical transfer Pillars

- …..To fully understand the effect of changes in method parameters on an analytical procedure, you should adopt a systematic approach for a method robustness study (e.g., a design of experiments with method parameters). You should begin with an ***initial risk assessment*** and follow with multivariate experiments. Such approaches allow you to understand factorial parameter effects on method performance.

- You should ***describe analytical procedures in sufficient detail*** to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria

Technology Transfer Analytical transfer Pillars

- **Three approaches** are suggested to be analyzed case by case:
  - *Analytical Validation (single lab or multi lab)*
  - *Method verification – compendial methods suitability verification*
  - *Analytical comparability exercise when validated method are transferred between two labs*
    - ✓ A sufficient number of representative test articles (e.g., same lot(s) of drug substance or drug product) are used by the originating and receiving laboratories. The comparative studies are performed to evaluate accuracy and precision

Technology Transfer Analytical transfer Pillars*

- The following is a list of essential information you should include when describing an analytical procedure:
  - Principle/scope
  - Equipment
  - Operating Parameters
  - Reagents and Standards
  - Sample preparation
  - Standards control solution preparation
  - Procedure
  - System Suitability
  - Calculation
  - Data Reporting

...list of variables to be considered in RA!

Technology Transfer Analytical transfer Pillars*

- ***Why speak about RA in Analytical transfer?***

The simplistic Validation/Comparability/Verification exercise without and additional consideration on level of method development, RU expertise and knowledge, method history and performance *is not enough* to guarantee a reproducible and effective analysis of our product during the transfer and during the commercial manufacturing production

Technology Transfer Analytical transfer Pillars

- Prior to initiation of method transfer / implementation a 'paper based' method Risk Assessment should be performed within the RU.

- Serves as both a 'knowledge transfer' document and a tool for identifying areas of concern / potential improvement prior to use in a GMP setting.

- Risks are evaluated on specific method parameters and classified based on potential impact and likelihood of occurrence:

Impact \ Likelihood	Certain (4)	Possible (3)	Unlikely (2)	Rare (1)
Critical (4)	16	12	8	4
Major(3)	12	9	6	3
Moderate (2)	8	6	4	2
Minor (1)	4	3	2	1

Impact	Score	Definition
Critical	4	Risk to quality/Regulatory compliance
Major	3	AD Method RFT failure
Moderate	2	AD Method RFT risk/Future method risk
Minor	1	Nice to have/Site Preference/Efficiency

- The competed risk assessment is shared with the SU and may drive the design of formal method evaluation / transfer / validation activities.

- Upon completion of the laboratory method implementation activities a RU version of the method incorporating any incremental changes and/or cautionary statements is forwarded to the SU for approval.

Technology Transfer Analytical transfer Pillars

Chromatographic conditions	Details/Information	Likelihood (L) of method issue (R=1; U=2; P=3; C=4)	Impact (I) of method issue (Min=1; Mod=2; Maj=3; Cr=4)	Risk Rating (L x I)	Acceptable Risk (Y/N)
Manufacturer of HPLC system defined/appropriate	See test procedure	1	2	2	Y
Relevant LC detection technique	See test procedure	1	3	3	Y
Appropriate LC detection wavelength (Assay and Rel Subs)	See test procedure	1	2	2	Y
Single method for assay and related substances	See test procedure	1	1	1	Y
Type of HPLC column acceptable for chemical structure	See test procedure	1	3	3	Y
HPLC column stable under conditions of method	See test procedure	1	2	2	Y
Column temperature acceptable	See test procedure	1	3	3	Y
Sample temperature acceptable	See test procedure	1	3	3	Y
Injection volume suitable for instrumentation	See test procedure	1	3	3	Y
Mobile phase constituents (complexity/additives etc)	See test procedure	1	3	3	Y
HPLC Method pre-column required	See test procedure	1	2	2	Y
Needle wash appropriate	See test procedure	1	2	2	Y
Length of HPLC run (Isocratic vs Gradient) acceptable	See test procedure	1	1	1	Y
Complexity of HPLC gradient acceptable (if appropriate)	See test procedure	1	1	1	Y
Robustness of method (If known)	pH of mobile phase Flow rate Mobile phase composition Column Temperature Wavelength	4 lack of Robustness details into the method validation provided	4	16	N

Technology Transfer Analytical transfer Pillars

- The RU should review the analytical information and perform an analysis to evaluate gaps

- Any gap identified should be assessed for risk of failure by both the SU and the RU.

- After the initial assessments of the methods, a pre-approved protocol will be prepared to describe the experiments to be performed.

There are a number of ways in which the transfer may be performed, you need to be sure you are taking the right one!

Technology Transfer Analytical transfer Pillars

Laboratory	Suggested Responsibilities
SU laboratory	• Assess feasibility/readiness • Compile QC/process data • Organize training, if required • Establish the transfer package • Write transfer protocol based on requirements of both laboratories and knowledge of method prior to transfer • Establish protocol acceptance criteria • Allocate resources for training and transfer study • Provide critical reagents and samples • Provide troubleshooting support • Approve the transfer report
RU laboratory	• Review the transfer package • Define the transfer process, including training requirements • Inform the donor laboratory of potential issues identified (such as different suppliers of critical equipment) • Allocate resources for training and transfer study • Analyze transfer data • Write the transfer report • Inform the donor laboratory of the outcome of the transfer • Approve the transfer report

Technology Transfer Analytical transfer Pillars

- Since a successful validation requires the ***cooperative efforts of several departments*** including Regulatory Affairs, Quality Control and Analytical Research and Development, it is essential that the organization has a well defined Validation Master Plan (VMP) for analytical methods.

- The ***Analytical strategy*** has to be detailed in a dedicated GMP document (Analytical transfer Plan/Protocol)

- A well developed VMP must clearly define the ***roles and responsibilities*** of each department and Units involved in the validation of analytical methods

- A well developed VMP must clearly define the activities to be done for each method to be imported in the RU with the ***scientific sound rationale*** used to establish it

Technology Transfer – PMO…one answer


I NEED MORE RESOURCES ON MY PROJECT.
I'LL GIVE YOU SOMEONE FROM ALICE'S PROJECT.
Dilbert.com DilbertCartoonist@gmail.com
THEN ALICE WON'T HAVE ENOUGH RESOURCES.
I CAN ONLY SOLVE ONE PROBLEM AT A TIME.
9-12-09 © 2009 Scott Adams, Inc./Dist. by UFS, Inc.
DID HE SOLVE YOUR PROBLEM?
I'M GOING TO SAY YES.

Index

What is the PMO?

An organizational body …

assigned various responsibilities related to the centralized and coordinated management of those projects under it's domain.

There in no such thing as a „universal solution".

To be effective, a PMO must be tailored to your organisation's project types, management/staff capabilities, and organisation culture

Why setup the PMO?

①	**Limited resources (financial, human staff, …)**
②	**Multiple projects**
③	**Time to market is a critical factor**

*** Condition is full executive support**

Time for Dilbert

What can the PMO be?

Supportive PMO

Generally provides support in the area of expertise, templates, best practices, access to information

Controlling PMO

It also requires that support to be used (pass the regular reviews, audits, …)

Directive PMO

Only professional project managers are assigned to the projects

High level of consistency across all projects because PMs are reporting back to the PMO

What would the PMO provide?

①	Methodology
②	Terminology
③	Project managenet processes
④	Supporting tools
⑤	Reporting
⑥	Training and mentoring
⑦	Best practices collecting
⑧	Project Managers services
⑨	Continuous improvement of level of sucess within organisation

Why does the PMO fail?

One example from many posibilities

Scope

Defining processes

Defining best practices

Have executive level support

Staffing

- Process oriented staff without significant experience in delivering projects, aren‘t respected
- Push to the teams to get information that the top management wants

PMO cops

Similar problem as IAD (Internal affairs department) **inside PD** (Police department)

Technology Transfer – day 2

Technology Transfer – day 2 – brief recap

Teamworking in TT

https://www.youtube.com/watch?v=nF_77OdTNS4

Technology Transfer – Feedback from PDA TT IG

Technology Transfer

Key factors for success no matter which kind of TT we are considering

- Sending unit and receiving unit work closely with each other.
- Clear understanding of roles and responsibilities of both sending unit and receiving unit team members.
- Complete technology transfer package.
- Quality Risk Management.
- Effective knowledge transfer and training.
- Stage Gate Approach

Technology Transfer

Why do we do TT

•Product life cycle management, from R&D through scale-up to routine manufacturing – Segmentation of Business Core Activites

•Post-approval changes to implement new process versions

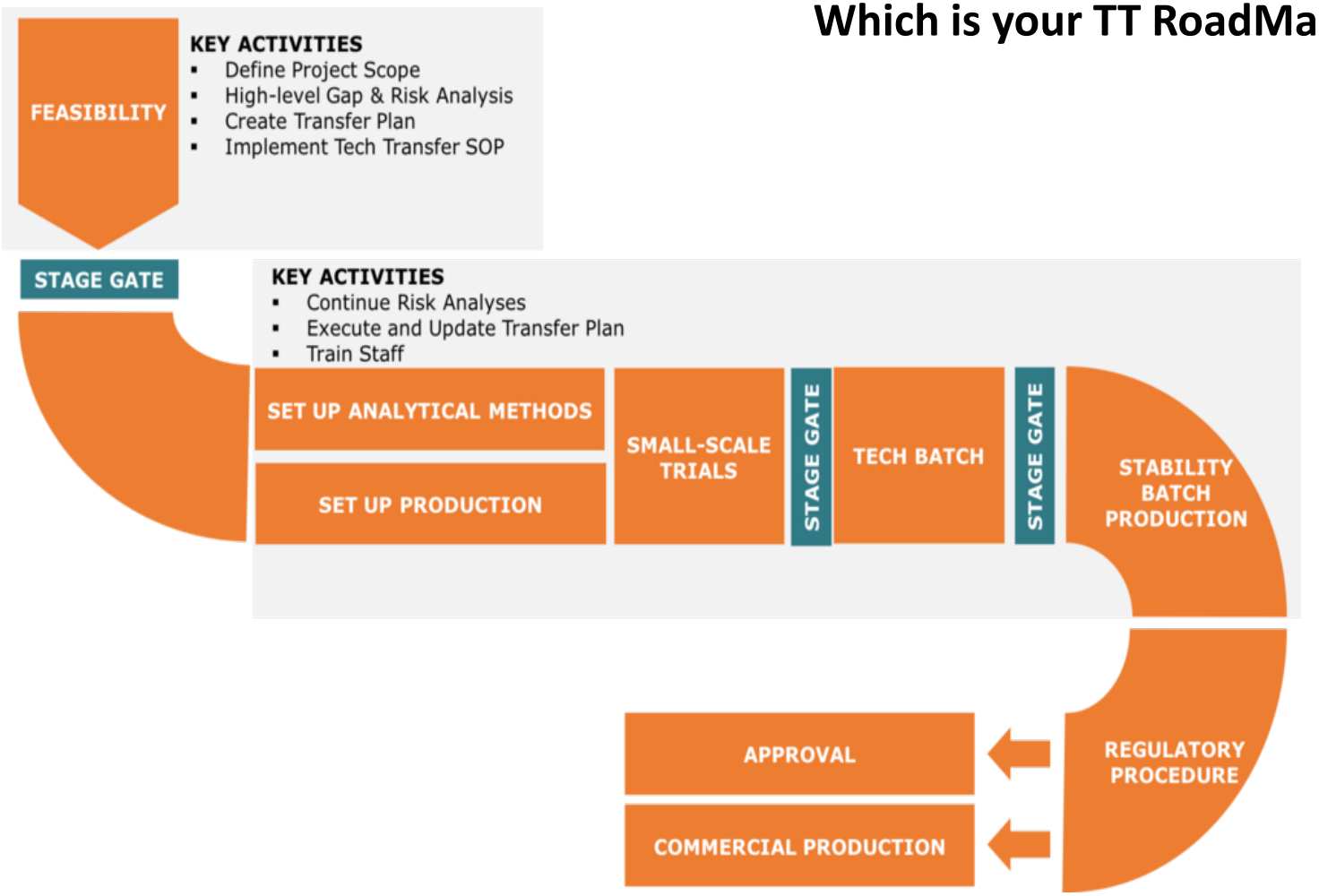
•Need for additional manufacturing capacity driven by increased demand or risk mitigation

•Strategic requirements to relocate manufacturing sites for rationalization or economic advantages in different regions of the world (e.g. market access, supply chain optimization, contract manufacturing)

•Needs of Technical competencies

Technology Transfer

Which is your TT RoadMap?



PDA TT IG Survey

1. Which is the main difficulty during a Development to Clinical phase TT?

   Lack of information regarding robustness of process

2. Which is the main difficulty during a Clinical Phase to Commercial TT?

   Appropriateness of batch scale based on market demand

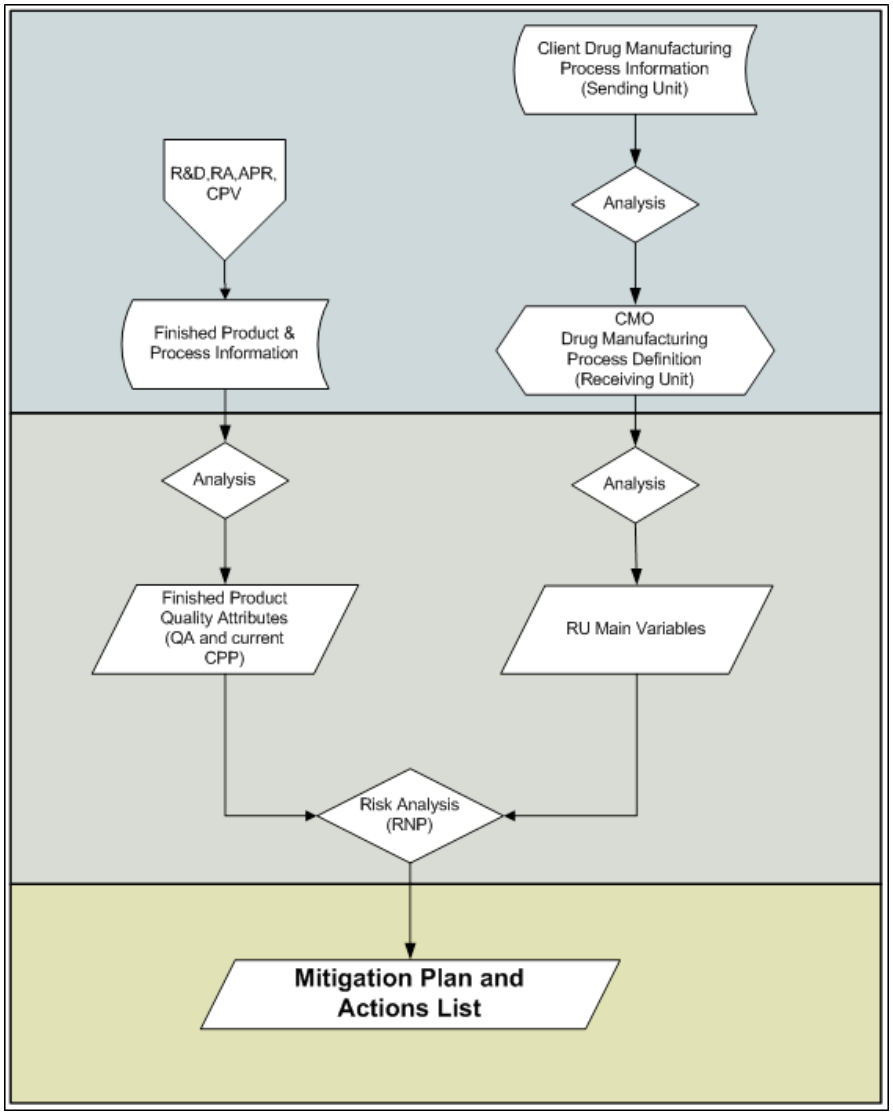
3. Which is the main difficulty during a Commercial to Commercial TT?

   MSA negotiation and agreement (in case of external TT)

   R&R between sites (in case of internal TT)

Technology Transfer – Recap on RA

Technology Transfer RA Approach



Data collection

Data evaluation

Data use

Technology Transfer – Risk Management

Severity considers the potential impact on the quality attributes of the product and hence on patient health.

It can be rate based on the table below

Severity	Risk Classification	Value
No impact on the product's quality attributes or on patient health	Negligible	1
Moderate impact on product's quality attributes and on patient health	Moderate	2
Severe impact on product's quality attributes and on patient health	Critical	3

Technology Transfer – Risk Management

The occurrence factor is defined as the frequency of occurrence of the event. In a TTP phase, occurrence is based on the combination of the SU knowledge of the product and the RU experience on process.

It can be rate based on the table below

Occurence	Risk Classification	Value
Highly improbable or impossible that the negative event occur	Remote	1
Some possibility that the negative event will occur	Medium	2
Highly probable or certain that the negative event will occur	High	3

Technology Transfer – Risk Management

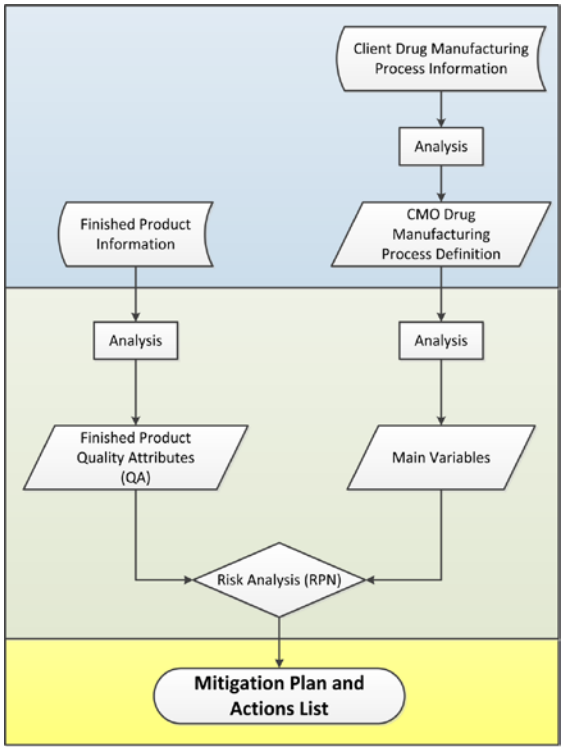
The detection factor is defined as the probability of detecting the events if they occur, based on the control system in place.

It can be rate based on the table below

Probability	Risk Classification	Value
Highly probable or certain that the negative event will be detected by the control system in place	Remote	1
Some possibility that the negative event will be not detected by the control system in place	Medium	2
Highly improbable or impossible that the negative event will be detected by the control system in place	High	3

Technology Transfer RA Approach

Our Risk Assessment and Mitigation approach is based on several Source of information, linked to create a TT Starting Story



Source 1 – Definition of the Main Process Variables of the product (SU -> RU) *(examples below)*

List of main items considered for the evaluation	Relative Variables		
Process	Mixing Holding Compounding Grade C filtration Grade A filtration	Filling Stoppering Crimping Solution transfer Steam terminal sterilization	Identification Wrapping Visual inspection Secondary packaging Line cleaning
Primary packaging and GMP materials	Stoppers Vials Seals	Filters Disposable tubes Disposable bag	Fixed tube Gasket
API and excipient attributes	API pH API appearance	API density API osmolality	Excipient attributes

Source 2 – Definition of the Quality Attributes (RU) *(examples below)*

Quality Attribute		
Appearance	pH	Volume in container
Identity	Density 20°C	Cosmetic appearance
Assay	Osmolality	Sterility
Impurity	Particle matter	Endotoxins

Technology Transfer RA Approach

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	Mixing and compounding	pH	Dissolution speed is insufficient for complete dissolution and a homogenous system.	3	3	1	9	During the performance qualification, the mixing device of the tank used in the RU will be challenged.
		Osmolality	Dissolution speed is insufficient for complete dissolution and a homogenous system.	3	3	1	9	Mixing studies will be agreed on by the SU and performed during the engineering batch.
		Appearance	Mixing system is not appropriate to guarantee uniform batch mixing	3	3	3	27	The user requirements of the RU tank have properly defined the mixing needs based on the characteristics of the colloidal system. The initial evaluation and information sharing between SU, RU, and the disposable technology Supplier have identified the appropriate mixing device. The PQ challenge of the mixing system will include appropriate tests suggested by the supplier/ owner of the technology
		Density	Temperature of the system is outside the range specified by the SU	2	1	1	2	No further action needed. The colloidal system is not sensitive to temperature. The RU WFI loop cooling and temperature control system will guarantee a 15-25°C range.
			Sampling mode device can affect the analysis	3	2	2	12	The sampling system will be made of pharmaceutical-grade glass. The SU has collected data on compatibility, and the solution is declared compatible with glass devices.
		Sterility	Preparation time can affect the bioburden level of the final compounded solution	3	2	2	12	Validation activities will include hold time challenges according to a dedicated protocol. Chemical characteristics and microbiological attributes of the solution will be analyzed.
		Particulate matter	Particles release from disposable hoses may impact the particulate matter profile	3	2	3	18	Use Silicon, platinum-cured, disposable hose certified for pharmaceutical use for solution transfer. To address particle release from the hoses used in grade C, filter the solution three times before filling (0.45 um + 0.22/0.2 um in grade C area and 0.22/0.2 um in grade A area). Regarding the particle release from the hoses used on the filling machine, a final 100% visual inspection will be done. Vials with a particle matter defect will be rejected.
			Mixing system shedding may impact the particulate matter profile	3	2	3	18	Supplier has provided leachable/ extractable documentation and certifications. Compatibility studies to be conducted with specified analytical methods with the supplier.

Technology Transfer RA Approach - OverReaction

Info coming from development department: API oxidizes quickly if exposed to Air/O2. Dispensing is done under N2. Small quantity per batch: approx. 0.8 g per 95Lt of bulk solution

- Main commercial variable considered: Dispensing
- QA Impacted: Impurity Profile & Assay
- Severity 3 – Occurance 3 – Detection is 1
- Risk acceptance level was < 6

Mitigation Plan: Purchase and installation of a Dispensing Hood allowing O2 residual less than 0,5% during dispensing

- QA Impacted: Impurity Profile & Assay
- Severity 3 – Occurance 1 – Detection is 1
- Risk acceptance level was < 3

Technology Transfer RA Approach - OverReaction

First TT Batch failed for API assay

Investigation identified the root cause in the Dispensing Hood

The N2 atmoshpere created with the hood enhances the «electrostatic charge environment» which impacts the accurancy of the API weight

Action: development activities to explore «API oxides quickly»

Mitigation Plan: Defined an appropriate holding time of dispensing based on degradation/stability of the API in Air

Technology Transfer – Some exercises

Workshop 1

Workshop

❑**Background:**

A product dedicated to EU market, has to be outsourced from one of your site in US. The manufacturing history of the product in the current manufacturing site is not robust.

❑**Questions**

❑Which Criteria will you use to select a partner?

- *US Regulatory History*
- *Technical expertise in process development*

Workshop 2

Workshop

❑**Background:**

A product dedicated to EU market, has to be outsourced from one of your site in US. The manufacturing history of the product in the current manufacturing site is not robust.

The partner has been identified and selected in US

❑ **Questions**

- ❑Describe the main milestones to bring the product from the SU to the RU including stage/gate and upper management main updates

Workshop 3

Workshop

❑**Background:**

A product dedicated to EU market, has to be outsourced from one of your site in US. The manufacturing history of the product in the current manufacturing site is not robust.

The partner has been identified and selected.

❑**Questions**

- ❑Group 1. SU Describe the project team member mainly impacted in each milestone with an “allocation curve”
- ❑Group 2. RU Describe the project team member mainly impacted in each milestone with an “allocation curve”

Workshop 4

Workshop

❑**Background:**

A product dedicated to EU market, has to be outsourced from one of your site in US. The manufacturing history of the product in the current manufacturing site is not robust.

The partner has been identified and selected. Agreement is in place, team members identified

❑**Questions**

- ❑Group 1. SU. Define the list of information/document you would prepare for the transfer
- ❑Group 2. RU. Define the list of information/document you would request for the transfer

Workshop 5

Workshop

❑**Background:**

A product dedicated to EU market, has to be outsourced from one of your site in US. The manufacturing history of the product in the current manufacturing site is not robust.

The partner has been identified and selected. Agreement is in place and path defined.

❑**Questions**

- ❑Group 1. SU. Define timelines for the main milestones of the project
- ❑Group 2. RU. Define timelines for the main milestones of the project

Workshop 7

Workshop

❑**Background:**

A product dedicated to EU market, has to be outsourced from one of your site in US. The manufacturing history of the product in the current manufacturing site is not robust.

The partner has been identified and selected. Agreement is in place and path defined; timelines are defined.

❑**Questions**

- ❑Group 1. Thinking as Prj manager, define your idea of Value/for the Project team
- ❑Group 2. Thinking as Project team member, define your expectation of support from the Prj Manager

Workshop 5 process transfer case study

Workshop

❑**Background:**

A product dedicated to EU market, has to be outsourced from one of your site in US. The manufacturing history of the product in the current manufacturing site is not robust.

The partner has been identified and selected. Agreement is in place…

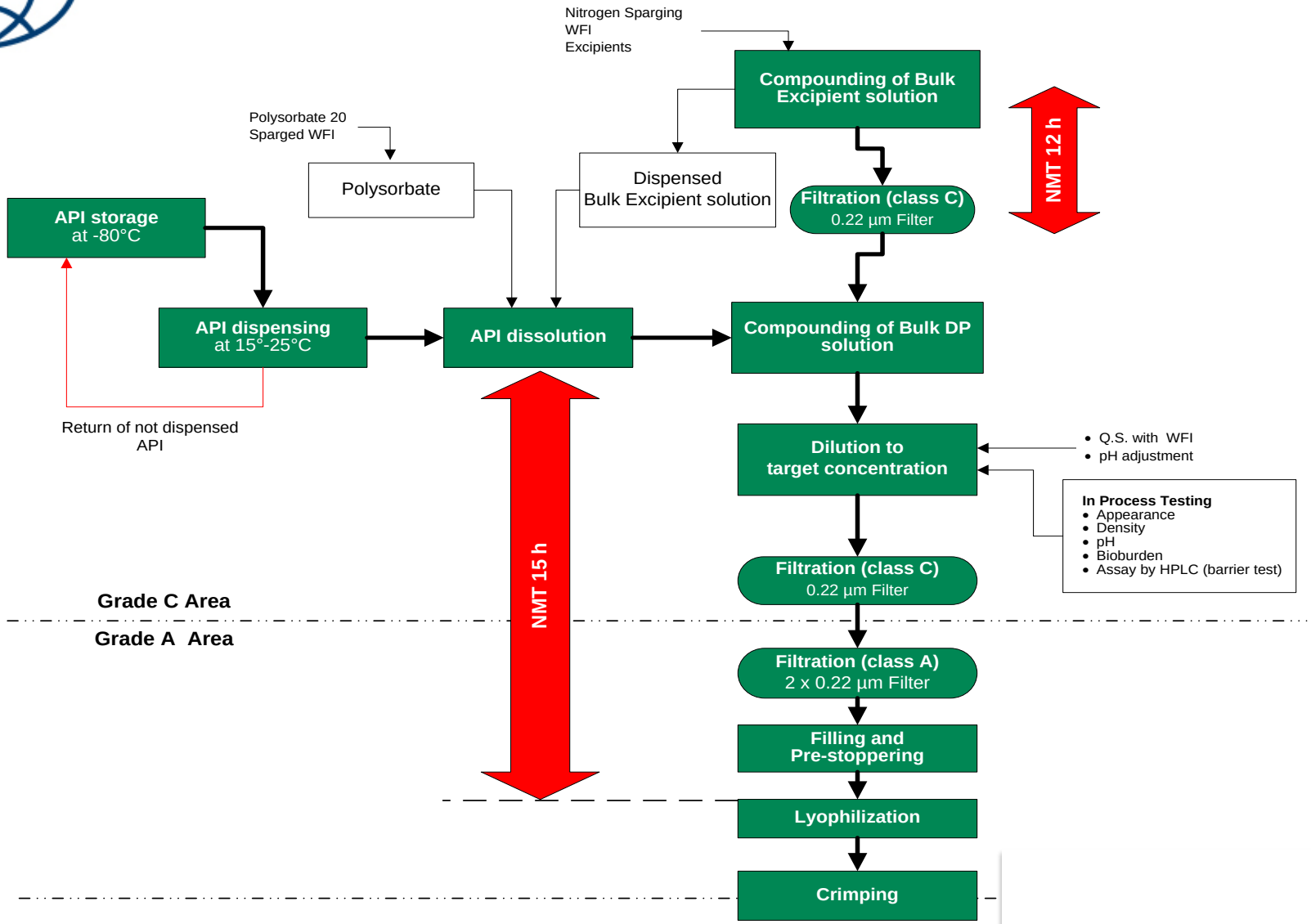
❑**Questions**

- ❑Define the Process Variables
- ❑Prepare a Risk Assessment based on the quality attributes defined by the SU and the Process Variables identified by the RU

Workshop

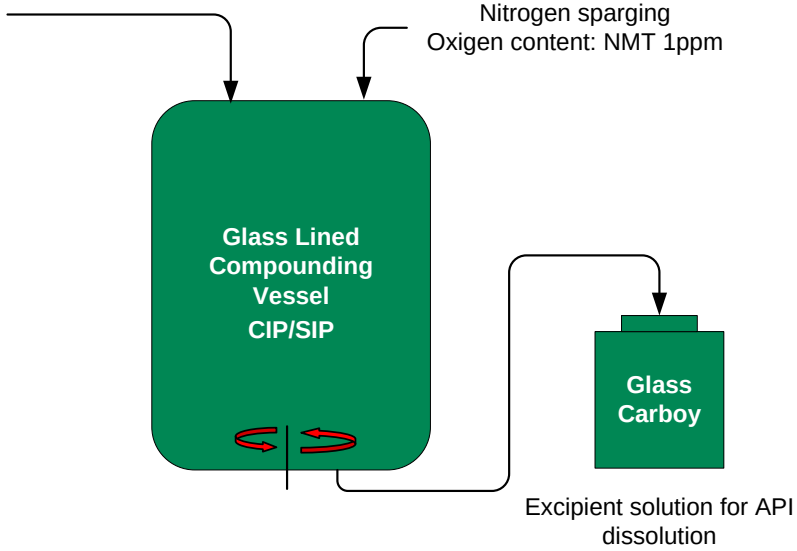
Product	YYY	
API and Pharmacological use	No special RA concern categories	
Pharmaceutical dosage form	Sterile lyophilized DP. 0.0050 mg/vial	
Product phase	Commercial	
Unit Dose composition	•API: 5.0 mg •Polysorbate 20: 0.8 mg •Sucrose:190.0 mg •Potassium Phospate, Dibasic: 18.0 mg	•Citric Acid: 22.8 mg •Phosphoric Acid: 7.0 mg •Vit E: 0.008 mg
Fill Volume (Including overfill)	10 mL	
Batch Size	120K Vials	
API Storage condition	-70°C	
Finish Product Storage	2-8°C	
Finish Product Shipment	2-8°C	

Workshop

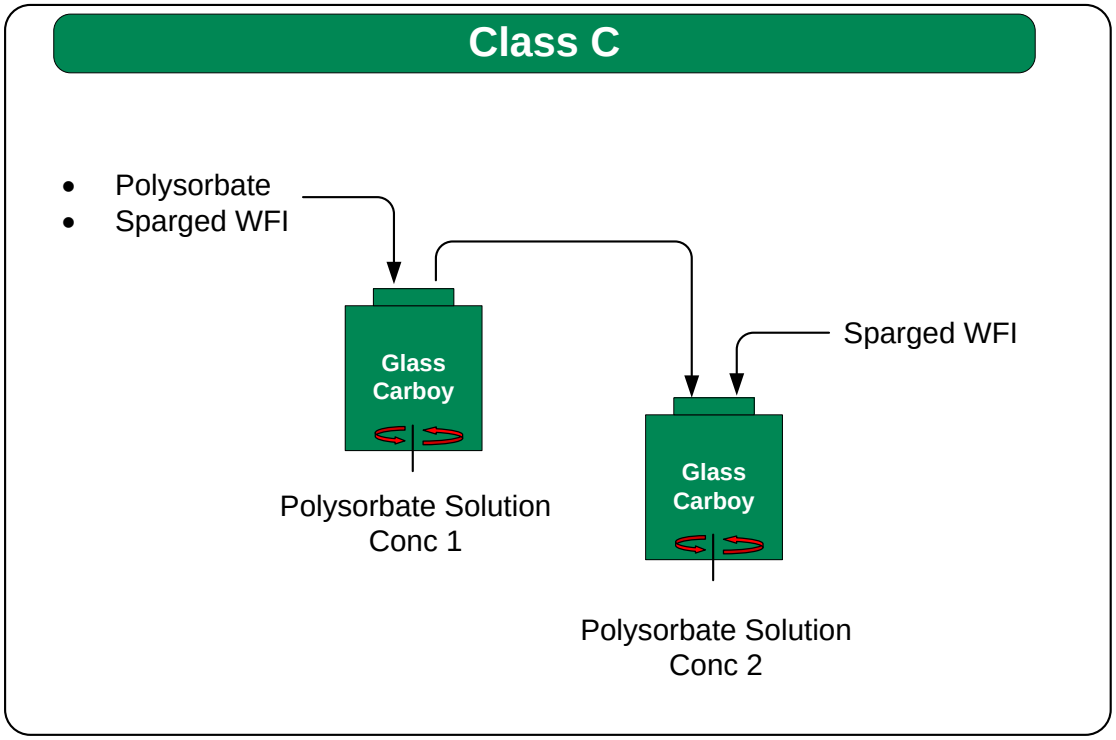

Nitrogen Sparging
WFI
Excipients
Compounding of Bulk Excipient solution
NMT 12 h
Polysorbate 20
Sparged WFI
Polysorbate
Dispensed
Bulk Excipient solution
Filtration (class C)
0.22 µm Filter
API storage
at -80°C
API dispensing
at 15°-25°C
API dissolution
Compounding of Bulk DP solution
Return of not dispensed API
Dilution to target concentration
Q.S. with WFI
pH adjustment
In Process Testing
Appearance
Density
pH
Bioburden
Assay by HPLC (barrier test)
NMT 15 h
Filtration (class C)
0.22 µm Filter
Grade C Area
Grade A Area
Filtration (class A)
2 x 0.22 µm Filter
Filling and Pre-stoppering
Lyophilization
Crimping

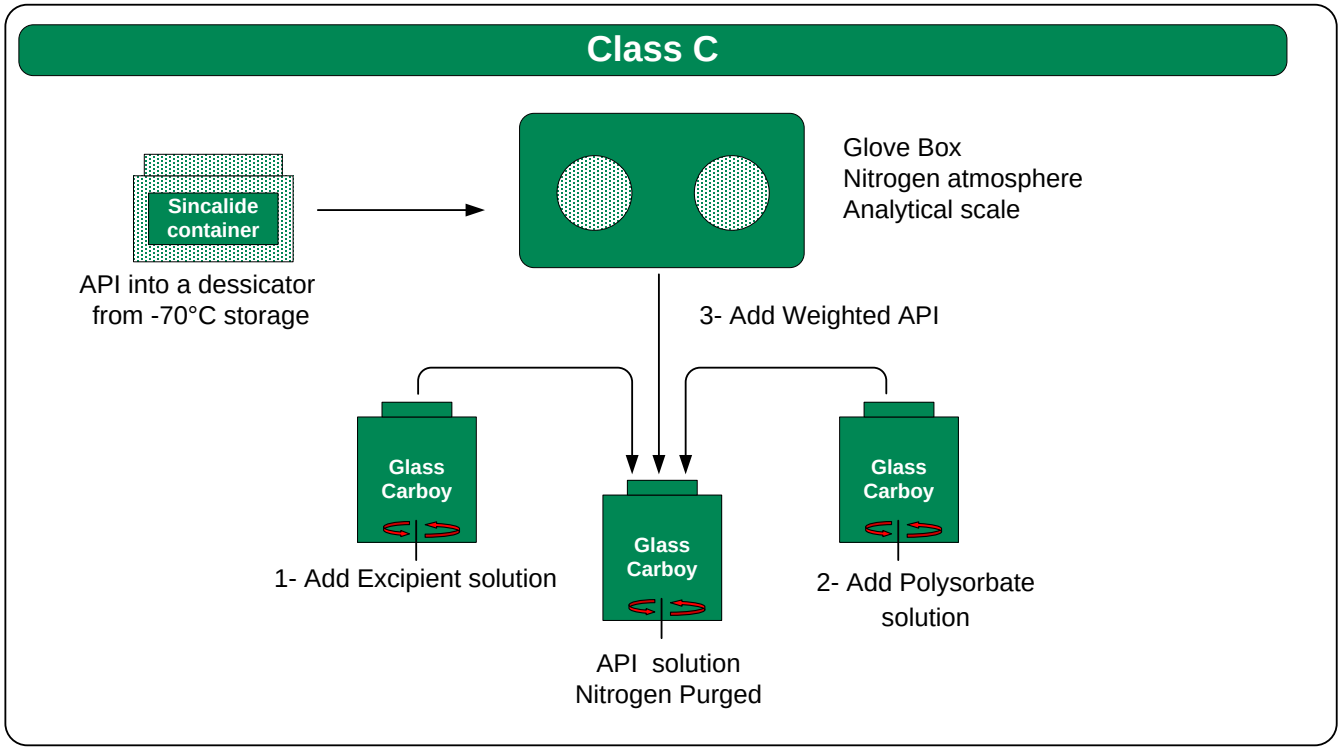
Class C

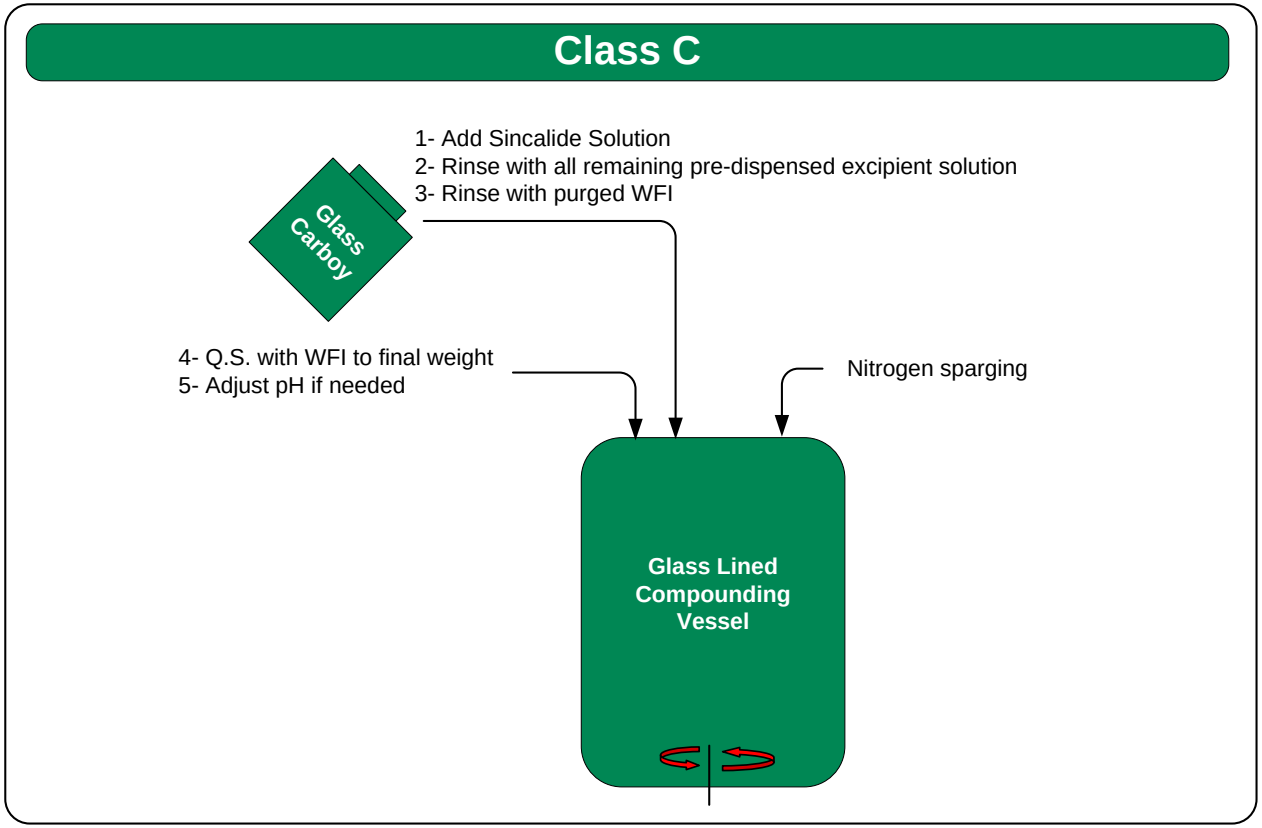
- Sparged WFI
- Excipients

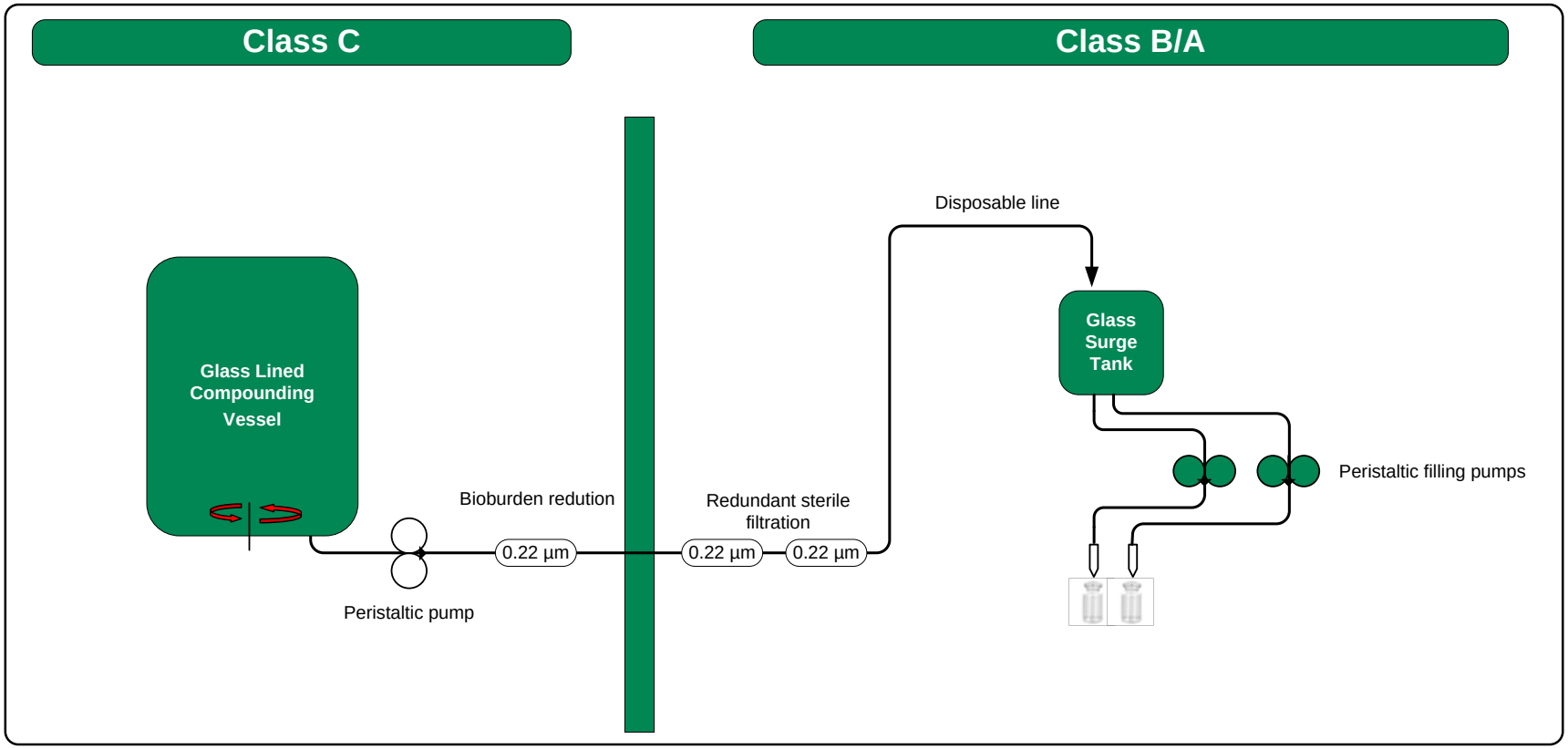


Workshop


Class C
Polysorbate
Sparged WFI
Glass Carboy
Polysorbate Solution Conc 1
Sparged WFI
Glass Carboy
Polysorbate Solution Conc 2


Class C
Sincalide container
API into a dessicator from -70°C storage
Glove Box
Nitrogen atmosphere
Analytical scale
3- Add Weighted API
Glass Carboy
1- Add Excipient solution
Glass Carboy
API solution
Nitrogen Purged
Glass Carboy
2- Add Polysorbate solution


Class C
1- Add Sincalide Solution
2- Rinse with all remaining pre-dispensed excipient solution
3- Rinse with purged WFI
Glass Carboy
4- Q.S. with WFI to final weight
5- Adjust pH if needed
Nitrogen sparging
Glass Lined Compounding Vessel


Class C
Class B/A
Glass Lined Compounding Vessel
Peristaltic pump
Bioburden redution
0.22 µm
Redundant sterile filtration
0.22 µm
0.22 µm
Disposable line
Glass Surge Tank
Peristaltic filling pumps

Workshop

Product Quality Attributes
Micro Attributes Endotoxins Sterility
Chemical & Physical methods • Moisture content by KF • Appearance of the solution (after reconstitution) • Density of the solution (after reconstitution) • pH of the solution (after reconstitution) • Appearance and colour of lyophilized cake (DP) • Particles of the solution (after reconstitution) • Oxygen in headspace of drug product vial (CCI test). • Uniformity of dosage units • Cosmetic appearance of the cake • Impurity profile and assay • Amorphous at X ray of the cake