

September 3<sup>rd</sup> and 4<sup>th</sup>, Mirko Gabriele

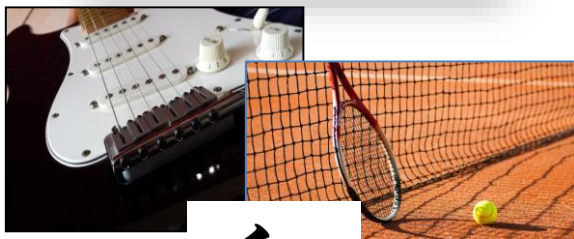
# Managing Technology Transfer Projects in Pharma



# Today's Agenda

9.00 – 9.15	Attendees introduction and course expectations
9.15 - 9.30	Course introduction
9.30 – 10.30	Pharma Management
10.30 – 12.00	Team role in pharma
12.00 – 13.00	PM Role in pharma tech transfer projects
13.00 – 14.00	<i>Lunch break</i>
14.00 – 15.00	Pharma Tech Transfer Projects governance
15.00 – 16.00	Pharma Tech Transfer Projects Risk Management
16.00 - 16.30	Change Management
16.30 – 17.00	Q&A and close out





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### How I'm used to introduce myself

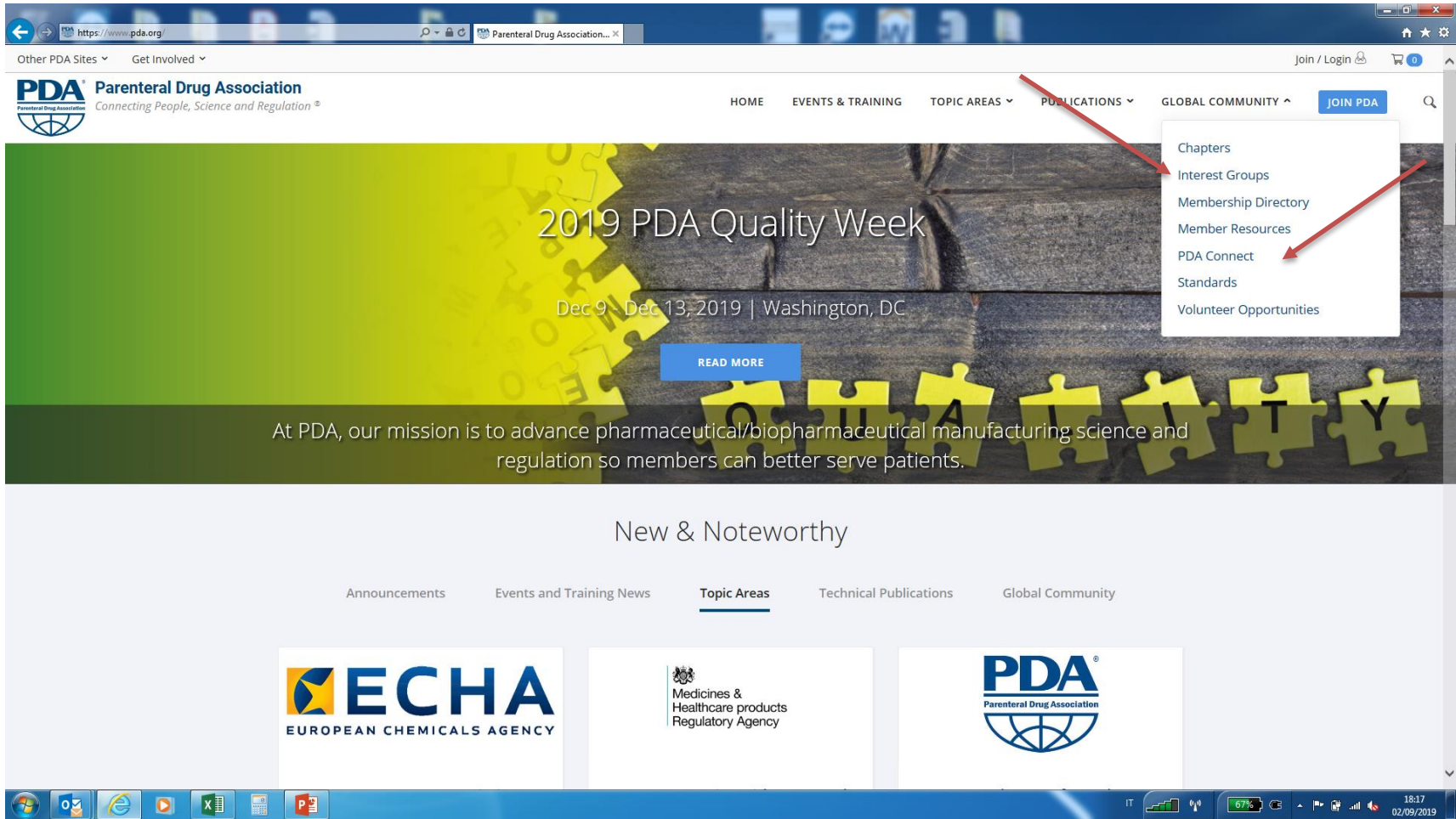
- *Pharmaceutical Chemist with MBA in Pharma Administration. Qualified Person since July 2015*
- *QC and R&D as first steps in my career then my true love: Patheon TT & BM since 2008*
- *TT PM, BM, TT Manager, Global TT Sr Manager, DPS*
- *Production Director since May 2017*
- *Next steps...Who knows??!*

### What the others say about me

- *You will rock being yourself*
- *One of the Best dressed man in the network (after Jim and Franco and some others...)*
- *Highly motivated and passionate about work...always hungry about Knowledge!*
- *Guilt-ridden...no matter how much he is accomplishing...never enough*
- *Visionary...always! Demotivating him? No way!*
- *Stubborn but... (my wife voice)*
- *Great dad (my personal interpretation of Andrea's smile – my kid 2 years old!)*

### About my PDA life

- *Team Leader for TR65 issuing*
- *PDA RAQAB Members since 2014*
- *PDA TT IG European Leader and European trainer on TT topics since 2016*
- *PDA Italy members*


















The screenshot shows the PDA website homepage. At the top, there is a navigation bar with links for HOME, EVENTS & TRAINING, TOPIC AREAS, PUBLICATIONS, and GLOBAL COMMUNITY. A dropdown menu is open under GLOBAL COMMUNITY, listing: Chapters, Interest Groups, Membership Directory, Member Resources, PDA Connect, Standards, and Volunteer Opportunities. A red arrow points from the PUBLICATIONS link to the dropdown menu, and another red arrow points from the dropdown menu to the PDA Connect link. Below the navigation bar is a large banner for "2019 PDA Quality Week" with the dates "Dec 9 - Dec 13, 2019 | Washington, DC" and a "READ MORE" button. Below the banner is a mission statement: "At PDA, our mission is to advance pharmaceutical/biopharmaceutical manufacturing science and regulation so members can better serve patients." Below the mission statement is a "New & Noteworthy" section with tabs for Announcements, Events and Training News, Topic Areas (which is selected), Technical Publications, and Global Community. Under the Topic Areas tab, there are three featured items: ECHA (European Chemicals Agency), Medicines & Healthcare products Regulatory Agency, and the PDA logo.

Browser address bar: <https://community.pda.org/#/group-listing> Groups - PDA Connect

Search: Search...

Hello Mirkol

 <p>Microbiology Environmental Monitoring IG</p> <a href="#">join</a>	 <p>Packaging Science IG</p> <a href="#">join</a>	 <p>Pharmaceutical Cold Chain IG</p> <a href="#">join</a>
 <p>Pharmaceutical Water IG</p> <a href="#">join</a>	 <p>Pharmacopeial IG</p> <a href="#">join</a>	 <p>Post Approval Change Interest Group</p> <a href="#">join</a>
 <p>Prefilled Syringe IG</p> <a href="#">join</a>	 <p>Process Validation IG</p> <a href="#">join</a>	 <p>Quality Risk Management IG</p> <a href="#">join</a>
 <p>Quality Systems IG</p> <a href="#">join</a>	 <p>Quality Systems IG Global</p> <a href="#">join</a>	 <p>Regulatory Affairs IG</p> <a href="#">join</a>
		

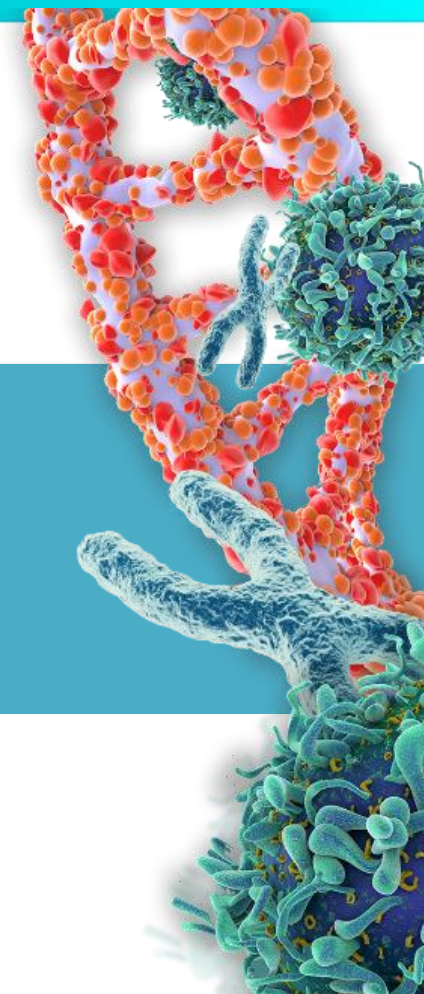
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Taskbar: 18:24 02/09/2019



Who we are...

**Mission:** We enable our customers to make the world healthier, cleaner and safer.



**\$22B**  
in revenues

**50**  
countries

**>\$900M**  
R&D investment

**>70,000**  
employees

**Our Customer Focus:**  
We help accelerate innovation and enhance productivity for our customers.

**ThermoFisher**  
SCIENTIFIC

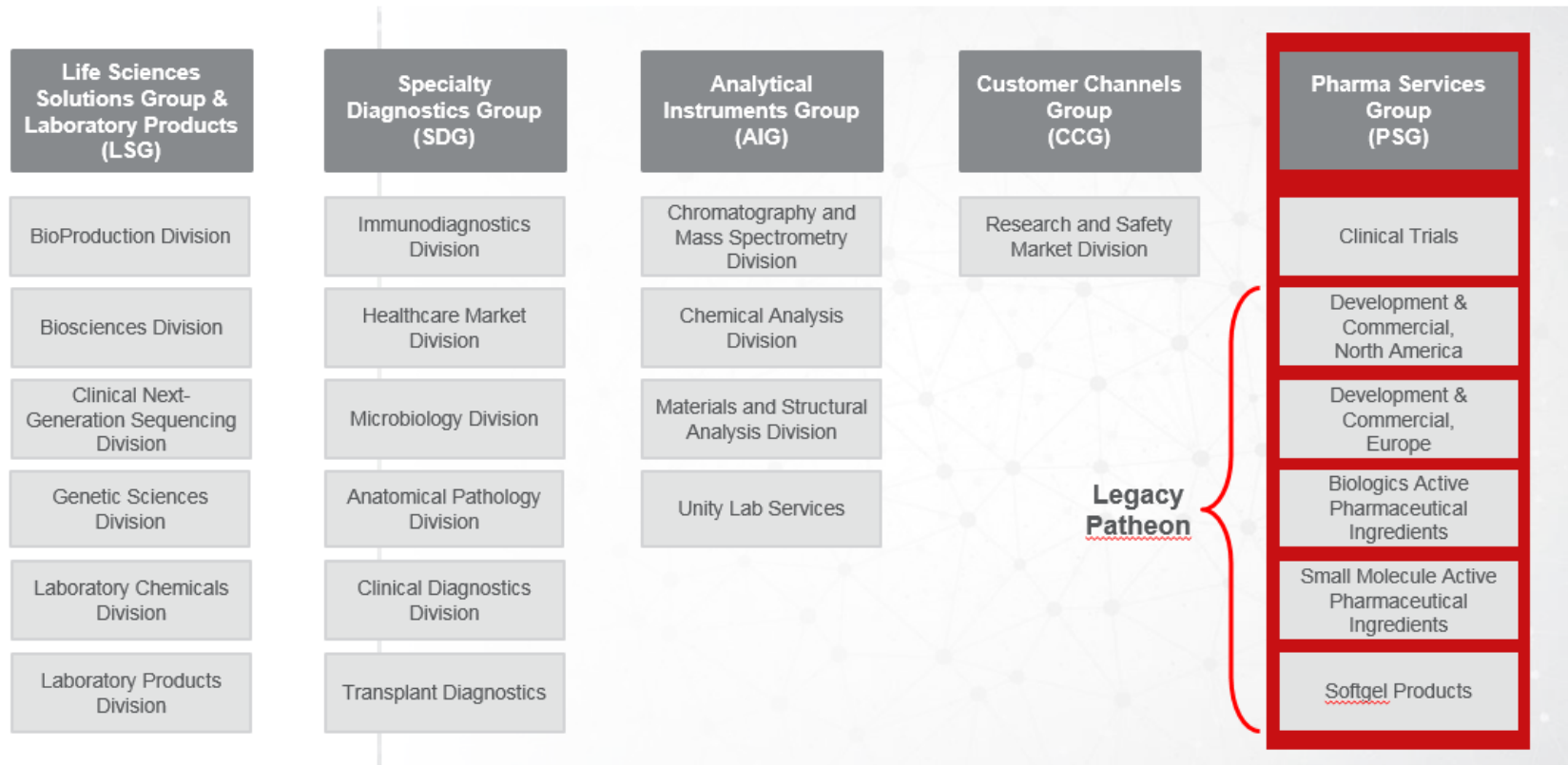
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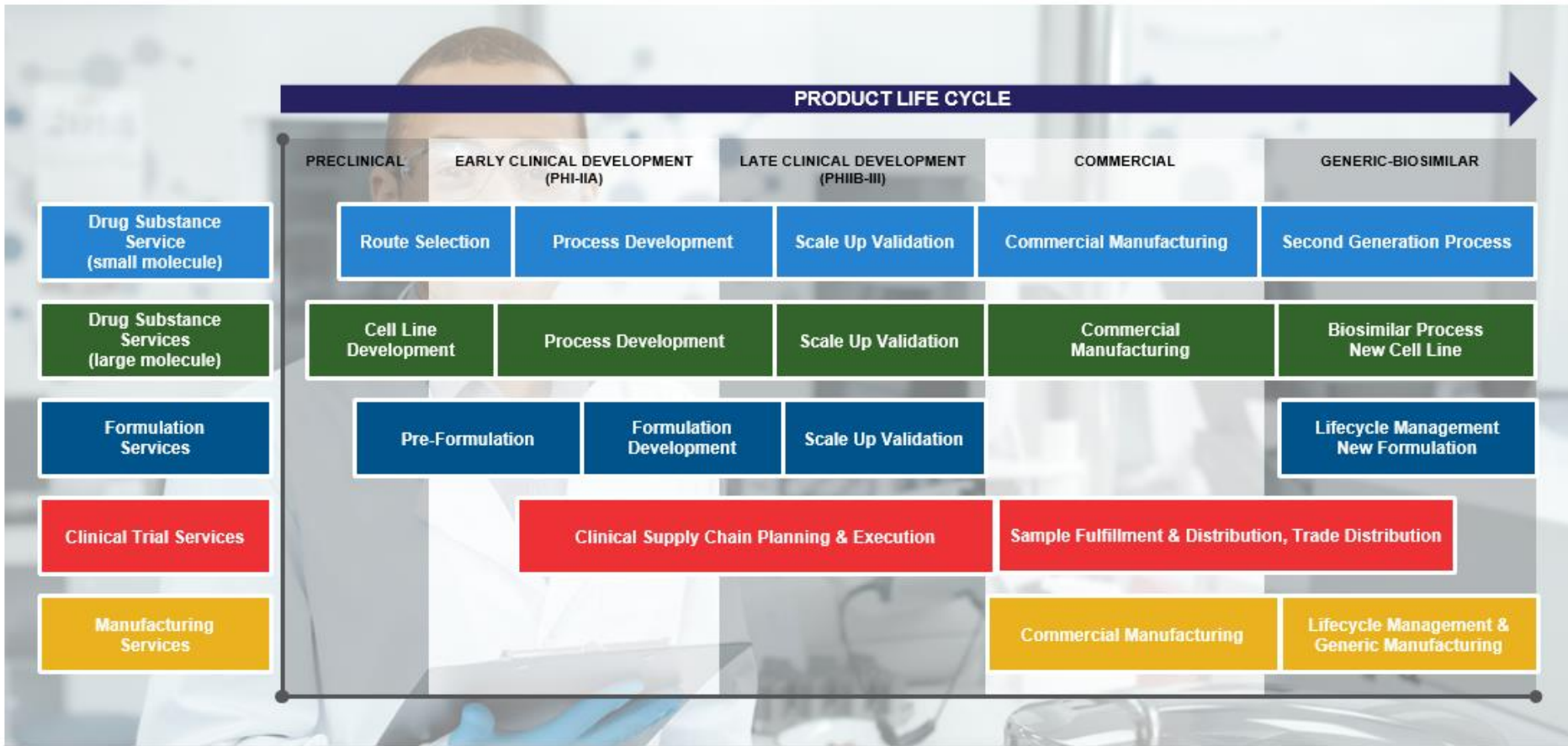
applied  
biosystems

invitrogen

 fisher  
scientific

unity  
lab services







# 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

***IT IS AND WILL BECOME A MORE CRITICAL BUSINESS NEED,  
A “BEST TO BEST DEAL” WITH CUSTOMERS, TOP PLAYERS  
LOOKING FOR CDMO TOP PLAYERS***

# Why Discuss about TT

***EVEN MORE TRUE, BASED ON PHARMA INDUSTRY DICHOTOMY  
PLANNED AS FUTURE SCENARIO***



**&**



- 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;
- **Business Opportunity** for big and small companies
- Project **complexity** is growing TT Experts have to be prepared to face challenges
- **Dynamic and challenge** environment



- TT was involved in the PDA PMCO program, as core activity of the Lifecycle Management of a Drug
- Get professionals experts in TT and define what RM means in TT;
- TR-65 was issue in August 2015
- TT Interest Group was started up in May 2016
- Training in Europe and US are organized yearly to maintain high the attention on this topic and to proceed defining best practices in TT
- TR-65 “revamping program”





## 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?*

# Pharma Management

What does project in pharma mean?

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*)



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:

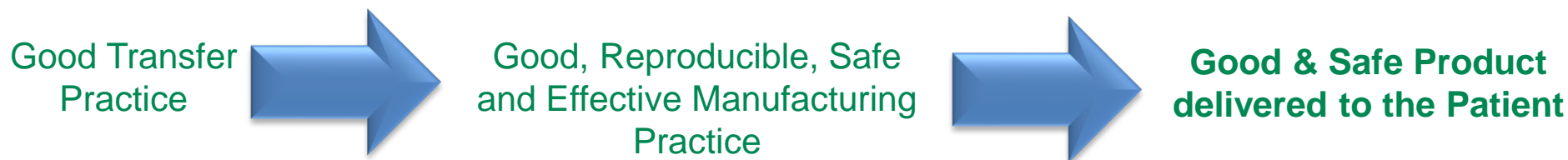
- Technical knowledge
- Documentation management
- Project management
- Personnel training and skills

*PDA – PMCO Program – Technical Report N.65*

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.



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.

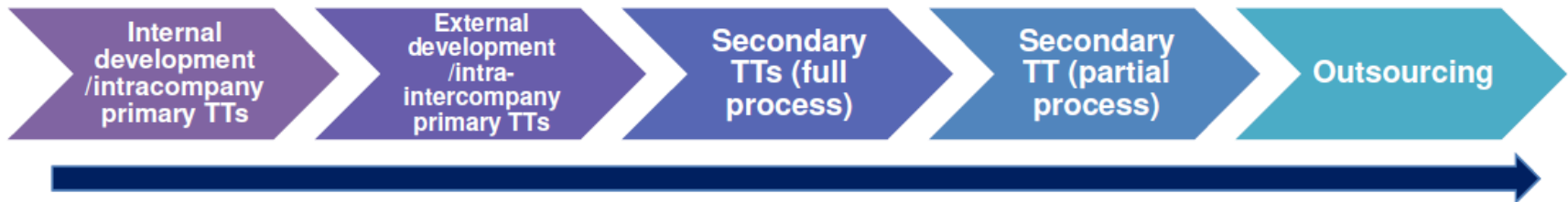
The Technology Transfer Project (TTP) is defined as a set of planned and controlled actions, based on well-defined acceptance criteria needed to transfer a technology from a sending unit (SU) to a receiving unit (RU).

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 main concepts

- |   |   |   |  |  |
|---|---|---|--|--|
| <ul style="list-style-type: none"> <li>• Big pharma (brand)</li> <li>• R&amp;D&amp;manuf in the same site</li> <li>• R&amp;D centric approach</li> <li>• Technical focus</li> <li>• High expertise</li> <li>• High specialization</li> <li>• High budget</li> </ul> | <ul style="list-style-type: none"> <li>• Big pharma (brand)</li> <li>• Generic market</li> <li>• R&amp;D centralization</li> <li>• R&amp;D&amp;manuf in different sites</li> <li>• TT Manager/PM</li> <li>• Increasing role of management and relationship aspects</li> </ul> | <ul style="list-style-type: none"> <li>• Outsourcing&amp;C MOs business</li> <li>• TT from different sites/companies</li> <li>• Higher impact of management aspects</li> <li>• Lower specialization</li> <li>• Higher attention to costs</li> </ul> | <ul style="list-style-type: none"> <li>• Outsourcing&amp;C MOs business</li> <li>• New type of products</li> <li>• TT from different sites and companies</li> <li>• New types of TT</li> </ul> | <ul style="list-style-type: none"> <li>• Outsourcing&amp;C MOs business</li> <li>• New types of companies</li> <li>• Higher importance of contractual aspects</li> <li>• Major focus on costs</li> </ul> |
|---|---|---|--|--|

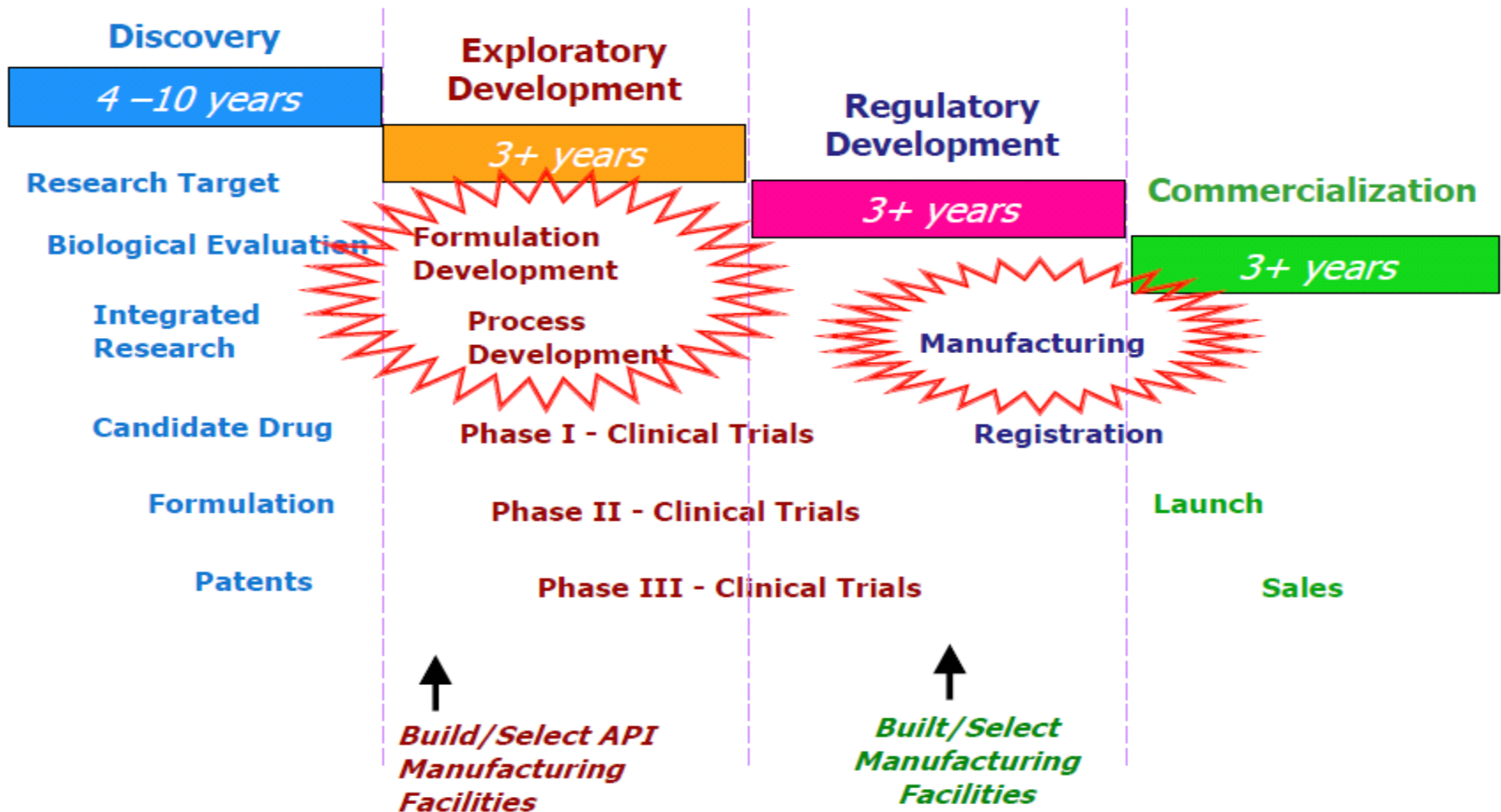


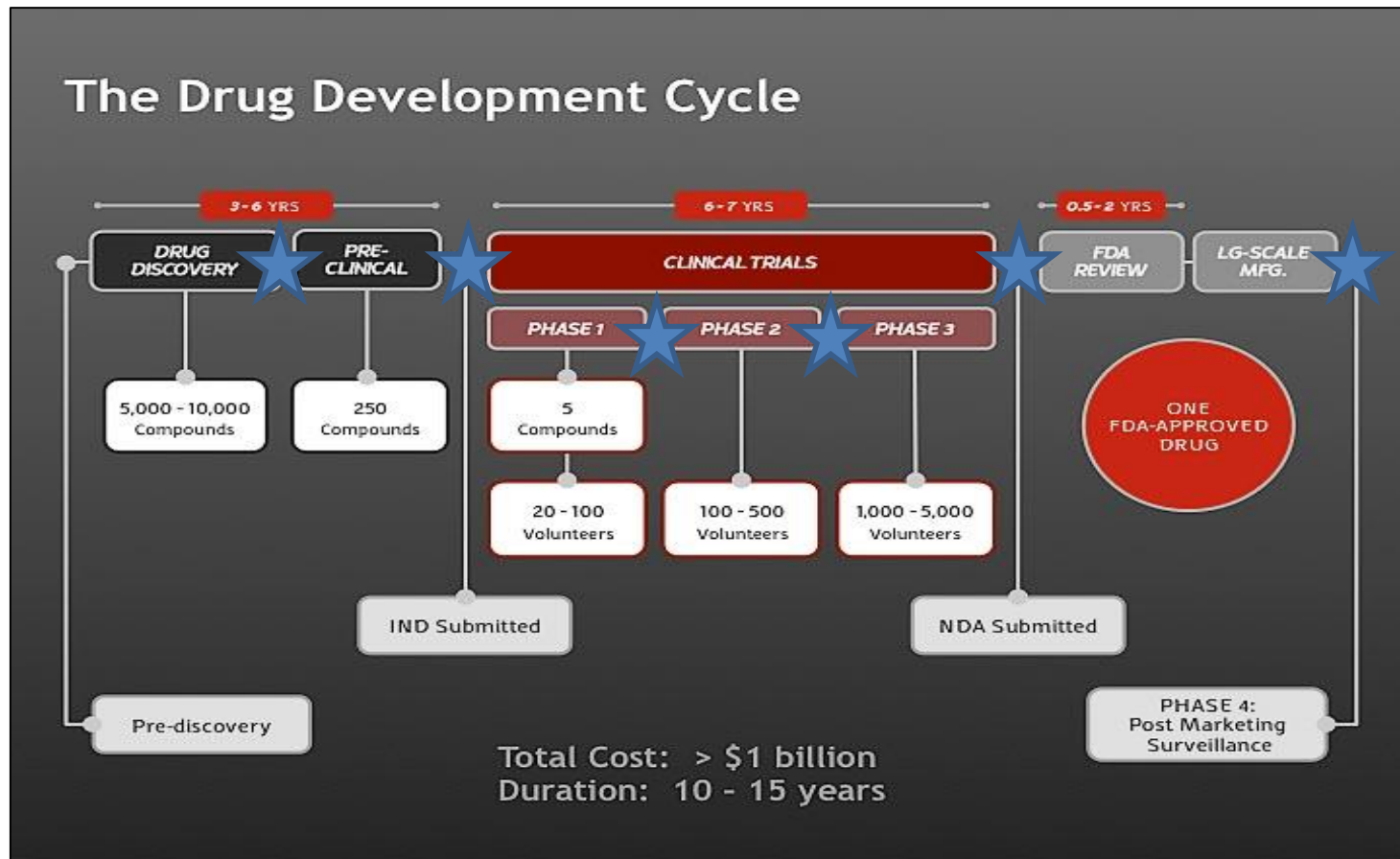
'70/'80

Today



## Stages in the Development of a New Medicine



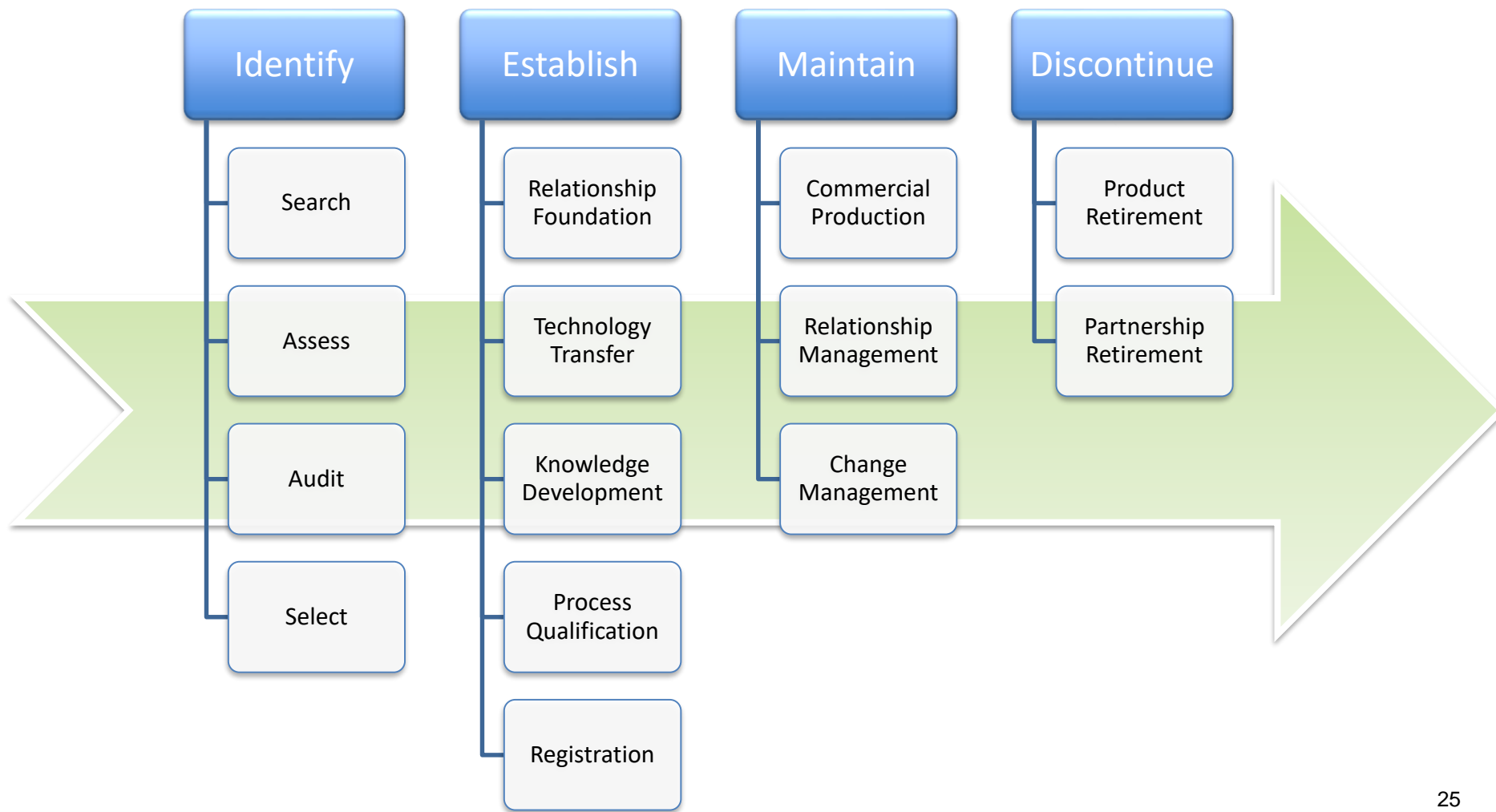


**Risk of Selection Partner!**





# 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*

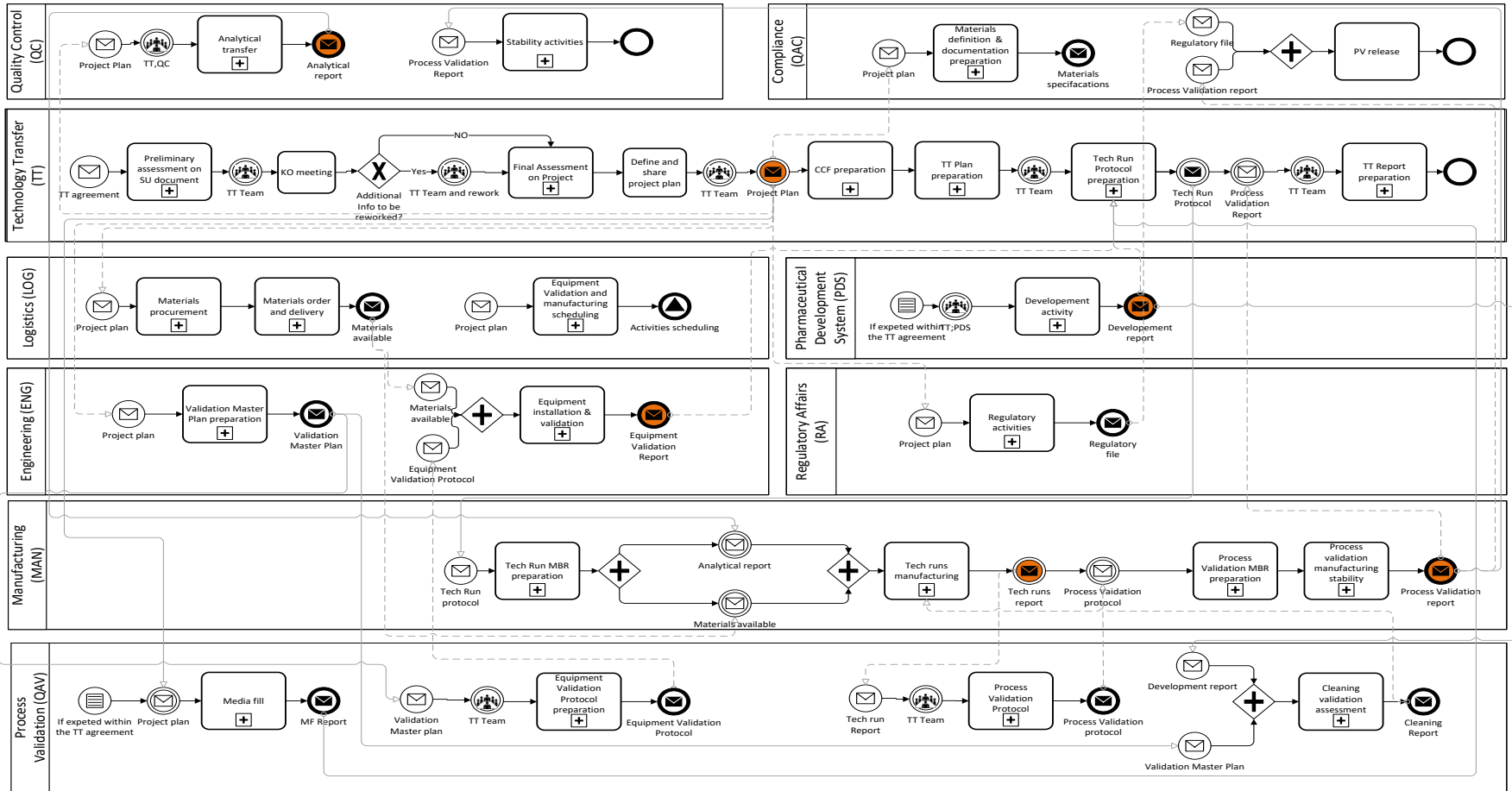


- **Receiving Unit (RU)**
  - The involved disciplines at an organization where a designated product, process or method is expected to be transferred.
- **Risk Management (RM)**
  - Risk is combination of severity of harm and probability of occurrence (ICH Q9).
  - Applicable to Technology Transfer Projects
    - 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



# 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. Deliverables defined
- d. Control philosophy agreed
- e. Risks evaluated and mitigation plan defined

## 5 main steps!



## 2. Process Readiness

- a. Control and Achieve the readiness set for the project
- b. Each TT phase and milestones has its own readiness
- c. Stage/Gate step along the project execution
- d. Process changes tracking and handling
- e. Training and expertise challenge



## 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

## 5 main steps!



## 4. Licensing & Manufacturing

- a. Regulatory submission
- b. Monitoring of the manufacturing batches

## 5 main steps!



## 5. Project Closure

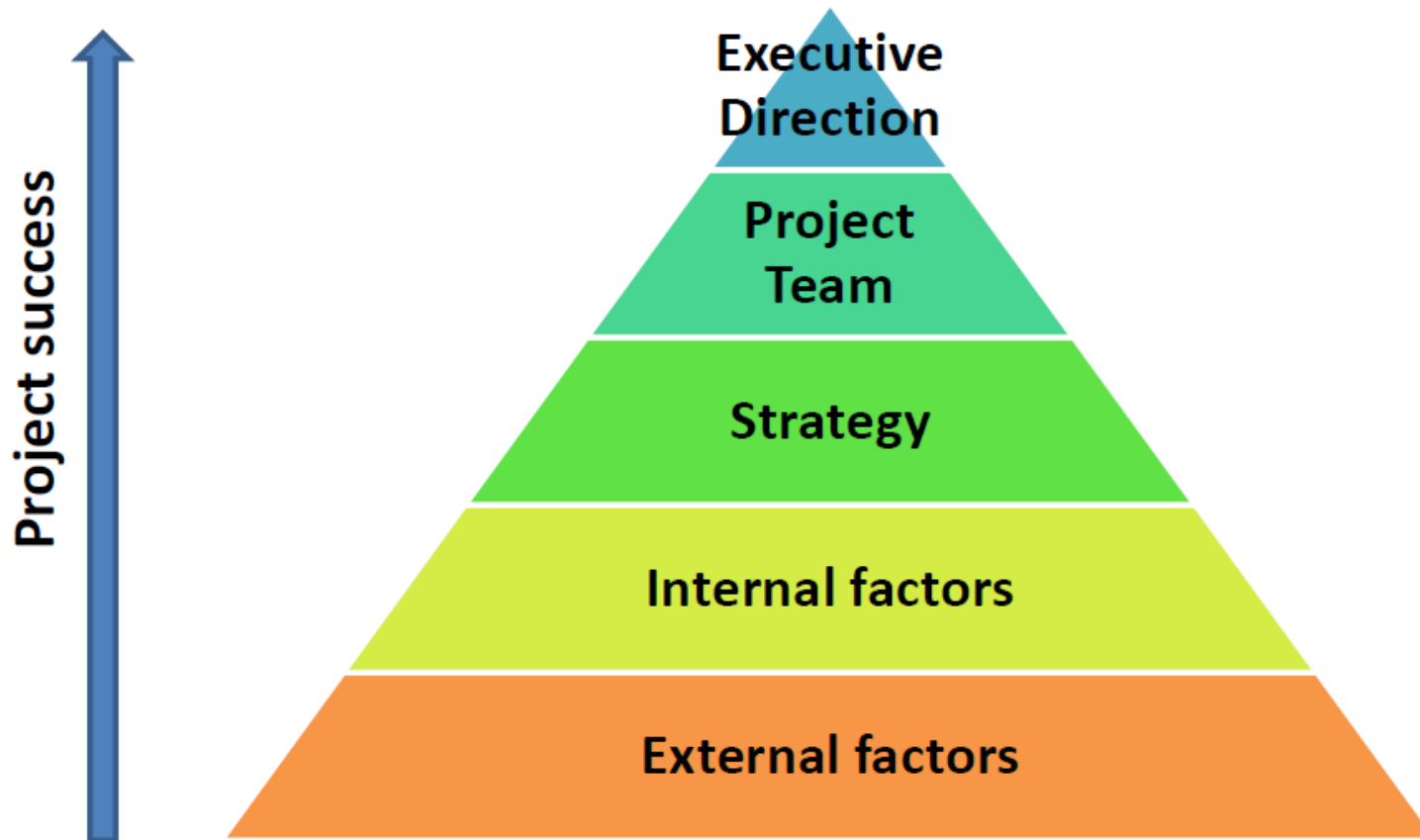
- a. Continuous improvement
- b. Lesson learned

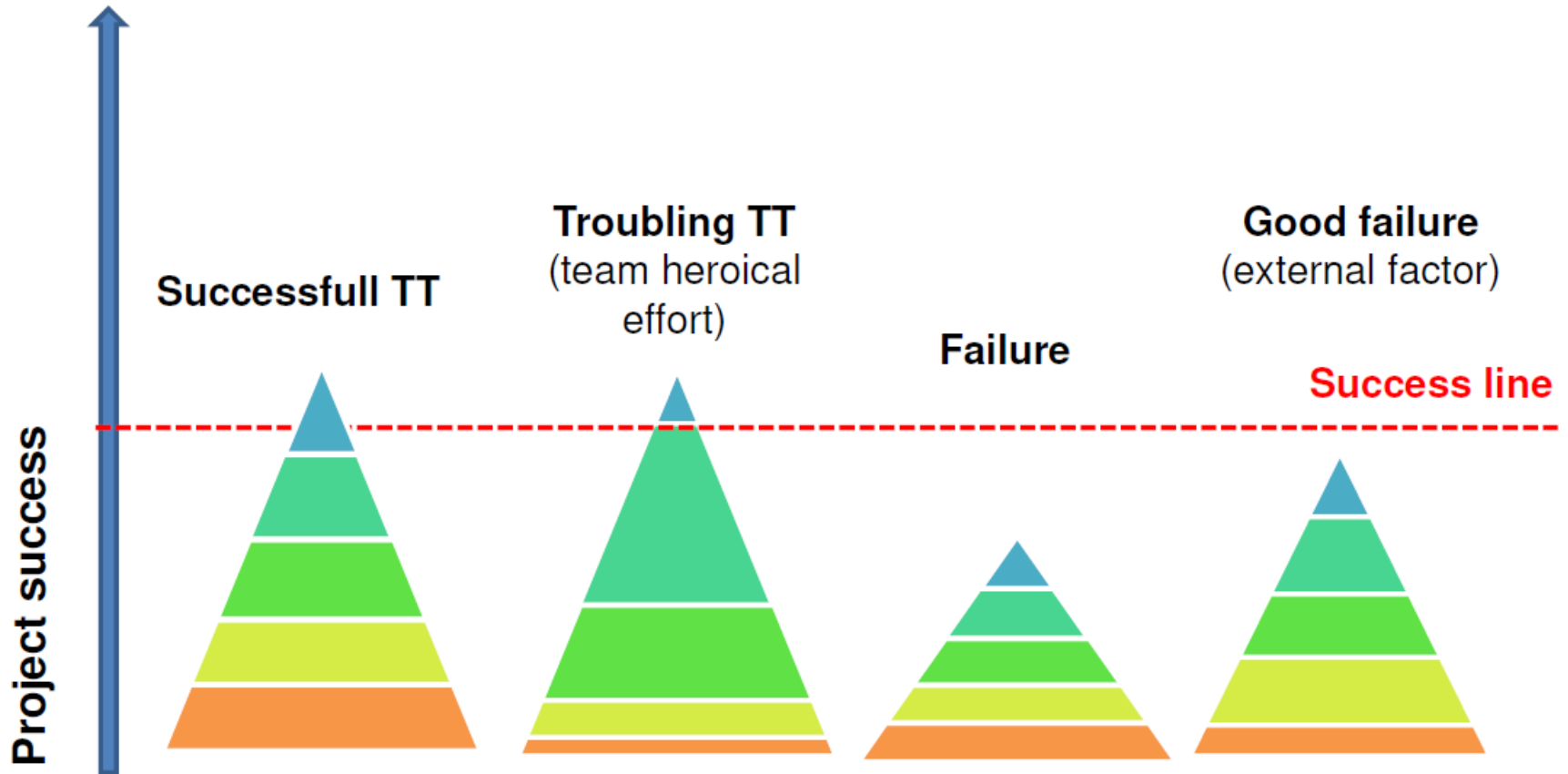
## 3.4.2 Multidisciplinary Technology Transfer Project Team

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

- 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 some cases project committee, which has a mainly consultant role, could be useful for the success of the project.







## 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!**





1. **EU GMP Guidance** for Medicinal Products for Human and Veterinary

- Vol 4, chapter 1, 4, 6 (Close to TT approach and definition)
- Vol 4, chapter III (Quality aspects, ie QAA, Management review)

2. **FDA Guidance** for Industry in Contract Manufacturing Arrangements for Drugs

3. **WHO Guidance** on TT in pharmaceutical manufacturing n.961, 2011

4. **TR-65 PDA**

5. **ISPE Technical documentation**

...under GMP!



# Technology Transfer ...in GMP

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 ...in GMP

- 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 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.**

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

## SOP for TT Protocol/report handling

- Chapter 1. *Application area*: Which kind of documents are needed
- Chapter 2. *Responsibilities*: Who is responsible 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

*What does project in pharma mean?*

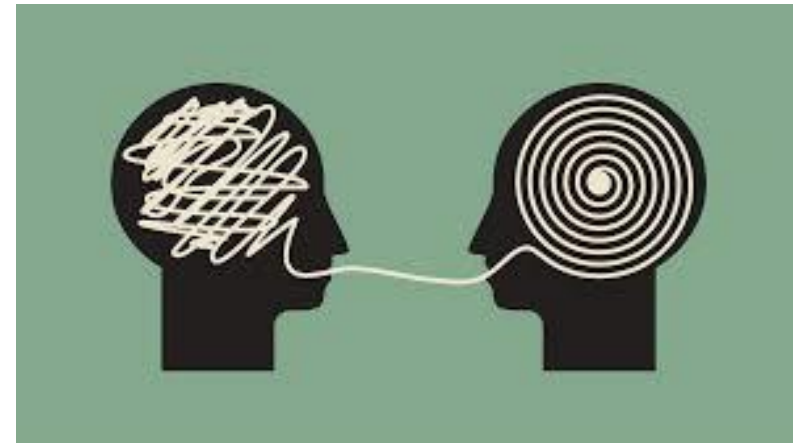
- *Multidisciplinary Context*
- *Be always focus on Patient as this is our final «Client»*
- *Dynamic and challenging environemnt*
- *5 main risks categories to be considered*
- *Map your internal & external factors to be sure we are taking the TT under control*

# Team role in pharma

Is the team critical for TT Project success?



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).

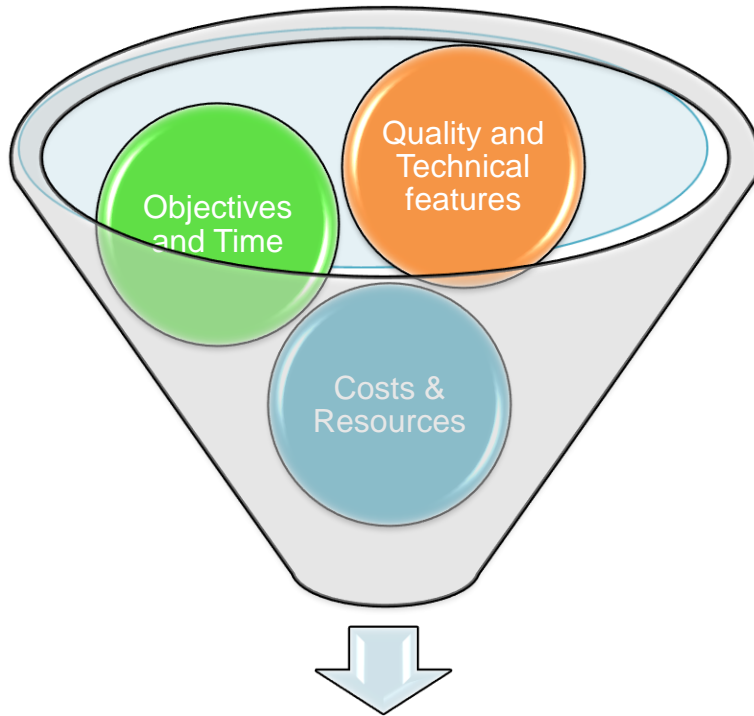


*Which are the main Project risks? – PDA TT IG 2018*

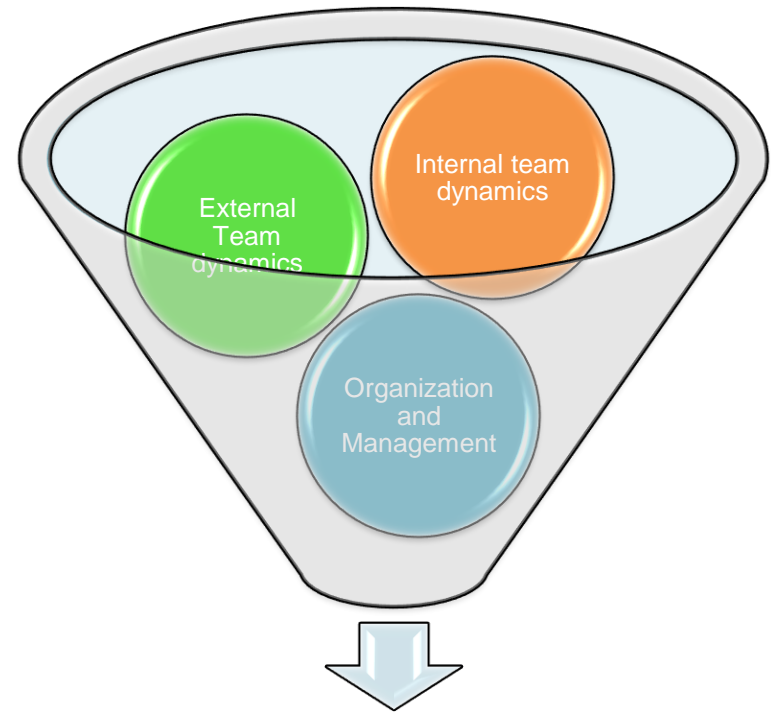
- 1. Project Scope missed or misunderstood*
- 2. Underestimating of new site/process impact on product attribute*
- 3. Lack of product/ process understanding*
- 4. Lack of communication*
- 5. Lack of escalation process*
- 6. Wrong estimation of time/resources/costs*
- 7. Lack of engagement of Team members*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



# Team role in pharma

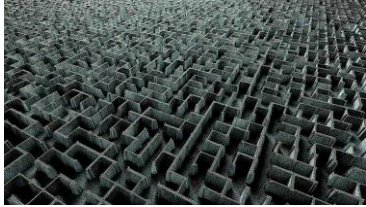


*Planning*



*Social Intelligence*

# Team role in pharma



Business

Regulatory  
Affairs

Manufacturing

Project  
Engineering

Quality

Development

Process  
Engineering

Regulatory

- *At each project phase, different functional areas need to interact to provide specific deliverables.*
- *Cross-functionality is a key component of all technology transfers requiring involvement from a wide range of functional areas*

Procurement

Analytical

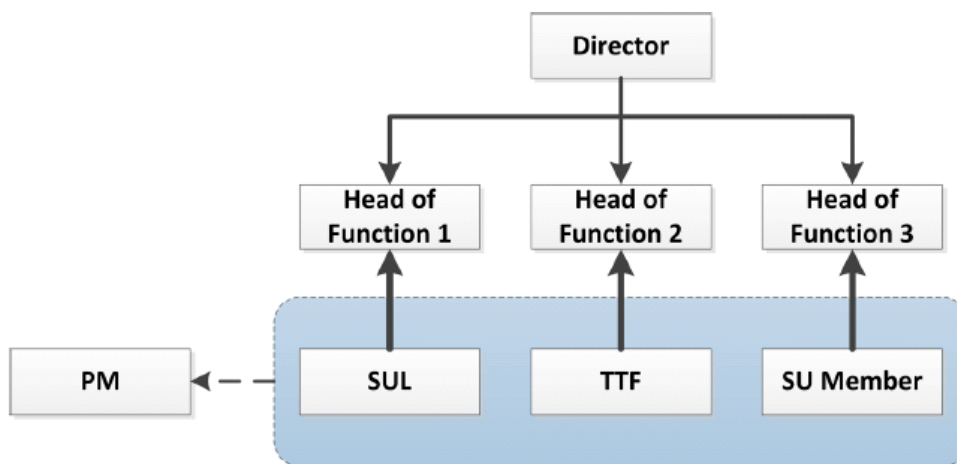
Supply Chain



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.

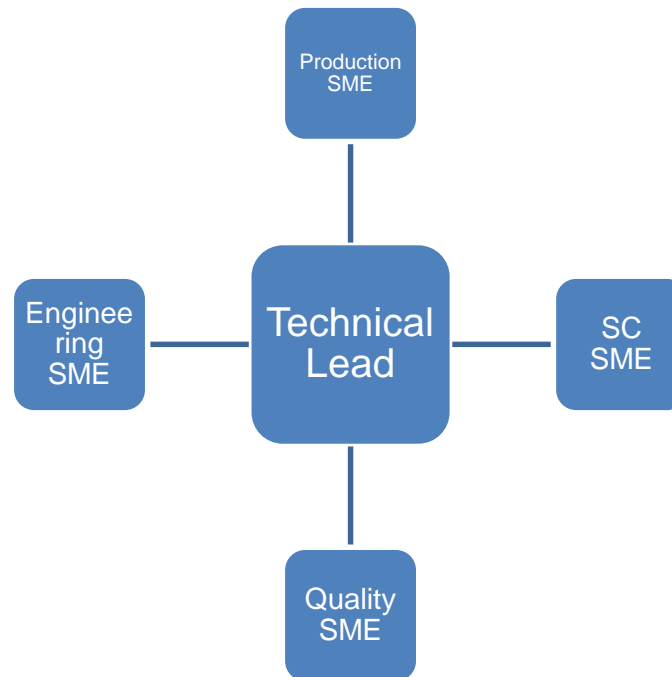
Two main organizational model are seen in the pharma environemnt: *light matrix* and *hard functional*

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



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.





# Team role in pharma

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.



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**



- 1) Weekly Technical Call
- 2) Weekly Project Management Call
- 3) Monthly Stirring Committee
- 4) Business Review meetings

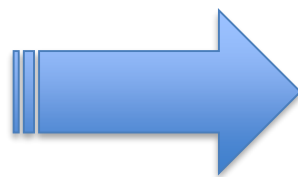


**Cultural / organizational differences to be considered and assessed!**

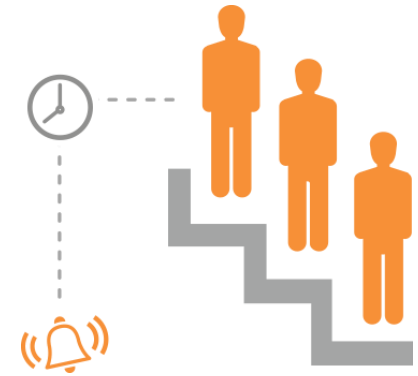
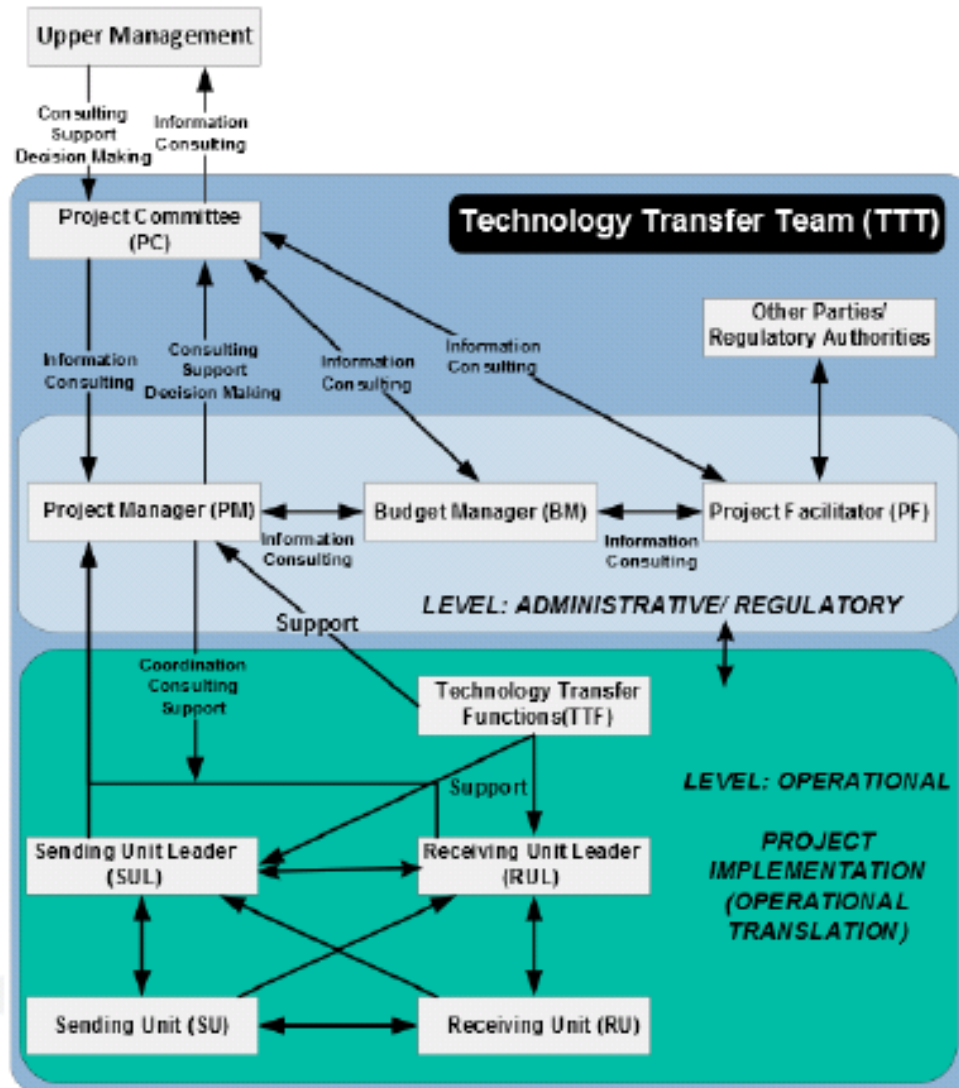


# Team role in pharma

#	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



# Team role in pharma



**Stakeholders** are individuals and groups, both inside and outside the Challenge team/start-up, who can:

- influence the success of the business plan and start-up
- be impacted by the new start-up
- actively support the start-up through funding, mentoring, etc.
- they are internal or external to the team/start-up



# Team role in pharma



**Stakeholders** are individuals and groups, both inside and outside the Challenge team/start-up, who can:

- influence the success of the business plan and start-up
- be impacted by the new start-up
- actively support the start-up through funding, mentoring, etc.
- handling of group dynamics is fundamental for process success
- they are internal or external to the team/start-up
- Stakeholder mapping is a key pharma process step
- Several tools are available to facilitate stakeholder mapping

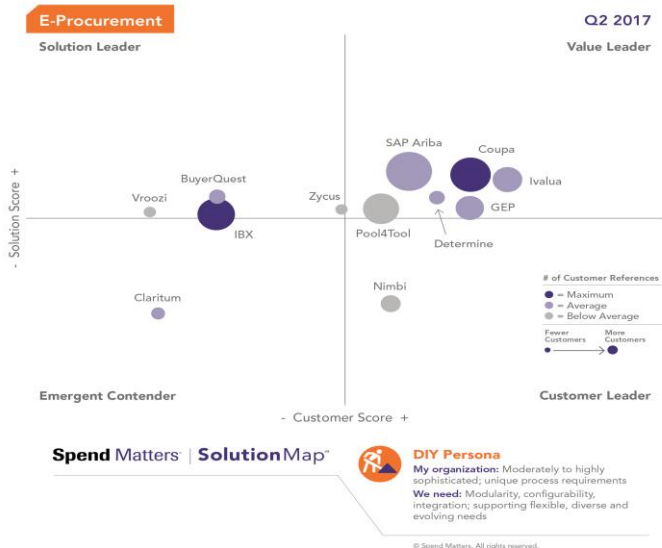


## The Stakeholder Analysis Process – tool 1

1. **Brainstorm** a list of Stakeholders, asking, “who can influence the success of my business plan and startup and who can be impacted by the project?” Segment the stakeholders into meaningful clusters as appropriate (functions, regions, etc.)
2. Ask, “to what degree do they have the **power to influence the success** of the ultimate startup?” Use the 1-5 scale shown on the Template (COLUMN O)
3. Next ask, “what is this stakeholder’s current **level of commitment to the startup**? How Favorably do they view the startup?” Use the 1-5 scale shown on the Template (COLUMN P)
4. Ask, “for our start-up, what does success look like to this stakeholder, what would **they consider to be wins**?” (COLUMN T)
5. Identify **proactive actions** to achieve these “wins”, and to engage them to increase their favorability.

## The Stakeholder Analysis Process – tool 2

1. **Brainstorm** on Stakedolders Dynamics
2. Track them with colored lines (influences, Defers, Antagonizes)
3. Track Power Level of each stakeholder identified
5. Identify **proactive actions** to achieve these “wins”, and to engage them to increase their favorability.



### 2. Prioritise your stakeholders



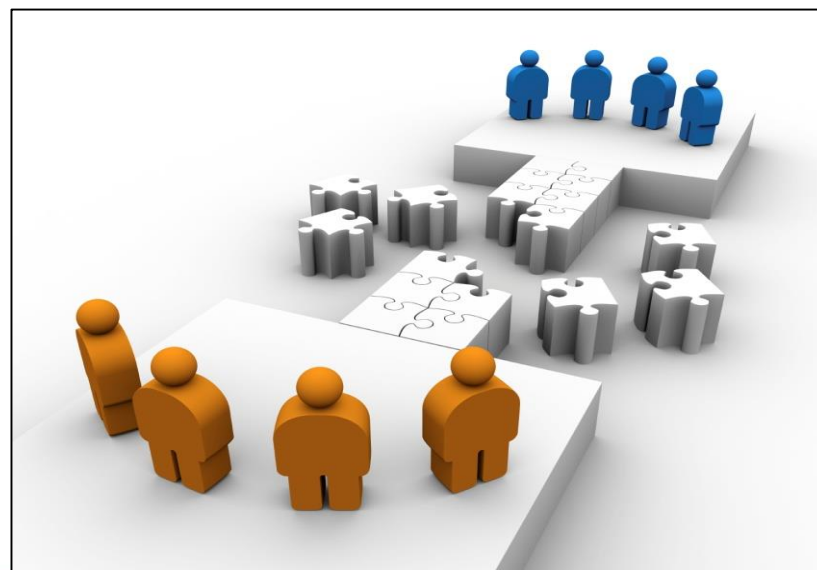


# PM Role in pharma tech transfer projects

Is the PM critical for TT Project success?

# PM Role in pharma tech transfer projects

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



- **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 manufacturing and routine supply**:
  - 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**

Role  Project Deliverable (or Activity)	Project Leadership									
	Technology Transfer (TT)	Business Management (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	IC
Meet the customer and verify information	A/R	A/R	I	I	I	C/I	I	I	C	IC
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	I
Materials Order and delivery	I/C	I/C	I	I	A	I/C	I	I	I	I
Equipment validation and manufacturing scheduling	I/C	I/C	I	I	R	A/R	I	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



## 1. Transactional Leader

The best way to understand transactional leadership is to think of a typical transaction: **I give you this, and you do this in return.**

**Pro:** Confusion and guesswork are eliminated, because tasks and expectations are clearly mapped out by the leader.

**Con:** Due to the rigid environment and expectations, *creativity and innovation are stifled.*

## 2. Transformational Leadership

Again, with this leadership style, it's all in the name: Transformational leaders seek to change (ahem, transform) the businesses or groups in which they lead by inspiring their employees to innovate.

These leaders are all about making improvements and finding better ways to get things done.

**Pro:** Leaders are able to establish a high level of trust with employees and rally them around a shared vision or end goal.

**Con:** In environments where existing processes are valued, this desire to change things up can ruffle some feathers.



# PM Role in pharma tech transfer projects

## 3. Servant Leadership

Servant leaders operate with this standard motto: ***Serve first and lead second***. Rather than thinking about how they can inspire people to follow their lead, they channel the majority of their energy into finding ways that they can help others.

**Pro:** This approach *boosts morale* and leads to a high level of trust, which results in better employee performance and a more positive company culture overall.

**Con:** *It's challenging*. Constantly pushing your own needs and priorities to the backburner isn't something that comes as second nature for most of us.

## 4. Democratic Leadership

You might also hear this leadership style referred to as “participative leadership.” Leaders in this category run groups and projects like...well, a democracy.

**Pro:** *Creativity and innovation are encouraged*, which also improves job satisfaction among employees and team members.

**Con:** Constantly trying to *achieve consensus* among a group can be inefficient and, in some cases, costly.

## 5. Autocratic Leadership

Autocratic leadership exists on the opposite side of the spectrum from democratic leadership.

You can think of this as a *“my way or the highway” approach*.

**Pro:** *Decisions are often made quickly and strategically*, and teams are kept on track as a result.

**Con:** *Employees can feel ignored, restricted*, and—in the absolute worst of cases—even abused.

## 6. Bureaucratic Leadership

Bureaucratic leadership goes “by the book,” so to speak. With this leadership style, there’s a *prescribed set of boxes to check in order to be a true leader*.

For example, bureaucratic leaders have hierarchical authority—*meaning their power comes from a formal position or title*, rather than unique traits or characteristics that they possess.

**Pro:** There’s *plenty of stability*. Since this is a systematized approach to leadership, things remain constant even through personnel changes and other shifts that threaten to rock the boat.

**Con:** It’s tempting to fall into the “we’ve always done it this way” trap. This *approach can be inflexible* and neglect to leave room for creativity or ideas from employees.

## 7. Laissez-Faire Leadership

Do you remember the term “laissez-faire” from your high school French or history class? If not, let’s refresh your memory. This is a French term that translates to “*leave it be,*” which pretty accurately summarizes this hands-off leadership approach. It’s the exact opposite of micromanagement.

**Pro:** This level of trust and *independence is empowering* for teams that are creative and self-motivated.

**Con:** *Chaos and confusion* can quickly ensue—especially if a team isn’t organized or self-directed.

## 8. Charismatic Leadership

You know what it means to have a *lot of charisma*, and that’s exactly what these leaders possess.

Charismatic leaders have magnetic personalities, as well as a lot of *conviction to achieve their objectives*.

Rather than encouraging behaviors through strict instructions, these leaders use eloquent communication and persuasion to unite a team around a cause.

**Pro:** Charismatic leaders are very inspirational and effective at getting an entire group invested in a shared objective.

**Con:** Due to their intense focus, it’s easy for these leaders to develop “tunnel vision” and lose sight of other important issues or tasks that crop up.



- **Is there a right style to lead a TT Project in pharma?**

**NO because....**

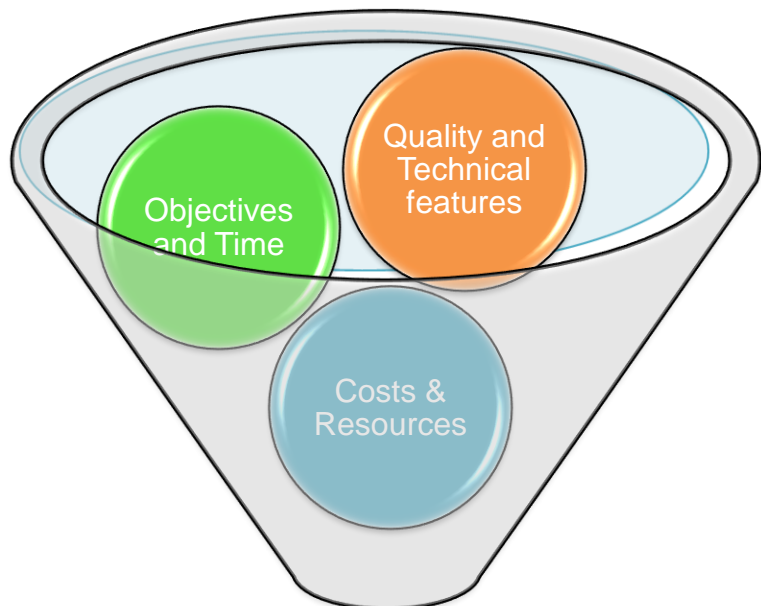
- Which is the best style I can use with this team?
- Which is the best style I can use in this situation?
- Which is the best style I can use with this RU or SU?
- What does it happen if I go against my Leadership Nature?



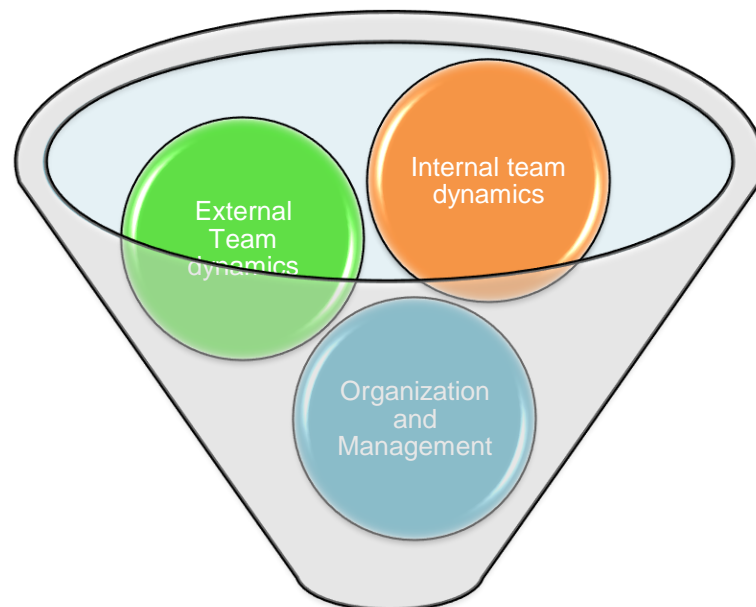
*Get the best from your personal style and leverage human being resilience to be flexible where project requires it!*

# Pharma Tech Transfer Projects governance

Which does governance mean in TT?



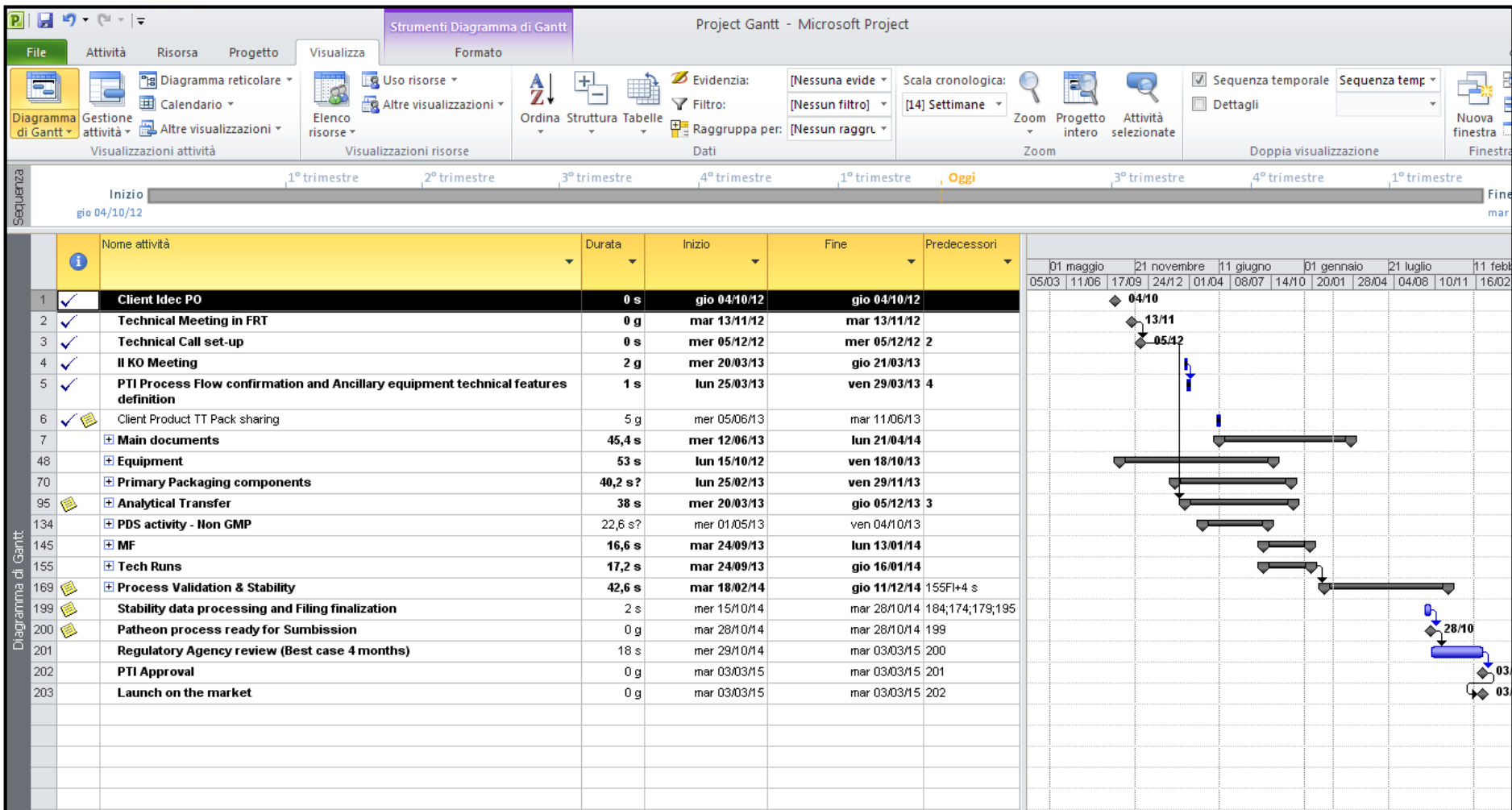
*Planning*



*Social Intelligence*

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

**Define scope, plan, execute and track**



action log - Microsoft Excel

Strumenti tabella

Home Inserisci Layout di pagina Formule Dati Revisione Visualizza Sviluppo Componenti aggiuntivi Progettazione

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Celle

Somma automatica Riempimento Cancellazione

Ordina e filtra Trova e seleziona

Modifica

F15

	A	B	C	D	E	F	G	H	I	J
1		Client: XXXX								
2		Project: YYYY								
3		Status	Action Item	Assigned To Company	Assigned to Team Member	Stream	Discussion Date	Due Date	Execution date (if applicable)	Comments and comment date
4	1	In process								
5	2	In process								
6	4	Done								
7	5	In process								
8	11	Done								
9	12	In process								
10	16	In process								
11	18	Done								
12	23	In process								
13	28	In process								
14	31	In process								
15	32	In process								
16	33	Done								
17	37	In process								
18	38	In process								
19	39	In process								
20	40	In process								

action log - Microsoft Excel

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Celle

Somma automatica Riempimento Cancella

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Modifica

B19

	A	B	C	D	E	F	G	H
1	Risk id	Risk status	Risk Description	Impact of risk	Mitigation plan	Mitigation completion date	comments	
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								




# Pharma Tech Transfer Projects governance




A	B	C	D	E	F
Docs/Info/Topic	YES	NO	N/A	Is there any disalignment/issue to be solved? (Y/N)	Action List (in case of naps in column E)
1.0 Environmental Health & Safety					
1.1 Complete EHS Questionnaire					
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 - CER, 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.g. 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			
Role	Project Leadership		
	Sending Unit	Receiving Unit	Sponsor
Project Deliverable (or Activity)			
<b>Project Assessment</b>			
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
<b>Project Planning</b>			
Overall Technical Assessment preparation		R/A	
		A	
		R/A	
		A	
		R/A	I
		A	I
		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



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	
[Redacted]	[Redacted]	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		
<b>Site Total</b>			75	90	91	38	40	52	17	56	56				50		
Measurement	Color Code	Range															
Red		Less Than 90%															
Yellow		90% - 94%															
Green		Over 95%															

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		
[Redacted]	[Redacted]	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				N/A	
		Registration	N/A	N/A	N/A	N/A	N/A	92	N/A	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				N/A	
		TT	N/A	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	N/A				100	
		TT	N/A	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				N/A	
		Development	N/A	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	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				N/A	
		TT	N/A	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	N/A	N/A				100
		<b>Site Total</b>			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%															

*Human Beings, who are almost unique in having the ability to learn from the experience of others are also remarkable for their apparent disinclination to do so..*

*Douglas Adams*

**What is lesson learned...**terminology to identify actions or activities related to the act of learning from experience to obtain improvements of the current way of working.

**Idea and main concept behind the definition...**using a robust, structured and formal process team can reduce risk of doing same mistakes and increase success rate of their projects

**LL circle:** Data Collection – Data Analysis – Action Plan definition – Plan Execution

- Data collection : Collect data, facts, from previous projects/TT
- Data Analysis : Analyze data to confirm event, measure severity and prevention rate
- Action Plan definition: Define improvements to the existing procedure or ways of working
- Plan execution: Execute plan changing internal procedure and adopting appropriate communication plan

**Lesson Learned Capability:** need to be established, trained and improved step by step.

# Pharma Tech Transfer Projects Risk Management

What does RM mean in TT?

- **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



## Welcome to the ICH official website

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development, so that the benefits of international harmonisation for better global health can be realised worldwide. ICH's mission is to achieve greater harmonisation to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. Download the [ICH 20th Anniversary Publication](#)

## Discover ICH Products



**M4: CTD**

The agreement to assemble all the Q, S, and E information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes... [\(more\)](#)

### Help to Shape the ICH Guidelines

by responding to one of our consultations. Your contribution will then be considered by the relevant ICH Working Group.

[Draft Guidelines](#)  
[Q&A Documents](#)



### Recent News

10 February 2014

[Invitation to Submit an Expression of Interest for the MSSO Tender](#)

ICH is considering a Call for Tender in 2014 for the contract for the MedDRA Maintenance...

## ICH Training



## Vision / [About ICH](#) / [Home](#)

### Mission

ICH's mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.

Launched in 1990, ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States.

Regulatory harmonisation offers many direct benefits to both regulatory authorities and the pharmaceutical industry with beneficial impact for the protection of public health. Key benefits include: preventing duplication of clinical trials in humans and minimising the use of animal testing without compromising safety and effectiveness; streamlining the regulatory assessment process for new drug applications; and reducing the development times and resources for drug development.

Harmonisation is achieved through the development of ICH Tripartite Guidelines. The Guidelines are developed through a process of scientific consensus with regulatory and industry experts working side-by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final Guidelines.

### Quote

*"Coming together is a beginning. Keeping together is progress. Working together is success."*

**Henry Ford**



### ICH at a Glance...

[Overview of ICH - Presentation](#)

[Overview of ICH - Summary](#)





Stability Q1A - Q1F	▼
Analytical Validation Q2	▼
Impurities Q3A - Q3D	▼
Pharmacopoeias Q4 - Q4B	▼
Quality of Biotechnological Products Q5A - Q5E	▼
Specifications Q6A- Q6B	▼
Good Manufacturing Practice Q7	▼
Pharmaceutical Development Q8	▼
Quality Risk Management Q9	▼
Pharmaceutical Quality System Q10	▼
Development and Manufacture of Drug Substances Q11	▼
Cross-cutting Topics	▼





- 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.



Two primary principles of quality risk management are:

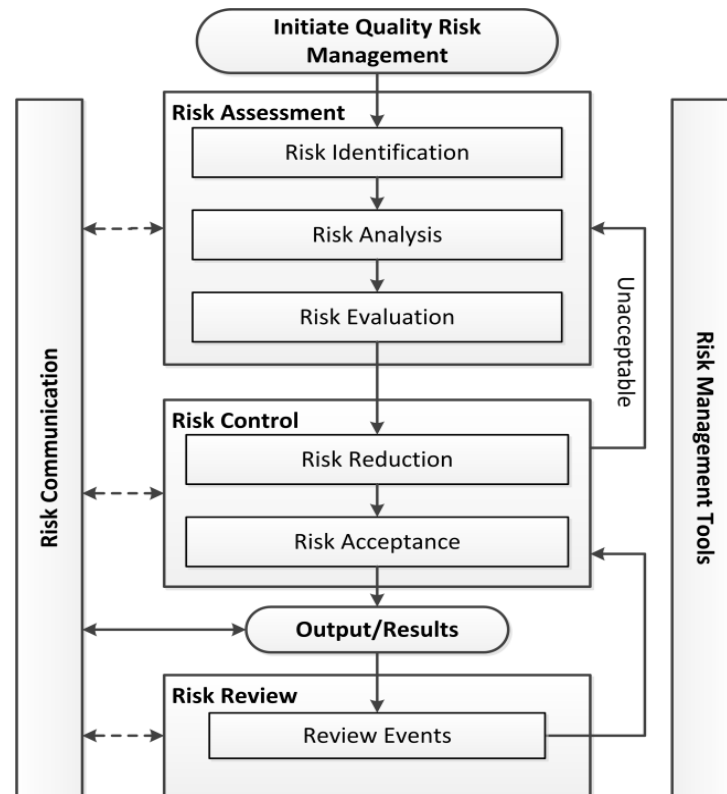
- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient;
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

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

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.”



## 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

- ❑ 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

Stage Gate	Strategy	Analytical and Quality Control Testing	Regulatory	Process	Facilities/ Engineering	Risk Management and Components
<b>1</b> Planning	Perform preliminary risk assessment prior to beginning late-phase development using risk ranking and/or preliminary hazards analysis approach.					
<b>2</b> 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
<b>3</b> TTP implementation and Qualification	Review and update risk assessment/PHA from stage gate 2 if necessary. Mitigate identified high risks.					
<b>4</b> 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



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)

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

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

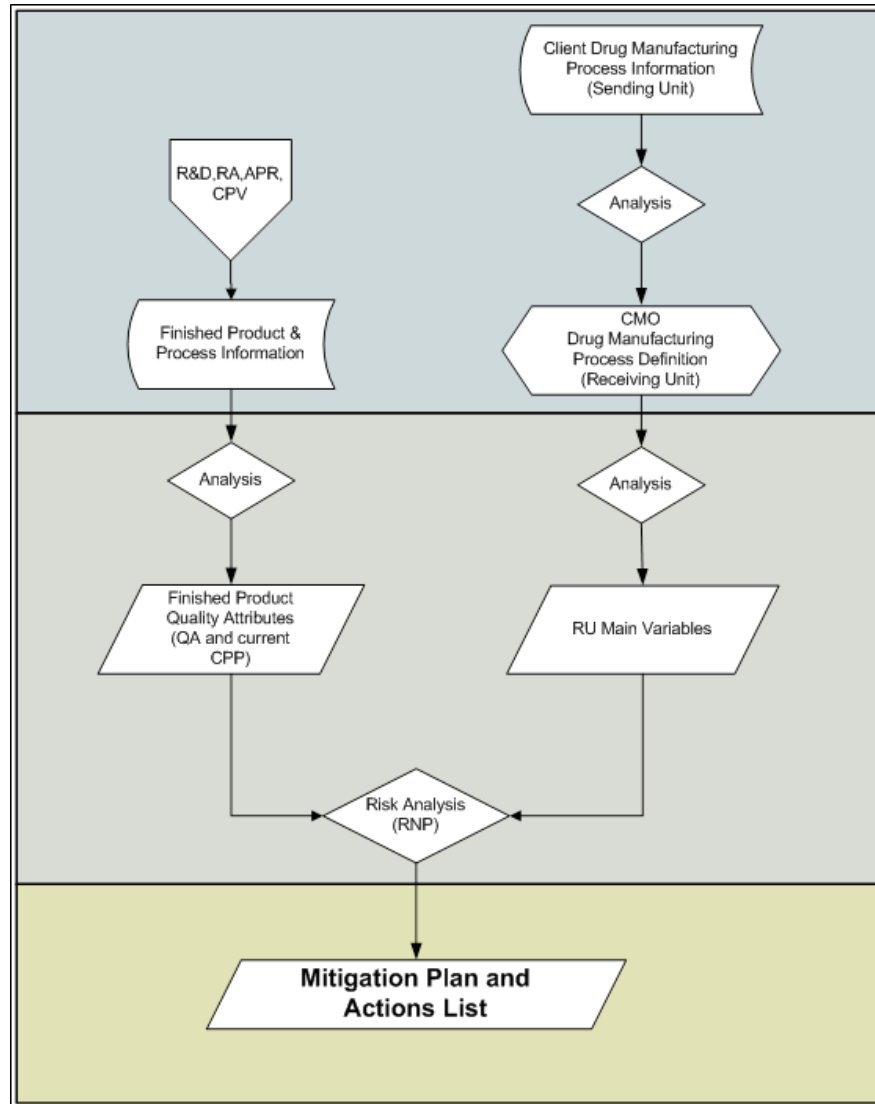
Occurrence	Risk Classification	Value
Highly improbable or impossible that the negative event occur	Remote	1
Some possibility that the negative event will occur	Medium	2
Highly probable or certain that the negative event will occur	High	3

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

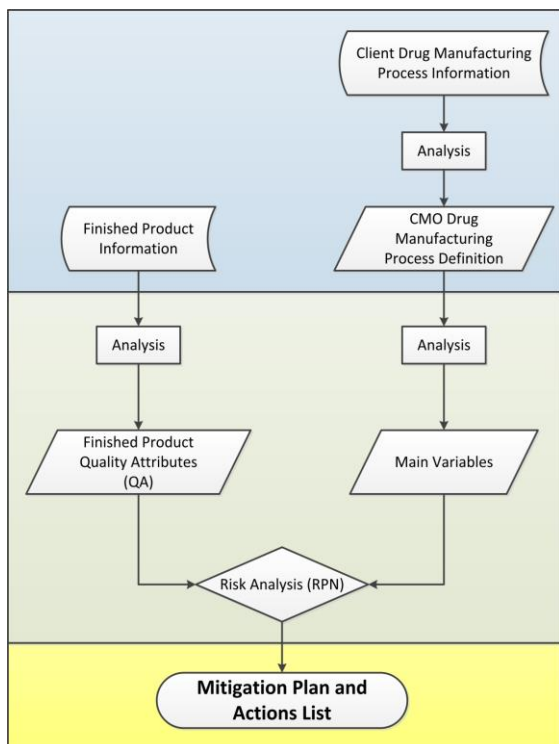


***Data collection***

***Data evaluation***

***Data use***

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

## 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/case of lack of quality attributes description	Severity	Occurrence	Detection	RPN	Consideration/Action	
Primary Packaging & GMP materials	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 coating material can modify the chemical solution profile	3	2	3	18	The same stoppers will be used to guarantee no anomalous interaction with stopper coating and rubber.	
	Appearance		Substances released from the stopper or from the coating can induce flocculation or coagulation events in the solution	3	2	1	6	Stability data were collected by the SU; no interaction issues were reported to RU.	
			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 sterilization 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.	
	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		
	Vials	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 ADLs for each defect. These ADLs are in line with the cosmetic requirements received by the SU.

Analysis				Risk Priority Number Evaluation				Mitigation Plan			
Item	Variable	QA Impacted	Potential criticality/case of lack of quality attributes 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.			
		Osmolality	Dissolution speed insufficient for complete dissolution and an homogenous system	3	3	1	9	The User Requirements of the RU tank have properly defined the mixing needs based on the characteristics of the colloidal system.			
		Appearance	Mixing system not appropriate to guarantee uniform batch mixing	3	3	3	27	The initial evaluation and information sharing between SU, RU and the disposable technology Supplier have identified the appropriate mixing device.			
	Density			Temperature of the system out of range specified by the SU	2	1	1	2	The PG challenge of the mixing system will include appropriate tests suggested by the supplier/owner of the technology.		
				Sampling mode device impact on the analysis results	3	2	2	12	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.		
				Preparation time impact on bioburden level of the final compounded solution	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.		
				Validation activities will include hold time challenges according to a dedicated protocol.	3	2	2	12	Chemical characteristics and microbiological attributes of the solution will be analyzed.		
				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.		
				Use Grade C, filter the solution 3 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

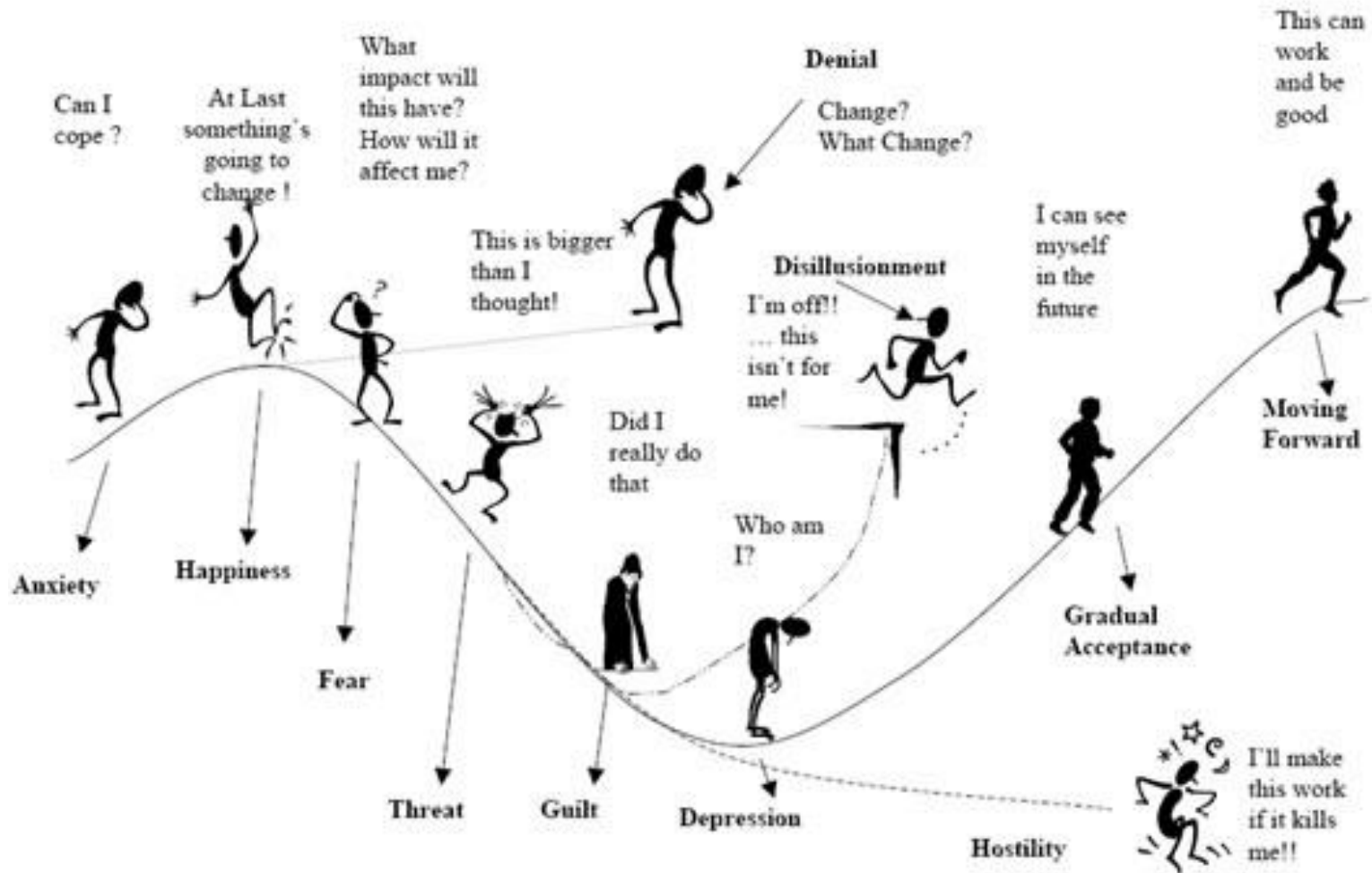
Analysis				Risk Priority Number Evaluation				Mitigation Plan
Item	Variable	QA Impacted	Potential criticality/cause of lack of quality attribute description	Severity	Occurrence	Detection	RPN	Consideration / Action
Process	Mixing and compounding	pH	Dissolution speed is insufficient for complete dissolution 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.
		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	<u>No further action needed.</u> 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 µm + 0.22/0.2 µm in grade C area and 0.22/0.2 µm 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.



# Change Management

Which does CM mean in TT?

# Change Management in TT



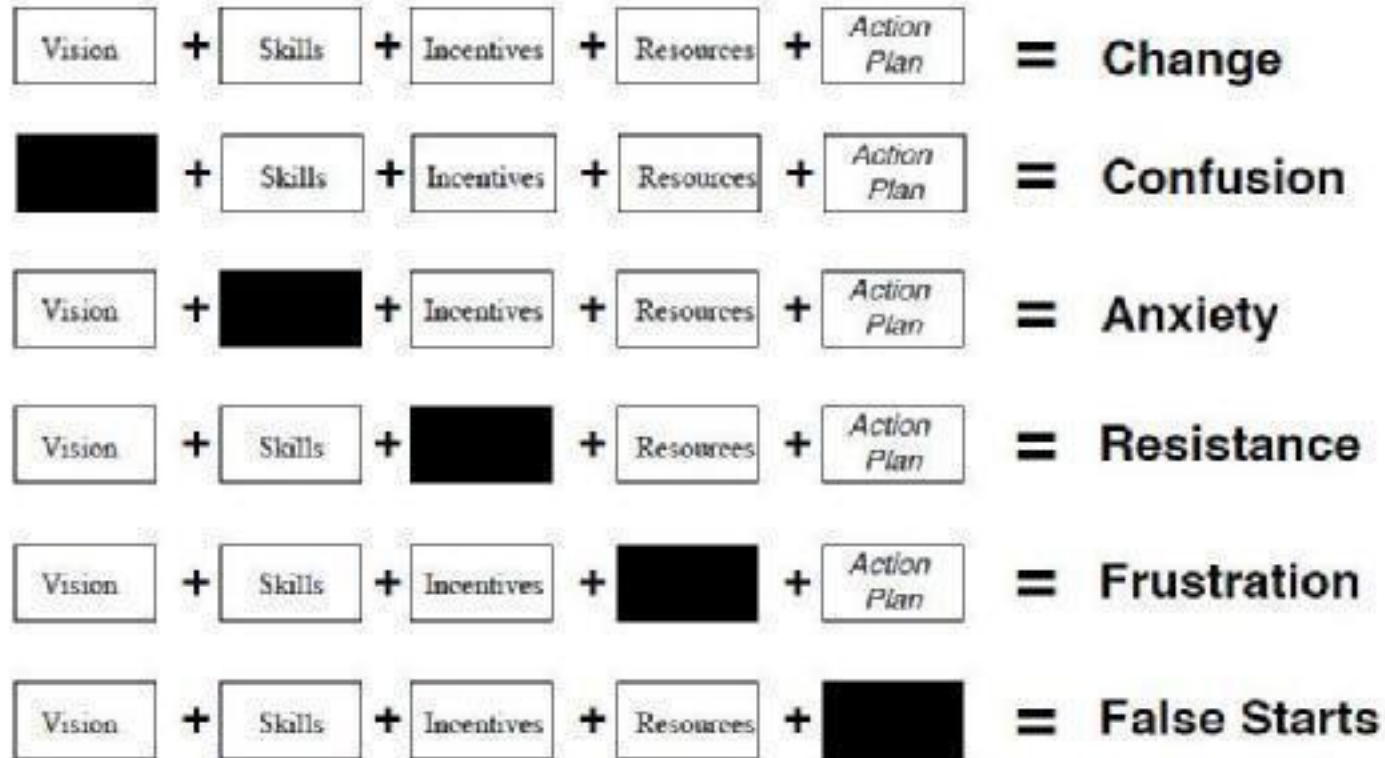
- Changes are frequent in TT project execution and can have big impact on project success
- Change management is not an easy skill to establish, train and improve
- Change management is time/costs/resources consuming
- Human nature tends to avoid or delay changes
- Team members are not challenged or selected for change management skills but based on technical skills usually



*Change Management is a quite big issue in TT Project and special focus has to be done on team ability to handle change*



## Managing Complex Change



Adapted from Knoeter, T., Villa R., & Thousand, J. (2000). A framework for thinking about systems change. In R. villa & J. Thousand (Eds.), *Restructuring for caring and effective education: Piecing the puzzle together* (pp. 93-126). Baltimore: Paul H. Brookes Publishing Co.

## Top three reasons which stops change management

- 1. Day-to-day tasks are overwhelming to most
- 2. There isn't a lot of alignment around what exactly organizational priorities are
- 3. Even if the executives understand the priorities, that doesn't mean there's alignment between that and the daily work

This is, in essence, why change management is hard. Moreover....

- Several terms connected with change management are “fluffy” (mindset, vision, strategy)



## Tips:

- Standard Procedures in place to handle changes from a Business (Costs/Timelines) perspective
- Standard Procedures in place to handle GMP changes
- Escalation process in place and standardized
- Communication process in place and standardized

*Change management does need to start with senior decision-makers, which is incredibly fraught: these guys are evaluated differently, their overall picture of issues and strategy is different from yours; overall they perceive the organization and its strengths/weaknesses at a much different level than the people who actually need to be boots on the ground in the change management process.*



## Always starts with three things:

- Care:** Why are we doing this change management process? Why are we doing it now? Is it because we might get disrupted? Are we fundamentally not able to compete anymore? Are we financially behind? What's the purpose of the change management now?
- Listen:** Listen all over the org. and listen to your team! These people are closer to the "floor" and know stuff. They get the pain points. They know what we need to change and how. Too often, we believe hierarchy = formal power (yes, still true) = those people know what's best. That's where the logic falls off a cliff. Listen to the upper management to understand long term strategy and mix the two levels...understand in the specific project moment you are which is the most important for the project success.
- Align:** Everyone misses this area, and it requires a lot of work...When I say "align," here's the deal.



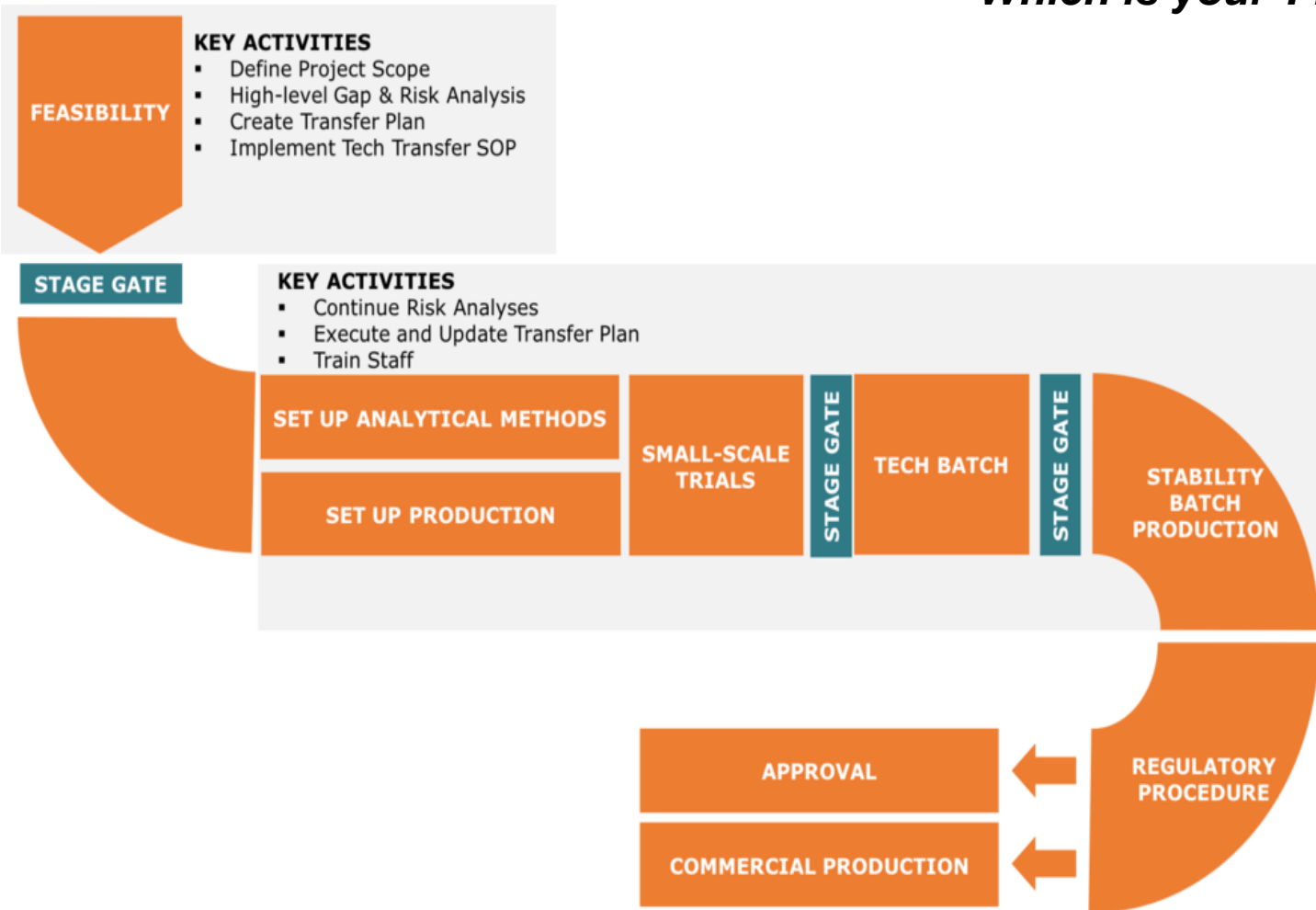
# Technology Transfer – Take Away from PDA TT IG



## **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

*Which is your TT RoadMap?*



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)*



- Risks can be overestimated and a new risk will come!
  - Pay attention...

**Info coming from development department:** API oxidizes quickly if exposed to Air/O<sub>2</sub>. Dispensing is done under N<sub>2</sub>. 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 O<sub>2</sub> residual less than 0,5% during dispensing

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

## First TT Batch failed for API assay



Investigation identified the root cause in the Dispensing Hood

The N<sub>2</sub> atmosphere created with the hood enhances the «electrostatic charge environment» which impacts the accuracy 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 – Risks can be hidden everywhere; 360 view is needed

- ❑ Commercial site (big pharma) located in EU
- ❑ The site is a center of excellence for Analytical technology within the network
- ❑ The site has an intense Innovation program on analytical technology and a periodic gap analysis is done on analytical equipment to identify “aged” instrumentation
- ❑ The current AA-ABS / IPC equipment was identified as critical → replacement program was put in place





***Major Risks/Actions identified:***

- Gap Analysis on all the methods done on the equipment and mitigation plan for implementation (including disposable equipment/reagents/utilities/Spare parts)
- Gap Analysis on the knowledge and training program within the lab
- RA Gap Analysis to identify RA actions
- Benchmarking on the network to get information available on same technique already in place somewhere else



***Results:***

- Technology replacement was successfully completed on time and on budget
- No issue in knowledge and use of the equipment
- One of the well established process in the plant starts to give issue in IPC
- IPC requires AA-ABS and was impacted by the replacement of the instrument
- The quantitation limit of the new equipment was 100x more than the old one
- Small variation of concentration ( $\Delta$ ppm) was detected and re-calculated based on the dilution steps done in lab, brings assay out of IPC range

*IPC assay range during process dilution was established based on the old analytical technique. No assessment was done during analytical method implementation on manufacturing process, impact on operations missed*



- Technology Transfer – Risks can be hidden everywhere; 360 view is needed

- Commercial site (CDMO) located in EU
- They receive a new process (lyo sterile small molecules) from a client in EU
- Process Technology is well known
- Process is already commercial with a good pack of technical information and well known commercial story (APR, dev, complaints, etc)
- Scale up or down are not part of the TT, same BS is transferred
- Analytical package is well transferred as well and not new methods are implemented in the R lab
- Process flow is maintained equal to previous one including equipment and primary packaging
- Secondary packaging is not part of the transfer
- Lyo cycle was developed and well established

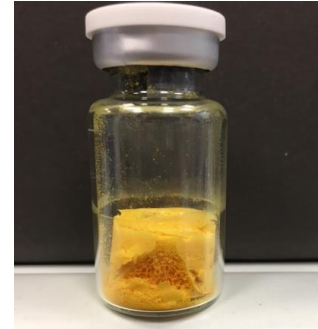
### ***Major Risks/Actions identified:***

- RA completed as one single team, between RU & SU; major risk was the difference in lyo equipment
- Development activities planned focusing on operative parameters during the cycle (T ranges and P ranges during lyo steps) and potential impact on product quality (KF, appearance, reconstitution, impurity profile, lyo texture)
- No concerns based on lyo small scale tests -> Pre-PPQ planned and done



## Results

- Pre-PPQ 28% of collapsed vials
- RC analysis -> Different T of the product during freezing and primary drying step
- Process Analysis ->  $\Delta T$  causes in the process ?
- *lyo chamber T at the beg of the lyo cycle after cip/sip cycle, due to different cooling down procedure. Evaluation done in small scale (not representative of real commercial conditions); robustness not repeated.*





- Technology Transfer – Risks can be hidden everywhere; 360 view is needed

- ❑ Medium-small company family owned – new product to be transferred to CDMO for capacity issue
- ❑ Basic Process Technology and well established
- ❑ Process characterization well done and scale-up studied already completed
- ❑ Analytical package is well transferred as well and not new methods are implemented in the R lab
- ❑ Process flow is maintained equal to previous one primary packaging





### ***Major Risks/Actions identified:***

- RA completed as one single team, between RU & SU; major risk was the difference in scale-up from SU and RU but studied already done to evaluate impact in QA
- Equipment gap analysis completed with no major risks
- Standard challenge pack considered in the first Eng batch due to scale-up
- Pre-PPQ planned and successfully completed
- PPQ completed successfully



### **Results**

- TT went very well, according to plan and budget

**SO WHAT?**

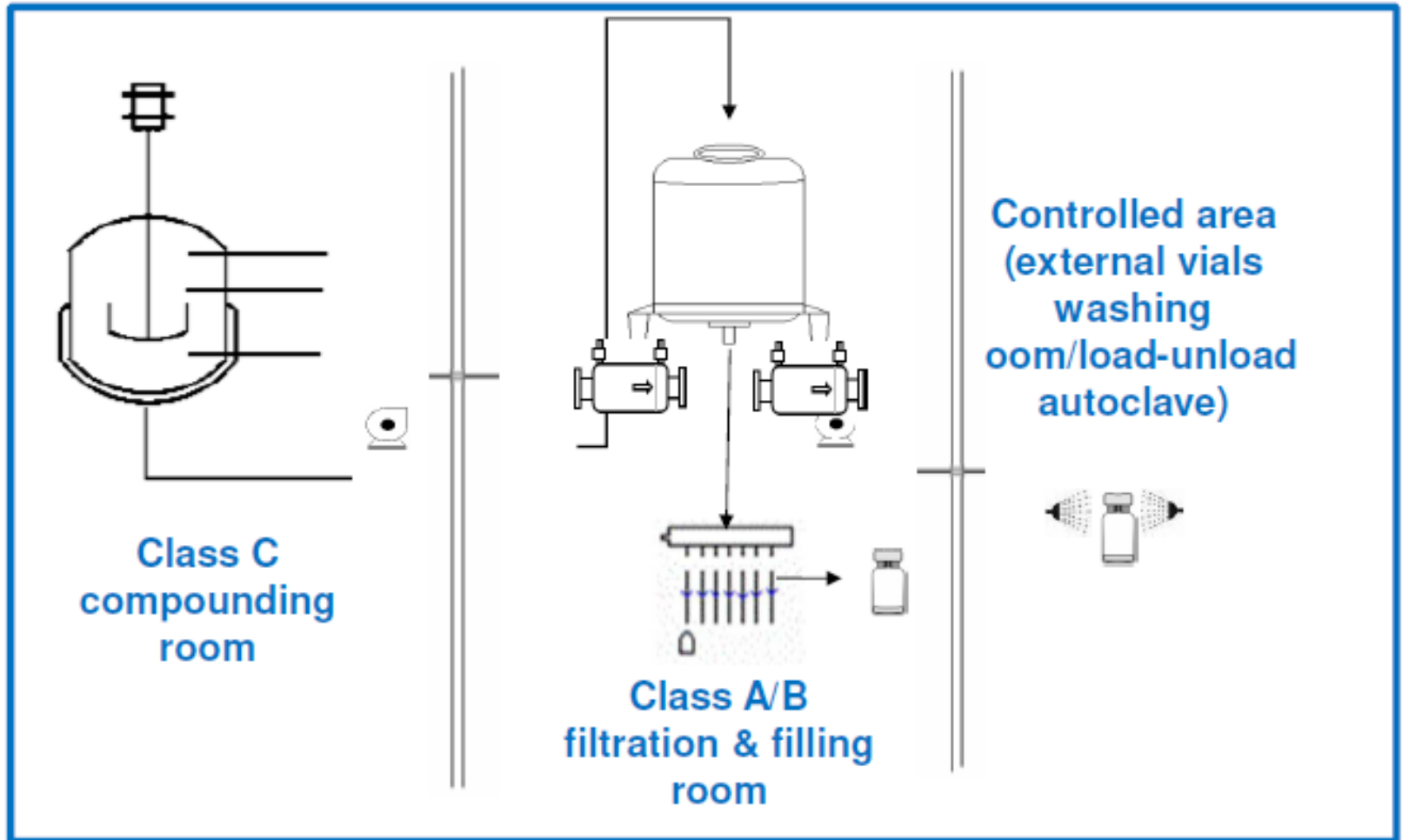
- Commercial production start delayed of 2 years
- API supplier had 483 due to compliance issue, not backup supplier validated to speed up the overall TT (DS+DP)
- New API supplier needed and commercial supply disrupted



- Technology Transfer – HL Risk Analysis

- **Product A:**
  - Sterile solution in vial
  - High potent drug
  - Complex formulation
- **Partial transfer:**
  - Fill&finish, analysis and release transfer
- **Partially blind transfer:**
  - No contact with the responsible CMO but only with the MAH
- **Intercompany transfer:**
  - The bulk manufacturing site, responsible also of product development, is external
- **Main challenges:**
  - Complex manufacturing process/new for the receiving site
  - Different manufacturing processes
  - Challenging timelines

## Receiving site equipment

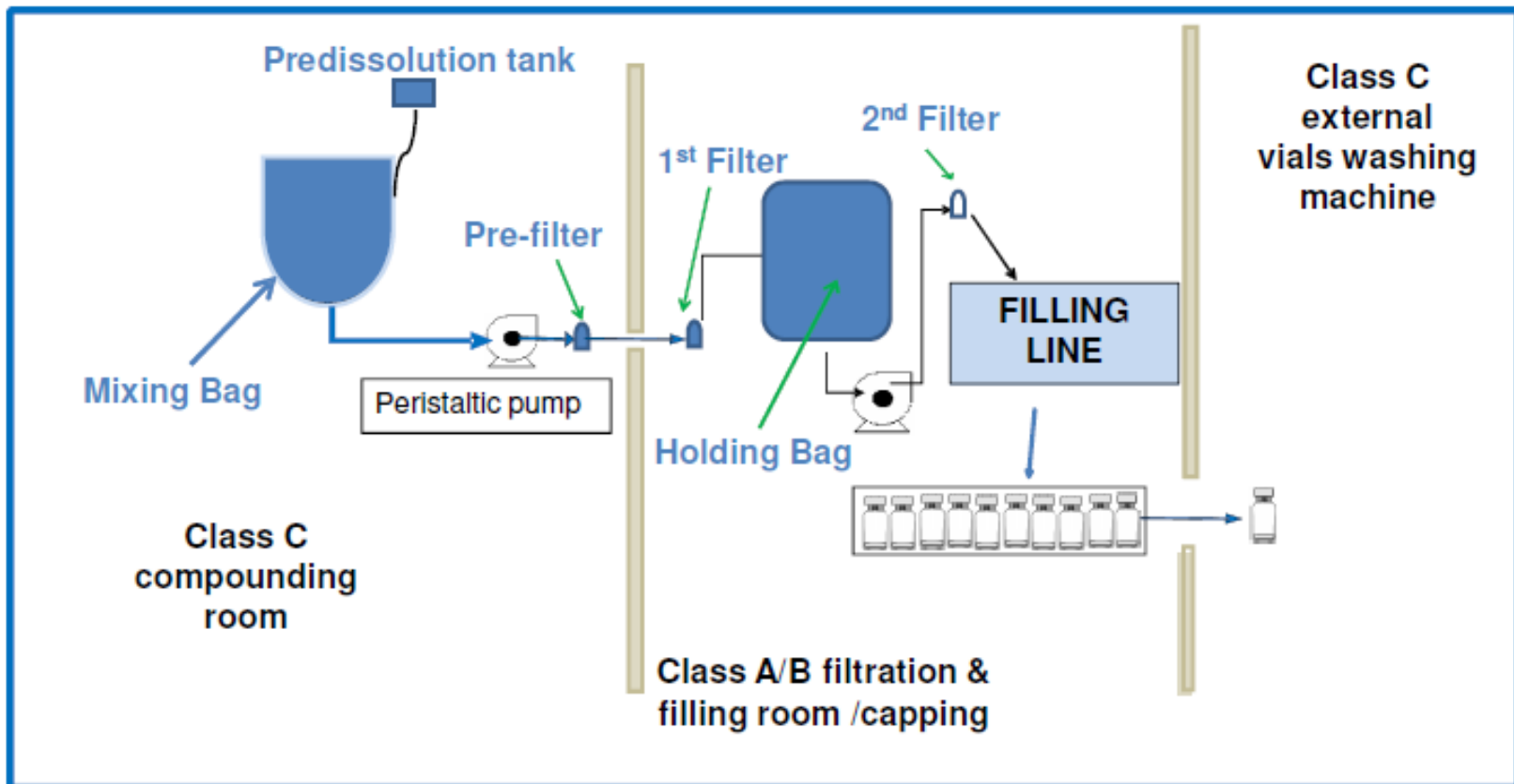


## Sending site equipment I

- Single Use materials used in all the manufacturing process (from bulk to filling) by the current CMO
- Strong knowledge and recommendation in Single Use use
- No data supporting the use of equipment and materials available at the receiving site
- Necessity of gentle mixing
- Cleaning difficulties
- Challenges in sterilizing filtration
- Preliminary compatibility data with Single Use materials



## Sending site equipment II



Major risks ?

- New technology for supplier
- Challenges in some process steps to be analyzed due to
- Partial Blind - TT

Actions?

- Challenge the network for similar product and similar product
- Training by suppliers and by consultants on technology
- Development plan defined and agreed with the Client to support data missed  
-> identification of pH range as CPP in a range different from the first received





- Technology Transfer – Some exercises



# 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 with several non conformity linked with product chemical characteristics.

## Questions

Which Criteria will you use to select a partner?

- *Good US Regulatory History (no 483, no warning letters, etc etc)*
- *Technical expertise in process development*



# 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

## **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 effort in each milestone with an “allocation diagram”

**Group 2. RU** Describe the project team member mainly impacted in each milestone with an “allocation diagram”

Colonna1 ▼	SME 1 ▼	SME 2 ▼	SME 3 ▼	SME 4 ▼	SME 5 ▼	SME 6 ▼	SME 7 ▼	SME 8 ▼
Milestone 1	100	50	75	100	100	100	100	100
Milestone 2	100	100	50	50	50	50	50	50
Milestone 3	100	25	100	75	75	75	75	75
Milestone 4	100	100	75	100	75	75	75	75
Milestone 5	100	100	75	75	25	25	25	25
Milestone 6	100	100	75	75	75	75	75	75
Milestone 7	50	50	50	50	50	50	50	50
Milestone 8	100	50	75	25	25	25	75	75
Milestone 9	100	50	75	100	25	75	75	75
Milestone 10	100	50	75	100	25	75	75	75
Milestone 11	75	50	75	100	25	75	75	75

## 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

## **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. Team allocation resources is completed and alignment between R and S units is in place

## **Questions**

- As RU, Design the Stakeholder Map of your TT

- As SU, Design the Stakeholder Map of your TT



# Workshop – Stakeholder Mapping

1. **Brainstorm** a list of Stakeholders, asking, “who can influence the success of my business plan and startup and who can be impacted by the project?” Segment the stakeholders into meaningful clusters as appropriate (functions, regions, etc.)
2. Ask, “to what degree do they have the **power to influence the success** of the ultimate startup?” Use the 1-5 scale shown on the Template (COLUMN 0)
3. Next ask, “what is this stakeholder’s current **level of commitment to the startup**? How Favorably do they view the startup?” Use the 1-5 scale shown on the Template (COLUMN P)
4. **Brainstorm** on Stakeholders Dynamics, track them with colored lines (Influences positively, Antagonizes)
5. Design some “Action Path” to influence positively key stakeholders



# Workshop – Stakeholder Mapping

