Sept 2024, Angela Molaschi

Managing Technology Transfer Projects in Pharma

PDA

About us

PDA at glance

- **The Parenteral Drug Association (PDA)** is the leading global provider of science, technology and regulatory information and education for the pharmaceutical and biopharmaceutical community.
- Founded in 1946 is a not profit organization.
- PDA commitment is to developing **scientifically sound, practical technical information and resources to advance science and regulation** through the expertise of its more than 9500 members worldwide.

Our mission:

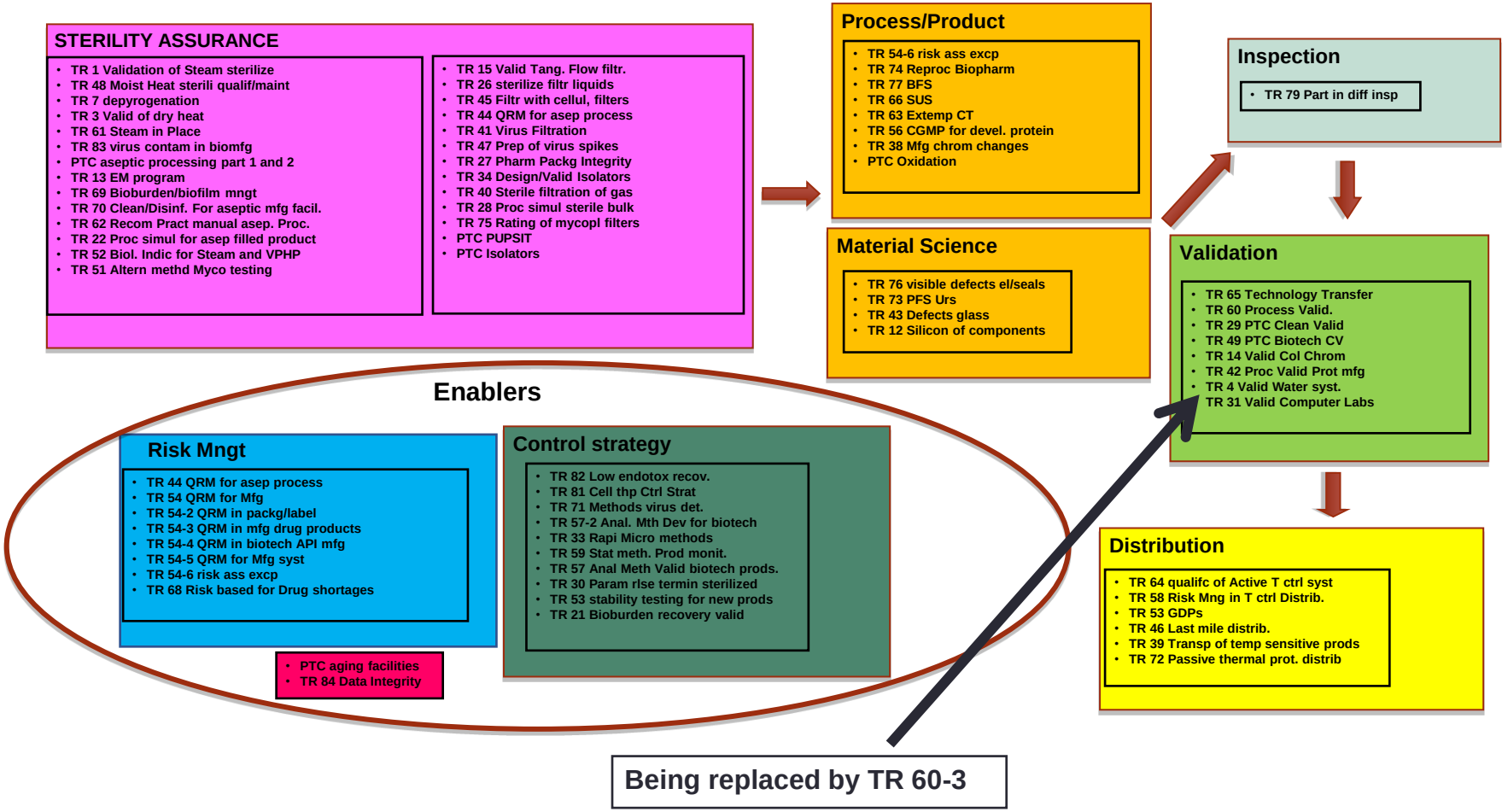
« Connecting People, Science and Regulation»

PDA governance/organization

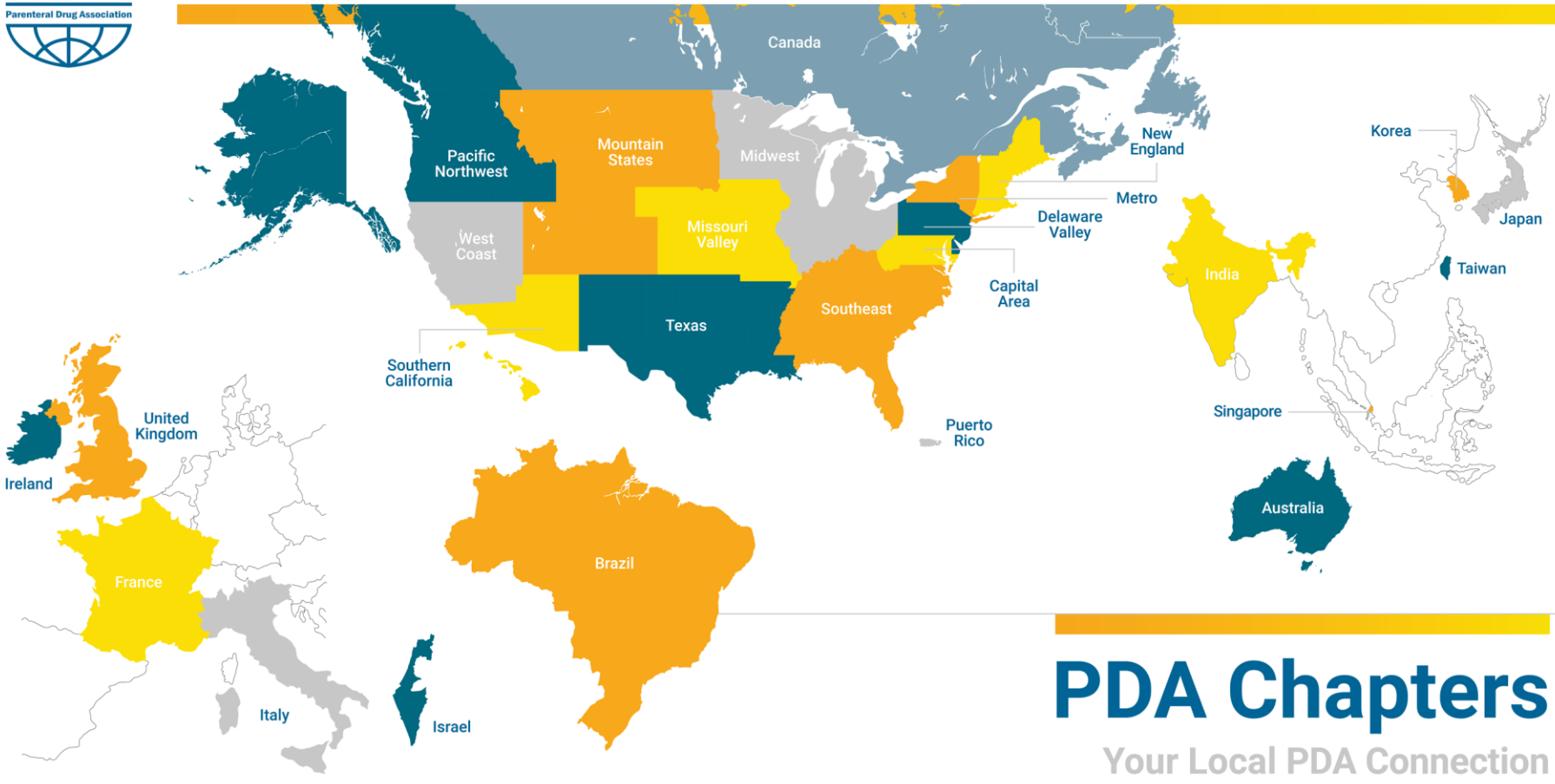
- PDA is based on 4 main boards, each overseeing Interest Groups covering specific topics. See link
- Technical Advisory Boards | Parenteral Drug Association (pda.org)
  - BioManufacturing Advisory Board (e.g. Vaccines, Fermentation, etc..)
  - Regulatory and Quality Advisory Board (Inspection Trends, Quality Risk Mngt, etc..)
  - Scientific Advisory Board (e.g. Process Validation, Visual Inspection, etc..)
  - Advanced Therapy Medicinal Products (ATMP)

- At geographical level, PDA is based on Chapters: there are 14 US Chapters, 4 European Chapters (France, Italy, Ireland, UK), Israel Chapter, 1 Chapter in Latin America and 6 chapters in Asia Pacific. See link
- PDA Chapters | Pharmaceutical Manufacturing Association

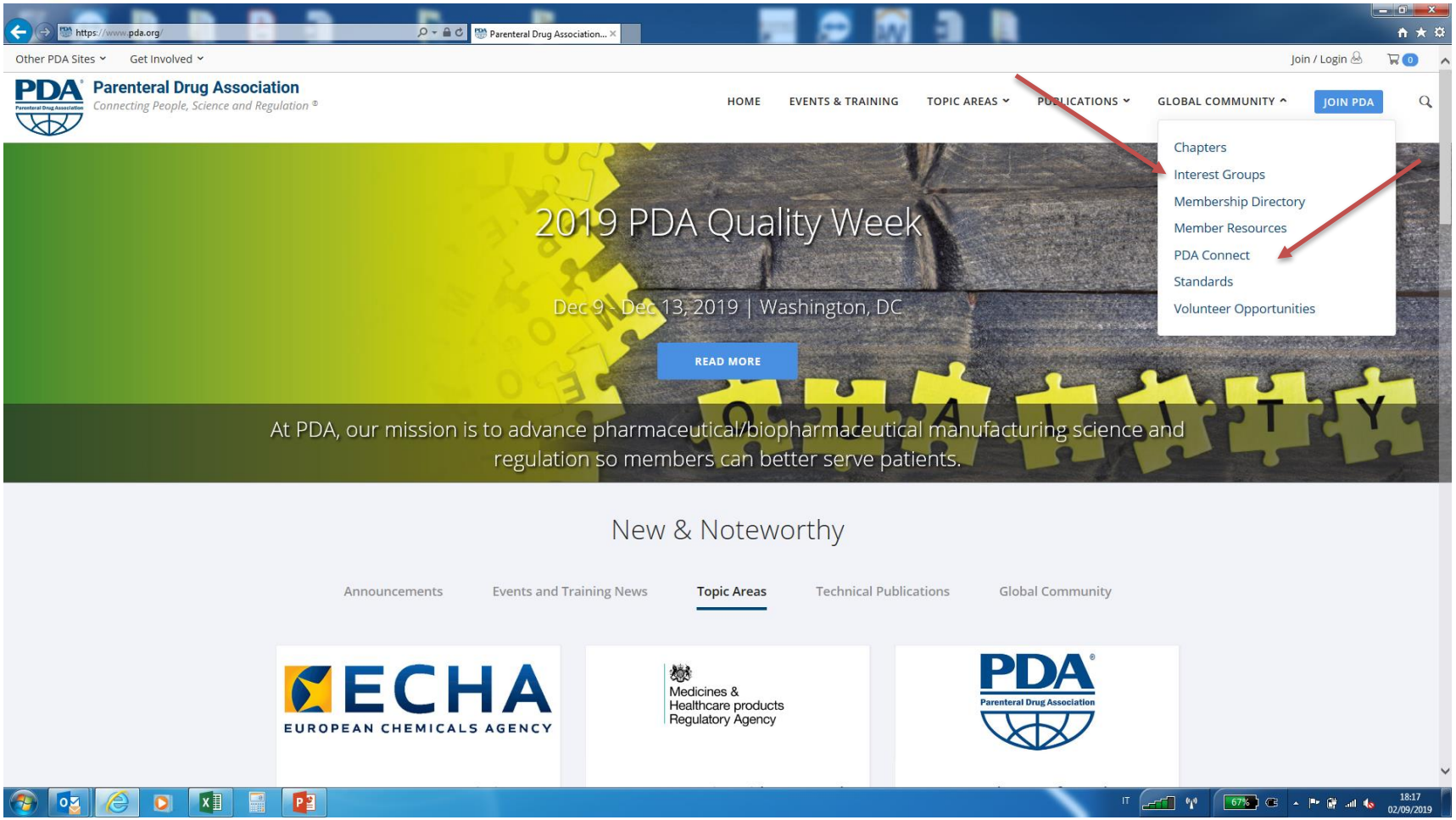
PDA technical reports



PDA chapters



About the Interest Groups



About the Interest Groups

PDA Interest Groups provide a unique forum for in-depth discussion on a wide range of industry-related topics. Interest Groups hold in-person meetings in conjunction with PDA conferences, virtual meetings, and communicate through discussion posts on PDA's online community, PDA Connect®. PDA Interest Group membership is open to all active PDA members.

Joining an Interest Group (IG) is quick and simple. Click the "Join/Manage My IGs" button below and follow the instructions provided. After joining you will receive invitations and emails related to IG activities.

Join/Manage My IGs

Biopharmaceutical IGs

- Advanced Manufacturing and Applied Process Digitalization
- ATMP
- Combination Products
- Vaccines

Regulatory & Quality IGs

- Data Governance, Management, Integrity, and Digitalization
- Drug Compounding
- GMP Links to Pharmacovigilance
- GXP Auditing and Inspections
- Management on Outsourced Operations
- Pharmacopeial
- Quality Risk Management
- Quality Systems
- Regulatory Affairs
- Supply Chain Management

Manufacturing Science IGs

- Annex 1 Implementation
- Facilities and Engineering
- Filtration
- Lyophilization
- Microbiology/Environmental Monitoring
- Packaging Science
- Pharmaceutical Water Systems
- Pre-Filled Syringe
- Process Validation
- Sterile Processing/Parenteral Drug Manufacturing

Quick Links

- Interest Group Leaders
- Joining an Interest Group
- PDA Connect

Join PDA Connect Forum

Discover, Discuss, and Connect with Fellow PDA Interest Group Members on PDA Connect – Your Hub for Meaningful Conversations and Insights.

Join Now

Volunteer Opportunities

Join us in making a difference! Explore our volunteer opportunities and contribute to our mission.

Get Involved

Introduction

Why we are here?

Why join this training?

$1T

Global Rx sales by 2022

$160B

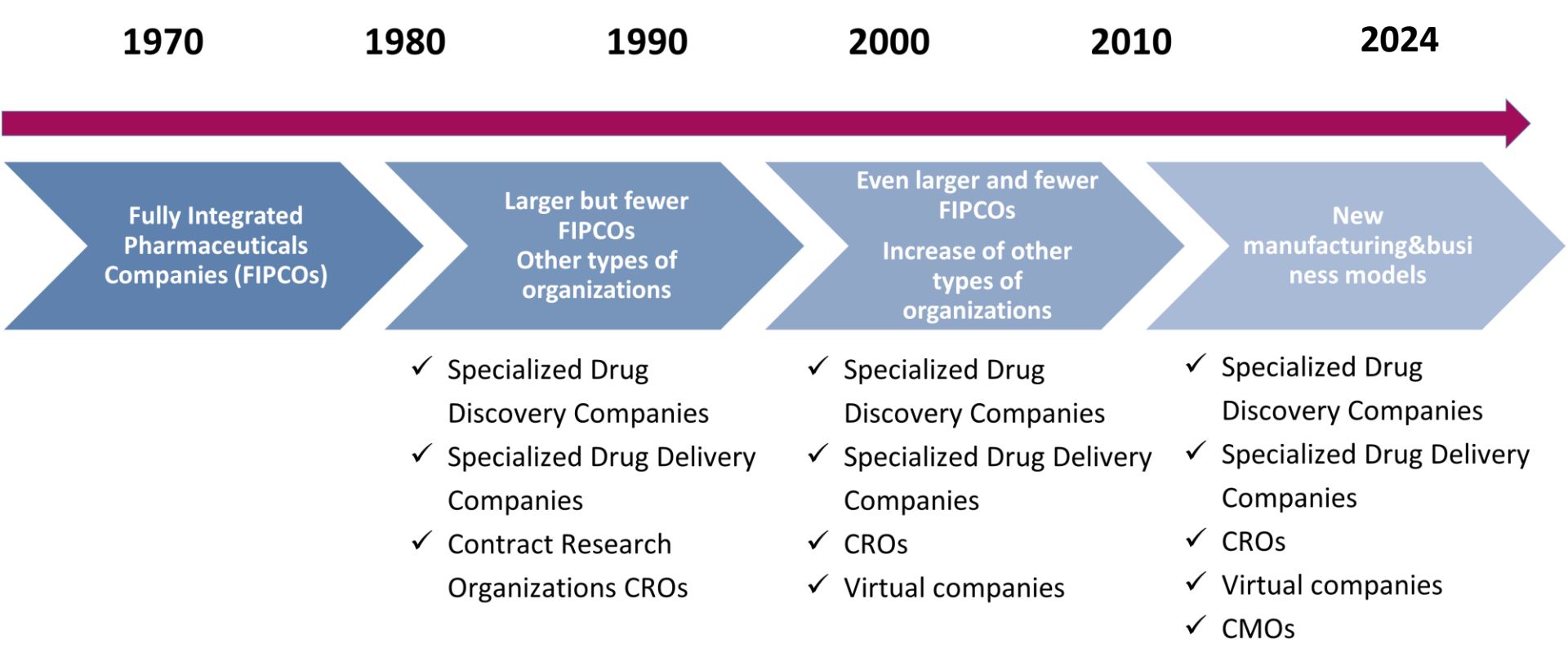
Global pharma and biotech R&D spend by 2022

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

Pharmaceutical world evolution



Evolution of the big pharma model

- Patents expirations and generic drugs
- Globalization
- Mergeries and aquisitions
- Huge increase of the development and registration costs
- More stringent and demanding regulatory requirements
- Competition:
    - Outsourcing increase
    - New markets and new competitors
    - New business models

…….all that and much more led to the evolution of the **Pharma world and models**

Pharma world today

- Increase of complexity and competition
- Different and new business models (i.e. equity funds)
- Outsourcing increase: CDMO model
- Production sites rationalization
- High specialization
- Hig value products VS medium/low value products
- Importance of the costs
- ….last but not least covid impact:
  - Big growth in vaccines sector
  - Big growth of CDMO model
  - Stable business in life-saving products
  - Impact on non life-saving products (need of conversion)
  - Priority investment in some areas

Pharma world today: CDMO I

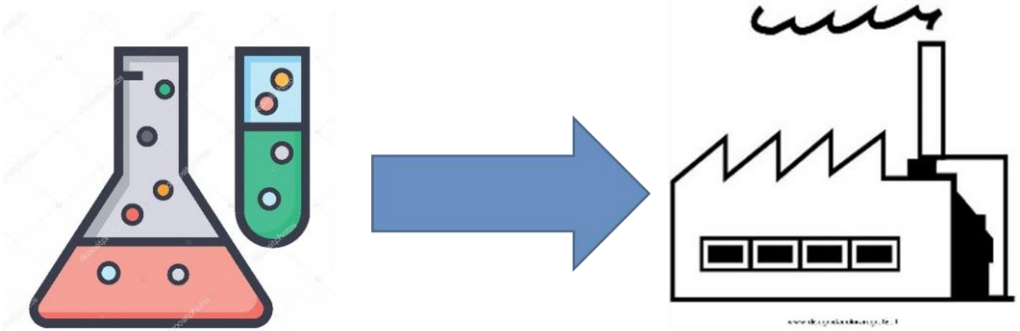
- According to a number of industry studies, the CDMO market, both in the API and FP product areas, is set for further growth in the coming years estimated **from $98.7 Mld (2018) to $157.7 Mld (2025)**
- This remarkable growth certainly can be attributed to an increase in the demand for pharmaceutical products, linked to various socio-economic factors, but it is also a clear sign of the further accentuation of the product-owning companies' willingness to use outsourced services to manufacture, reducing costs, risks and internal complexity. The growth of "Business To Business (B2B)" business models has further accentuated this trend
- From 2020 onward, moreover, the Covid19 pandemic generated the need for **massive vaccine production** and thus gave further impulse to the CDMO sector

Pharma world today: CDMO II

- The growth of the CDMO specifically at the European and Italian levels is attested by a study conducted by Prometeia and Farmindustria in 2020 and repeated in 2022. The Italian pharmaceutical CDMO sector developed a turnover close to 2.7 Mld€ in 2022, higher than the €2 Mld€ in 2020, and accounting for 22.8% of total European turnover in the same year. On the strength of this value, Italy retains its lead at the EU level, followed by Germany (2.5 Mld€) and France (2.1 Mld€), respectively, also in 2022
- The CDMO sector also confirmed a strong propensity for investments: 15% (relative to turnover) in 2020, 21% in 2021 and 15% in 2022

How Technology Transfer was born

- Born in Fully Integrated Pharmaceuticals Companies (FIPCOs) as transfer/scale up from development to production/industrial scale
- Usually within the same site
- Managed by R&D
- High specialization and technical expertise of who is managing and executing TT
- Very specific activity
- High budget and resources
- Long timelines



Technology Transfer evolution I

With the pharmaceutical world evolution Technology Transfer has become:

- More frequent and with increased values (acquistions, mergeries, new strategies, outsourcing, shorter products life..)
- More international
- More complex (different sites, different cultures, different procedures, different technologies and equipment)
- A fundamental part of pharmaceutical processes
- Globally recognized in the pharmaceutical business: Technology Transfer dedicated functions

Technology Transfer evolution II

- In the complex and fast pharmaceutical business the development and technology transfer of rubust formulations and processes is «critical»
- Due to high differentiation of current pharmaceutical business different Technology Transfer types were born
- All the main Pharma companies have created their own technology transfers models and culture

Technology Transfer evolution III

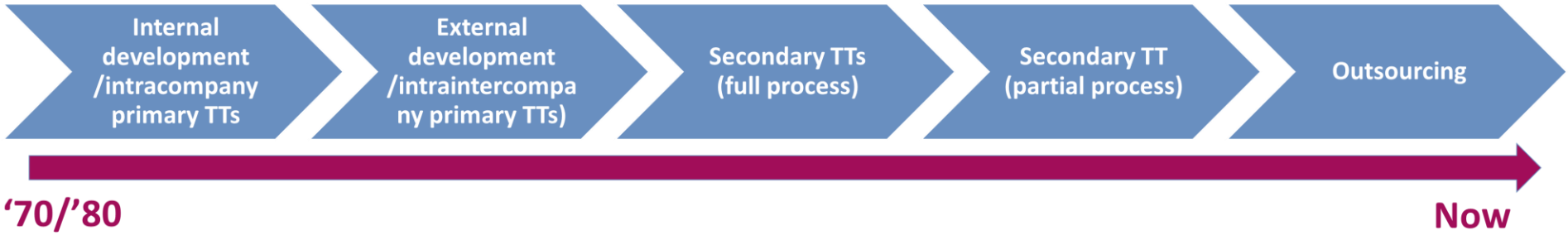
- Big pharma (brand)
- R&D and production in the same site
- R&D focus
- High technical skills
- Focus tecnico
- High budget

- Big pharma (brand)
- Generic market
- Development centralization
- R&D and production in different sites
- TT Manager/PM
- Growing importance of management and relationships

- Outsourcing
- CMOs business
- TT among different sites and companies
- Higher organization and management activities
- Less technical
- Higher attention on costs

- CMOs business
- New products and technologies (biologics, biosmililars)
- TT among different sites and companies
- Different TT types

- CMOs business
- New business and companies types
- High importance of the contractual part
- Focus on budget and costs



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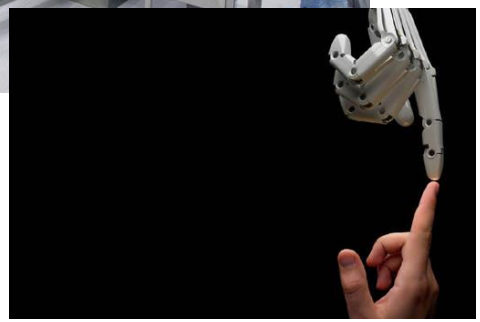
Why discuss about RM in TT

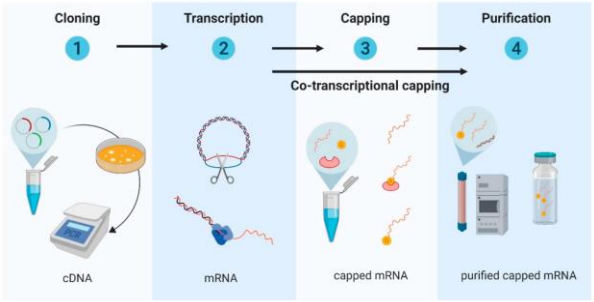
EVEN MORE TRUE, BASED ON PHARMA INDUSTRY DICHOTOMY PLANNED AS FUTURE SCENARIO

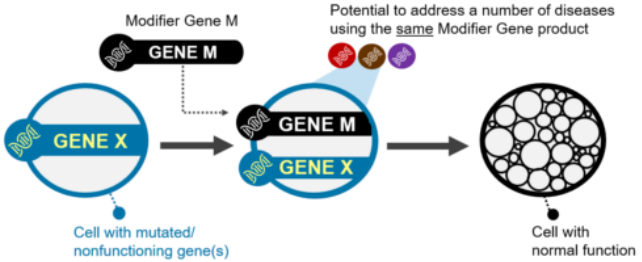
&



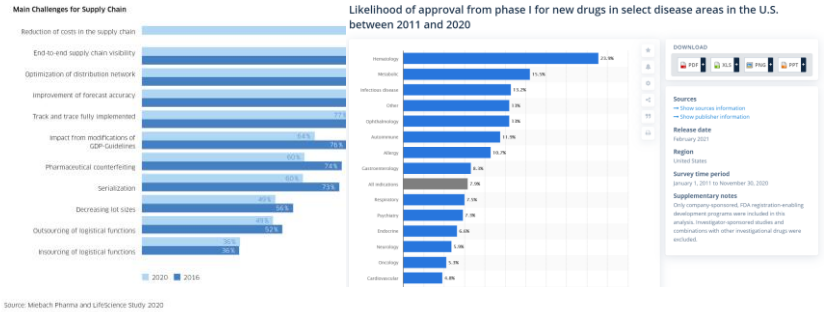
Why discuss about RM in TT

NEW PLATFORMS COMING UP WITH NEEDS OF QUICK AND CONSISTENT SCALE UP

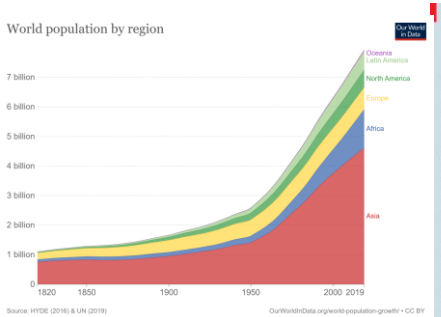


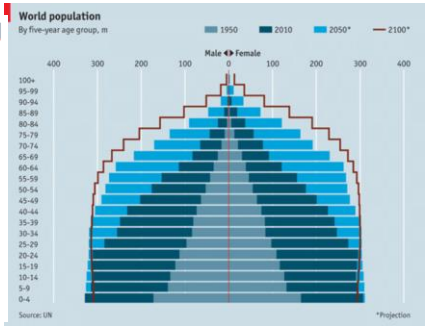


OPTIMIZATION PRESSURE IN PHARMA

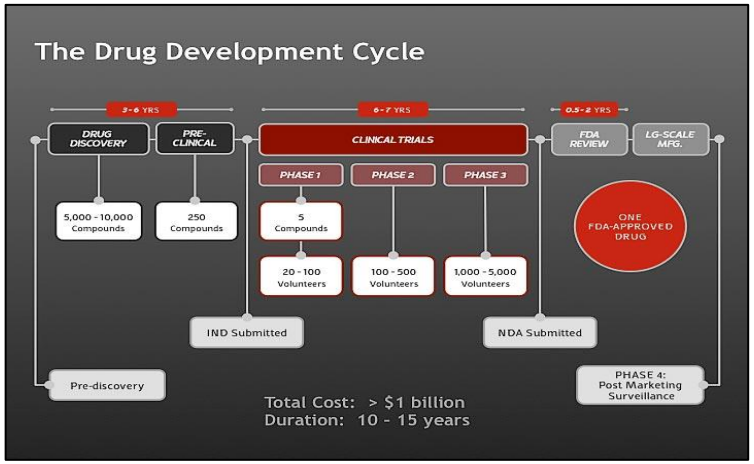


CAPACITY NEEDED FOR DRUG SUPPLY TO PEOPLE DUE TO EPIDEMIOLOGY AND DEMOGRAPHY TRENDS





Why discuss about TT



- **PATIENTS DIFFULTIES TO GET MEDICINES**
  - SUPPLY CHAIN DISRUPTION
  - LOW CAPACITY AVAILABLE FOR A CERTAIN MANUFACTURING
  - DELAY IN NEW DRUG APPROVAL AND DISTRIBUTION
  - DELAY IN CLINICAL STAGE
  - DELAY IN NEW DRUG DEVELOPMENT

In other words…

- 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
- Applicable to **different** types of products (APIs, Intermediates, FPs, services….)
- Project **complexity** is growing TT Experts have to be prepared to face challenges
- **Dynamic and challenge** environment

PDA and Technology Transfer group I

- 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, vs 02 issued in June 2022
- 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

PDA and Technology Transfer group II

Purpose

This interest group has as its main objective to capture the opportunity given by the benchmarking of our experience in Technology Transfer projects; with potential opportunity like TR, articles, position papers, training sections, and lectures.

The group will discuss the technology transfer projects topics, from manufacturing process to analytical transfer, from equipment user requirements definition to process validation, from Contract Manufacturing Organization selection to Business Discontinuity, from appropriateness of the documentation to lesson learnt approach and statistical data analysis, without never forget the ethic behind our job.

Pharmaceutical Technology Transfer Projects consist of planned and controlled actions that are based on well-defined acceptance criteria to convey a Pharma technology with all its attributes from a sending unit to a receiving unit and involve a complex group of internal and external stakeholders. Risks are hidden everywhere; it's mandatory to have a robust and efficient methodology to identify, mitigate and control them.

For that reason we think a Technology Transfer Interest Group will help all of us find best practices, monitor worldwide trends, analyze clusters of peculiarities based on companies, countries, dosage forms, drug entities.

Join this Interest Group | Follow Discussion

An active PDA membership is required to join an Interest Group. Not a member? Join today.

Interest Group Leaders

Mirko Gabriele, PhD
InfiniteVision

Beth Kramer
Eli Lilly

Quick Links

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- PDA Connect

Biopharmaceutical IGs

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Regulatory & Quality IGs

- Data Governance, Management, Integrity, and Digitalization
- Drug Compounding
- GMP Links to Pharmacovigilance
- GXP Auditing and Inspections
- Management on Outsourced Operations

My expectations for the two days…

- Share experience on TT
- Benchmarking on TT organization, Approaches
- Understand opportunity for improvements
- Discuss challenges and practical cases
- Learn from each other experience
- Networking

What about you?

What is your expectation?

Technology Transfer in Pharma: main concepts

What is a Technology Transfer?

Discussion

What is Technology Transfer?

Technology Transfer definitions I

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*)

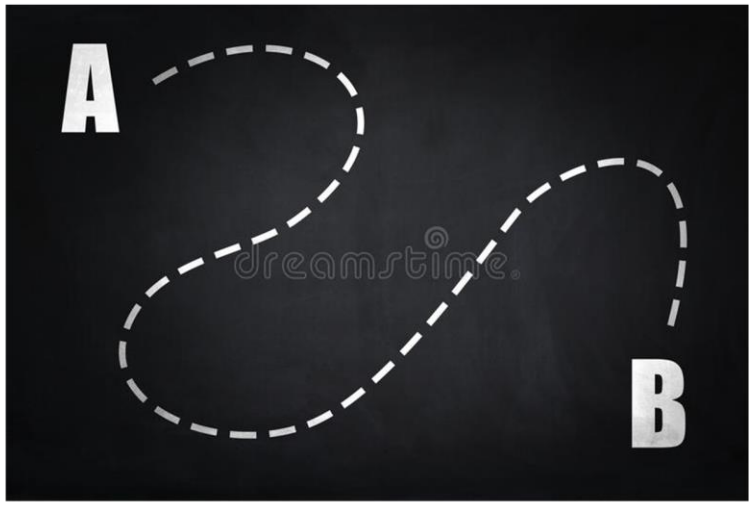
A logical procedure that controls the transfer of an established process together with its documentation and professional expertise to a site capable of reproducing the process and its support functions to a predetermined level of performance

(WHO Guideline on transfer technology, 2008)

Technology Transfer definitions II

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).

Sending unit



Receiving unit

PDA – PMCO Program – Technical Report N.65

Technology Transfer definitions III

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** is a systematic procedure that shall be executed with the aim to transfer knowledge and experience related to a pharmaceutical process from one organization to another. Technology transfer includes documentation transfer and proven ability of the receiving unit to execute what has been transferred»

Technology Transfer definitions IV

«Technology Transfer is a learning and growing experience for both the units involved»

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Technology Transfer definitions V

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 definitions VI

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
- Are managed by a team

Technology Transfer and Risks I

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 and Risks II

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 extimation of time/resources/costs*
7. *Lack of engagement of Team members*
8. *Lack of performance monitoring during execution*

Technology transfer success factors

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).

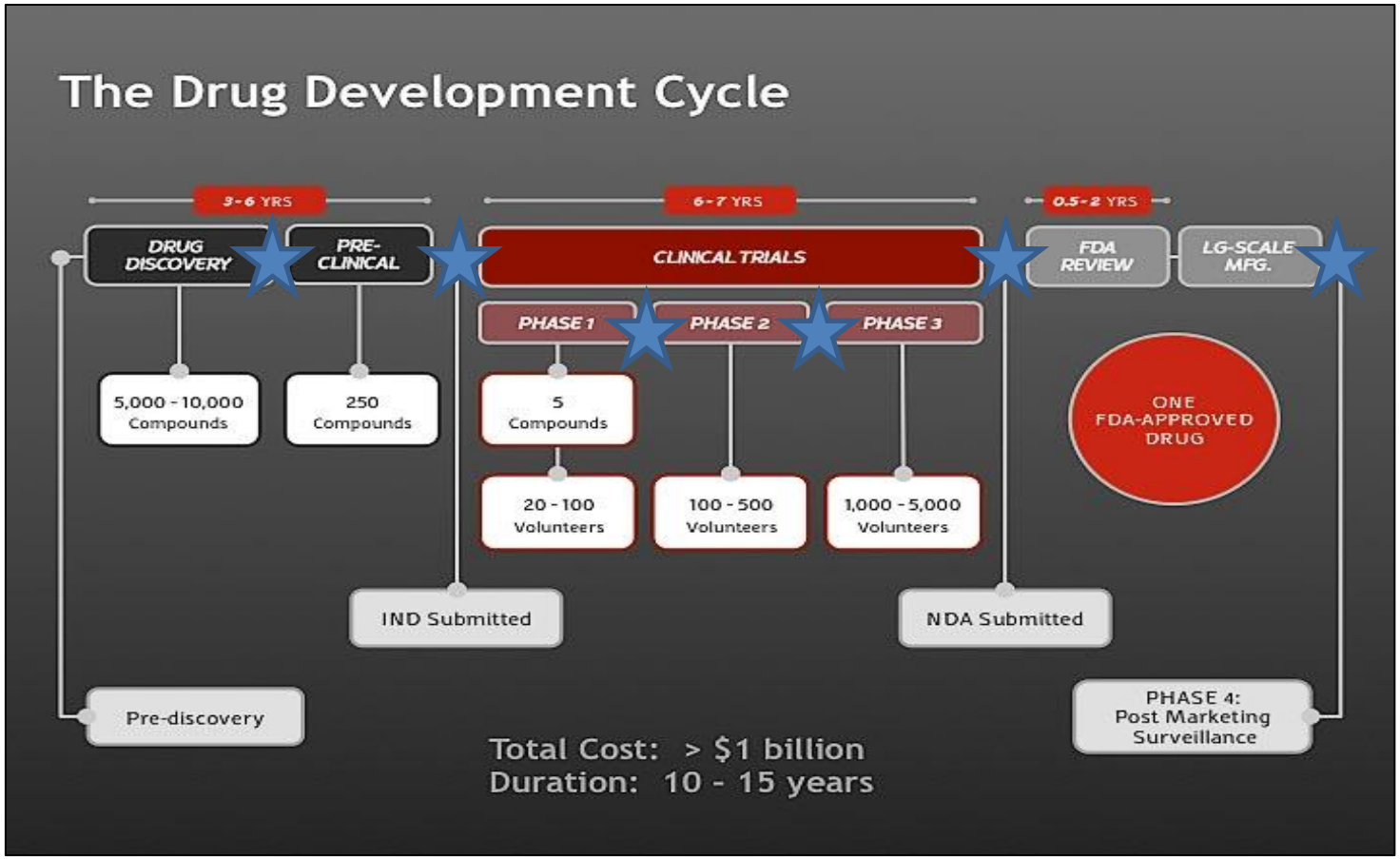
Success factors:

- Fulfilling **regulatory and qualitative requirements**
- Meeting **projects goals** (timelines, budget, people)
- Fulfilling **technical requirements** (production and analysis)

Technology Transfer – What?

- API/Drug Substance
- Drug Product (small molecules):
  - Solids, non sterile liquids, sterile liquids, sterile powders, emulsions, suspension…..
- Drug Product (large molecules):
  - Biologics, biosimilars…..
- Production phase:
  - Entire production process
  - Part of the production process (manufacturing, analysis, packaging….)

Technology Transfer – When?



Technology Transfer – When?

For different type of products and phases, 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*

Technology Transfer – What and When?

SO HOW????

DIFFERENT EXPERTISE BUT COMMON PRACTICES

Terminology I

Primary Technology Transfer:

- From R&D to production site (industrialization process)
- Intracompany o intercompany

Secondary Technology Transfer:

- From production site to production site
- Intracompany o intercompany
- Pre-submission, post-submission
- Pre-commercialization or during commercialization

Complete and partial Transfers:

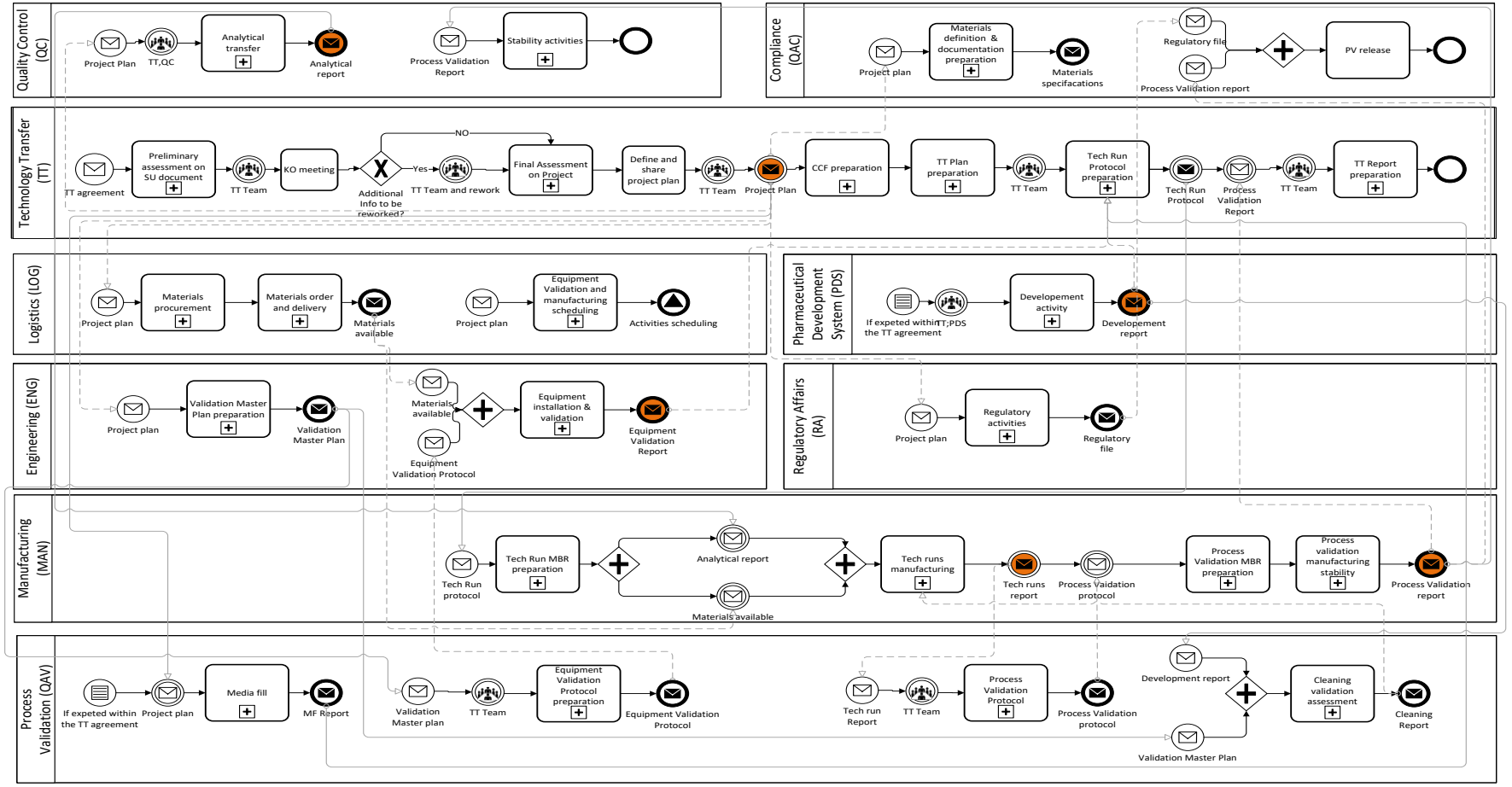
- Full manufacturing
- Partial (analytical, release, secondary packaging)
- **Open transfer VS blind transfer**
- **Transfer IN vs Transfer OUT**

© Can Stock Photo - csp25964108

Terminology II

- **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



Discussion

What are the main aspects/characteristics of Technology Transfer?

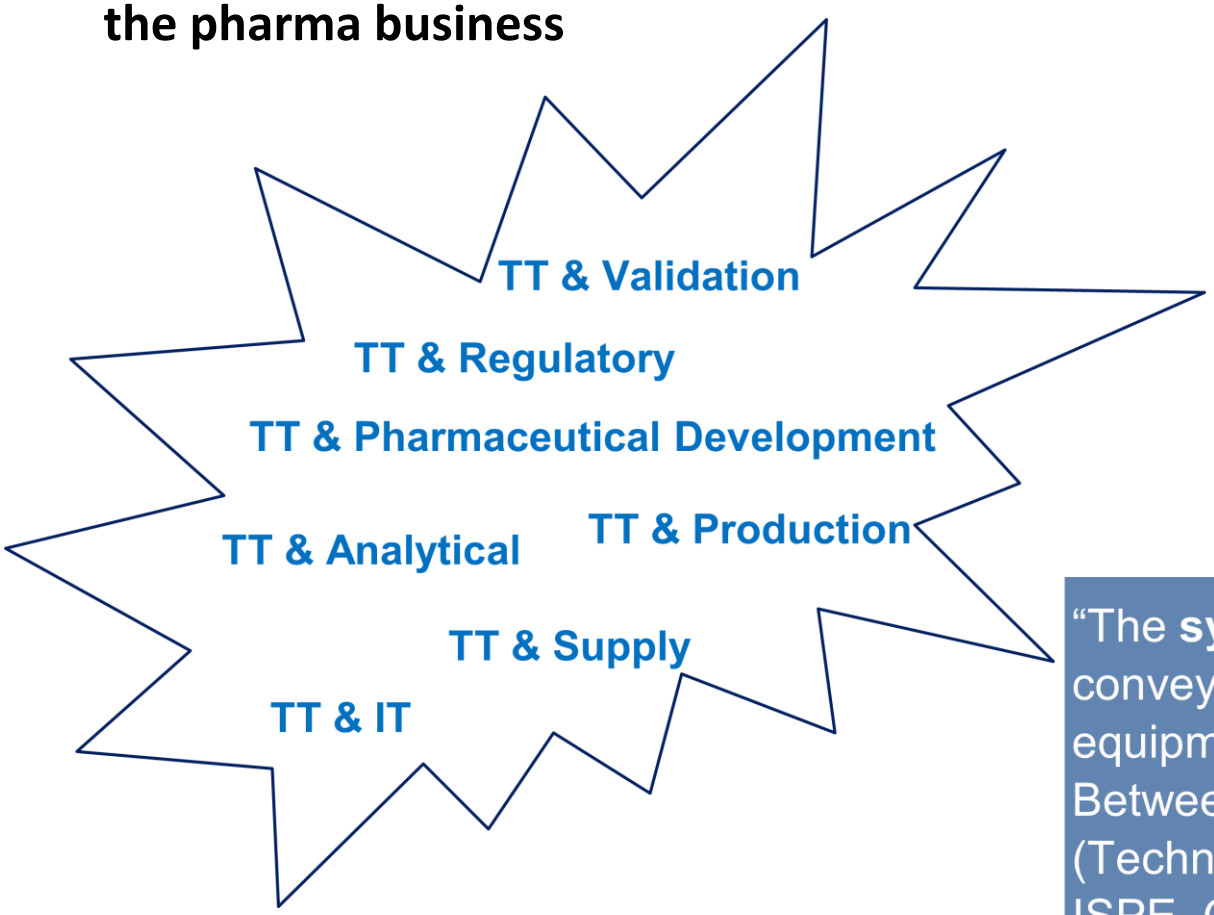
What makes the Technology Transfer different from the other activities?

Main aspects of Technology Transfer

- Integration and multidisciplinarity
- Extraordinary activity VS operations
- Complexity
- Unique
- Project Management
- Start-end
- Technical, communication and management aspects
- Hard and soft skills
- ……other…..

Multidisciplinarity and integration I

An integrated process that involves different functions and that is part of the pharma business



"The **systematic** means of conveying ability, documentation, equipment, skills, and systems Between parties"
(Technology Transfer, ISPE, Good Practice Guide, 2003)

Multidisciplinarity and integration II

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:

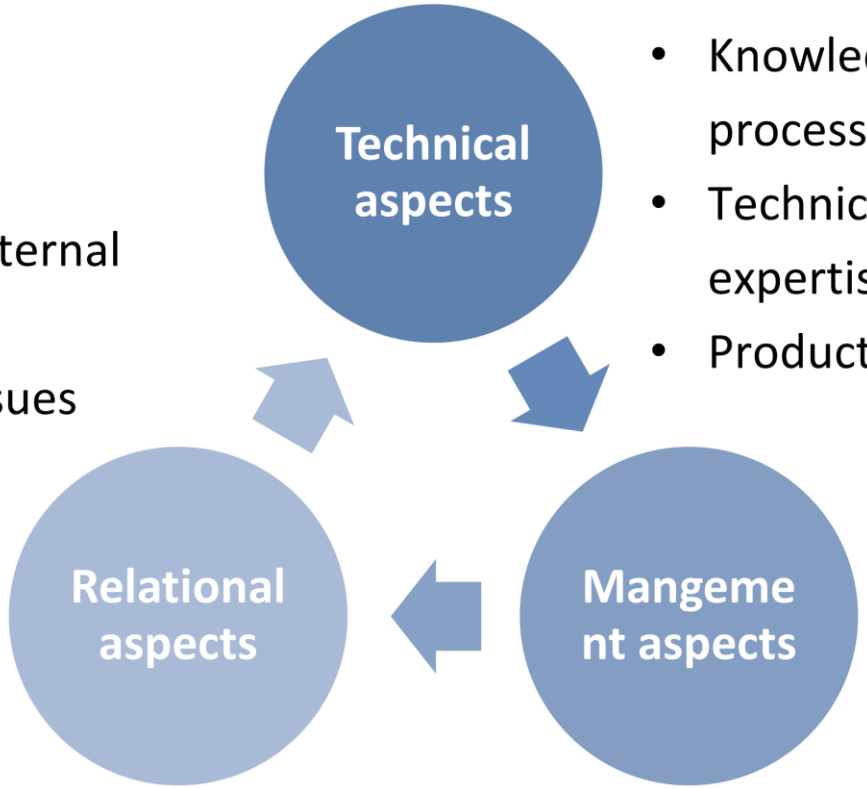
- Quality assurance
- Quality control
- Manufacturing
- Engineering
- Finance
- Maintenance
- Environment, health, and safety
- Research and development
- Regulatory affairs
- Legal issues
- Project management

Multidisciplinarity and integration III

- 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.

Main aspects of Technology Transfer

- Internal and external comunication
- Relationship issues
- SPOC



- Knowledge of technologies and processed
- Technical, quality and regulatory expertise
- Products knowledge

- People management
- Problem solving
- Working on priority
- Project Management
- 360° vision

Technical aspects I

- **Technology aligments and related evaluation:**
  - Equipments comparison between Sending and Receiving units
  - Scale up evaluation
- **Suppliers:**
  - Evaluation of the suppliers
- Analytical transfer
- Identification of **critical quality attributes**
- Identification of **critical process parameters**
- **Technical batches**

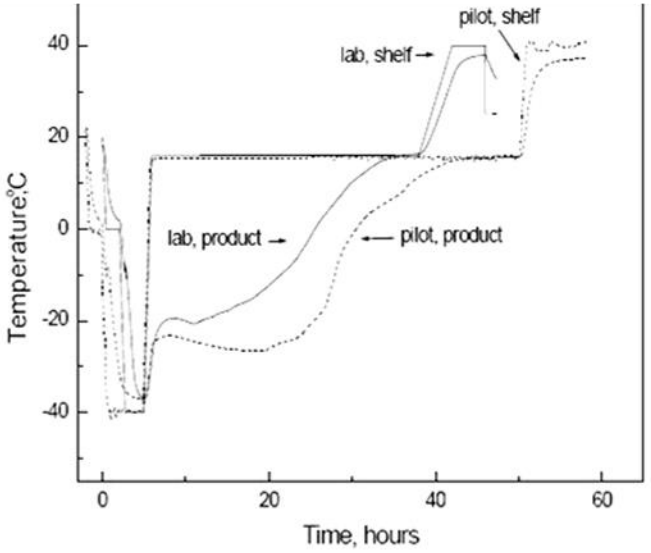
Technology alignment: size matters I

- **Primary technology transfer:**
  - Same type of technology
  - Scale down process
- **Secondary technology transfers:**
  - Which are the equipment in the two units?

Granulator

Technology alignment: size matters II

Lyophilizer



4 Shelfs – 0.5 m²

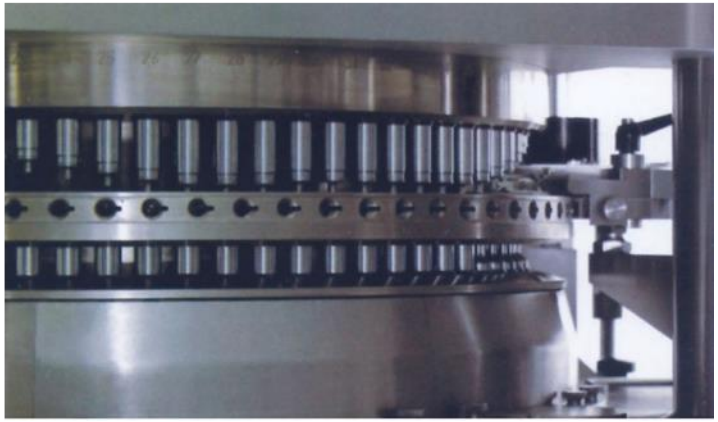
14 Shelfs - 23 m²

Example of industrial scale lyophilization chamber

Technology alignment: size matters III

Loading

Compression



Technical batches and submission batches I

TECHNICAL BATCHES

Definition: batches manufactured at the receiving unit using industrial equipment with the aim to test the process

- ✓ Strategy is defined depeding from process, risks and budget
- ✓ Goal is to test the process:
  - ✓ The first technical batches are necessary to test the process and highlight the challenges: problems are welcome
  - ✓ “Challenge” the process and its limits and to propose solutions
- ✓ They are a knowledge opportunity for both the units

Technical batches and submission batches II

SUBMISSION BATCHES

Definition: batches manufactured at the receiving unit to support product registration

- ✓ Strategy is different depending from type of registration, product and market
- ✓ The can be validation batches also
- ✓ They are stability batches
- ✓ They shall be manufactured at industrial scale, with the final process and once analytical transfer is complete

⇒ Both technical and submission batches are part of the Technology Transfer!

Analytical transfer

- It is a crucial phase of the Technology Transfer
- Usually is considered not so impprtant but it is one of the crucial aspects that leads to a successful Technology Transfer
- Different SOPs and practices at Sending and Receiving units can make it complicate
- No connection between Sending and Receiving units can make it more complicate
- Issues in methods validation or not rubust methods can cause issues during the Analytical transfer
- Analytical transfer must be completed before the production of the submission batches

Analytical transfer definition and types

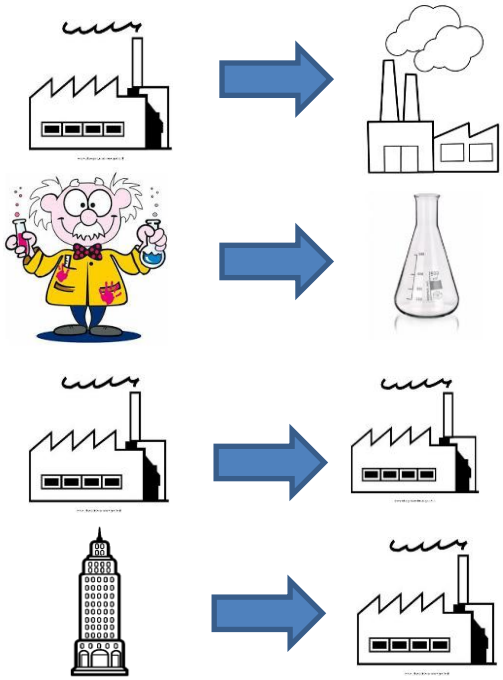
Definition: The analytical transfer is the proven transfer of the analytical technology from one site/organization/lab to another.

It involves tranfer of the knowledge and of the documentation.

It is the process through which the RECEIVING LAB is qualified to the use of an analytical procedure trasnsferred from a SENDING LAB

Types:

- From one site to another
- Within laboratories of the same company
- Transfer to back up sites
- Transfer of laboratories
- Use of external laboratories

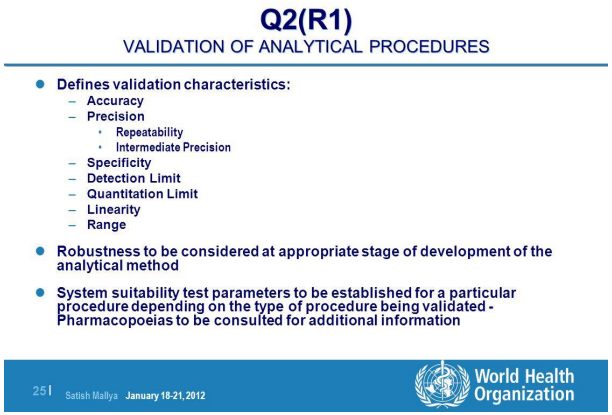


International guidelines

© World Health Organization WHO Technical Report Series, No. 961, 2011
Annex 7 WHO guidelines on transfer of technology in pharmaceutical manufacturing
6. Quality control: analytical method transfer

Analytical Procedures and Methods Validation for Drugs and Biologics
Guidance for Industry
U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) , July 2015

USP <1224>
Transfer of analytical procedures



How to manage an analytical transfer

- **Comparative test**
- **Inter-laboratory transfer**
- **Familiarization**
- **Transfer omission**
- **Revalidation (complete or partial)**

Reference USP 1224

1. Comparative test

- **More common practice**
- **When:**
  - Method is validated and in use
  - Sending and receiving lab have a contact
  - Sending site has product available
- **How:**
  - Analyze same batches in both the laboratories in a set up timeframe (usually 3 batches)
  - If no product is available CoAs from sending site can be used

2. Interlaboratory validation

- **When:**
  - If method validation has not been completed yet
  - If there is a cooperation among the laboratories (no blind transfers)
- **How:**
  - The receiving lab is involved in the riproducibility validation (ICHQ3(R1)

"Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology)"

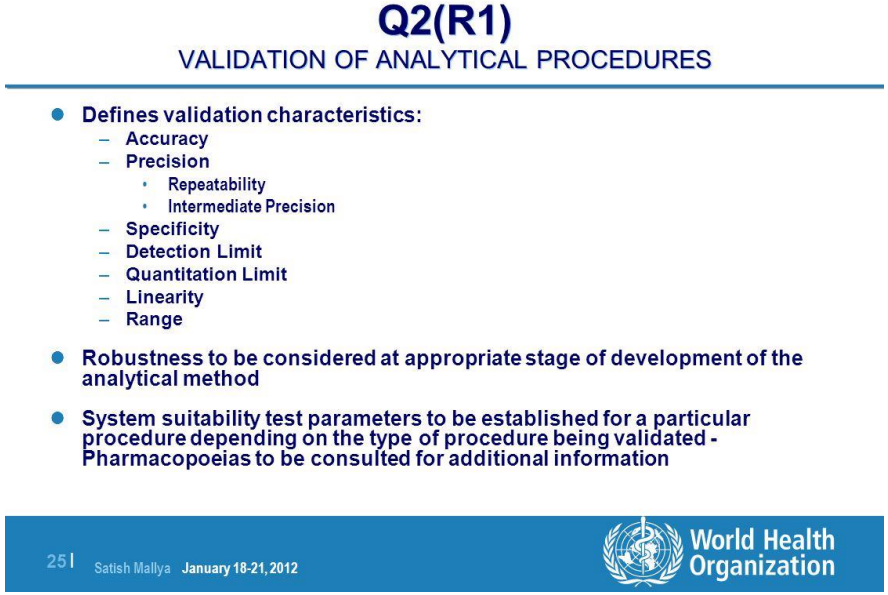
"Reproducibility is assessed by means of an inter-laboratory trial. Reproducibility should be considered in case of the standardization of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias. These data are not part of the marketing authorization dossier"

3.4. Familiarization and transfer omission

- **Familiarization:**
  - Simple and compendial methods
  - Receiving lab shall prove familiarization with trials
- **Transfer omission:**
  - Receiving lab is familiar with the method
  - Method is similar to method in use
  - Transfer of personnel or equipment to receiving lab

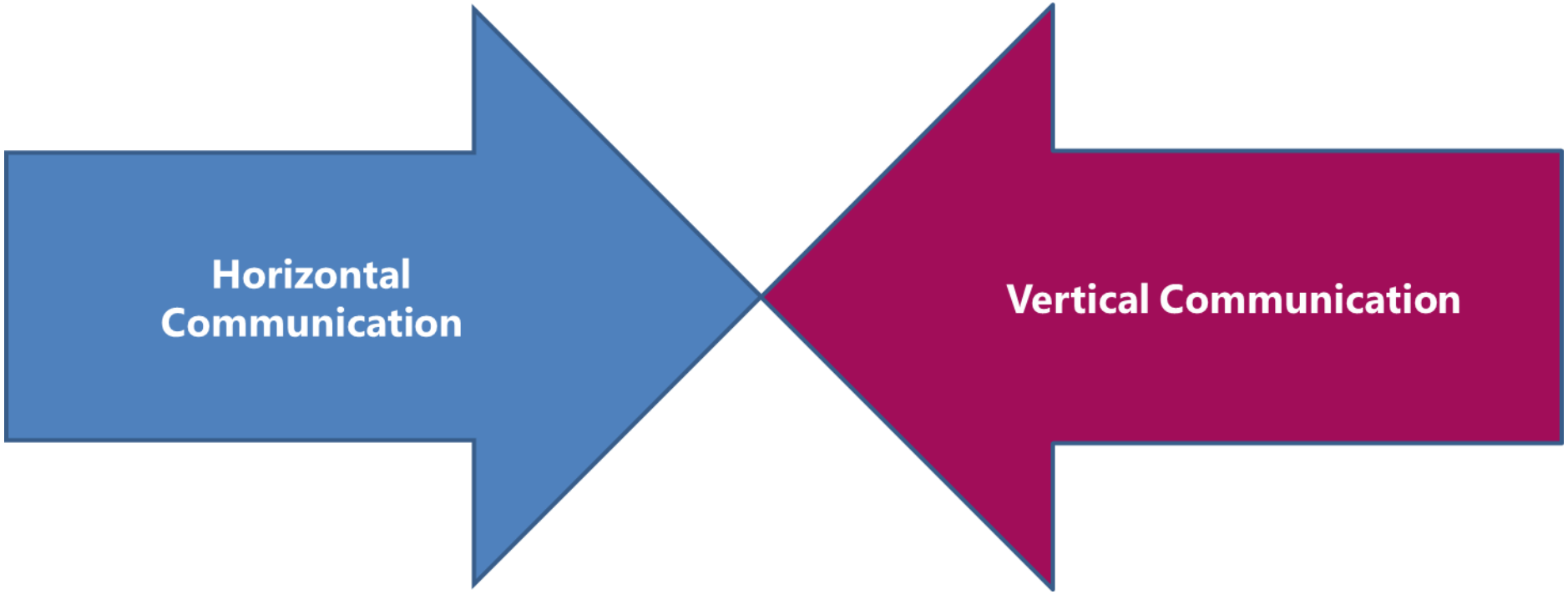
5. Complete or partial revalidation

- **When:**
  - No support or cooperation between the laboratories (i.e. blind transfers)
  - Complex method with criticities
  - «Poor validation» of the method
- **How:**
  - Complete or partial



Organizational aspects I

Organizational aspects II



Organizational aspects III

Team construction and management (dedicated slides)
PM role (dedicated slides)
Common goals between the parties:

- Different missions of the parties (i.e. Sending and Receiving units)
- Transfer strategy
- Tech Transfer plan
  - Flexible and agreed
  - Ruled by “change control”
- Status and goals clear and controlled in each phase of the project

Company culture:

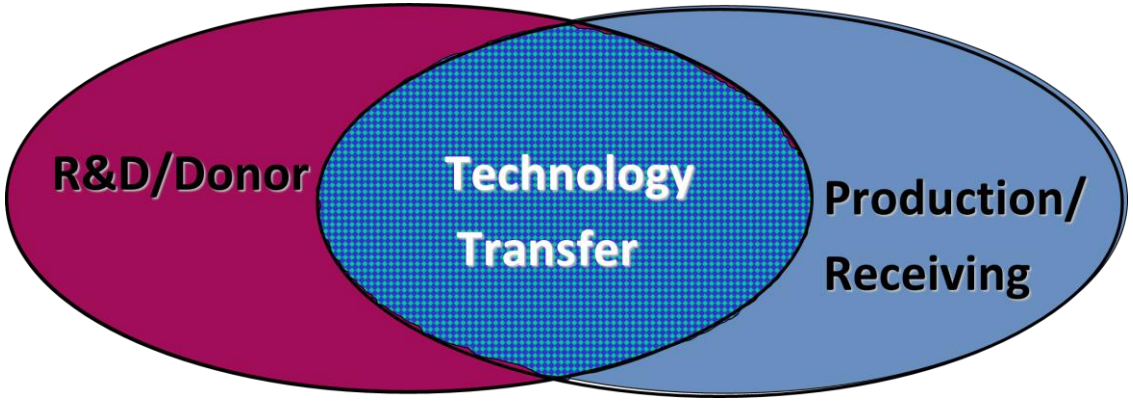
- Without a focus of the company there is no success: Technology Transfer is a company project
- Built in long times and with efforts
- Communications barriers shall be destroyed

Organizational aspects IV

When to start a Technology Transfer?

- Depening from type of technology transfer: primary, secondary, intercompany o intracompany…..
- **Primary technology Transfer:**
  - Advanced start allows more alignment between development and manufacturing, reduce risk of failures and gives usually better results

  BUT
  - Usually triggers higher investments….and in case of failure?



Discussion

Which are for you the main areas of concern in Technology Transfer: technical, organizational or other?

Technology Transfer in Pharma: main phases

How is a Technology Transfer structured?

Technology Transfer main phases I

5 main steps according to PDA TR!

1. Planning

a. Evaluation phase

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

c. Technology and Knowledge clearly stated

d. Delvierables defined

e. Control philosophy agreed

f. Risks evaluated and mitigation plan defined

Technology Transfer main phases II

5 main steps according to PDA TR65!

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 phases III

5 main steps according to PDA TR65!

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 phases IV

5 main steps according to PDA TR65!

4. Licensing & Manufacturing

a. Regulatory submission

b. Monitoring of the manufacturing batches

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Technology Transfer main phases V

5 main steps according to PDA TR65!

5. Project Closure

a. Continuous improvement

b. Lesson learned

Take Away of this first session

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).

- Be always focus on Patient as this is our final «Client»
- Multidisciplinary Context
- Dynamic and challenging environment
- Different types of Technology Transfer
- Technical, relational and management aspects
- 2 main risks categories to be considered: project and process risks

Technology transfer GMP aspects

How to manage a Technology Transfer in GMP?

Technology Transfer …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 …in 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 …in GMP

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 …in GMP

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 …in GMP

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*

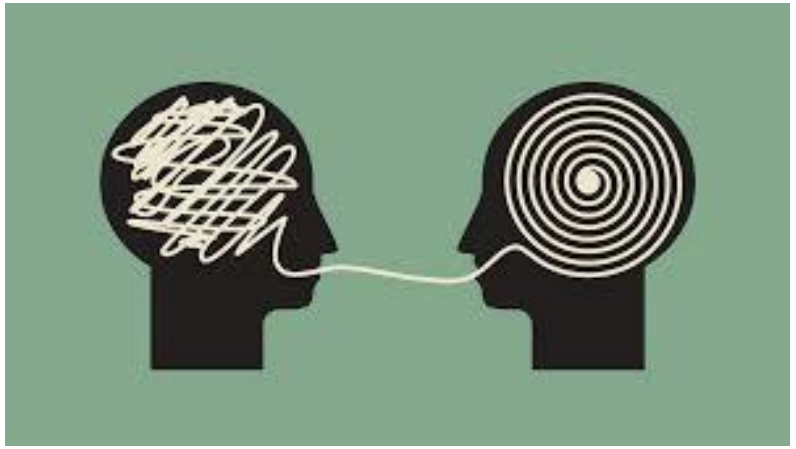
- ❑ Chapter 4. Project Story
- ❑ *Chapter 5.* Project Results
- ❑ *Chapter 6.* Lesson Learnt and CPV
- ❑ Chapter 7. Document Closure
- ❑ Chapter 8 . Document History

Team role in Technology Transfer

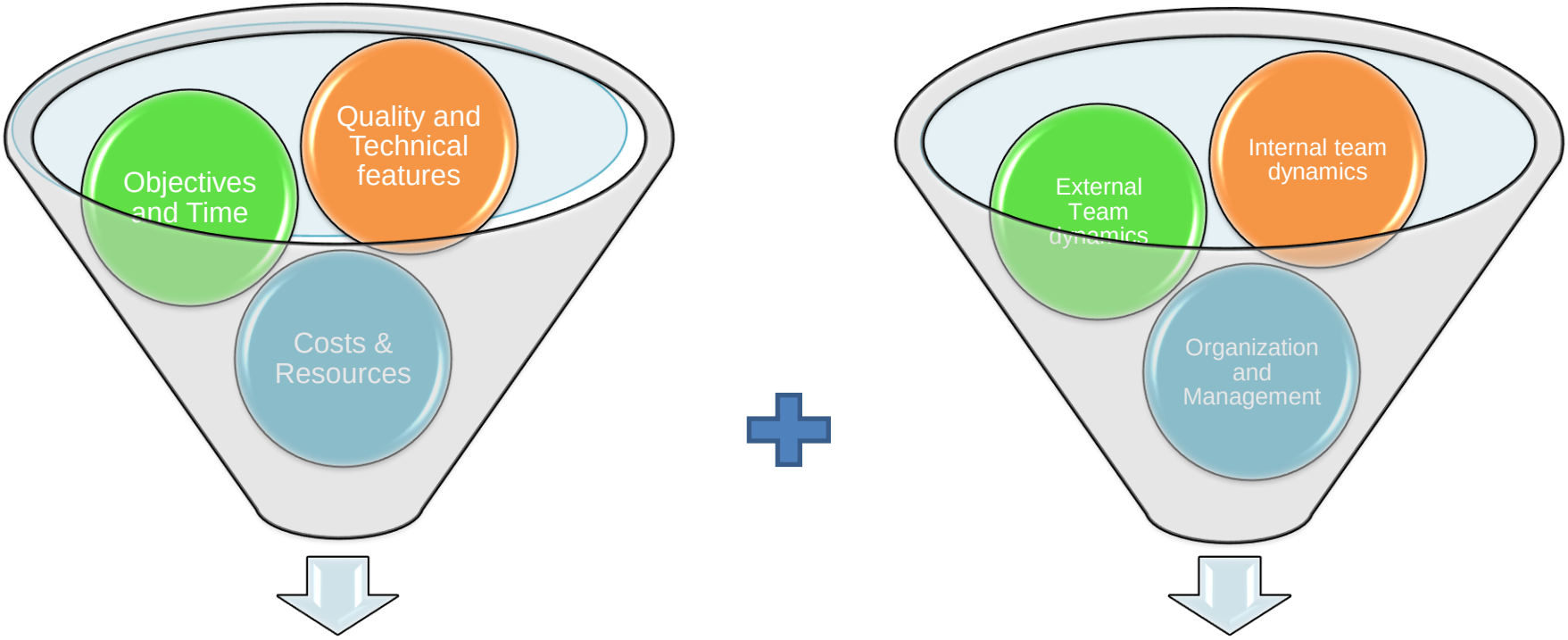
Is the team critical for TT Project success?

Team role in Technology Transfer I

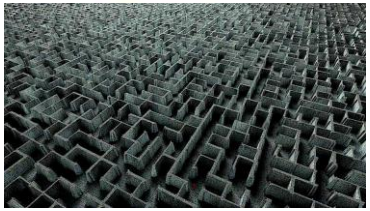
The Technology Transfer Project (TTP) is defined as a set of planned and controlled actions, based on well-defined acceptance criteria needed to transfer a technology from a sending unit (SU) to a receiving unit (RU).



Team role in Technology Transfer II



Team role in Technology Transfer IV



Business

Regulatory Affairs

Manufacturing

Project Engineering

- *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*

Quality

Development

Process Engineering

Regulatory

Supply Chain

Procurement

Analytical

Team setting I

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.

Team setting II

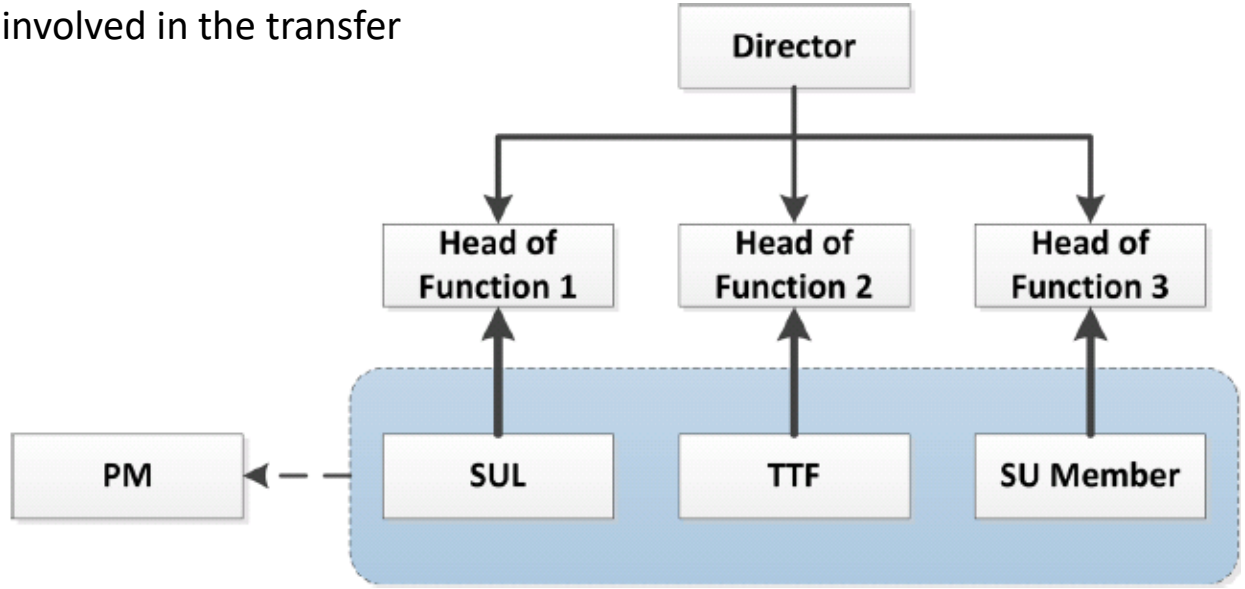
- **PM definition:**
  - PM in Receiving site
  - Endorcement del Management=Sponsor
  - Intracompany o intercompany
- **Team definition:**
  - Receiving Unit
  - Sending Unit
  - SPOC=single point of contact in each of them
  - Corporate functions
  - Others

Organization structure I

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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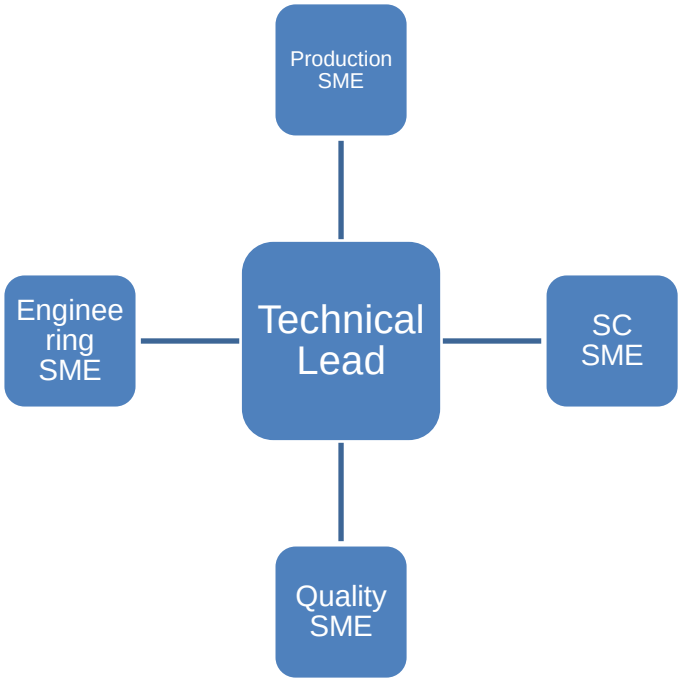
Organization structure II

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.



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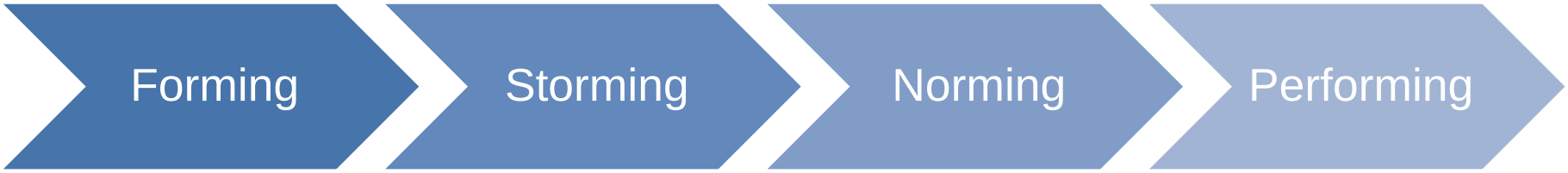
Team main phases

«Group of motivated people that work for a common goal and that cooperate to reach excellents results»

Team lifecycle phases:



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Team relationship and management I

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

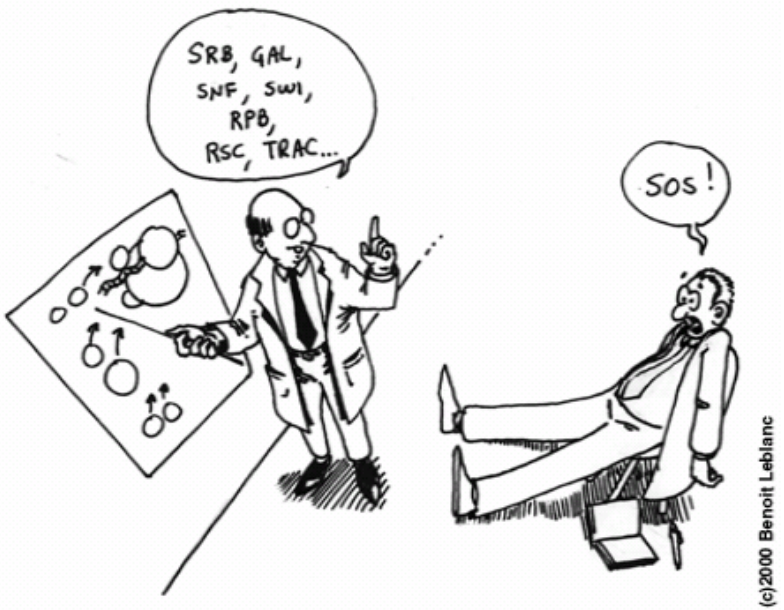
Team relationship and management II

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 relationship and management III

#	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

Discussion

What kind of team do you manage? Which organizational structure do you use?

Which are the main difficulties in team management?

Stakeholders analysis

Who are the stakeholders and how to manage them?

Stakeholders definition I

«Stakeholder: people or organization that is actively involved in the project or whose interests may be positively or negatively affected by execution or completion of the project» PMBOK® del PMI®

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

Stakeholders definition II

SU Team Members

Suppliers

Unions

Upper Management

Regulatory Agency

RU Team Members

Competitors

Corporate Experts

Employees

Business Partners

Stakeholders definition III

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

Stakeholders analysis I

The Stakeholder Analysis Process – tool 1 (Make a stakeholders map)

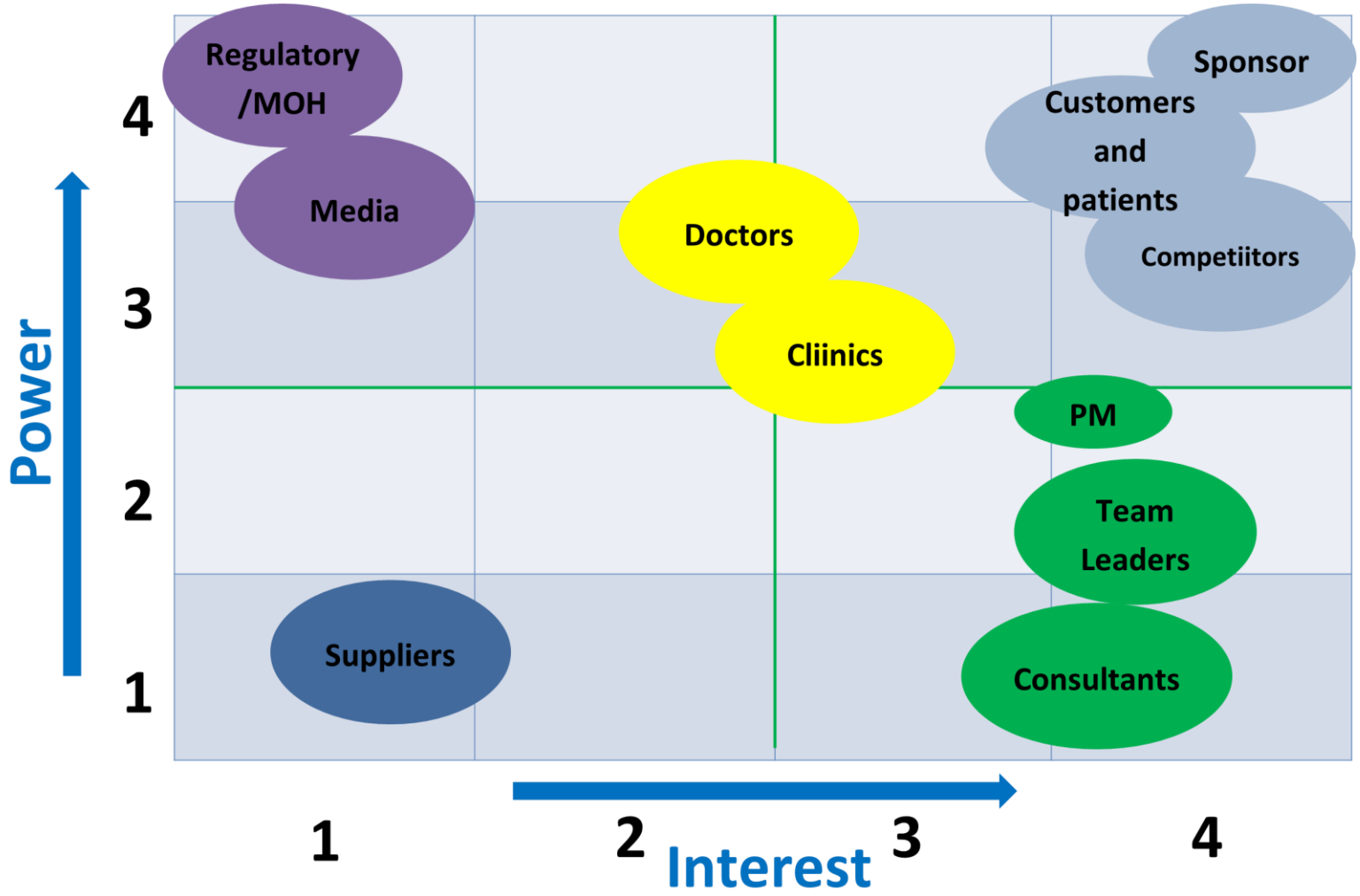
1.**Brainstorm** a list of Stakeholders, asking, “who can influence the success of my project and who can be impacted by the project?”

2.Ask, “to what degree do they have the ***power to influence the success*** of the ultimate startup?” I.e. use the 1-4 scale and place it on Y axis shown on the Template

3.Next ask, “what is this stakeholder’s current ***level of interest in the project***? I.e. use the 1-4 scale on X axis shown on the Template

4. Segment the stakeholders into meaningful clusters as appropriate (functions, regions,etc.)

Stakeholders analysis II



Stakeholders analysis III

The Stakeholder Analysis Process – tool 2 (Define stakeholders classes and how to manage them)

1.**Brainstorm** on Stakedolders Dynamics

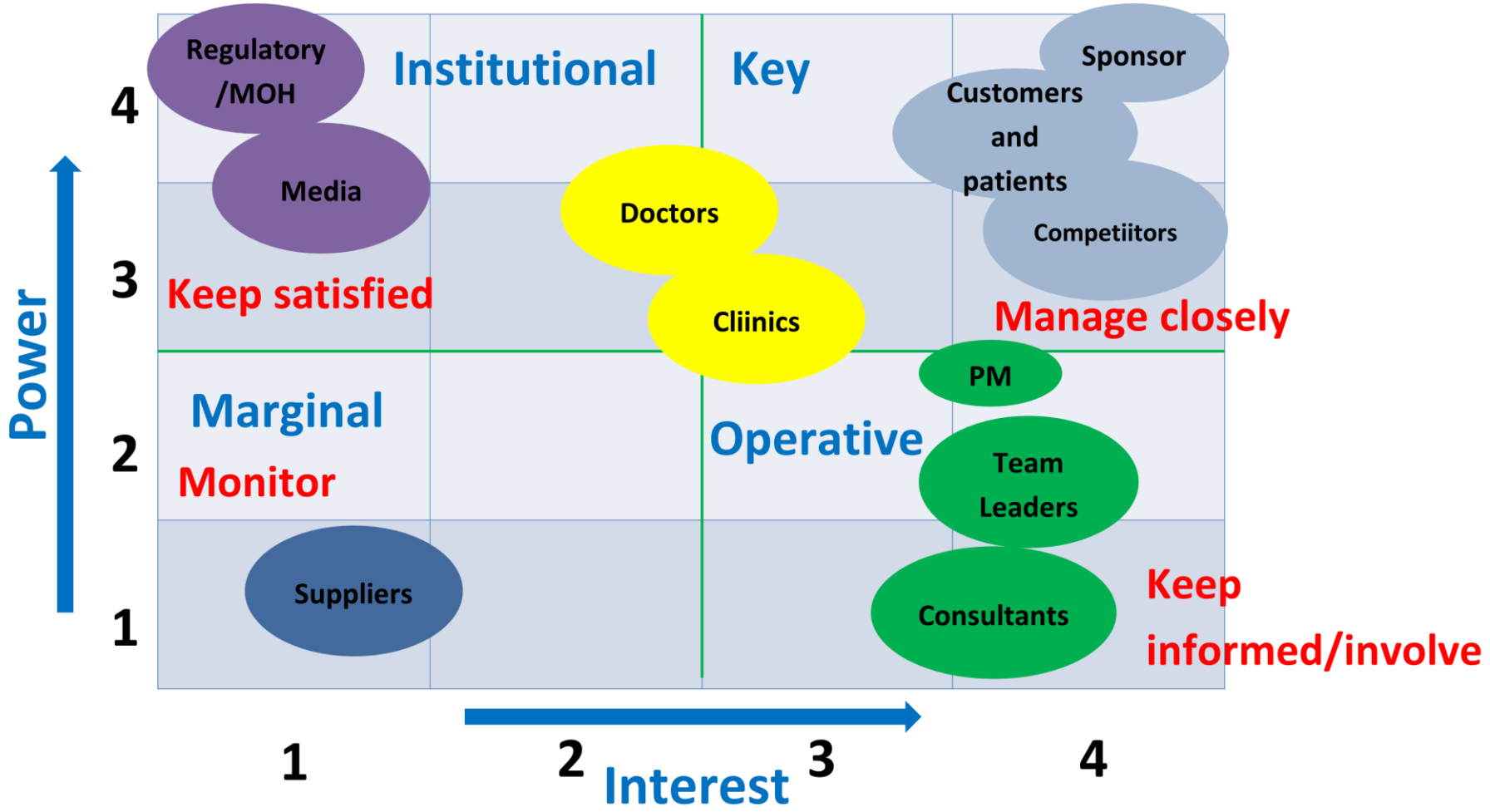
2. **Identify stakeholders classes**

3. Define **stakeholders level of involvment**

4. Define how to **manage them**

5. Make them **change!**

Stakeholders analysis IV



Stakeholders register

Stakeholder	Stakeholder type	Interest (1-4)	Power (1-4)	Engagement (U, R, N. S. L)
Regulators/MoH	Institutional	1	4	N
Press	Institutional	1	3	N
Suppliers	Marginal	1	1	U
Physicians/Clinics	Institutional/key	2	3	U
Experimental clinica	Institutional/key	3	3	S
Sponsor	Key	4	4	S
Customers/patients	Key	4	4	N
Competitors	Key	4	3	R
PM	Operative	4	2	L
Team Leaders	Operative	4	2	L
Trainers	Operative	4	1	S

U= Unaware, R=Resistant, N= Neutral, S=Supportive, L=Leading

Workshop: stakeholders analysis

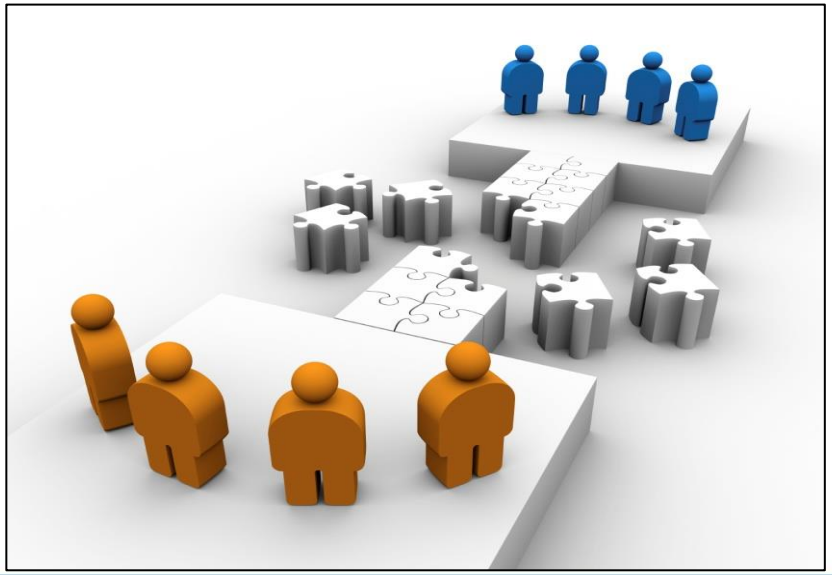
- ❑ **Step I:** select one technology transfer projects among the ones you managed
- ❑ **Step II:** perform stakeholders analysis, defining main stakeholders you identified
- ❑ **Step III:** draw your stakeholder map
- ❑ **Step IV:** among the defined stakeholders select one/one category and define which actions to take
- ❑ **Step V:** discussion

PM Role in pharma Technology Transfer projects

Is the PM critical for TT Project success?

PM Role in pharma tech tranfer projects

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



PM Role in pharma tech tranfer projects

- **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**

PM endorcement and Project charter

«Project charter: document issued by the Project Initiator or Sponsor that formally authorizes the existence of the project and provides the PM with the authority to apply organizational resources to project activities» PMBOK® del PMI®

Why to issue a Project Charter?

- To endorce the PM
- Nominate the team
- Get the Management approval
- Agree the main pillars with the Sponsors
- Define and officialize Technology Transfer project goals, budget and timelines

NO PROJECT CHARTER NO PARTY

PM and responsibilities: RACI I

«**RACI =** responsibility matrix where single functions and levels of responsibilities are listed»

R (responsible)

C (consultable)

A (accountable)

I (informed)

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PM and responsibilities: RACI II

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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PM and Leadership 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 and Leadership II

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.

PM and Leadership III

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.

PM and Leadership IV

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.

PM Role in pharma tech tranfer projects

- **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!

Take Away of this second session

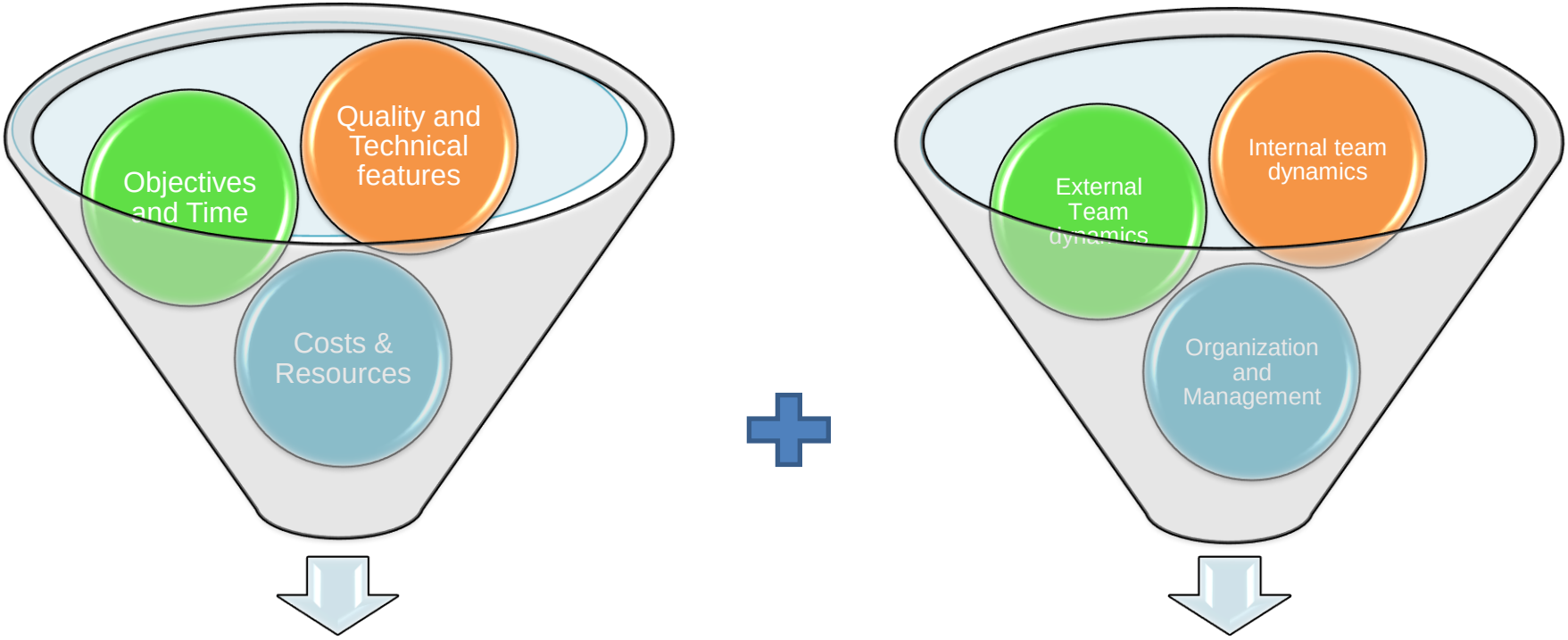
- Technology Transfer is not possible without a team
- Team shall be managed, organized and motivated
- Role and leadership of the PM are crucial for Technology Transfer success
- Stakeholders are different and shall be managed

PEOPLE ARE CRUCIAL FOR A SUCCESSFULL TECHNOLOGY TRANSFER

Technology Transfer in Pharma: projects governance and tools

Which does governance mean in TT?

Pharma Tech Transfer Projects governance



Pharma Tech Transfer Projects governance

Define scope, plan, execute and track

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

Define the scope: WBS I

Define what is TO BE be done and **Define what IS NOT to be done**

DELIVERABLE: «Any unique or verificable product, result or capability, to perform a service that must be produced to complete a process phase or project»

WORK BREAKDOWN STRUCTURE (WBS):

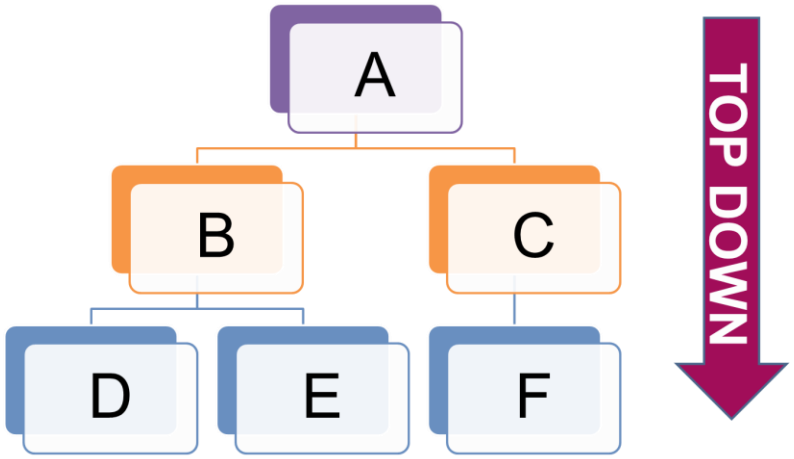
- Activities are detailed
- Scope is formalized

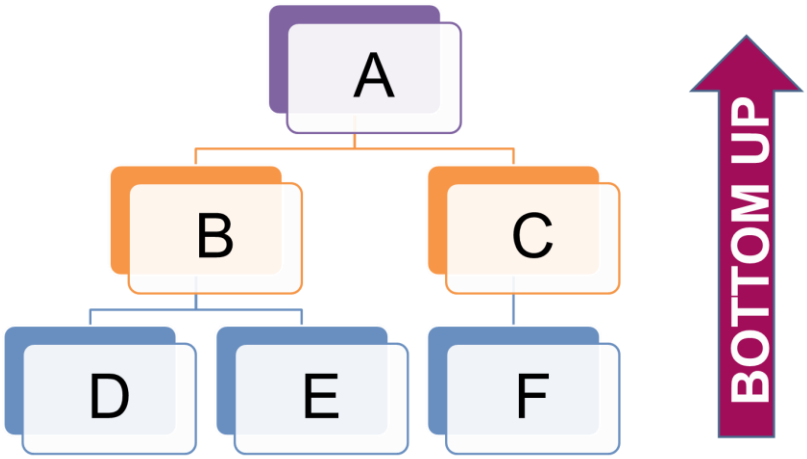
Define the scope: WBS II

Work Breakdown Structure:

- Logical structure used to define project deliverables, till the needed level of detail, and to list main project activities needed to reach the goal
- It is necessary to assign responsibilities, define work load and subsequently create the gaant
- It is necessary to formalize the «TT scope» defining not only the deliverables but also the activities needed to reach them

How to create a WBS?

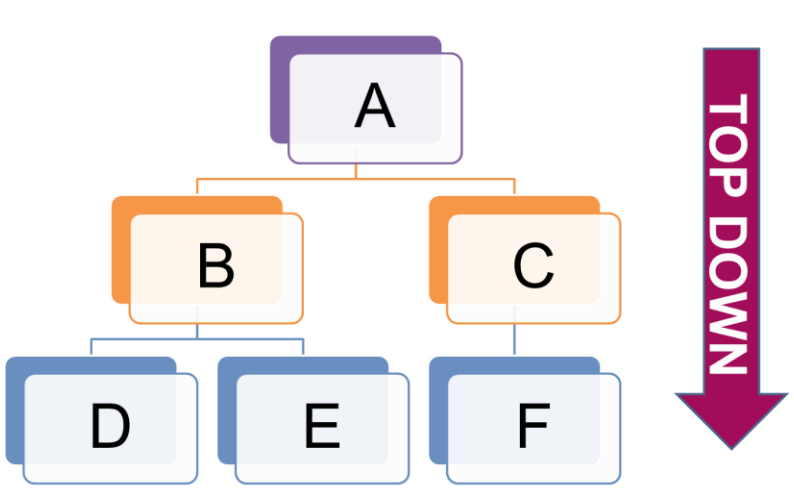


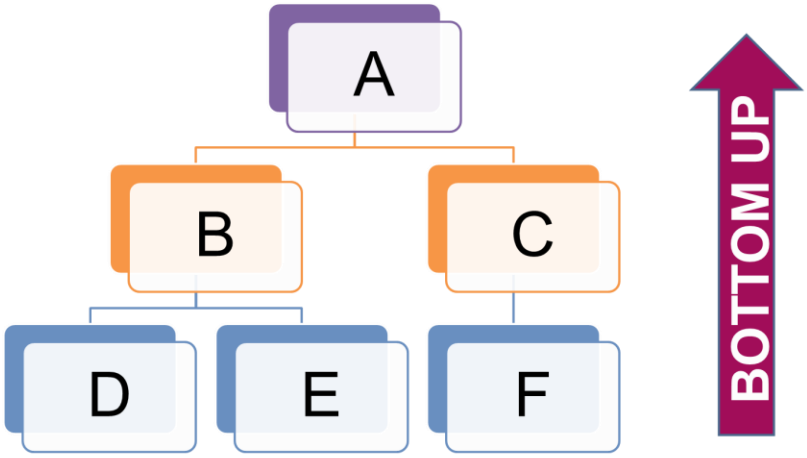


Define the scope: WBS III

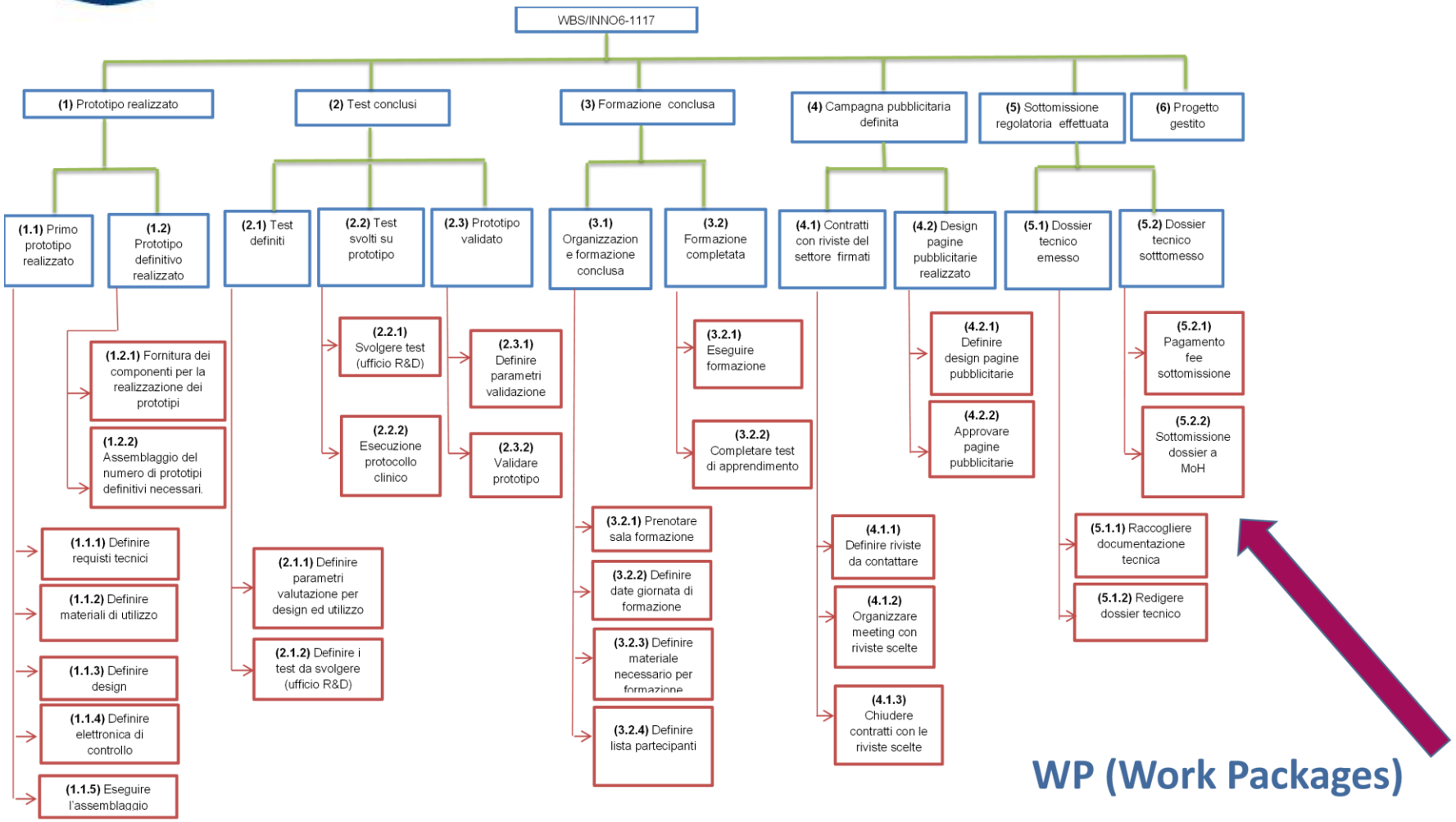
How to create a WBS:

- Start from the first level and then move to the others
- Follow logical or temporary sequence
- Stop when you think is needed





Define the scope: WBS IV



Plan: different steps

ASSIGN RESPONSIBILITIES

- For each of the activity assigned clear resposnibility (RACI or other models)

ESTIMATE THE EFFORTS:

- Expert judgment:
- Parametric estimation
- Analogous estimation
- Lesson learned
- Bottom up estimation
- Top down estimation

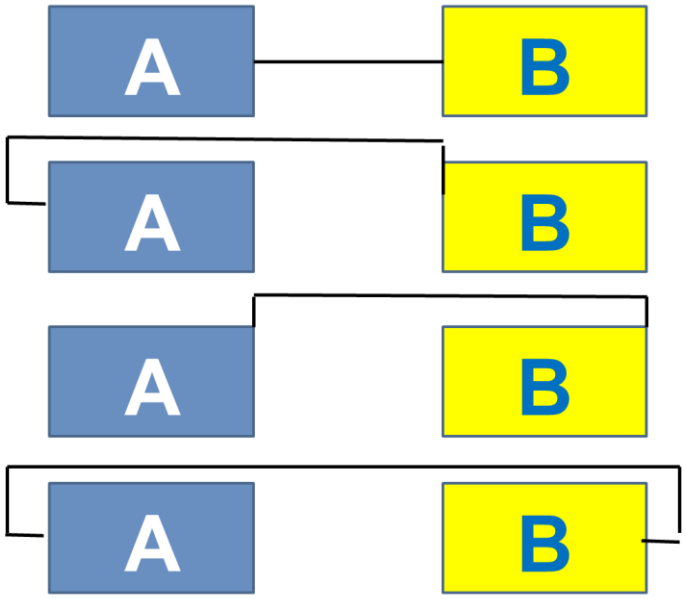
ASSIGN THE RESOURCES

CONVERT THE EFFORTS IN DURATION

ESTABLISH THE RELATIONSHIP BETWEEN THE ACTIVITIES

DEFINE THE PROJECT PLAN

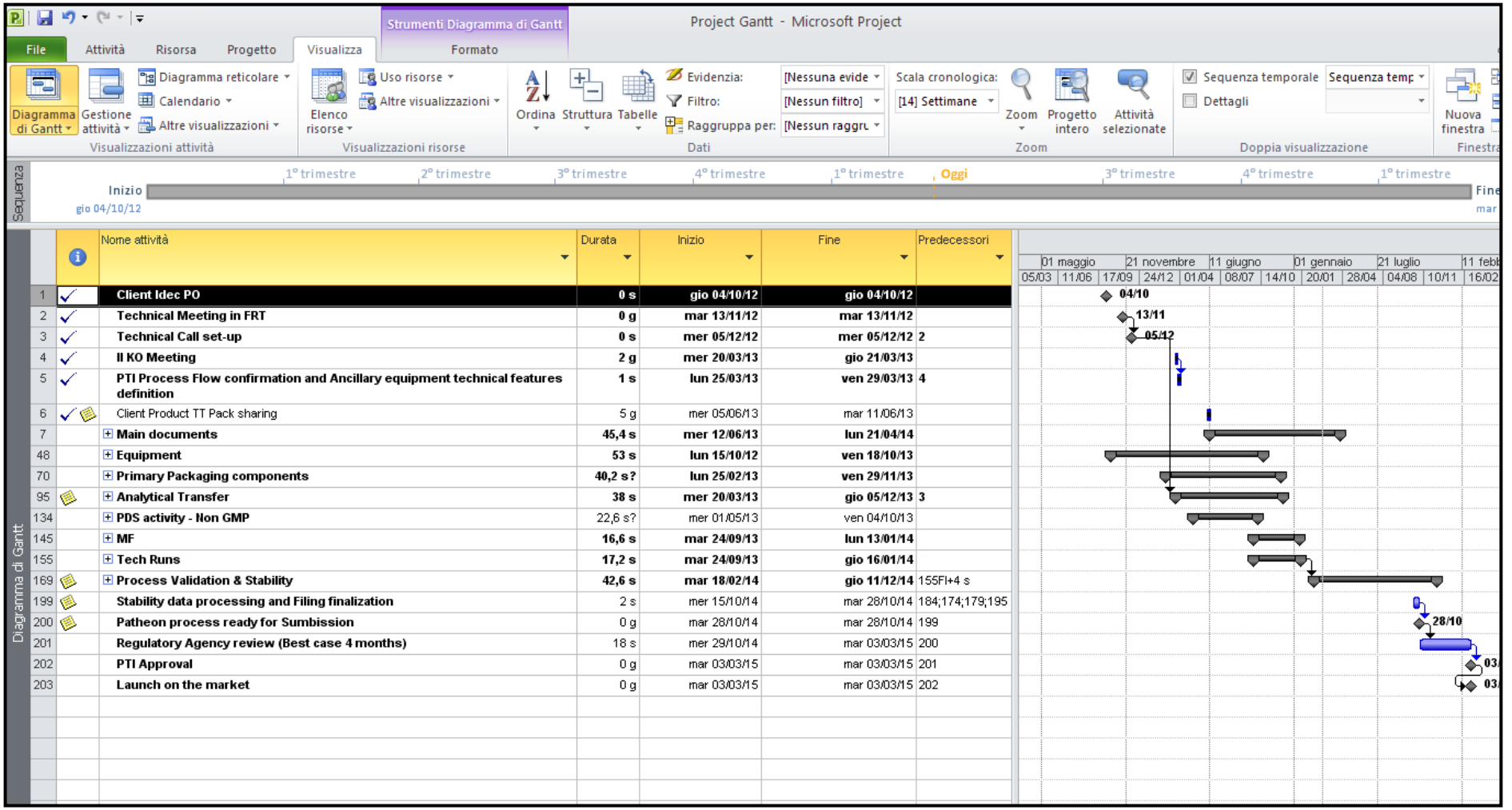
Activities relationships



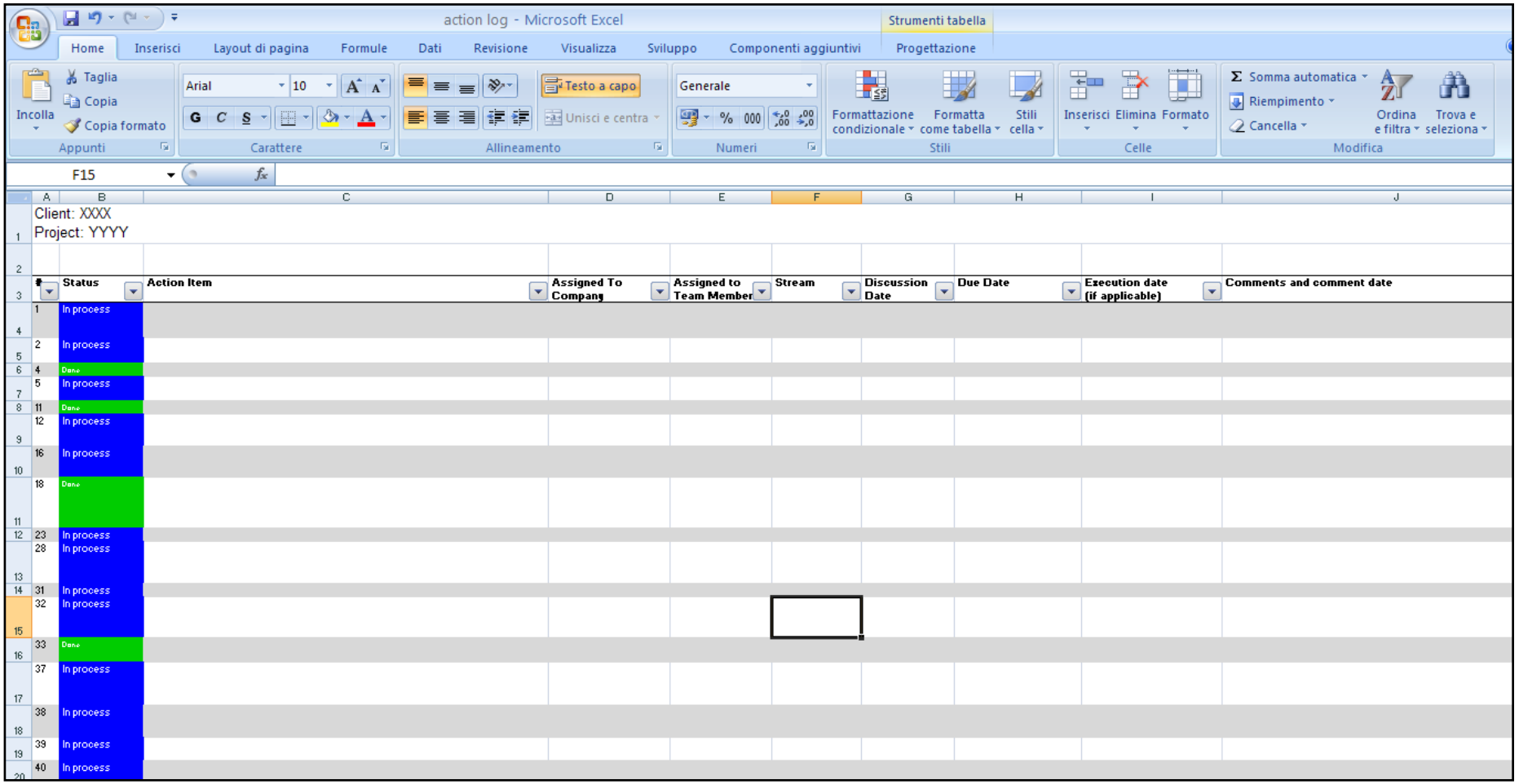
Plan: efforts and duration

ACTIVITY LIST	PM	HR	ING	MAN	QA	PROCUR	FIN	MARKETING	IT	QA/VAL	R&D	PROD	COMM	RA	CLINIC
(1.1.1)			120	80	120					80	80		40		
(1.1.2)			120	80	40					80	80		40		
(1.1.3)			80								120		40		
(1.1.4)			40		160										
(1.1.5)			20	20	20							200			
(1.2.1)						80	80								
(1.2.2)			20	20	20					40	40	200			
(2.1.1)			60					20		40	160		40		
(2.1.2)			120							40	80			40	40
(2.2.1)			40	20	20				10	80	200				
(2.2.2)			160							40	80				220
(2.3.1)			8							16	8	8		16	
(2.3.2)			50	50	50	50		20		160	40	40	40		
(3.1.1)		20											20		
(3.1.2)		40											20		
(3.1.3)		40				40		40					40		
(3.1.4)		40											80		
(3.2.1)		160	40	40	40				20	20	40	40	80		
(3.2.2)		160	20	20	20					20	20	20	40		
(4.1.1)								40		20	20		20		
(4.1.2)								80					20		
(4.1.3)						40		80							
PM	720														
N° hour/am	720	460	1258	390	550	210	120	520	70	776	1028	508	560	536	300
Cost/hour	€ 30,00	€ 20,00	€ 30,00	€ 30,00	€ 30,00	€ 16,00	€ 16,00	€ 30,00	€ 16,00	€ 40,00	€ 26,00	€ 26,00	€ 50,00	€ 30,00	€ 60,00
Total cost/area	€ 21.600	€ 9.200	€ 37.740	€ 11.700	€ 16.500	€ 3.360	€ 1.920	€ 15.600	€ 1.120	€ 31.040	€ 26.728	€ 13.208	€ 28.000	€ 16.080	€ 18.000

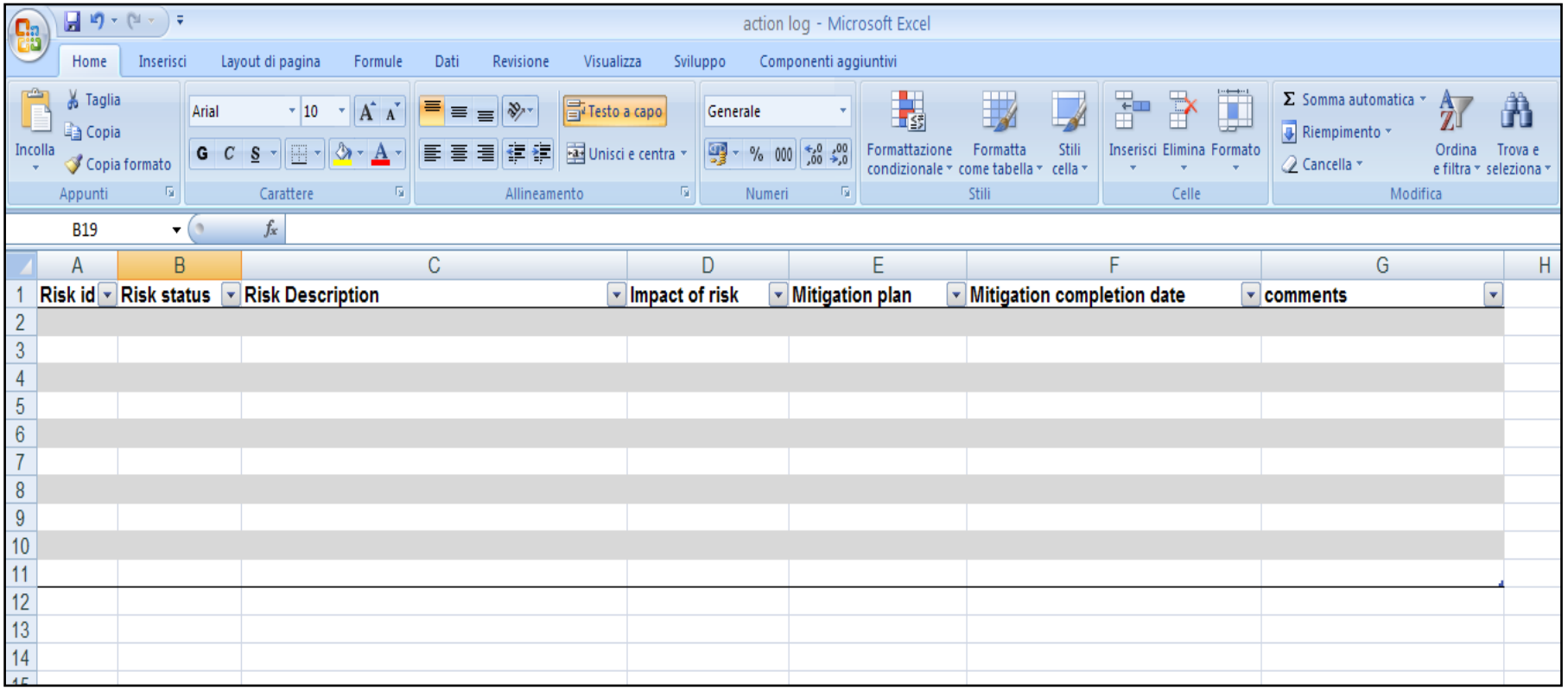
Plan and track diagrams I



Plan and track diagrams II



Plan and track diagrams III



Plan and track diagrams IV

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 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 : CEP, DMF, scientific data)					
2.1.10 API Letter Stating Stability Data, including the requirement of temptales 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

Plan and track diagrams V

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%

Plan and track diagrams VI

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%

Workshop: TT WBS

- **Background:**

Think about one Technology Transfer project you managed or you experienced in your professional life

- **Questions:**
  - Briefly describe it
  - Prepare a WBS

- **Discussion**

Execute: some tools

TECHNICAL DATA PACKAGE:

- Package that includes all the main information about the product, process, specifications etc from the Sending Unit
- Different dipending from the type of project

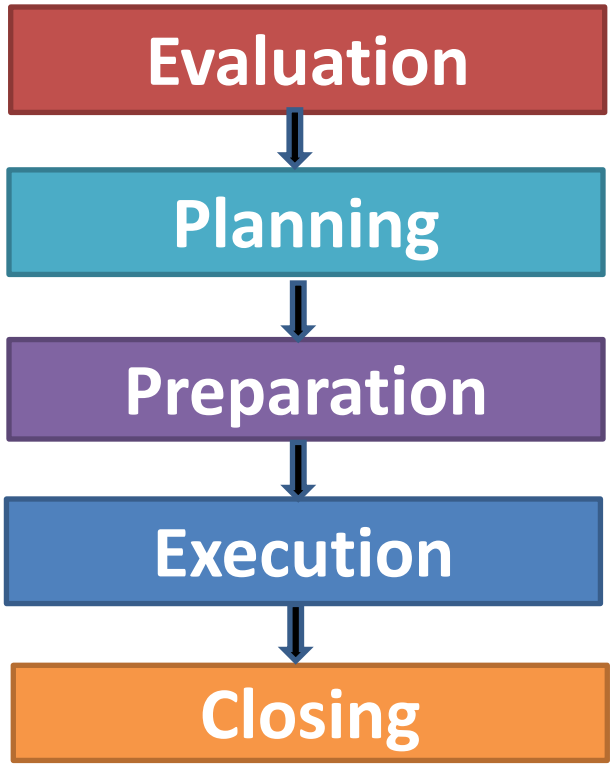
TECHNOLOGY TRANSFER PLAN OR PROTOCOL:

- Document that list scope, timelines, activities, responsibilities…..all about the project
- Management document or technical document?
- Different depending from the type of the project
- Different in different organizations

TECHNOLOGY TRANSFER REPORT:

- Document that sum up project conclusions and results
- Management document or technical document?
- Different depending from the type of the project
- Different in different organizations

Technology Transfer structure: recap



1. Evaluation

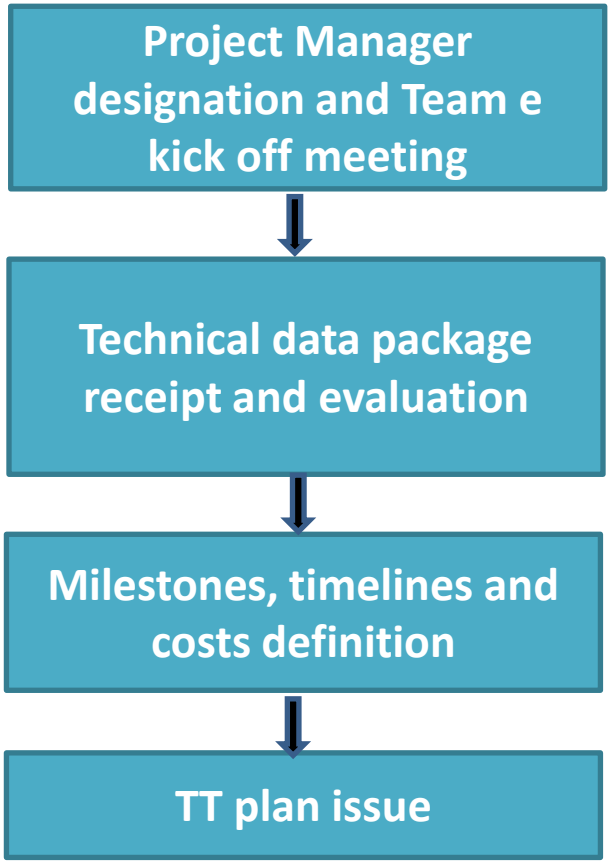
Microsoft Word
7 - 2003 Documen

Transfer request

Feasibility evaluation

- Technical
- Regulatory
- Qualitative
- Engineering
- Safety
- Costs and resources

2. Planning


Project Manager designation and Team e kick off meeting
Technical data package receipt and evaluation
Milestones, timelines and costs definition
TT plan issue

3. Preparation I

Preliminary activities

- Regulatory authorization request
- EHS authorization
- Regulatory assessment
- URS definition and issue
- Materials evaluation
- Change opening

Process and technology

- Evaluation of technical info
- Evaluation of available equipment and comparison
- In case they are different:
  - Act on the existing equipment
  - Buy new ones

3. Preparation II

Which are the main activities? Which is the proper sequence of work?

Examples and discussion

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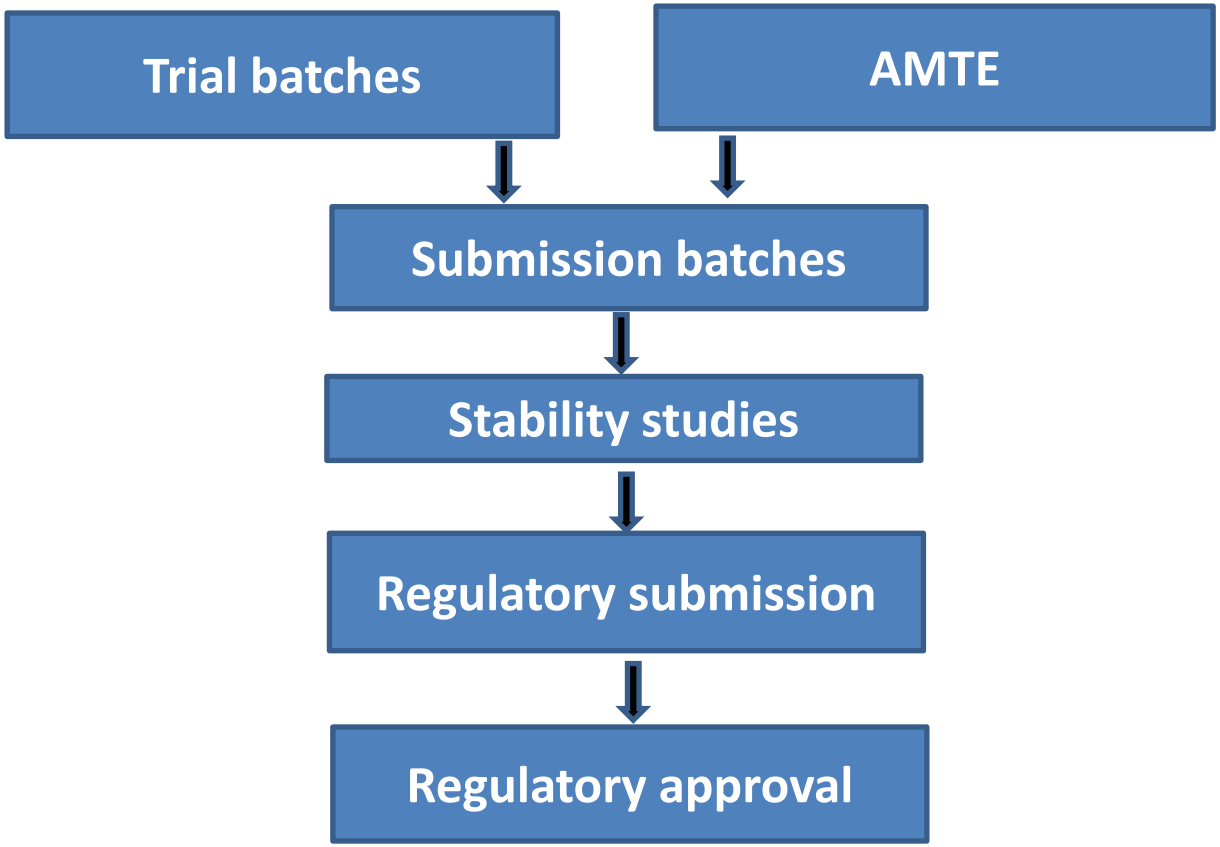
4. Execution I



4. Execution II

TECHNICAL BATCHES

Definition: batches manufactured at the receiving unit using industrial equipment with the aim to test the process

- ✓ Strategy is defined depeding from process, risks and budget
- ✓ Goal is to test the process:
  - ✓ The first technical batches are necessary to test the process and highlight the challenges: problems are welcome
  - ✓ “Challenge” the process and its limits and to propose solutions
- ✓ They are a knowledge opportunity for both the units

4. Execution III

SUBMISSION BATCHES

Definition: batches manufactured at the receiving unit to support product registration

- ✓ Strategy is different depending from type of registration, product and market
- ✓ The can be validation batches also
- ✓ They are stability batches
- ✓ They shall be manufactured at industrial scale, with the final process and once analytical transfer is complete

⇒ Both technical and submission batches are part of the Technology Transfer!

4. Execution IV

REGULATORY REQUIREMENTS AND STRATEGIES

Strategy is different depending:

- ✓ On type of registration, product and market
- ✓ Pharmaceutical form
- ✓ Status of product registration/dossier
- ✓ Type of transfer
- ✓ Level of risk
- ✓ Other

4. Execution IV

Which strategy to follow for trial/technical and submission batches? Examples and discussion

Which are possible regulatory strategy? Examples and discussion

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5. Closure

And once the transfer is completed?

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Post Technology Transfer

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.

Post technology transfer

MONITORING PRODUCT, PROCESS, RESULTS
CLOSING PHASE
LESSON LEARNED

….LEARNING IS A CONTINUOUS PROCESS…..

Pharma Tech Transfer Projects governance

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

Tech Transfer in CDMO

- **Types:**
  - From to R&D a CMO (primary)
  - From CMO a CMO (primary or secondary)
- **Request:**
  - From MAH
  - From licensee
  - Other
- **Key aspects/challenges:**
  - Technical data package availability (or not!) and communication with sending site: lack of information (blind transfer)
  - Technology transfer proposal and negotiaition: costs competition
  - Project complexity (differenet markets, strategies, customers…)
  - Challenging timing
  - Dossier status
  - Virtual companies

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Tech Transfer in CDMO: proposal

Main aspects and phases
1. Background: customer request and company introduction
2. CMO evaluation
3. Activities proposal
4. Technology Transfer quote and assumptions
5. Supply Price quote and assumptions
6. Timelines
7. Contractual aspects

Tech Transfer in CDMO: contractual aspects

- **Type of contracts:**
  - Master Service Agreement or Technology Transfer Agreement
  - Quality Technical Agreement
  - Supply Agreement
- **Key aspects/challenges of the Technology Transfer Agreement**
  - Responsibilities definition (not only for the CMO!)
  - Term and timelines: properly manage respect of timelines, what will happen in case of delay, incude the timelines or not (examples)
  - Failure of the technology transfer and selection of a new CMO
  - Penalties, liabilities and their limitation (i.e. penalties in case of delay and related limitations)
  - Termination clause and consequences (examples)
  - Impact of the technology transfer on the supply price

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Technology Transfer in Pharma: projects risk management

What does RM mean in TT?

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

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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...

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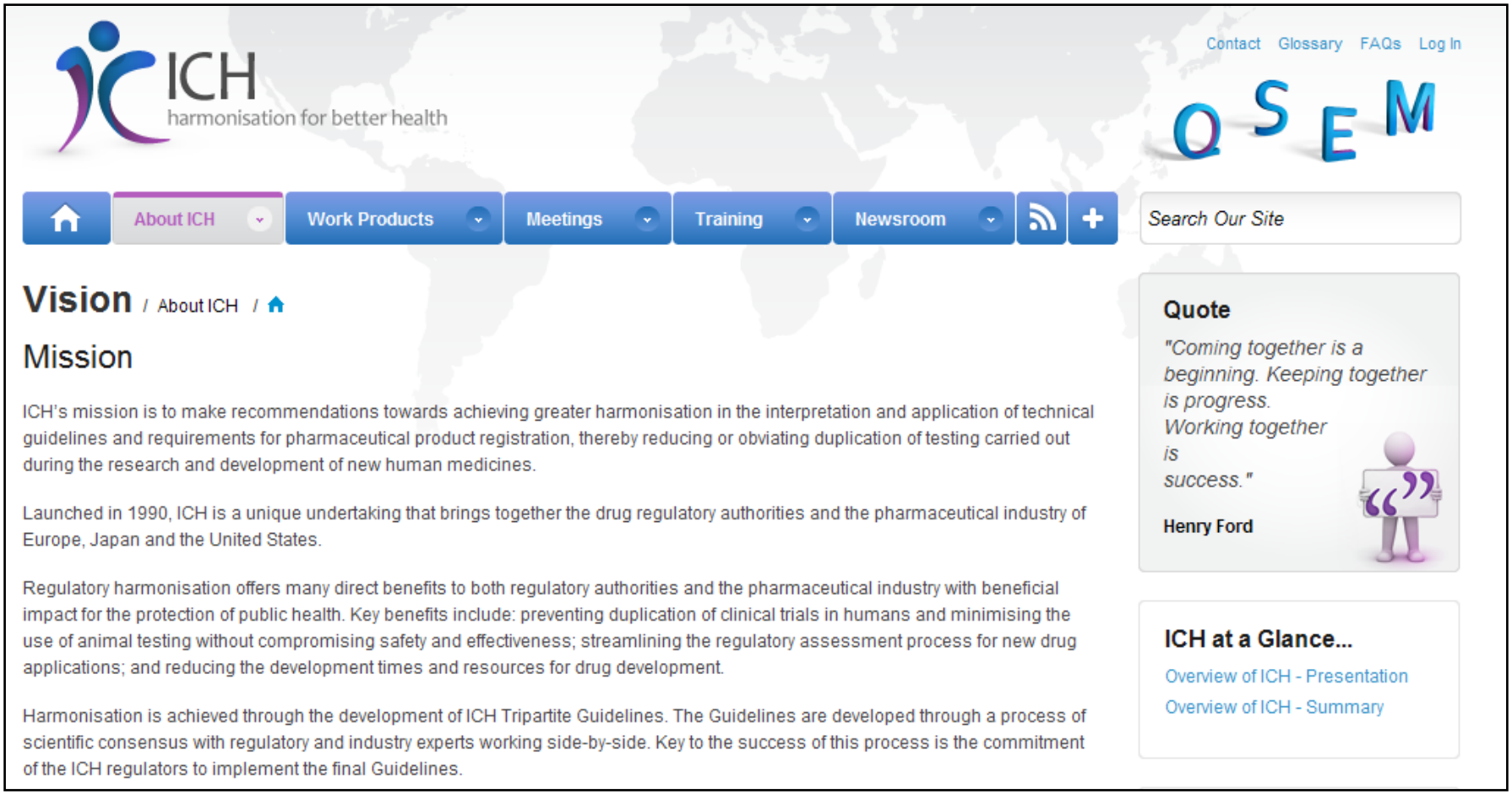

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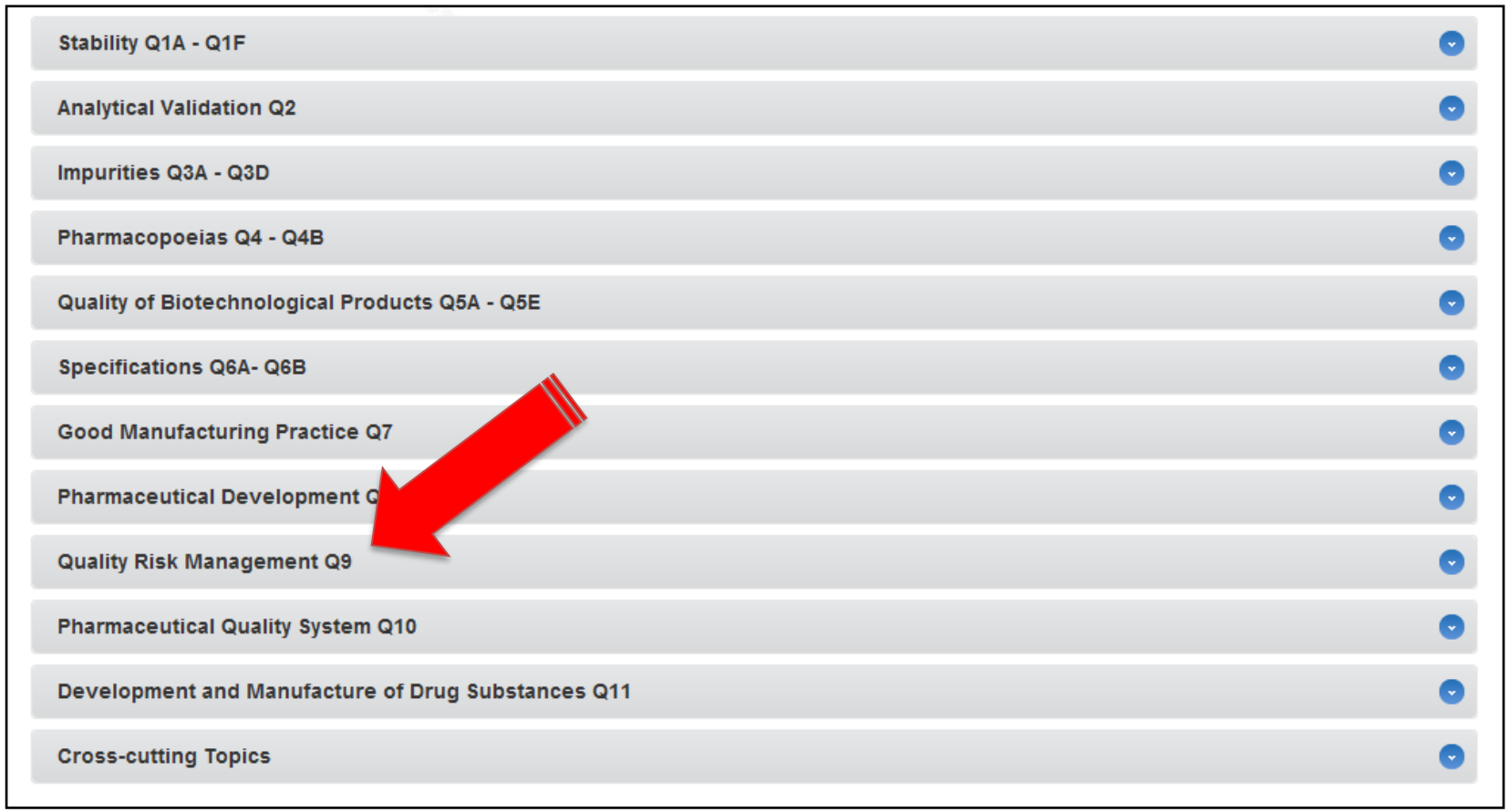

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- It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.
- In relation to pharmaceuticals, although there are a variety of stakeholders, including medical practitioners 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.

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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.

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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

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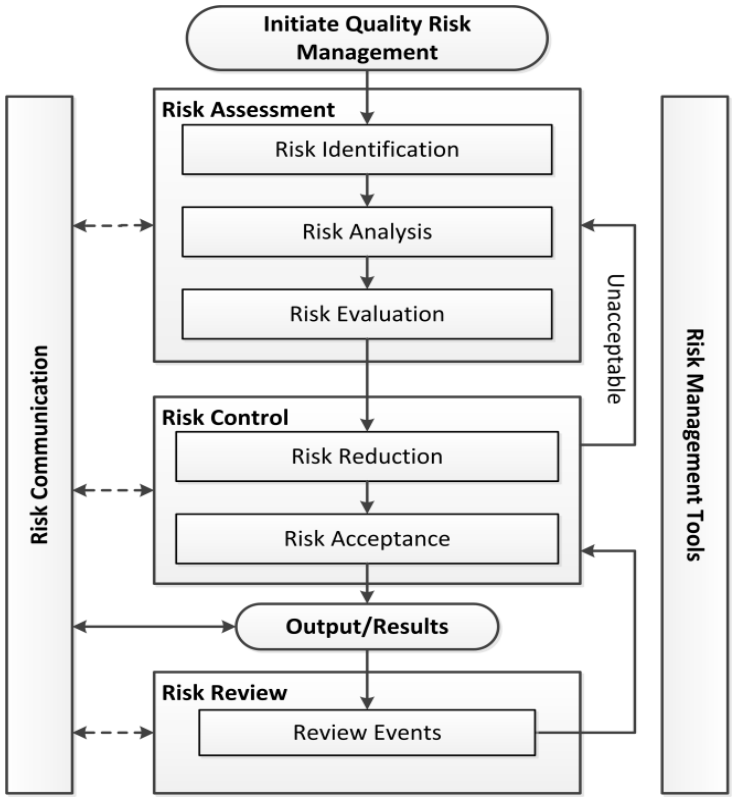
The quality risk management (QRM) is “a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.”



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

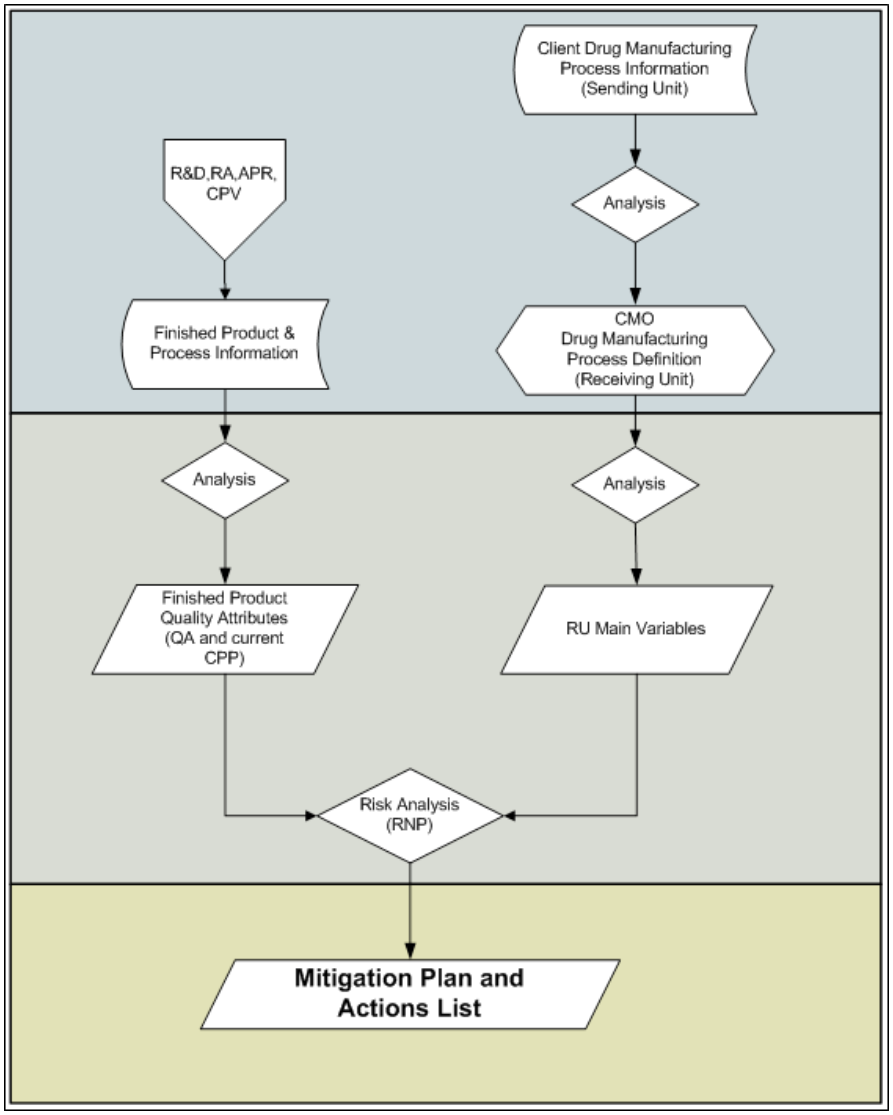
Technology Transfer – Risk Management

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



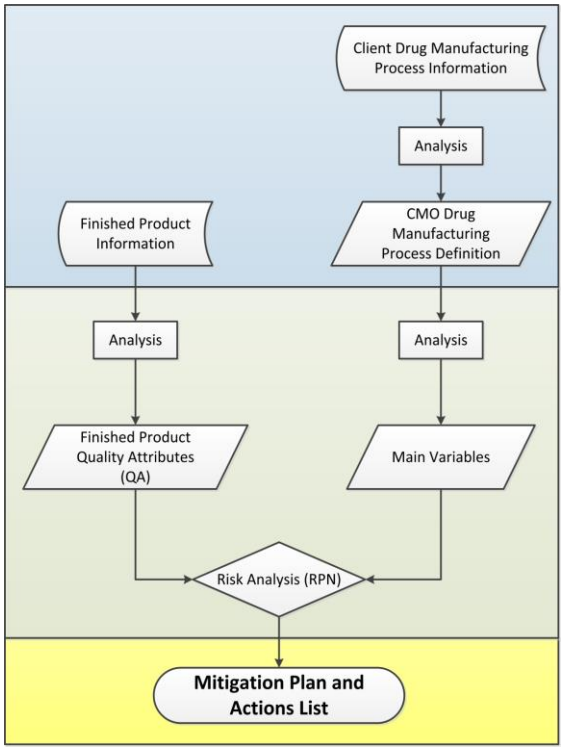
Data collection

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.
		Osmolality	Dissolution speed insufficient for complete dissolution and an homogenous system	3	3	1	9	Mixing studies will be agreed with the SU and performed during the engineering batch.
		Appearance	Mixing system 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 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 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	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 and type of risks

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

Process risks are specific for each transfer while project risks are common to all the transfers!

Workshop and discussion

Examples of process and project risks

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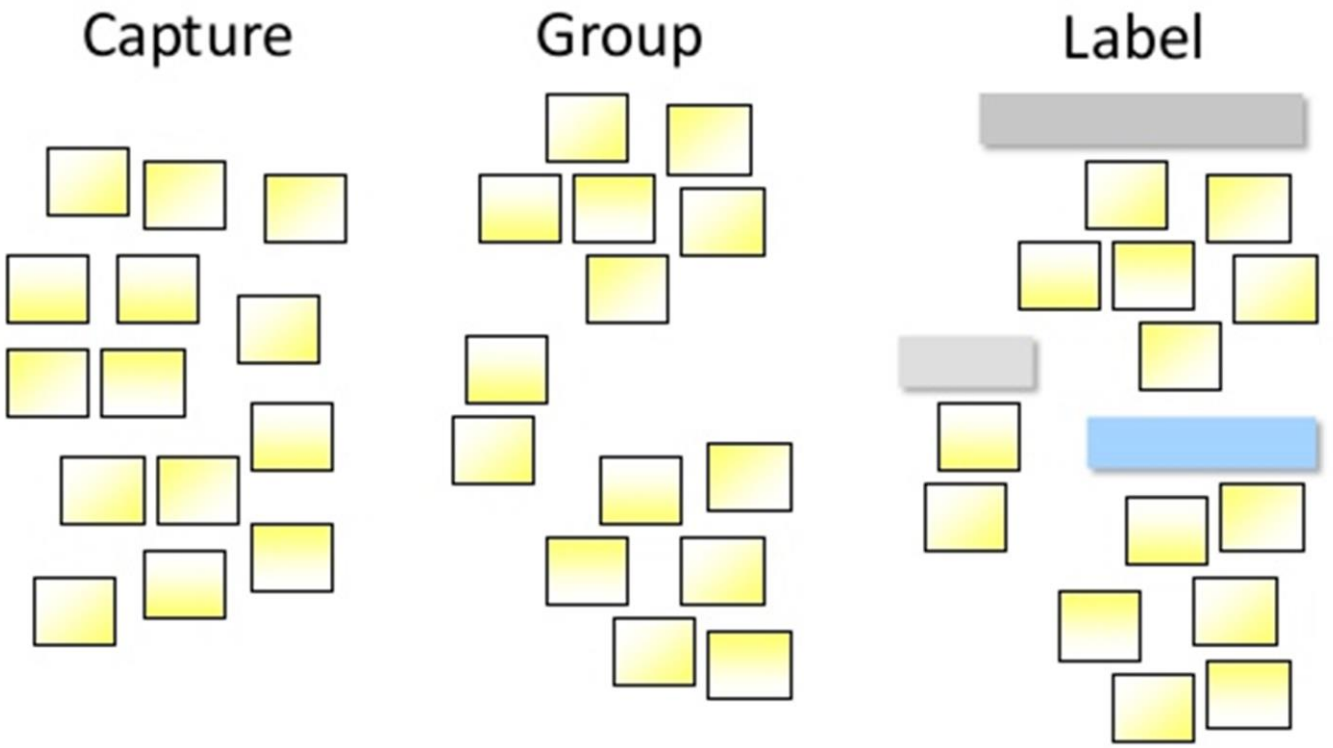
Workshop and discussion

Identify the risks using affinity diagram



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Workshop: Risk analysis part I

- **Step I:** split in three groups
- **Step II:** group focus
  - Group I: primary technology transfer (from R&D to industrial phase of a new product) I within the same company and site
  - Group II: secondary technology transfer (commercial phase) from one CMO to another CMO (blind transfer)
  - Group III: secondary technology transfer (pre-commercial phase) between two sites of the same company
- **Step III:** within the same group identify the project risks using the affinity diagram
- **Step IV:** present the results to the other groups
- **Step V:** discussion

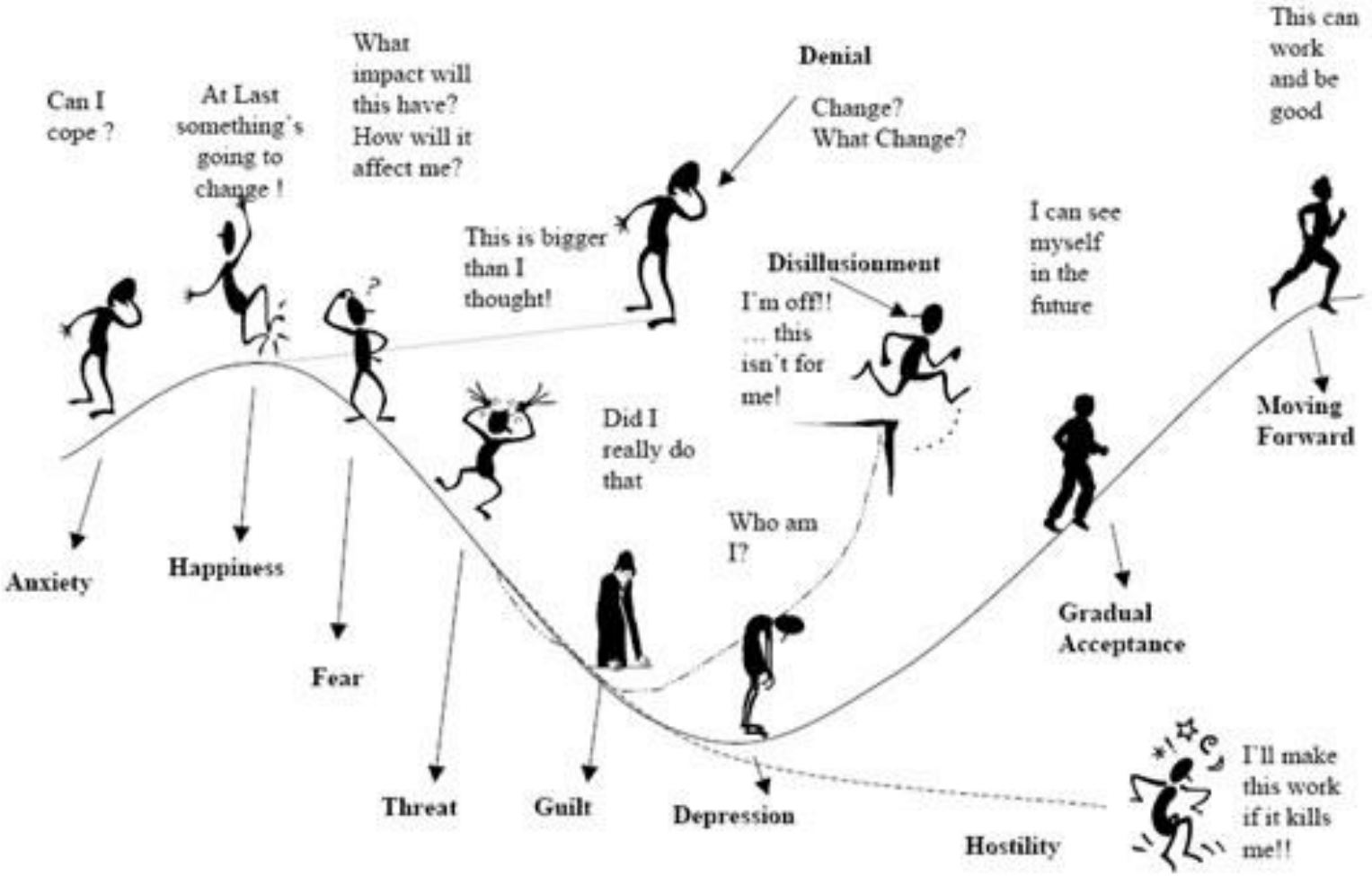
Workshop: Risk analysis part II

- **Step I:** keep same three groups and focus
- **Step II:**
  - Select 3 risks among the discussed ones (1 for each category)
  - Perform risk analysis with a special focus on project perspective (how and how much the risk will impact the project)
  - During risk analysis select define an action plan (risk avoidance, mitigation, reduction..)
- **Step III:** present the results to the other groups
- **Step IV:** discussion

Change Management in Technology Transfer

How to manage changes?

Change Management in TT I

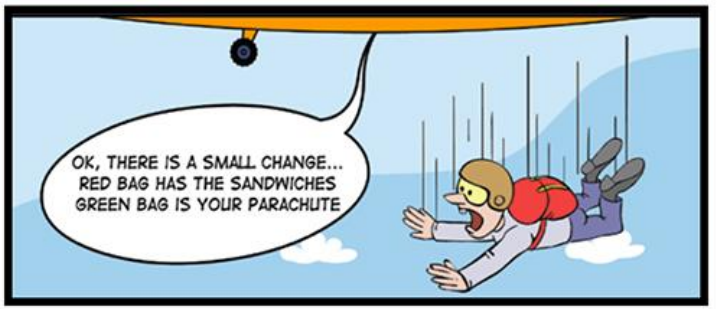


Change Management in TT II

Focus on changes in Technology Transfer Projects

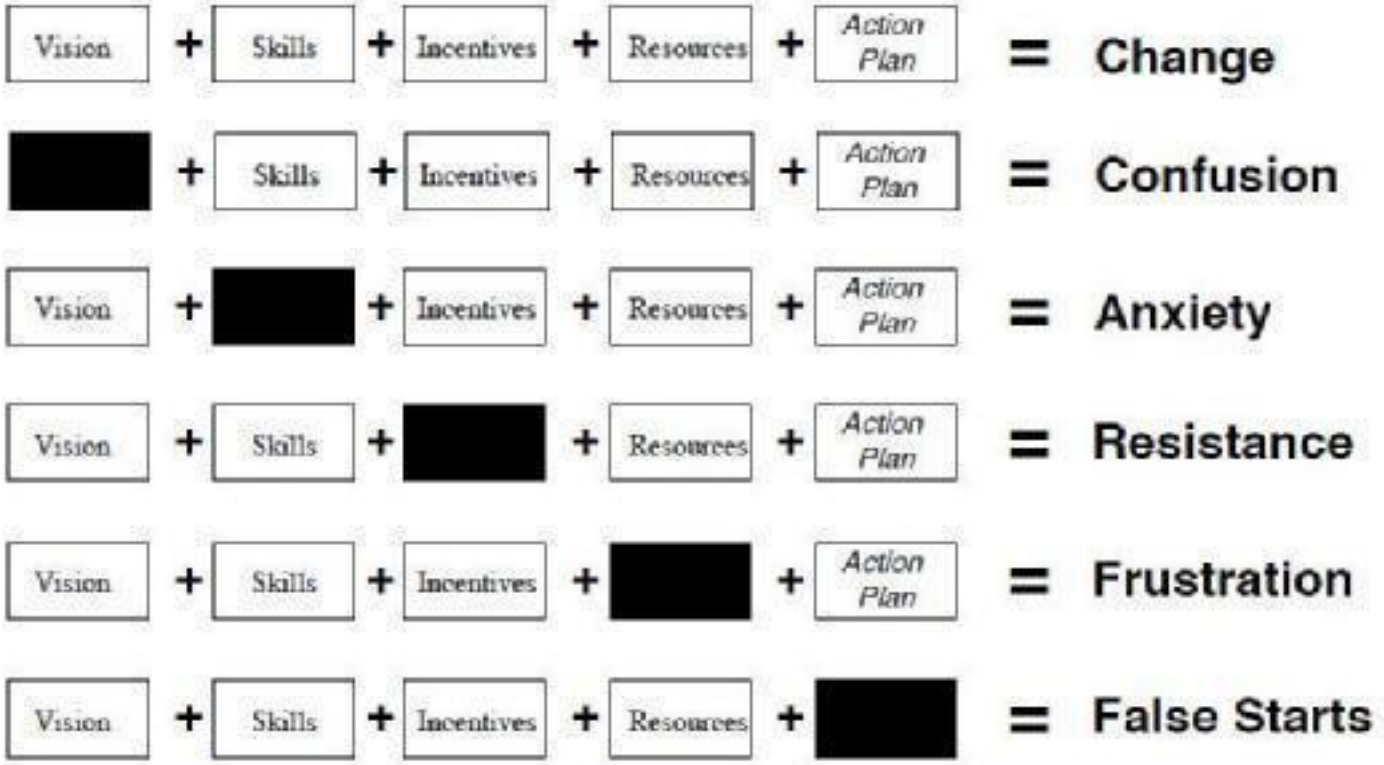
- Changes are frequent in TT project execution and can have big impact on project success
- Change management is not an easy skill to establish, train and improve
- Change management is time/costs/resources consuming

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



Change Management in TT III

Managing Complex Change



Adapted from Knoster, 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. 93-128). Baltimore: Paul H. Brookes Publishing Co.

Change Management in TT IV

Top three reasons which reduce acceptance of changes:

- Day-to-day tasks are overwhelming to most
- There isn't a lot of alignment around what exactly organizational priorities
- 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)

Change Management in TT V

Tips:

- Standard Procedures are always in place to handle GMP changes but

WE NEED

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

Change Management in TT VI

Always starts with three things:

- **Care:** Why are we doing this change management process? Why are we doing it now? What's the purpose of the change management now?
- **Listen:** Listen all over the organization and listen to your team. 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**

Technology Transfer and Risk management in real life

Case studies

- Risks can be overestimated and a new risk will come!
- Pay attention…
- Risks can be hidden everywhere: 360 view is needed

Case studies: examples of mistakes

- Use of excipeint different from the one used by Sending unit (different content in water) in Injectable product alcohol based: results at the limit of specifications → **MISTAKE IN COMMUNICATION**
- Delay in the project related to lack of communication on lab instrument needed and so bought with delay → **LACK OF COMMUNICATION**
- Low yieald and high % of breackage on Mannitol based Lyo product due to reduced N° trials and demo batches → **TECHNICAL MISTAKE**
- Delay in the project due to change in regulatory strategy → **WRONG STRATEGY**

Case study I: analysis and background

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

Case study I: results

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

Case study II: background

- 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

Case study II: risks analysis

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 technique already in place somewhere else

Case study II: results

- Technology replacement was succesfully completed on time and on budget
- No issue in knowldege 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 that the old one
- Small variation of concentration (Δppm) 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 establishes based on the old analytical technique. No assessment was done during analytical method implementation on manufacturing process, impact on operations missed

Case study III: background

- 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 knwon 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 mantained equal to previous one including equipment and primary packaging
- Secondary packaging is not part of the transfer
- Lyo cycle was developped and well established

Case study III: risks analysis

Major Risks/Actions identified:

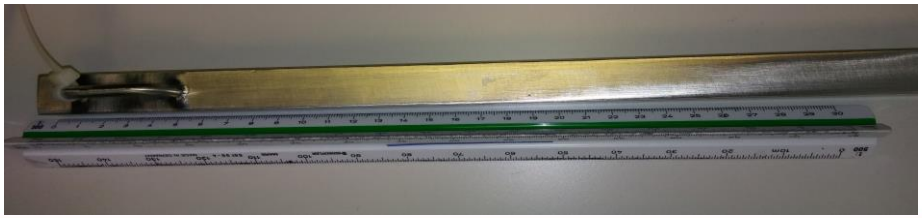
- RA completed as one single team, between RU & SU; major risk was the difference in lyo equipment
- Development activities planned focusing on operative parameters during the cycle (T ranges and P ranges during lyo steps) and potential impact on product quality (KF, appearance, reconstitution, impurity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

Case study III: results

Results

- Pre-PPQ 28% of collapsed vials
- RC analysis -> Different T of the product during freezing and primary drying step
- Process Analysis -> ΔT 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 rapresentative of real commercial conditions); robustness not repeated.



Case study IV: background

- Medium-small company family owned – new product to be transfered 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 mantained equal to previous one including equipment technology and primary packaging

Case study IV: risks analysis

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 succesfully completed
- PPQ completed succesfully

Case study IV: results

Results

- TT went very well, according to plan and budget

- 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

Case study V: background

Product A:

- Sterile solution in vial and high potent
- Complex formulation

Partial Technology Transfer:

- Production splitted in: bulk production and fill&finish
- Transfer of fill&finish, analysis and release

Partially blind transfer:

- No contact with the current manufacturer but only with the MAH

Main Challenges:

- Complexity of the production process (new for the receiving site)
- Manufacturing process defined by MAH and current manufacturer with no involvment of the receiving unit
- No contact with the current manufacturer/information only from MAH
- Strict timelines

Case study V: technology strategy

Collect information

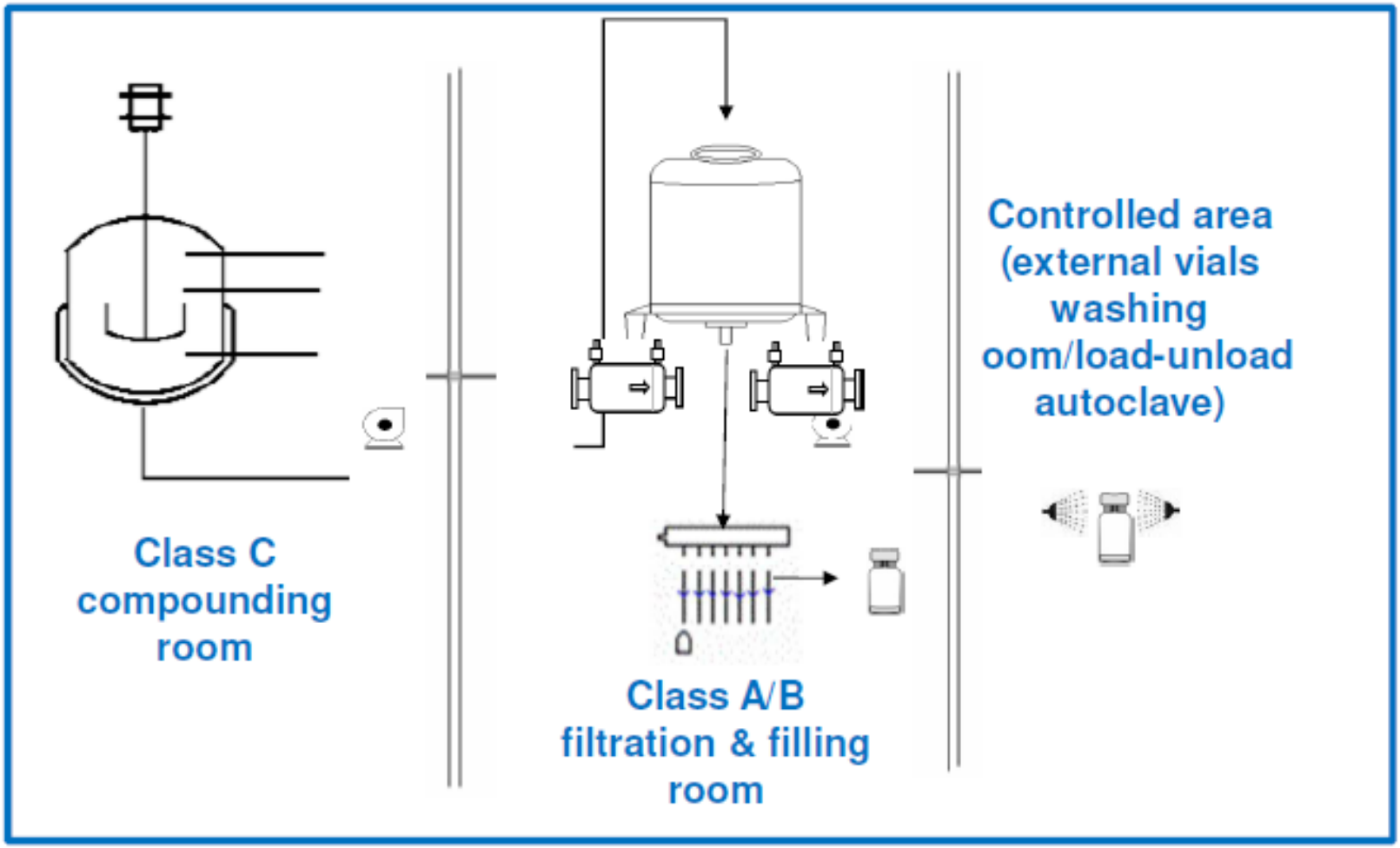
- Collect as much info as possible from MAH
- Involve MAH in all the discussions with suppliers and technical decisions
- Get knowledge on the new manufacturing process

Definition of manufacturing equipment:

- Carefully evaluate data received from MAH
- Comparison of the two sites equipment
- Evaluate the two options in case of difference:
- Use available equipment
- Introduce new ones

Case study V: equipment comparison

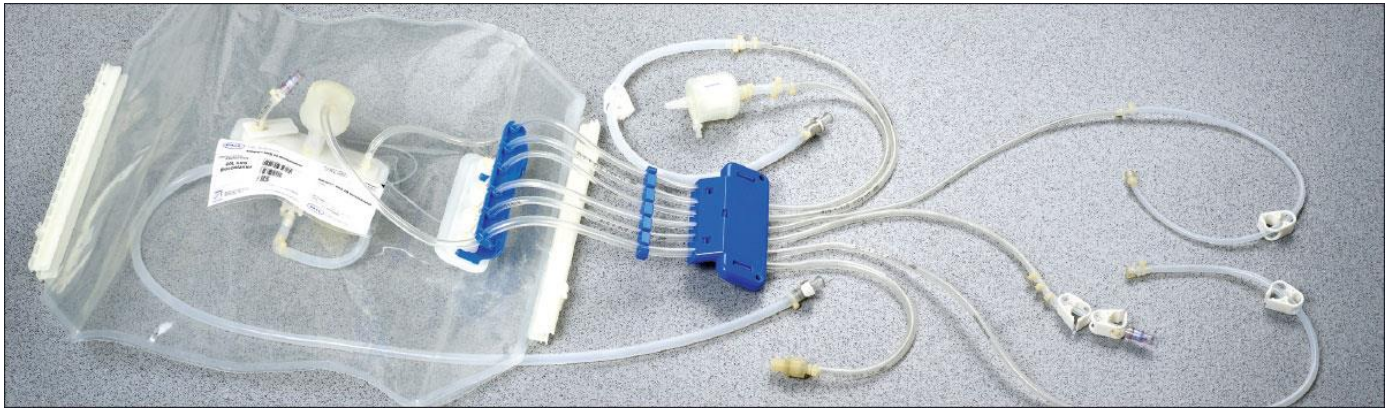
Receiving site equipment



Case study V: equipment comparison

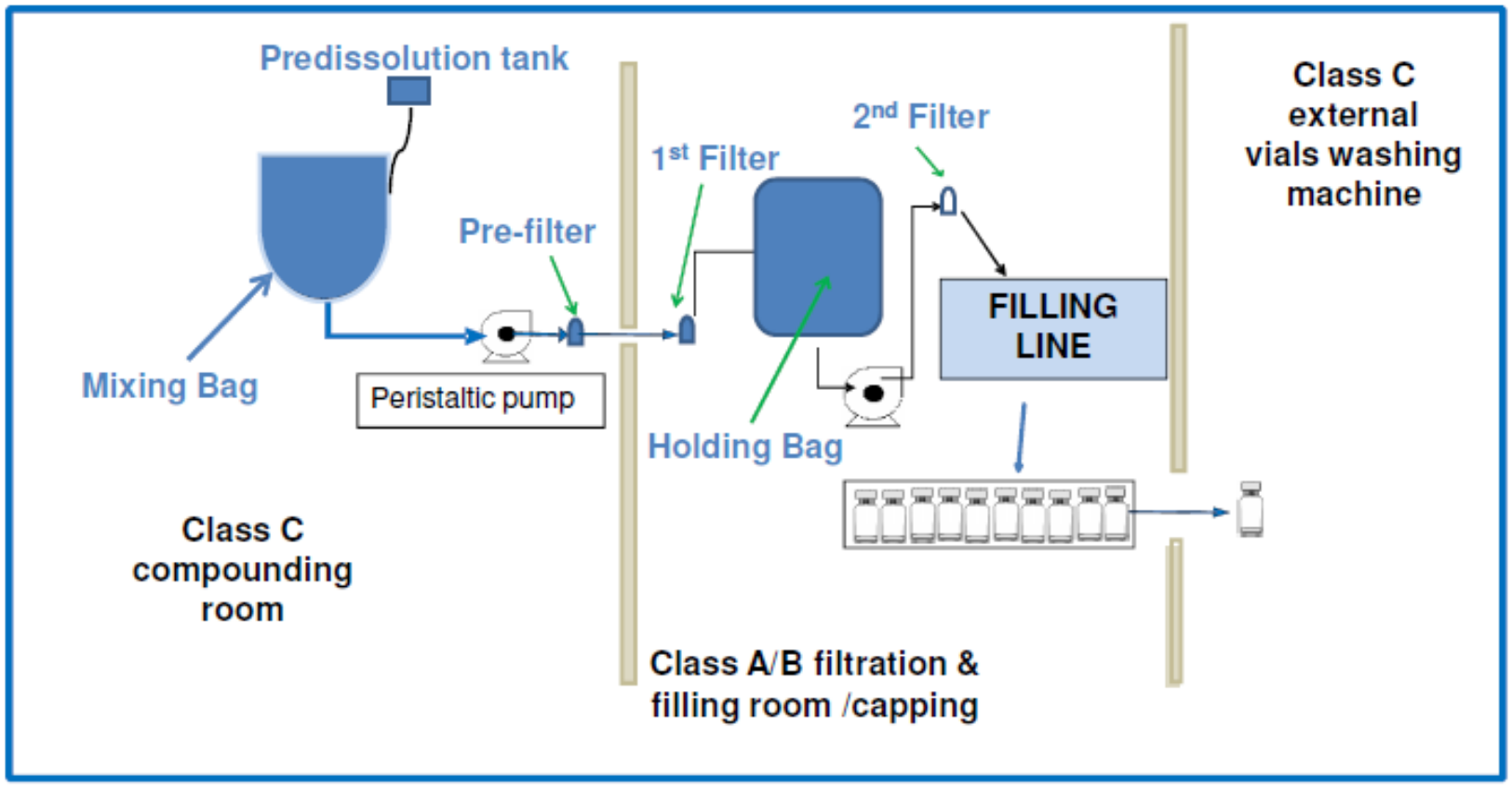
Sending site equipment

- Single Use materials used in all the production process
- Strong knowledge and recommendation to use Single Use
- No data available in the receiving unit supporting use of this new type of technology
- “Gentle” mixing needed
- Cleaning difficulties
- Difficulties in sterilizing filtration
- Preliminary compatibility data with Single Use available



Case study V: equipment comparison

Sending site equipment



Case study V: results

Major risks

- New technology for the receiving unit
- Challenges in some process steps to be analyzed due to partial blid TT
- Strict timelines and no possibility of mistake

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
- Execution of preliminary trials with “small scale” system before the production of technical and submission batches

Workshop: your case studies

- ❑ **Step I:** split into three groups
- ❑ **Step II:** among each group each one proposes one case study from real life/experience possibly that is still open/has not been solved yet
- ❑ **Step III:** each group select one case study and define possible actions and plan
- ❑ **Step IV:** present the case study to the other groups
- ❑ **Step V:** discussion

Technology Transfer Workshop

Let’ do exercise

Workshop: TT start

❑**Background:**

A sterile suspension product dedicated to US market, has to be outsourced from one of your site in EU. The manufacturing history of the product in the current manufacturing site is not robust with several non conformity in production process. You are entitled to select the new manufacturing site

❑ **Question:**

- ❑Which Criteria will you use to select a new manufacturing site? List at least three main criteria

❑**Discussion**

Workshop: TT technical package

❑**Background:**

A product dedicated to Japanese market, which is currently under development, has to be outsourced from one of your site in EU

❑ **Step I:** split into two groups:

- ❑Group 1 is part of the sending unit
- ❑Group 2 is part of the receiving unit

❑ **Step II:**

- ❑Group 1: define the list of information/document you would prepare for the transfer
- ❑Group 2: define the list of information/document you would request for the transfer

Step III: discussion

Workshop: TT milestones

- **Step I:** split in three groups
- **Step II:** group focus
  - Group I: primary technology transfer (from R&D to industrial phase of a new product) I within the same company and site
  - Group II: secondary technology transfer (commercial phase) from one CMO to another CMO (blind transfer)
  - Group III: secondary technology transfer (pre-commercial phase) between two sites of the same company
- **Step III:** within the same group describe the main milestones to bring the product from the SU to the RU including stage/gate
- **Step IV:** discussion

Workshop: TT allocation diagram

❑**Background:**

Think about one Technology Transfer project you managed or you experienced in your professional life

❑**Questions: on** the basis of the WBS already prepared focus on one area and prepare an allocation diagram, defining efforts

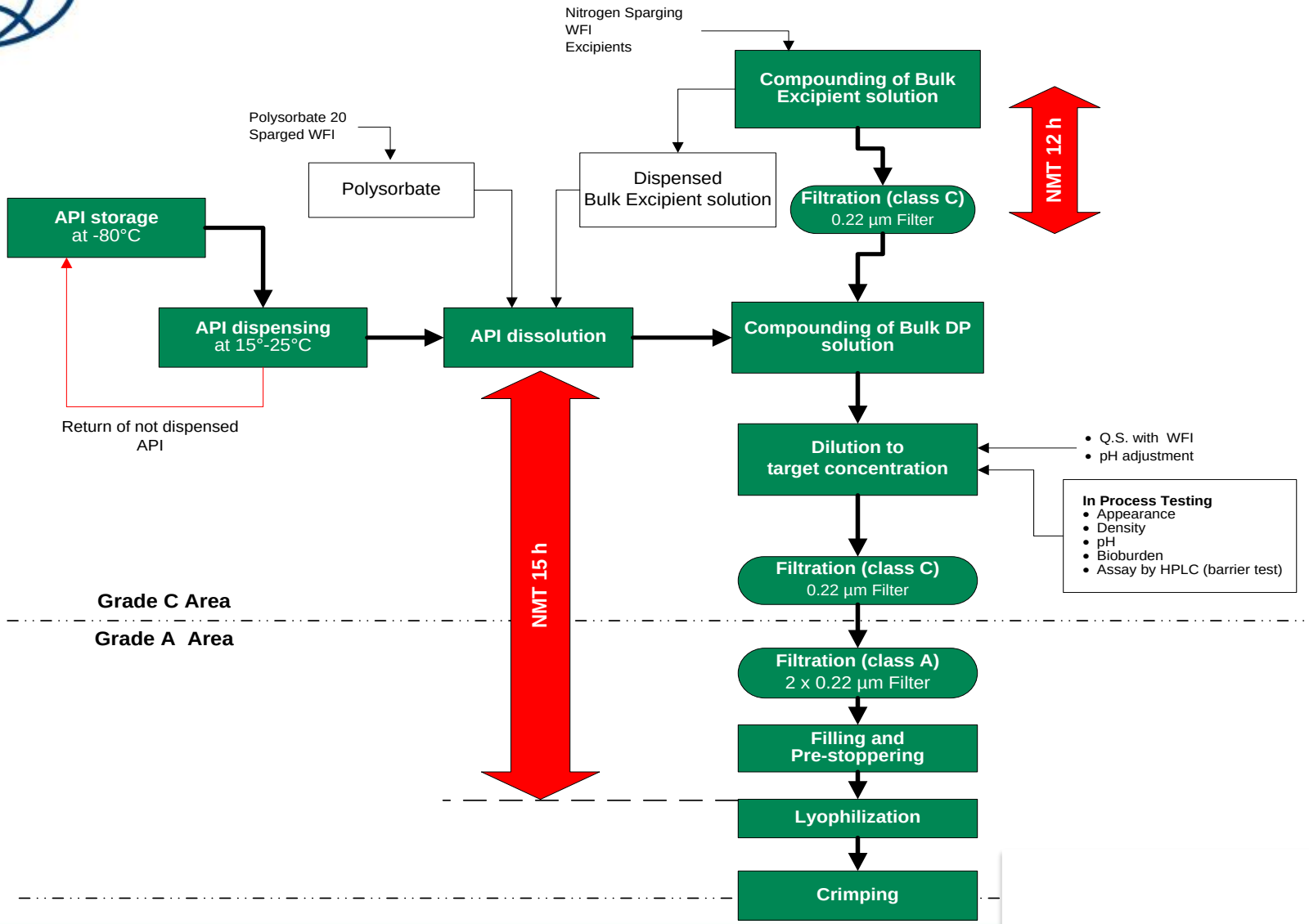
❑ **Discussion**

Back up

Technical Workshop Tech Transfer Case Study

Workshop

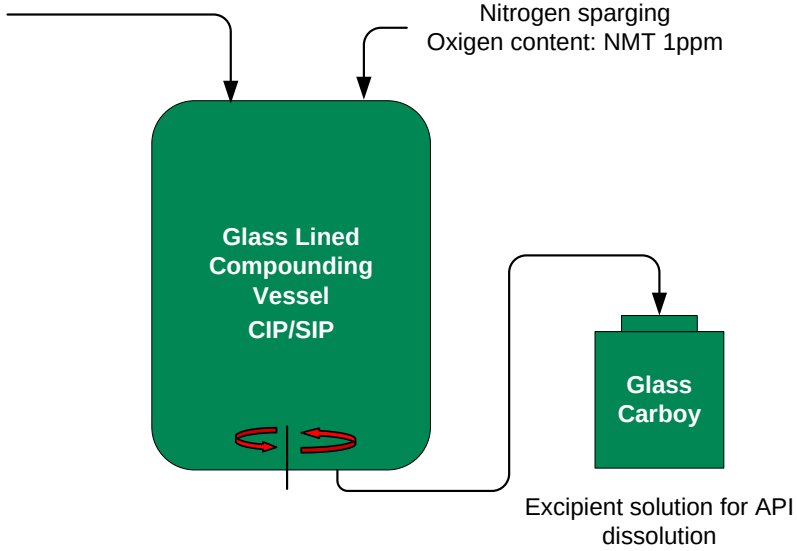
Product	X	
API and Pharmacological use	No special RA concern categories	
Pharmaceutical dosage form	Sterile lyophilized DP. 0.0050 mg/vial	
Product phase	Commercial	
Unit Dose composition	•API: 5.0 mg •Polysorbate 20: 0.8 mg •Sucrose:190.0 mg •Potassium Phospate, Dibasic: 18.0 mg	•Citric Acid: 22.8 mg •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	


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

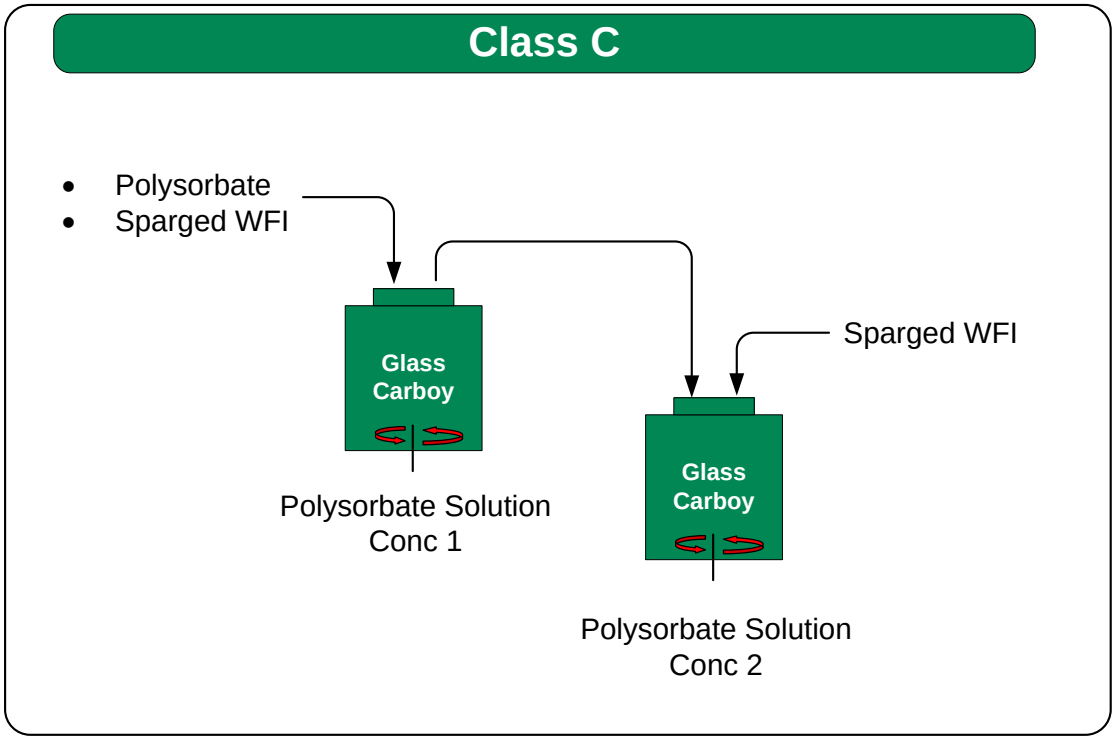
Workshop

Class C

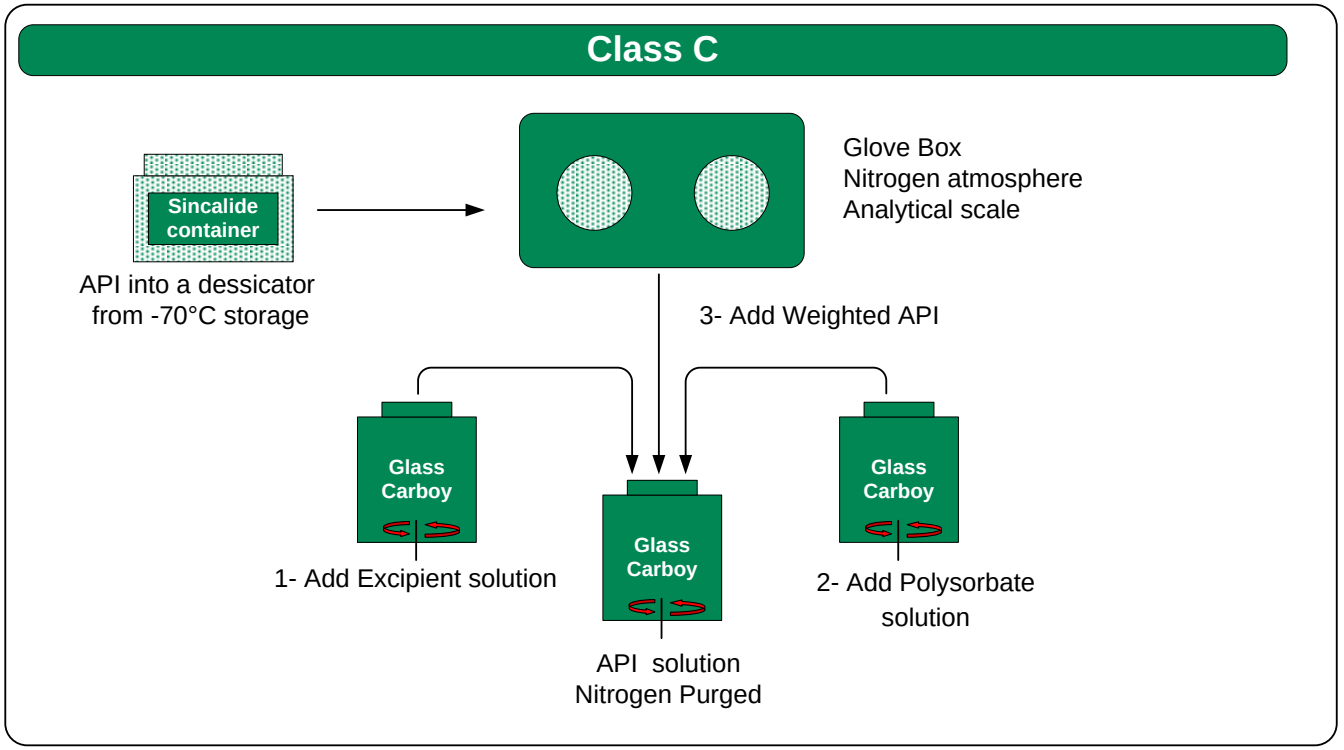
- Sparged WFI
- Excipients



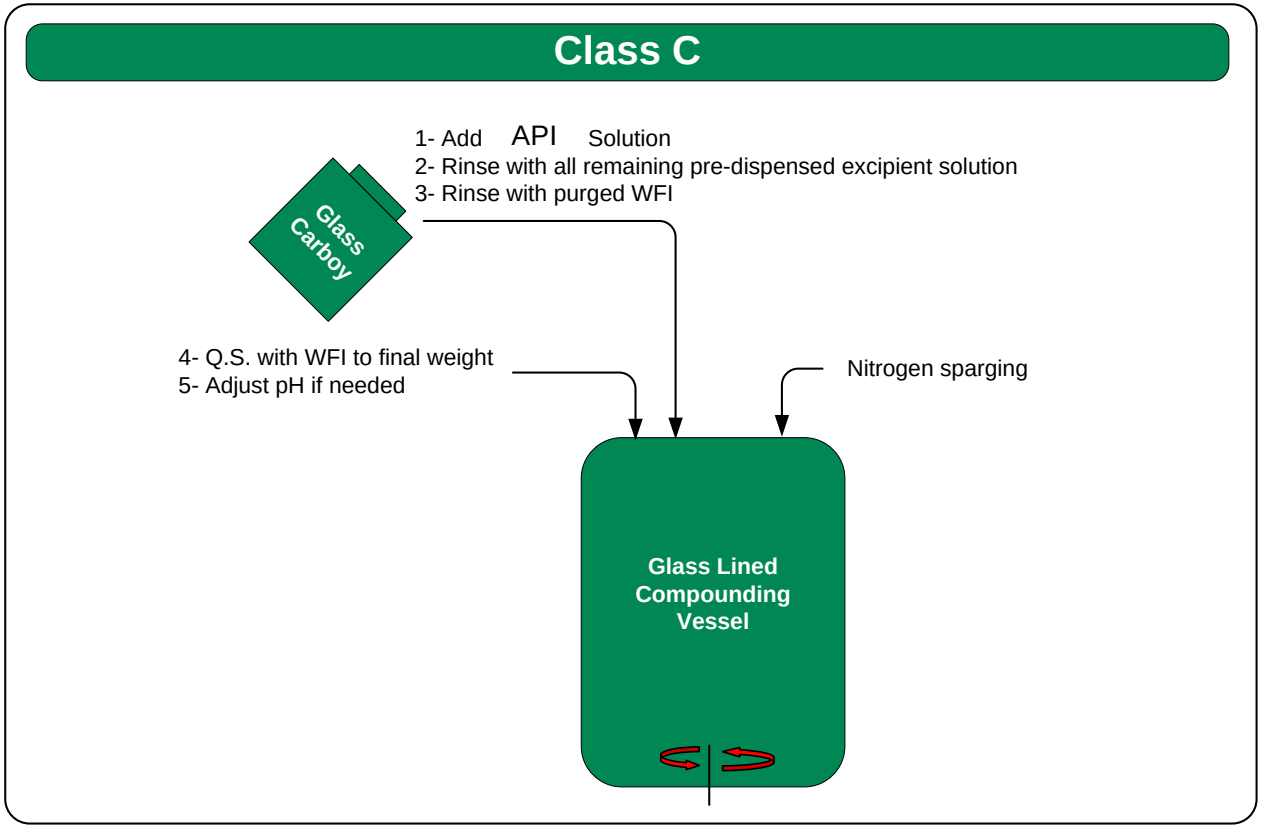
Workshop


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

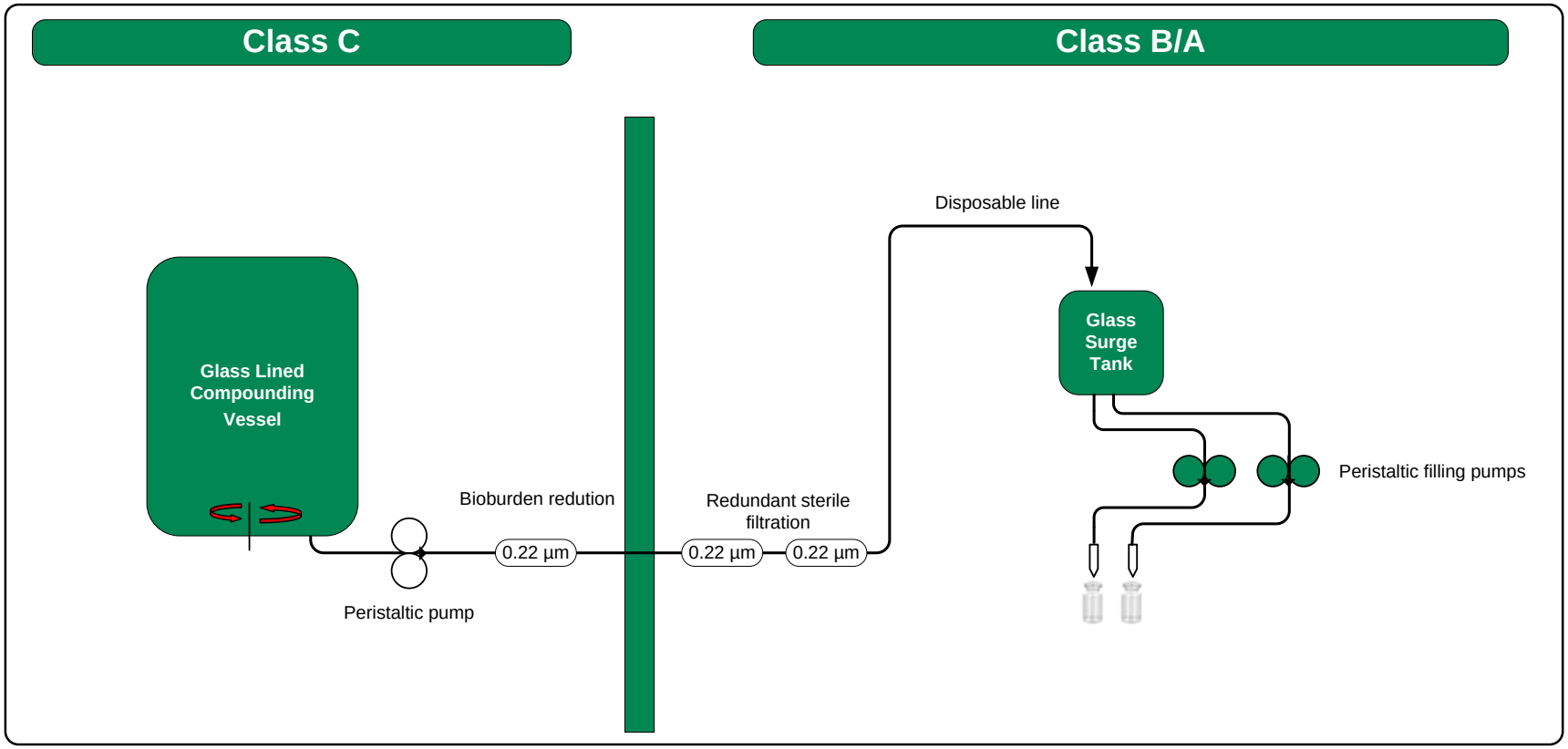
Workshop


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

Workshop


Class C
1- Add API 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

Workshop


Class C
Class B/A
Glass Lined Compounding Vessel
Bioburden redution
0.22 µm
Peristaltic pump
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

Workshop: risk management

❑**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 for one of the phase of the process

Technology Transfer: take away from TT IG

Case studies

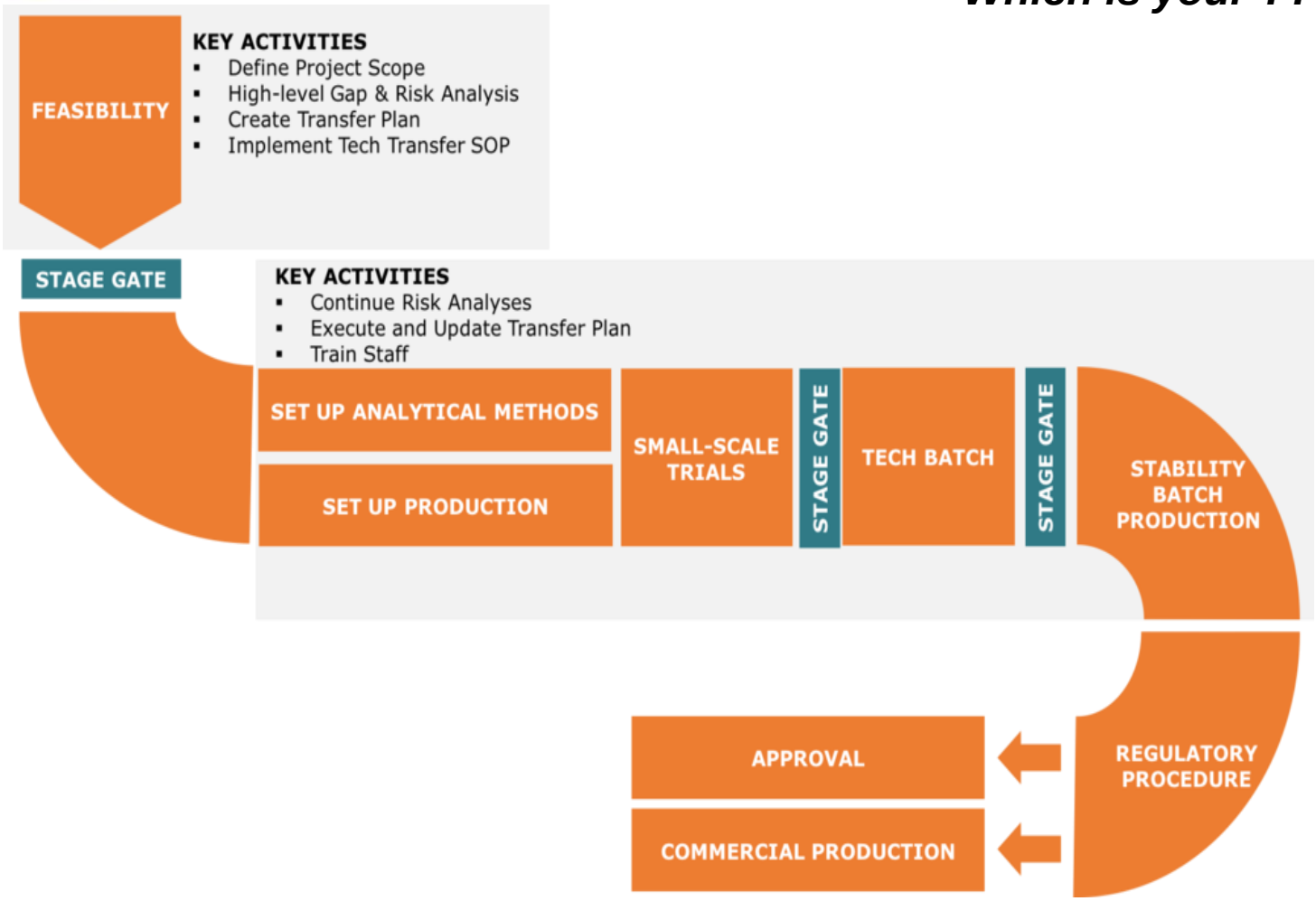
Technology Transfer I

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 II

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)

Discussion

What are the key factors for a successful Technology Transfer in your experience?

What are the main difficulties in a Technology Transfer in your experience?

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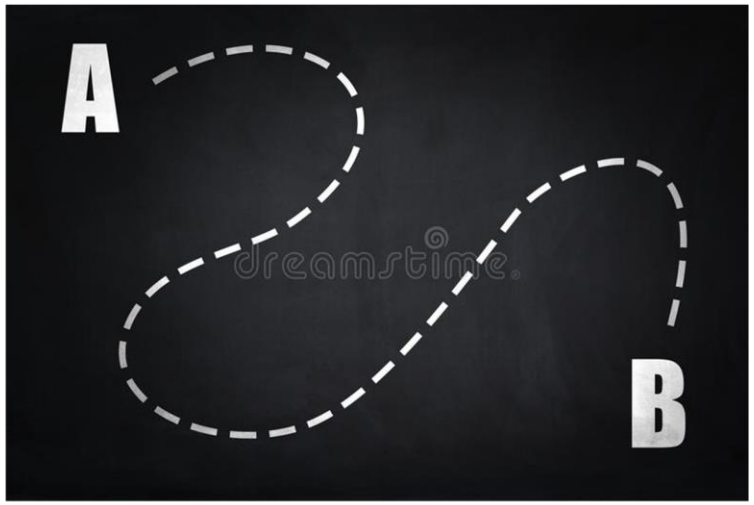
Conclusions

Technology Transfer definitions II

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).

Sending unit



Receiving unit

PDA – PMCO Program – Technical Report N.65

Technology Transfer definitions III

The Technology Transfer implies four main topics:

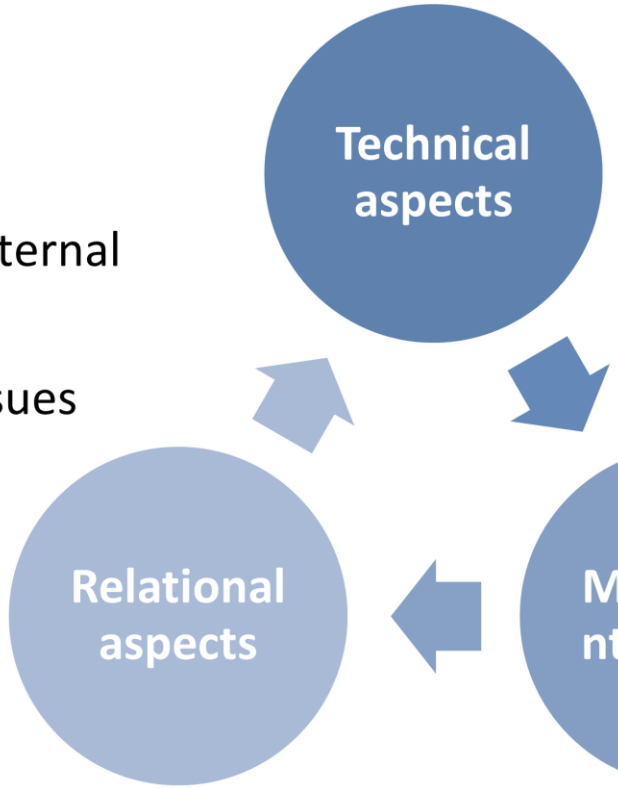
Technical knowledge

- Documentation management
- Project management
- Personnel training and skills

PDA – PMCO Program – Technical Report N.65

«**Technology Transfer** is a systematic procedure that shall be executed with the aim to transfer knowledge and experience related to a pharmaceutical process from one organization to another. Technology transfer includes documentation transfer and proven ability of the receiving unit to execute what has been transferred»

Main aspects of Technology Transfer



- Knowledge of technologies and processed
- Technical, quality and regulatory expertise
- Products knowledge

- People management
- Problem solving
- Working on priority
- Project Management
- 360° vision

- Internal and external comunication
- Relationship issues
- SPOC

People role in Technology Transfer

- Technology Transfer is not possible without a team
- Team shall be managed, organized and motivated
- Role and leadership of the PM are crucial for Technology Transfer success
- Stakeholders are different and shall be managed

PEOPLE ARE CRUCIAL FOR A SUCCESSFULL TECHNOLOGY TRANSFER

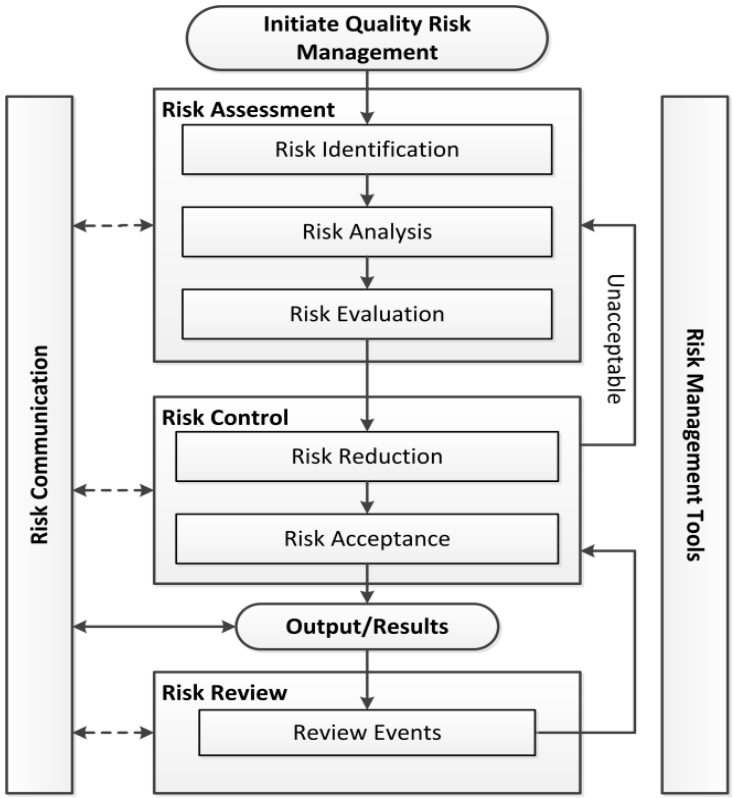
Pharma Tech Transfer Projects governance

Define scope, plan, execute and track

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

Role of 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.”



Final messages

The relationship between Technology Trasfer and Project is very close: there is no Technology Transfer without management and planning → **Be prepared**

Leadership is essential → **Take the lead**

Technical aspects are important and shall be deeply evaluated → **Devil is in the details!**

Role of the people and responsibilities are crucial → **Take care**

Lesson learned role → **Humility is a must!**

Challenges are many…… → **Be brave!**

Final messages

Technology Transfer is a wonderful trip!

Enjoy it!

Thank you!!

Angela Molaschi
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