Biotecnologie applicate

Plant Molecular Farming:
Pre-clinical and clinical development
Out-of-the-lab

Trieste, 06° May, 2025

Sara Raccovelli, PhD, MBA

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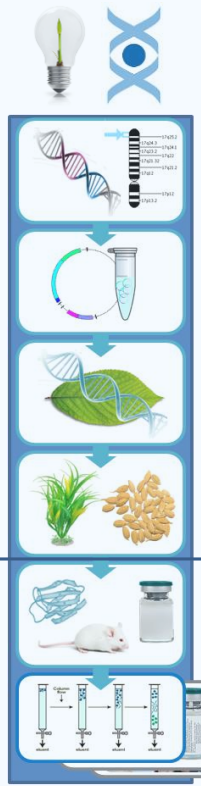
Course overview



Introduction: history of a biotech company / technology overview

Definition of **target protein**

DNA **optimization** and handling

Plant biomass transformation

Bioreactor cultivation and expansion

29/4/25

Preliminary **purification** and **characterization**

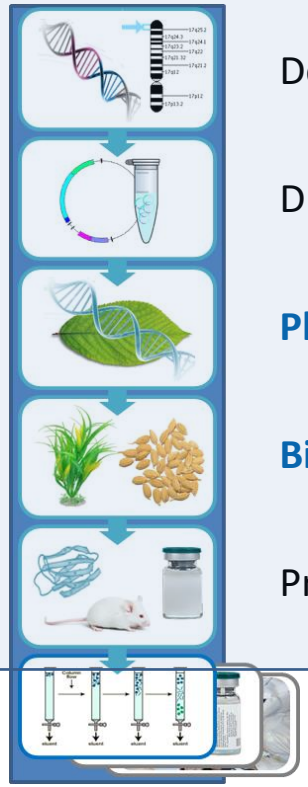
06/5/25

Next steps - out of the lab / **other applications** / exam simulation

Next steps: out of the lab

- **Proof of concept**, **pre-clinical** and **clinical** development
  (focus: biosimilarity)
- **Production** phase
- **Regulatory** framework
- Other PMF **applications**
- **Intellectual Property** (IP) framework
- ***Wrap-up - Exercise***

From idea to prototype: the pipeline



Definition of **target protein**

DNA **optimization** and handling

Plant biomass transformation

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Proof of concept
Scalable prototype

Prototype is ready to be out-licensed to client pharma

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Proof of concept: preclinical pre-regulatory

PoC

Pre-regulatory

Regulatory

Preclinical

Clinical

Pharma approval

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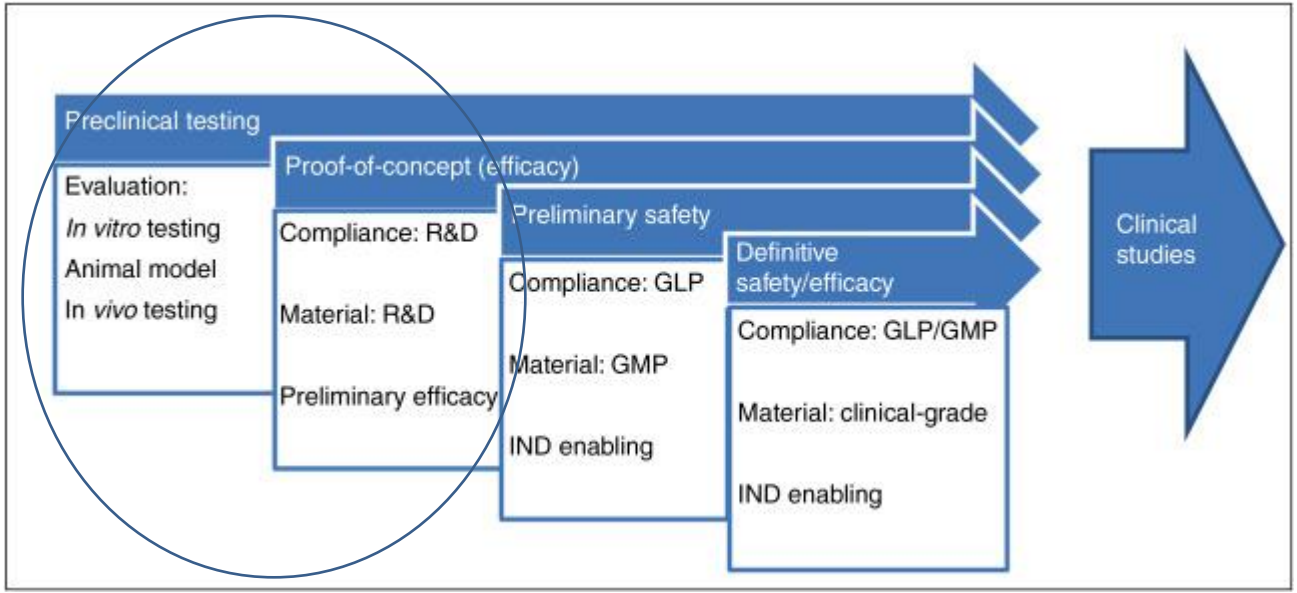
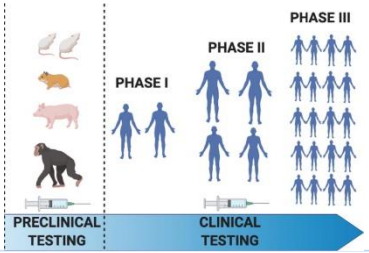
Proof of concept: preclinical pre-regulatory



PoC

GOOD MANUFACTURING PRACTICE GMP



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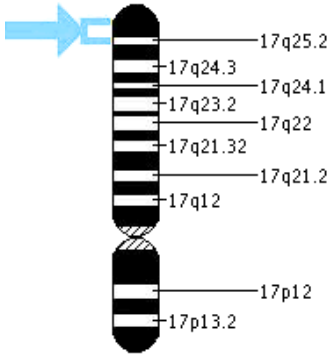
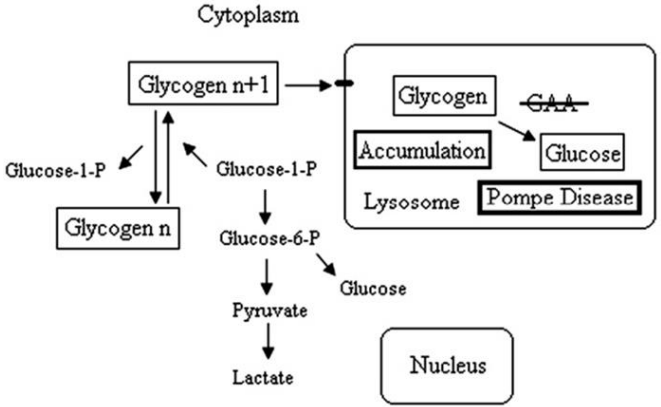
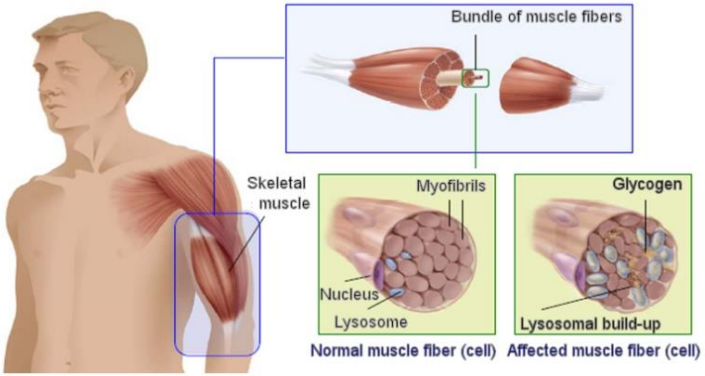
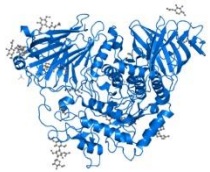
Proof of Concept: preclinical pre-regulatory

Example: rice_GAA / Pompe Disease









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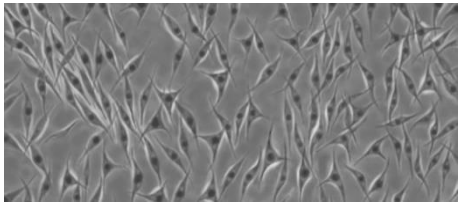
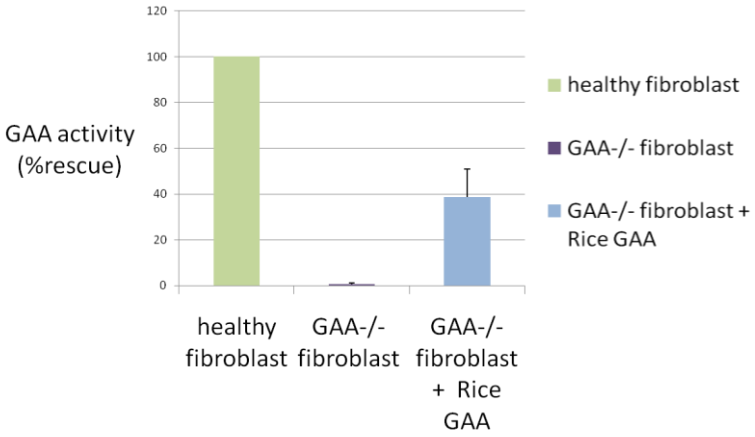
Proof of Concept: preclinical pre-regulatory

Example: rice_GAA / Pompe Disease



IN VITRO uptake

GAA-/- fibroblast



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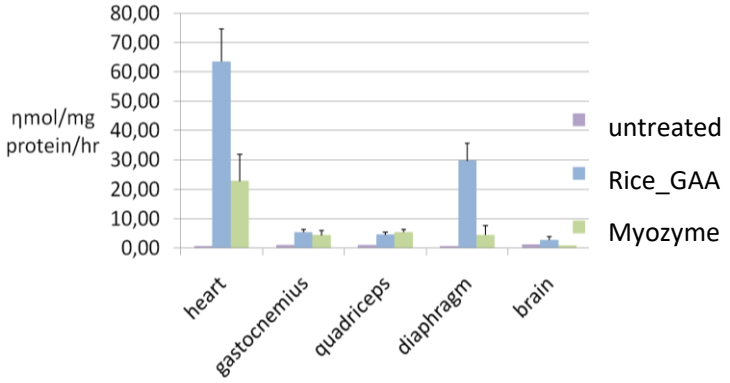
Santa Maria della Misericordia di Udine

IN VIVO activity

$6^{neo}/ 6^{neo}$ mice



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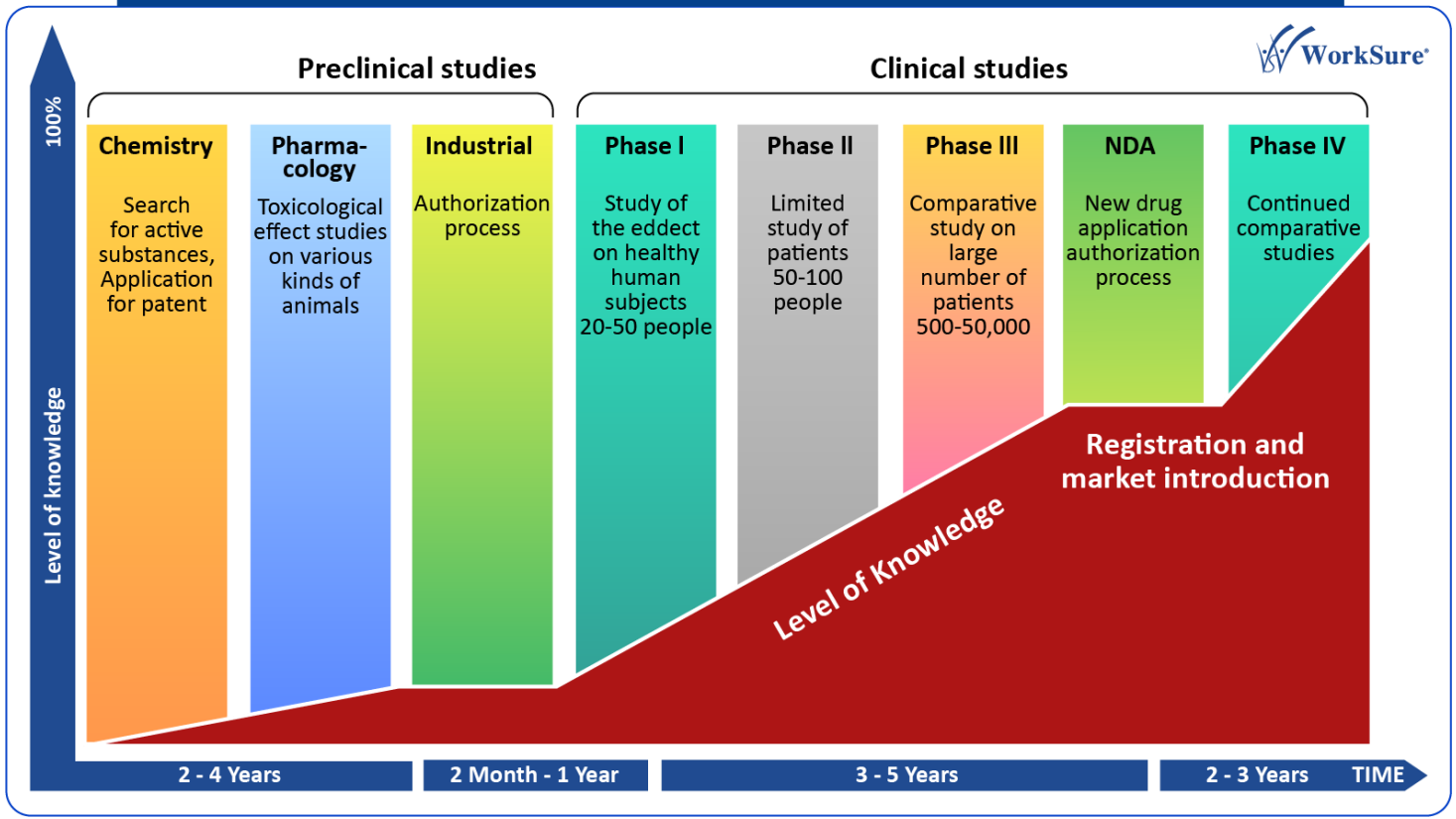
The Process of Drug Development



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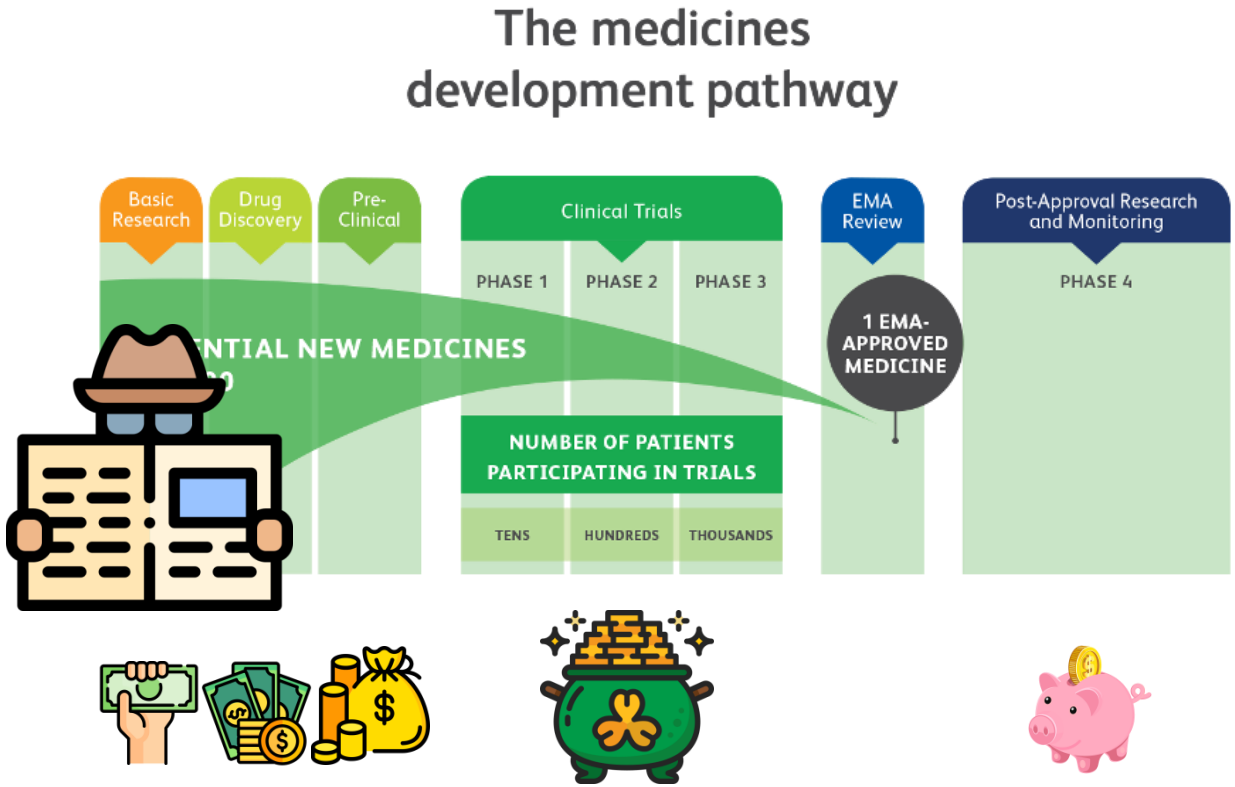
Drug Development: how much does it cost?



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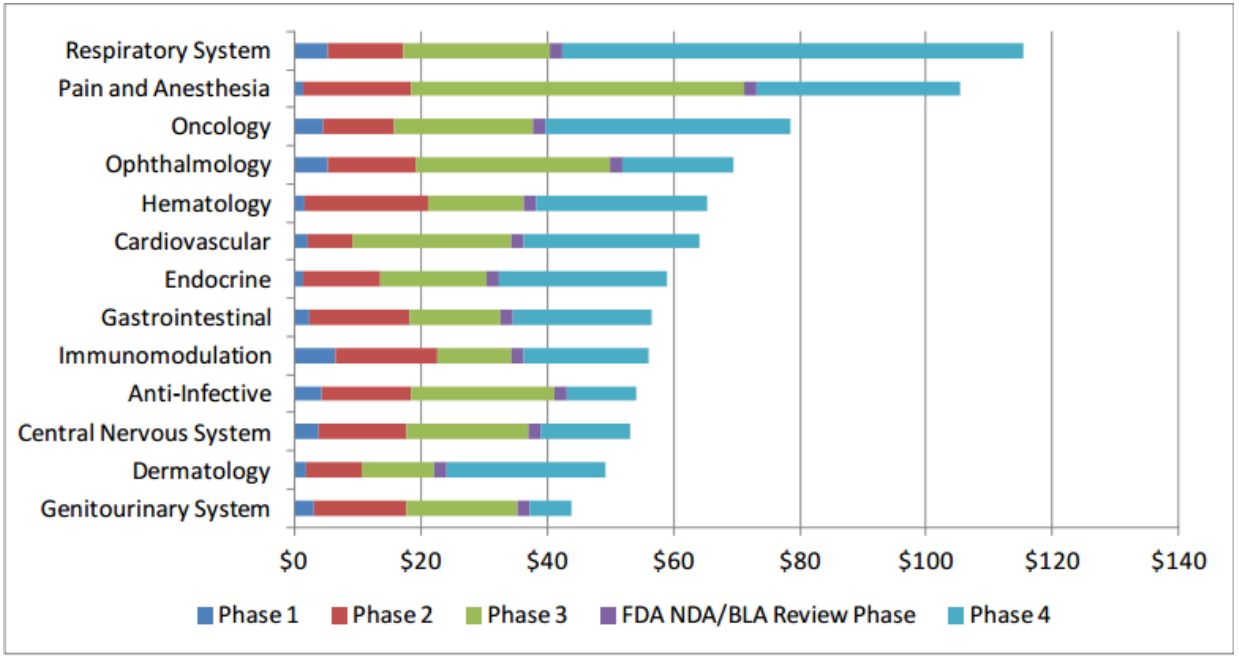

Clinical Trial Costs (in $ Millions) by Phase and Therapeutic Area

Source: "Examination of Clinical Trial Costs and Barriers for Drug Development", U.S. Department of Health and Human Services
https://aspe.hhs.gov/reports/examination-clinical-trial-costs-barriers-drug-development-0

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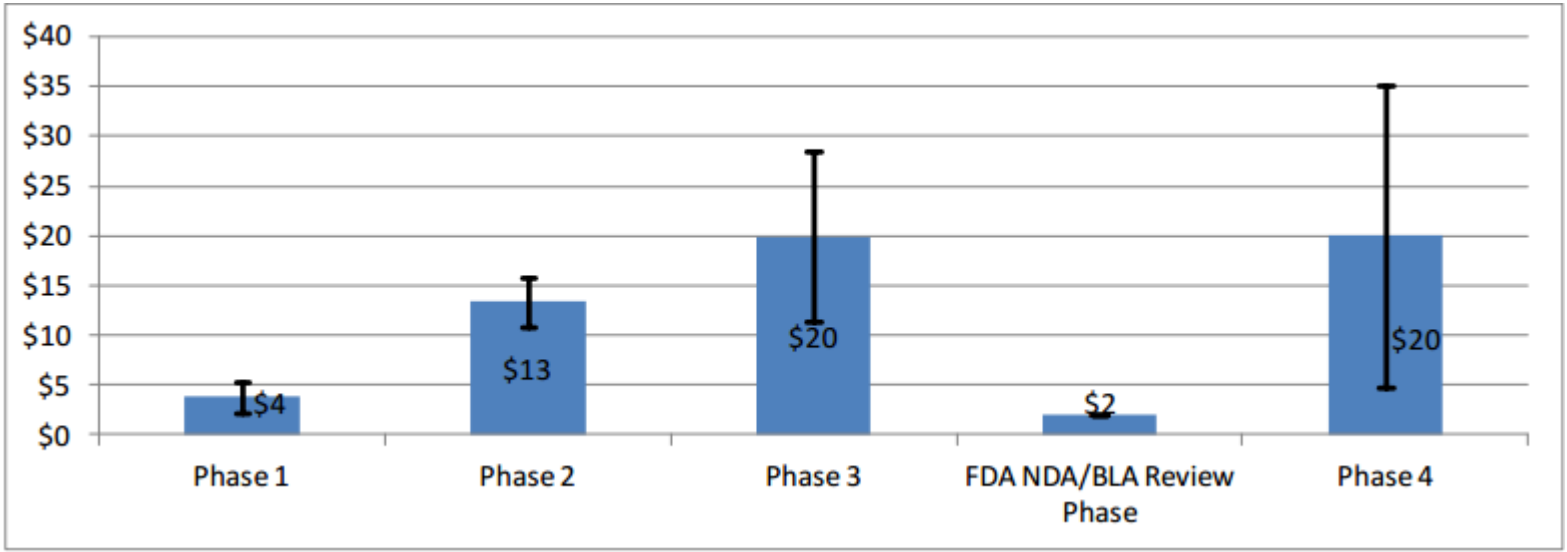
Drug Development: how much does it cost?



Average Per-Study Costs by Phase (in $ Millions) Across Therapeutic Areas

Source: "Examination of Clinical Trial Costs and Barriers for Drug Development", U.S. Department of Health and Human Services
https://aspe.hhs.gov/reports/examination-clinical-trial-costs-barriers-drug-development-0

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Development pathway: new drug vs biosimilar?

An example / exercise

A **biosimilar** is a biological medicine
highly similar
to another already approved biological medicine
(the 'reference medicine').

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Strategies for approval

Example: mAb

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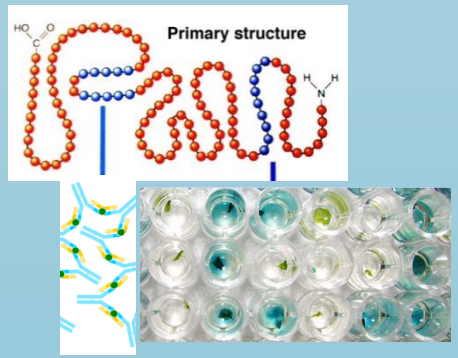

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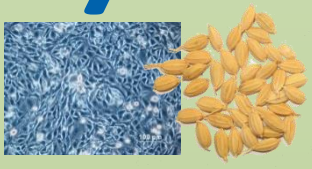

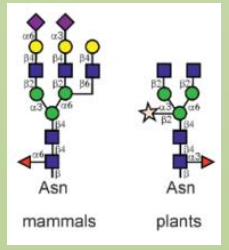

1. Biosimilar

2. New drug

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Different requirements for different regulatory agencies

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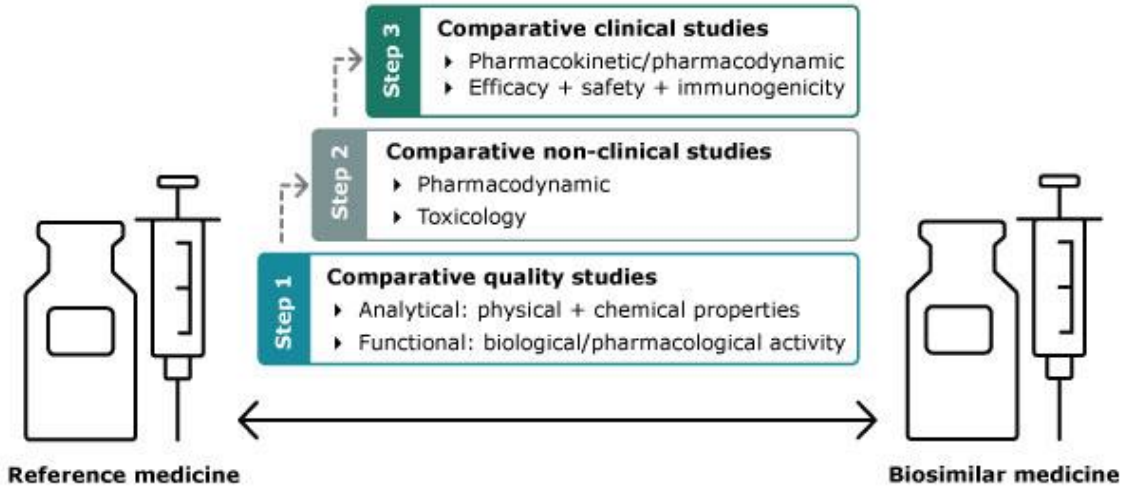

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EMA biosimilarity requirements

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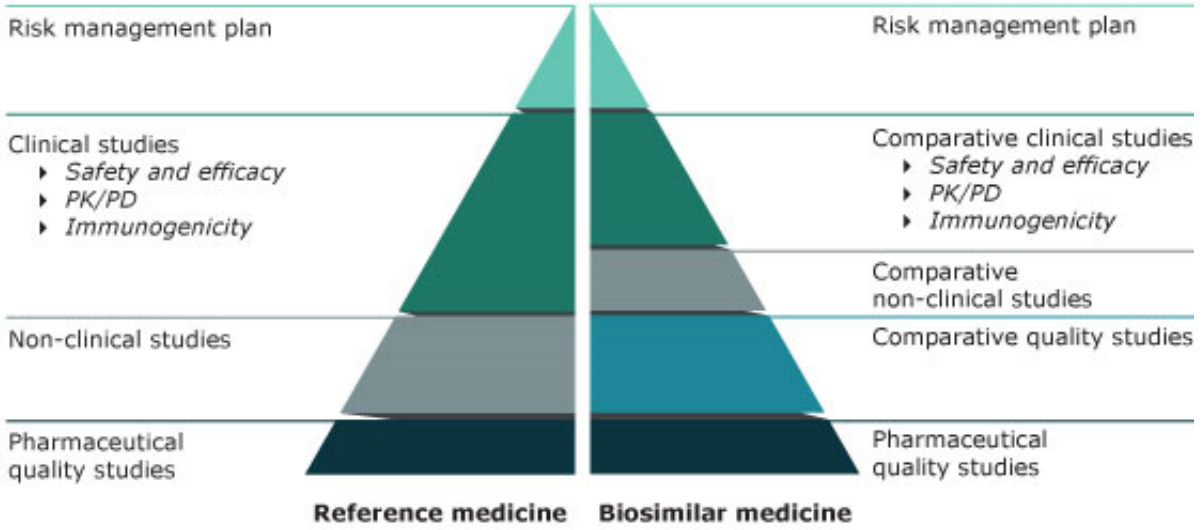

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EMA biosimilarity requirements

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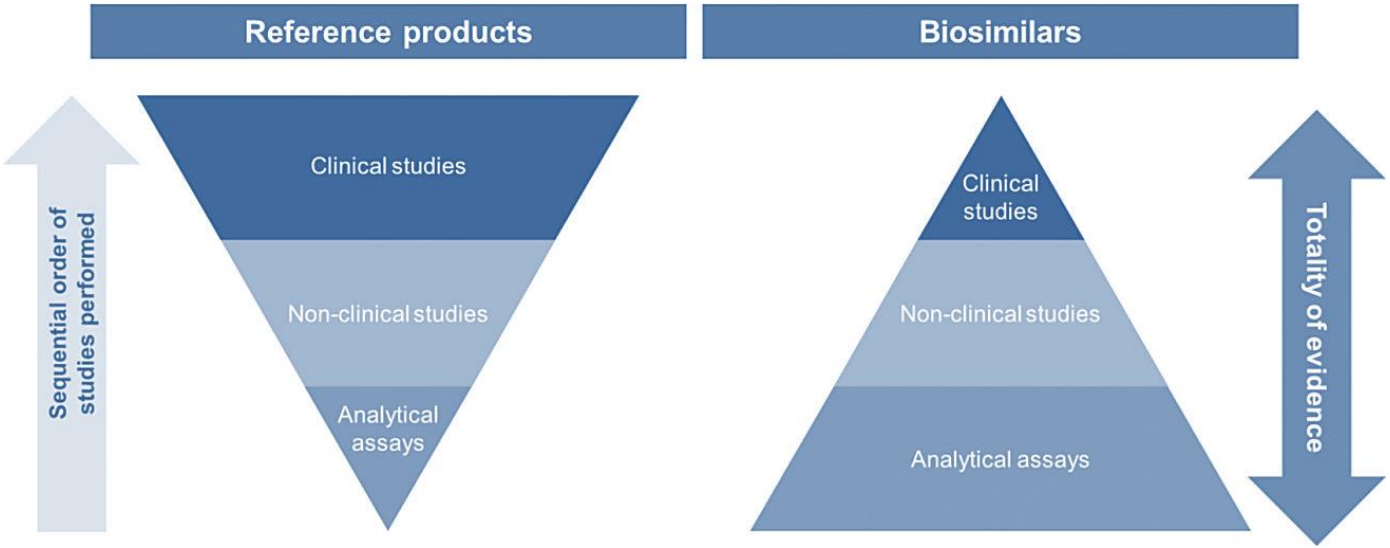

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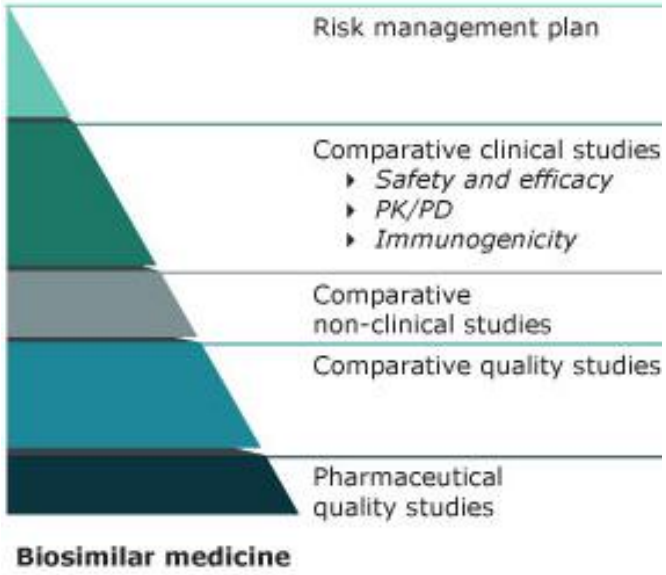
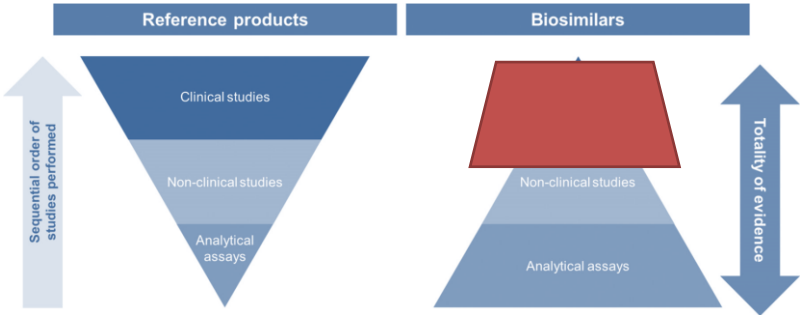
Risks of the biosimilariy path for Plant-Derived Biopharmaceuticls





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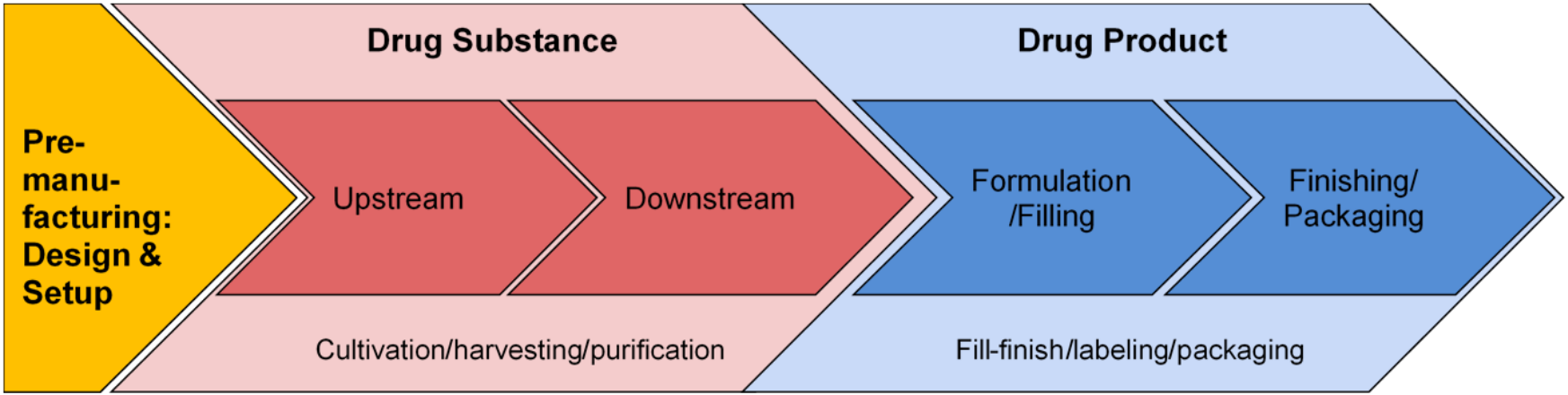
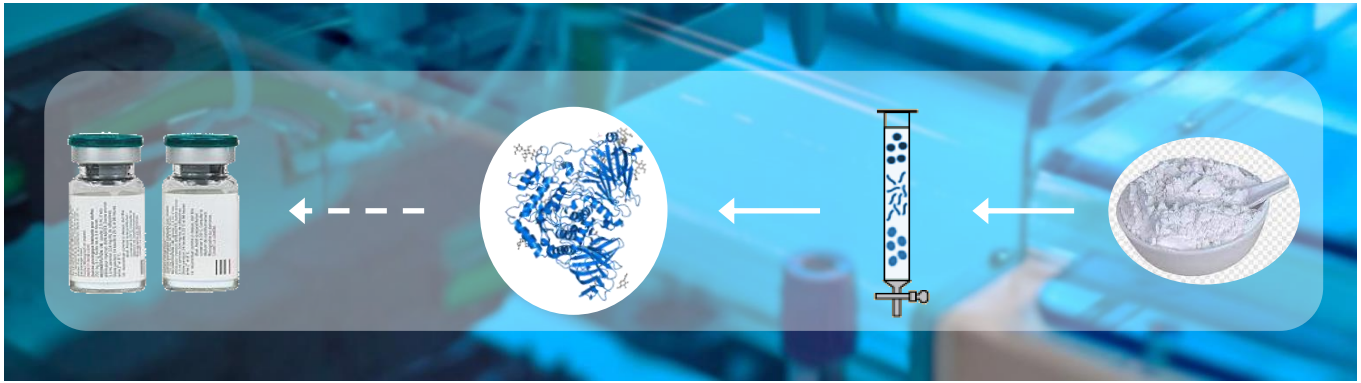
Drug Manufacturing

After drug development: Production of an approved drug



How does PMF fit into that framework?



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Regulatory framework:

requirements for plant-derived bioactives

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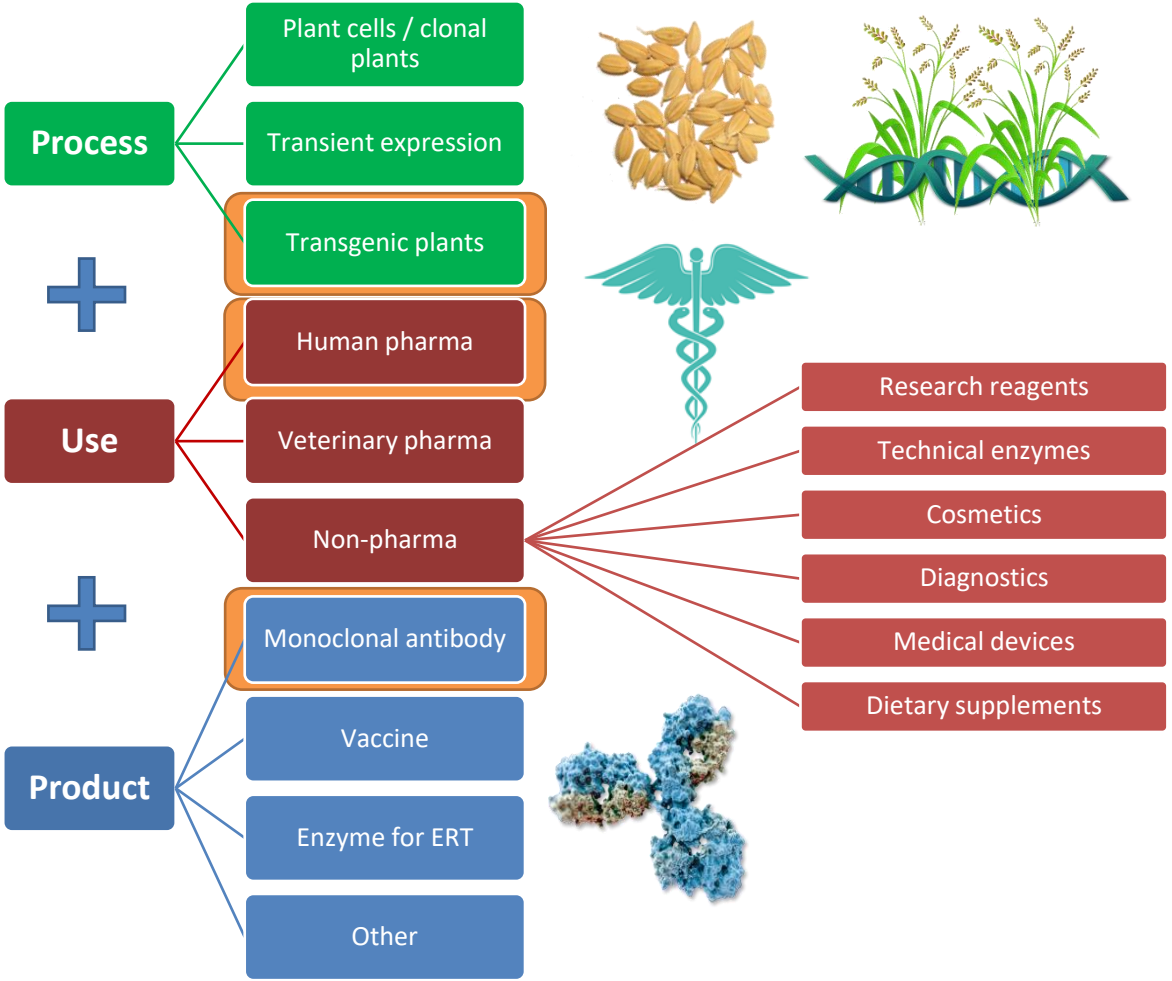
Plant-molecular farming

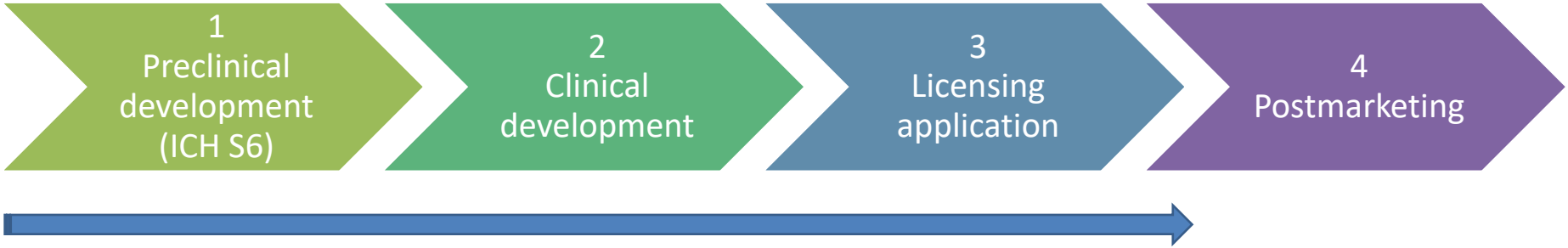
Regulatory framework



Focus: pharmaceuticals for human use

ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

4 steps approval process



Accelerated approval routes:
orphan drugs // temporary emergency approval // COVID19

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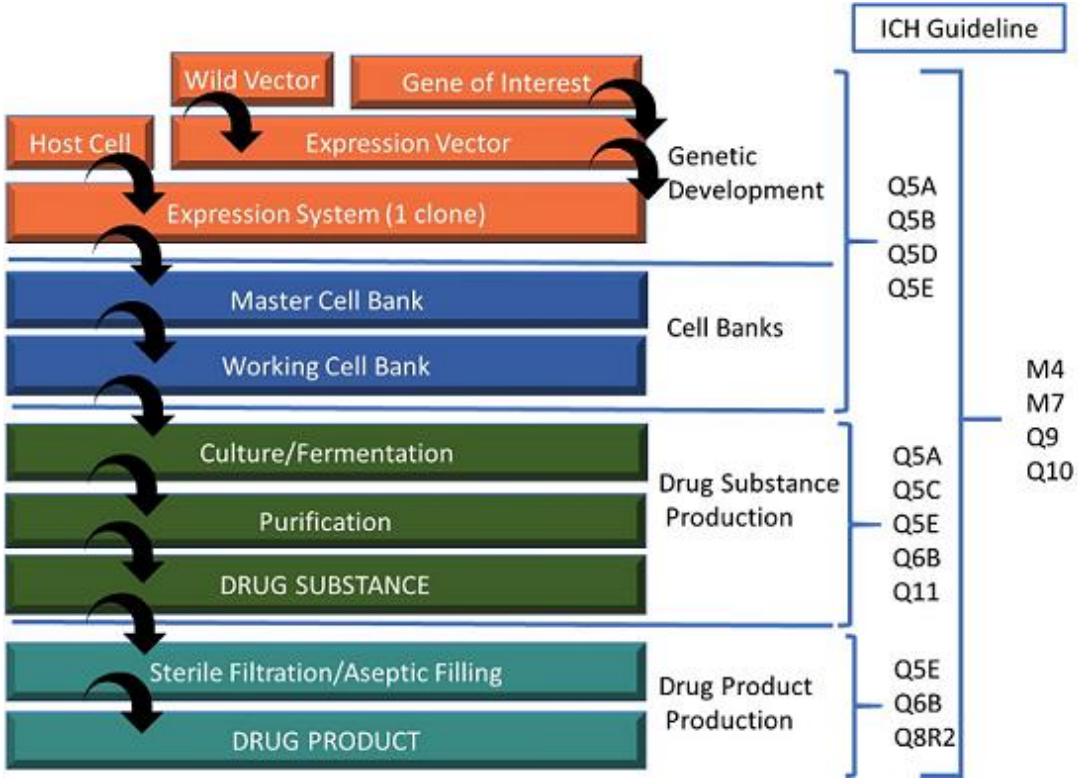
Drug Manufacturing



Focus: pharmaceuticals for human use derived from transgenic plants

EU biopharmaceuticals from **molecular farming** fall under the same regulation as all other biologics:

- **Directive 2001/83/EC**
  Community code relating to medicinal products for human use
- **Regulation (EC) No 726/2004**
  Community procedures for the authorization and supervision of medicinal products for human and veterinary use

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EMA Specific guidelines

- EMEA/CHMP/BWP/48316/2006 Guideline on the **quality** of biological active substances produced by **stable transgene expression in higher plants**
- EMA/CHMP/BWP/532517/2008 Guideline on development, production, characterisation and specification for **monoclonal antibodies** and related products

+ All the other relevant guidelines for **biopharmaceuticals / downstream**

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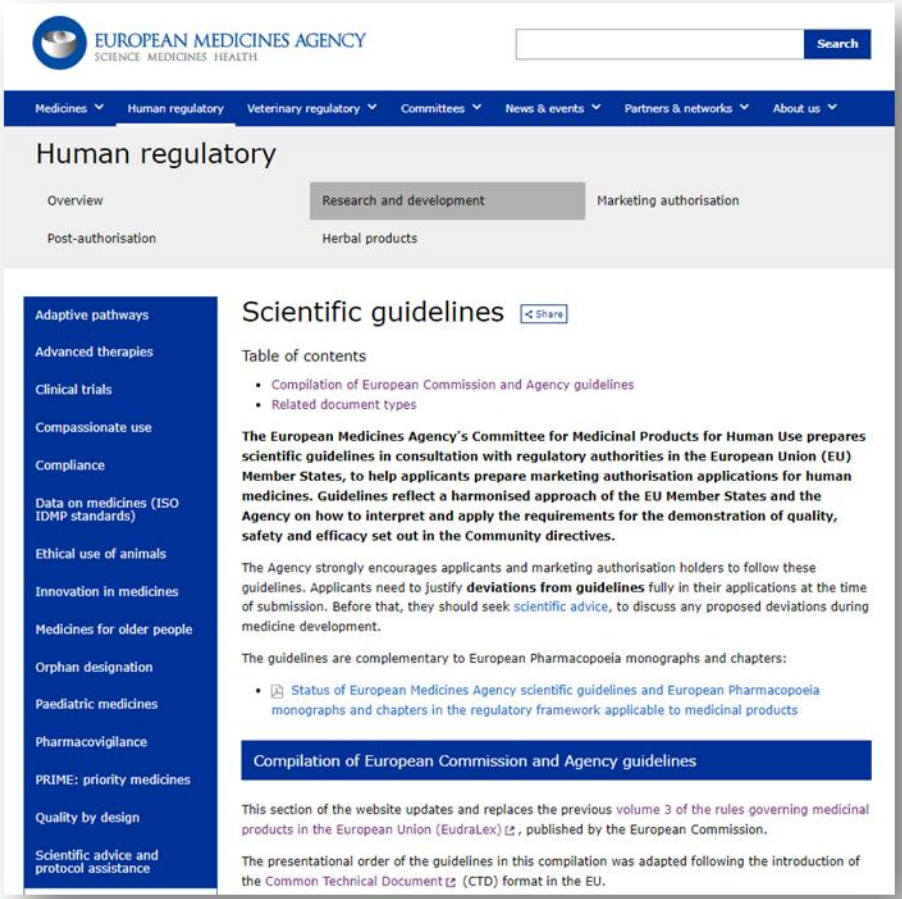

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Search

Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

Human regulatory

Overview | Research and development | Marketing authorisation | Post-authorisation | Herbal products

- Adaptive pathways
- Advanced therapies
- Clinical trials
- Compassionate use
- Compliance
- Data on medicines (ISO IDMP standards)
- Ethical use of animals
- Innovation in medicines
- Medicines for older people
- Orphan designation
- Paediatric medicines
- Pharmacovigilance
- PRIME: priority medicines
- Quality by design
- Scientific advice and protocol assistance

Scientific guidelines

Share

Table of contents

- Compilation of European Commission and Agency guidelines
- Related document types

The European Medicines Agency's Committee for Medicinal Products for Human Use prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing authorisation applications for human medicines. Guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives.

The Agency strongly encourages applicants and marketing authorisation holders to follow these guidelines. Applicants need to justify **deviations from guidelines** fully in their applications at the time of submission. Before that, they should seek scientific advice, to discuss any proposed deviations during medicine development.

The guidelines are complementary to European Pharmacopoeia monographs and chapters:

- Status of European Medicines Agency scientific guidelines and European Pharmacopoeia monographs and chapters in the regulatory framework applicable to medicinal products

Compilation of European Commission and Agency guidelines

This section of the website updates and replaces the previous volume 3 of the rules governing medicinal products in the European Union (EudraLex), published by the European Commission.

The presentational order of the guidelines in this compilation was adapted following the introduction of the Common Technical Document (CTD) format in the EU.

EudraLex - EU Legislation

PAGE CONTENTS

- Body of European Union legislation
- Guidelines
- Latest updates
- Documents

Body of European Union legislation

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union":

- Volume 1 - EU pharmaceutical legislation for medicinal products for human use (EN)
- Volume 5 - EU pharmaceutical legislation for medicinal products for veterinary use (EN)

Guidelines

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use (EN)
- Volume 3 - Scientific guidelines for medicinal products for human use (EN)
- Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use (EN)
- Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use (EN)
- Volume 7 - Scientific guidelines for medicinal products for veterinary use (EN)
- Volume 8 - Maximum residue limits (EN)
- Volume 9 - Guidelines for pharmacovigilance for medicinal products for human and veterinary use (EN)
- Volume 10 - Guidelines for clinical trial (EN)

Medicinal products for paediatric use (EN), orphans (EN), herbal medicinal products (EN) and advanced therapies (EN) are governed by specific rules.

Focus: pharmaceuticals for human use derived from transgenic plants

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Additional EU compliance for **leveraging plants** for **molecular farming** - **upstream**

If grown *outdoors*:

- **Directive 2001/18/EC**
  On the deliberate release into the environment of genetically modified organisms
- **Directive 1829/2003/EC** (if crop can be used as food/feed)
  On genetically modified food and feed

If grown *in containment*:

- **Directive 2009/41EC**
  On the contained use of genetically modified micro-organisms

Guidelines on pharmaceuticals for human use derived from transgenic plants

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EMA upstream for plants: focus on **quality**, **consistency** and **treaceability** of **raw materials**

- GMP-like standards for **characterization** of stock plants
- Seeds from an accredited source → **Seed banking** system (MSB / WSB)
- **Segregation** of GMP and non-GMP parts of the process

UPSTREAM

- Plant cultivation
- Harvest
- Primary processing
- (Initial extraction)

DOWNSTREAM

- GMP begins with sterile extract
- No additional regulatory burden
- (Some unique steps)

Guidelines on pharmaceuticals for human use derived from transgenic plants

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EMA upstream guidelines for plants:

- Ensure the **maximum reproducibility** in plant growth conditions
  - ✓ Clear definition of the manufacturing process
  - ✓ Applications of GMP-like principles
- Generate a defined **biological starting material** suitable for downstream under GMP conditions

Quality and **consistency** assurance:

Good **A**gricultural and **C**ultivation **P**ractices

Quality System in the upstream process

GACP

Developed by the WHO in 2003 as a reaction to substandard herbal medicines entering the market

AUTHORITY	DOC REF	TITLE
AHPA AMERICAN HERBAL PRODUCTS ASSOCIATION	AHPA GACP-GMP Guidance Document - May 2021 (Revised)	Good Agricultural and Collection Practices and Good Manufacturing Practices for Botanical Materials
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	EMEA/HMPC/246816/2005	Good agricultural and collection practice for starting materials of herbal origin
	EMA/HMPC/398706/2021	Concept paper on the revision of the Guideline on Good agricultural and collection practice for starting materials of herbal origin
	01 September 2009	EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use - Annex 7: Manufacture of Herbal Medicinal Products
EUROPEAN HERB GROWERS ASSOCIATION EUROPAM	25 NOVEMBER 2019 Version 7.3	EUROPAM Good Agricultural and Wild Collection Practice (GACP)
	17 SEPTEMBER 2020	EUROPAM Practical GACP Implementation Guide
	03 MAY 2019	EUROPAM position paper on necessary batch document information
World Health Organization	WHO	WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants

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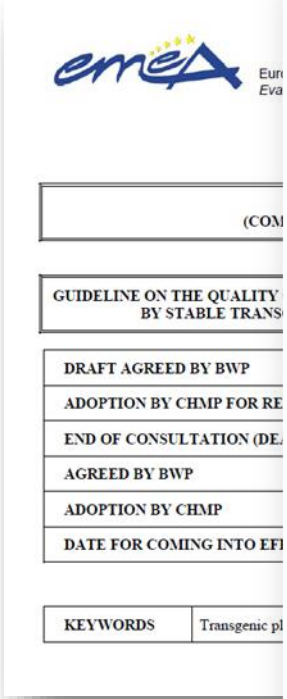
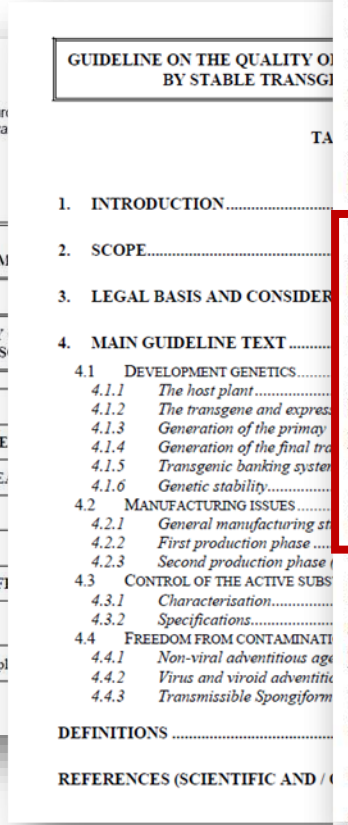


GUIDELINE ON THE QUALITY
BY STABLE TRANS

DRAFT AGREED BY BWP	
ADOPTION BY CHMP FOR RE	
END OF CONSULTATION (DE	
AGREED BY BWP	
ADOPTION BY CHMP	
DATE FOR COMING INTO EF	

KEYWORDS	Transgenic pl



GUIDELINE ON THE QUALITY O
BY STABLE TRANSG

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4.1.5 Transgenic banking system

Where possible and unless otherwise justified, a banking system should be included in the batch-to-batch consistency assurance strategy. Depending on the production strategy, there may be a need to bank both the production strain and an elite line. The fundamental principles underlying banking systems for substrates and materials used in the production of biological medicinal products are outlined in CHMP guidelines, and should be taken into account by manufacturers of transgenic plant-derived active substances when designing their systems.

Manufacturers should therefore establish a master and working transgenic bank of plant material derived from the final transformant, capable of long-term storage and of providing consistent and sufficient starting material for a number of production runs which is sufficiently large to ensure long-term continuation of supply.

The generation, establishment and maintenance of both the master and the working transgenic banks should be defined and clearly described. The approach applied to characterising and testing the master transgenic bank and the working transgenic bank should take into account the guidance outlined in CHMP guidelines, with adaptation to the particular transgenic plant production system in question. The plant material used to establish the master transgenic bank should be thoroughly characterised genotypically and phenotypically. The characterisation of the material used to form the master transgenic bank should include a comparison of its botanical, horticultural, agricultural and phytochemical characteristics with its natural counterpart, with a view to identifying any emerging characteristics which might have significance for the production crop, such as gene silencing activity or pleiotropic effects resulting from the presence of the transgene, which might have consequences for the quality, and safety of the active substance.

This study should include an analysis of the transgene (for example, sequence(s), integrity, site(s) of insertion, copy number, and fates of marker sequences), its expression (tissue/organ specific, regulation, and expression level), plant gene silencing effects, over-expression of other proteins, ploidy, and karyology).

The stability behaviour of the banked material should be investigated and on the basis of the results the following should be defined:

- Specifications for container and closure systems.
- Storage conditions

Other relevant regulations

National specifications for the cultivation, containment, import and export of GMOs

- Servicio Nacional de Sanidad y Calidad Agroalimentaria
- Comisión Nacional Asesora de Biotecnología Agropecuaria (CONABIA)

Example:

+ Other requirements for specific areas/markets

CASE-TO-CASE NEGOTIATIONS WITH REGULATORY AUTHORITIES ARE RECOMMENDED

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Other PMF applications

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PMF:
non-food, non-feed, non-fibre

Use

- Human pharma
- Veterinary pharma
- Non-pharma
  - Research reagents
  - Technical enzymes
  - Cosmetics
  - Diagnostics
  - Medical devices
  - Dietary supplements

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Active Cosmetic Ingredients

They fall under the regulations for chemicals

- **Commission regulation (EU) 2020/878** concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
- **Regulation (EC) No 1272/2008** of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (CLP)

They have to be compliant with the cosmetics regulation → **Regulation (EC) No 1223/2009** of the European Parliament and of the Council on cosmetic products

Art 18

NO ANIMAL TESTING

Art 20

PROVEN CLAIMS

- Forbidden ingredients (Annex II)
- Ingredients with limited use (Annex III)
- Allowed preservatives (Annex V)

The market requires that they are

- **SAFE** → **In vitro** safety: cytotoxicity, mutagenicity, phototoxicity, skin sensitivity, skin irritation, ocular irritation. **In vivo** safety on human: patch test or repeated insult patch test
- **EFFECTIVE**
  - **In vitro** activity test
  - Activity test on **volunteers** (min 20 people)
- **STABLE** → **Accelerated** stability (3-6 months 40°C)

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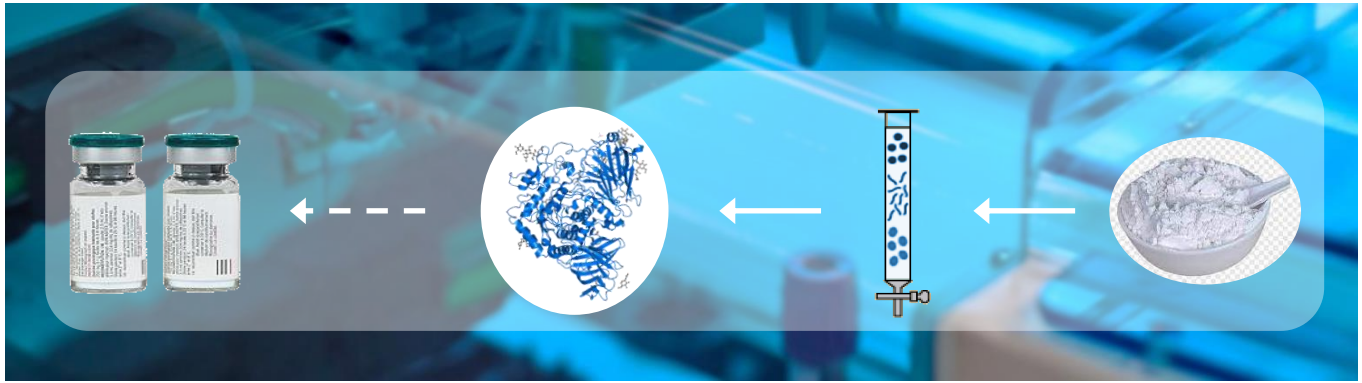
Intellectual Property (IP) framework

Intellectual Property: Patent or Secret?



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Transactiva's IP framework

Proprietary Patents:

- ✓ National + PCT, **whole recombinant antibody** in a cereal endosperm
- ✓ National + PCT, **recombinant human lysosomal enzyme** in a cereal endosperm
- ✓ National + PCT, **synthetic promoter** for heterologous protein expression

Patent title	Patent number	Priority date
A method for the production of a human protein in a plant, in particular a human recombinant lysosomal enzyme in a cereal endosperm	WO/2009/112508	13/03/2008
Expression vector and method for the stable production of a protein in a plant, in particular a whole recombinant antibody in a cereal endosperm	National deposit (IT) IT102017000042052	14/04/2017
Synthetic promoter for the expression of heterologous proteins in plants	National deposit (IT) IT102021000022157	20/08/2021

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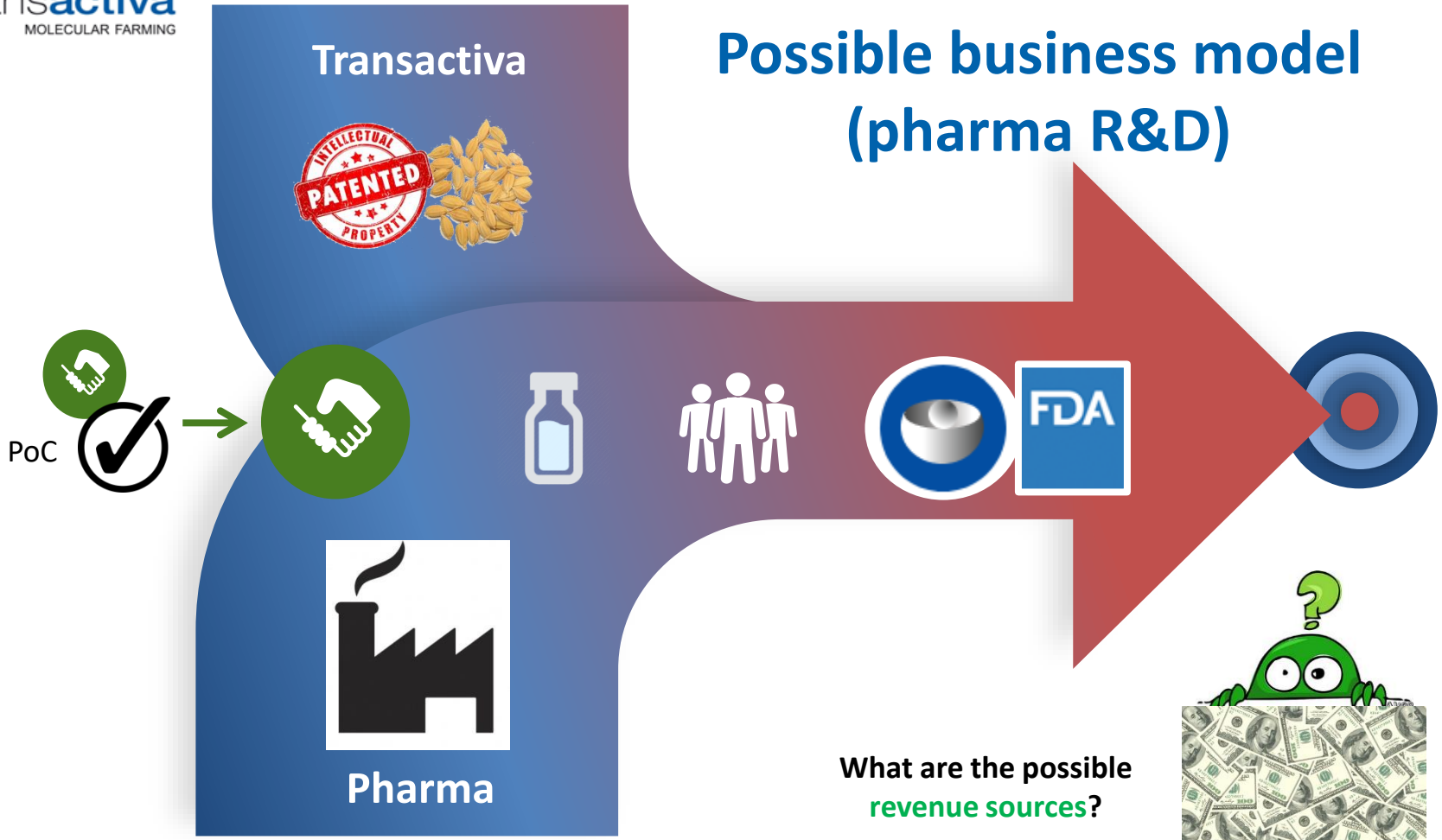
Possible business model (pharma R&D)



What are the possible revenue sources?

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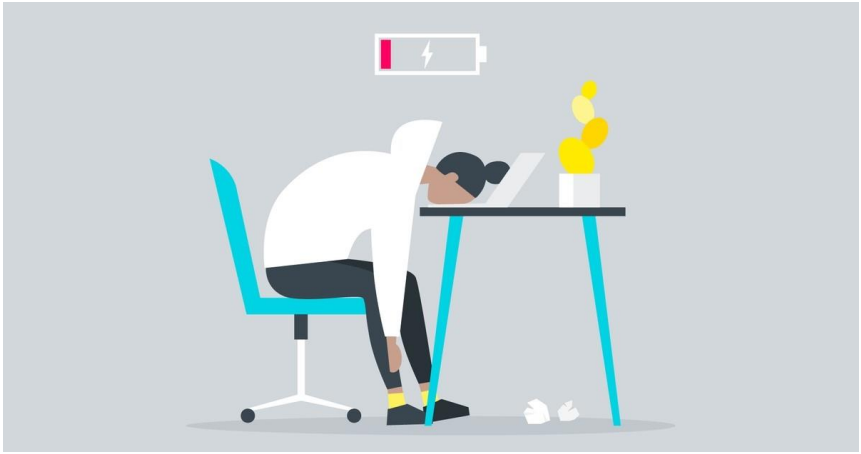
Wrap-up and exam simulations



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Exercise 1

L'azienda di biotecnologie vegetali **DSPrates** ha sviluppato una **linea di mais OGM** esprimente a livello di seme un fattore di crescita ematopoietico, il **GM-CSF**.

Risultati preliminari *in vitro* mostrano come la molecola sembri sovrapponibile in attività e funzionalità all'analogo umano.

L'hanno sviluppato come progetto interno, senza committente, sfruttando un **brevetto di metodo** da loro sviluppato anni prima, e ora vorrebbero cercare di farlo fruttare commercialmente.

Come **nuovo business development manager della DSPrates**, devi decidere se e come procedere.

Rifletti sulle **potenzialità commerciali** (farmaceutiche o meno) della molecola e proponi una o più **strategie**, evidenziando i possibili **fattori limitanti**.

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Exercise 2

Nell'ambito di un **progetto europeo** sullo sviluppo di piattaforme innovative per la produzione di biofarmaci, il gruppo di ricerca di biotecnologie agro-industriali della **Miskatonic University** ha ottenuto un contratto di servizio dall'**azienda farmaceutica MoreVil**.

L'obiettivo è quello di **risolvere un problema**: la MoreVil ha provato ad esprimere la **Trombopoietina umana** in **semi di orzo**, ma non ha ottenuto alcun segno di espressione (la proteina non dà segnale in ELISA o WB, e gli estratti proteici non mostrano attività specifica legata alla presenza della proteina).

Il gruppo di ricerca ha il compito di **ottenere una piattaforma vegetale** che esprima la trombopoietina umana.

Che approcci seguiresti?

Immagina di avere **un anno di tempo** ma **budget illimitato**.

Thanks and good luck!

Sara Raccovelli, PhD, MBA

sraccovelli@transactiva.it

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