Biomedical E&I BMEI-2022

Manufacturing/Delivery
QC release and stability

November 29, 2022

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Skoltech

BMEI STRUCTURE AND TOPICS

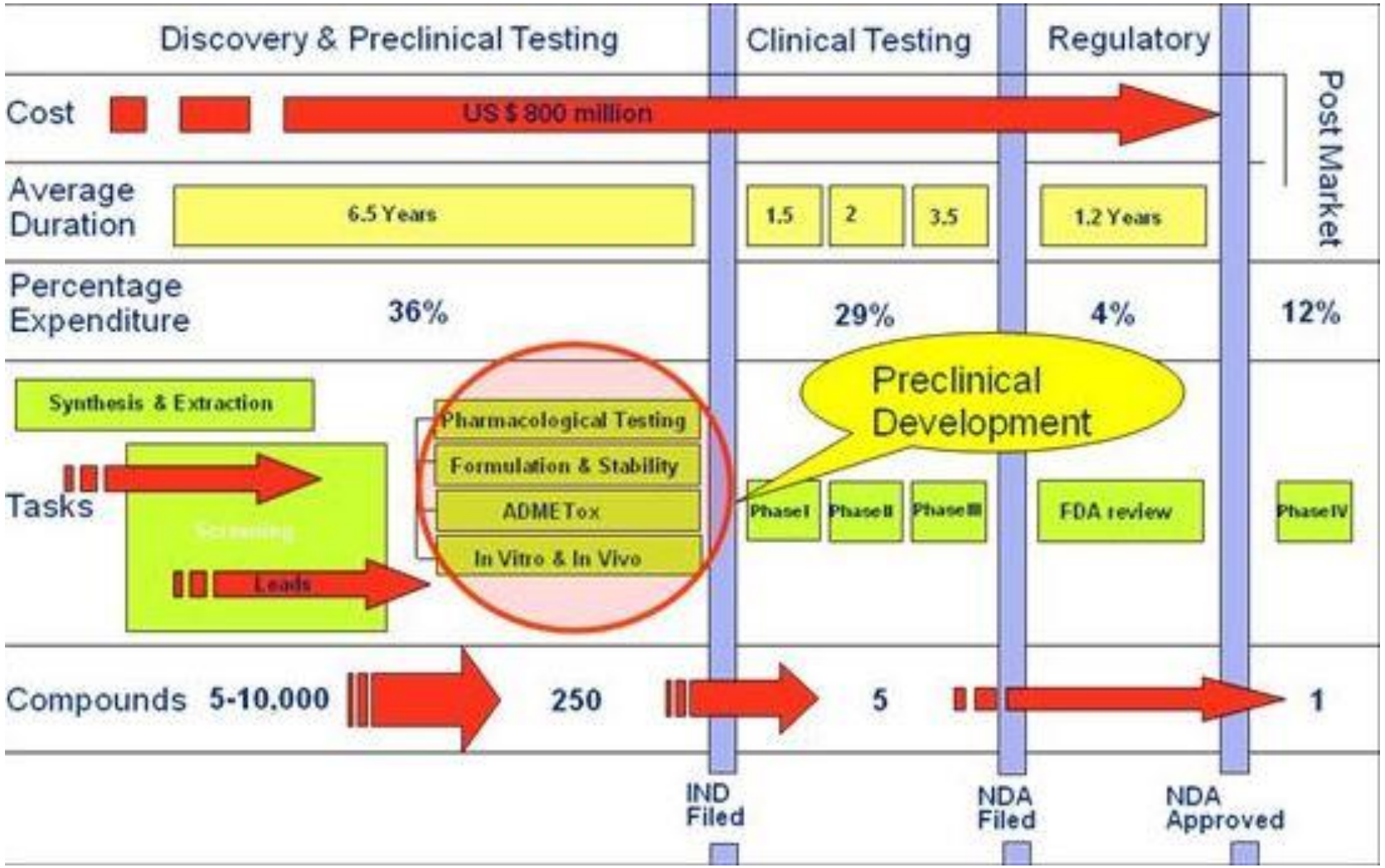
- MONDAY
  - mentoring by request
- TUESDAY
  - lecture of the topic of the week
    - Indication + MOA + POC
    - Patent
    - Formulation + Manuf + QC
    - Reg guidances + Preclin + Clin
    - Value chain + Value delivery
- THUR
  - mentoring by request
- FRIDAY
  - Team presentation
    - **Last course activity day: Wed Dec 16th**

		TUE-FRI 9-12	
week 1	1	Onco/Tobacco game + BMEI course intro	
	4		
week 2	8	ELP	
	11	LECT: Indication + POC experiment + charact	
week 3	15	PRESO: Ind + POC experiment + valid QC	Michail Grubman
	18	LECT: Grubman	Michail Grubman
week 4	22	LECT: PATENT	
	25	PRESO: PATENT three claims	
week 5	29	LECT: Reg + Guidances + Preclin + Clin	
	2	PRESO: Reg + Guidances + Preclin + Clin	Sophia Yartseva
week 6	6	LECT: Formulation + Manuf + QC release	Sophia Yartseva
	9	PRESO: Formulation + Manuf + QC release	
week 7	13	LECT: BMEI career	
	16	FIN PRESOS	Michail Grubman

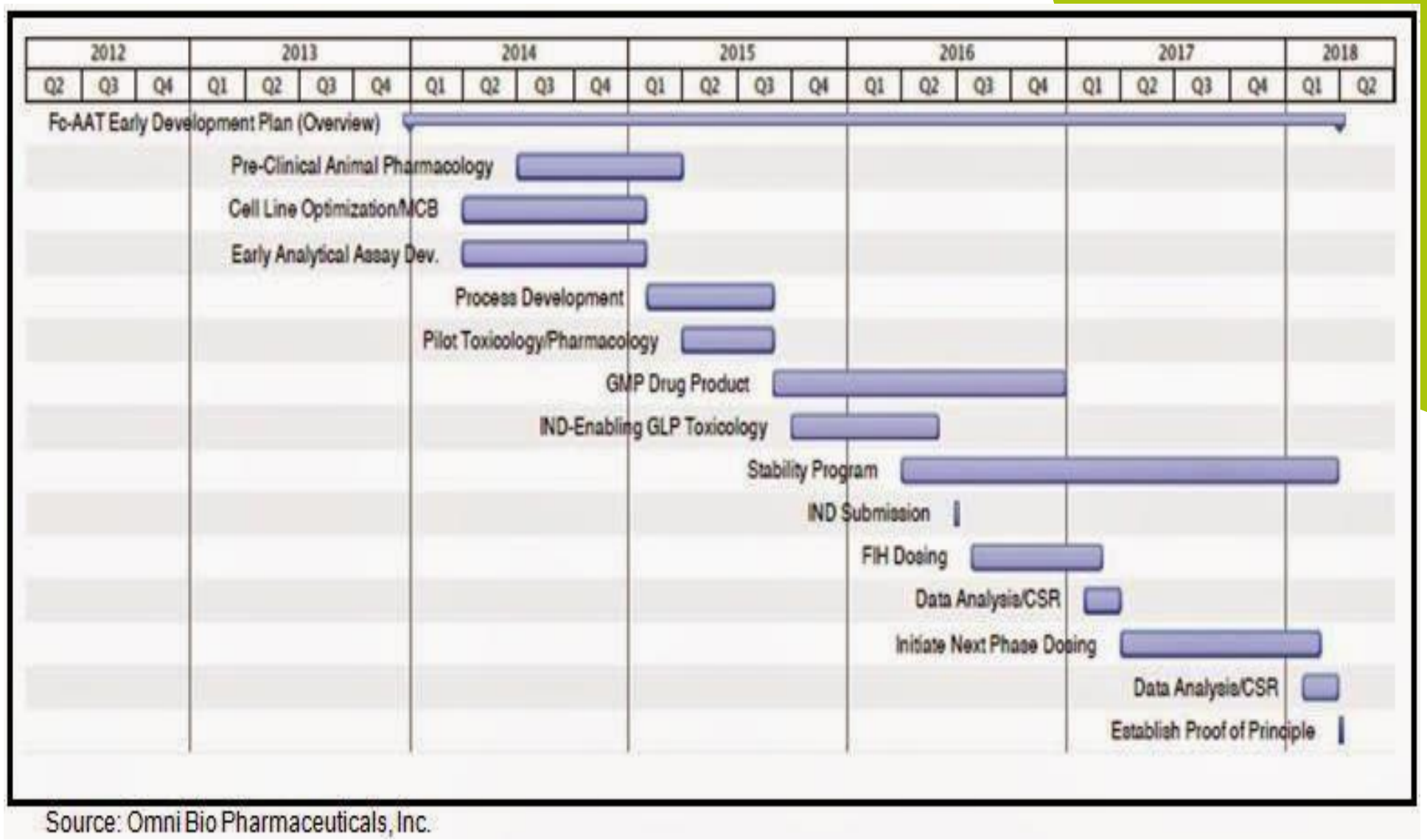
NEXT DAYS

- Friday Dec 09: Presentation MANUF + QC
  - graded submission in Canvas: Monday Dec 12
- **Monday Dec 12, 11pm:**
  - **Graded submission of the MANUF+QC presentation in Canvas**
- Tuesday Dec 13: final integrative lecture
  - broad Q&A
- Friday Dec 16: FINAL presentation
  - graded submission in Canvas: Monday Dec 19

The long and windy road of BMEI product/service



Pre-IND = Preclinical + Manuf + QC



Source: Omni Bio Pharmaceuticals, Inc.

MANUFACTURING CAN MAKE OR BREAK YOUR INNOVATION VALUE

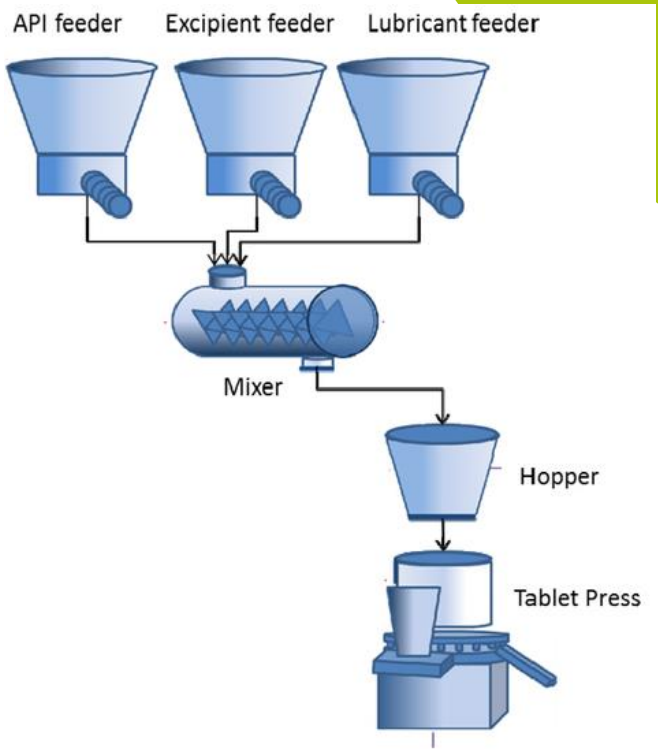
- Unbearable cost of production
  - *long modified peptides*
- Unbearable cost of delivery
  - *CARTs and other cell therapies*
- Unbearable cost of registration
  - *novel production strains with marginal cost effect*
  - *novel molecules with marginal therapeutic effect*
- Highly attractive to regular customer
  - *MS tablets vs biologics*
  - *anticoagulant tablets vs biologics*

BMEI Careers by function

	MOA + POC + IP	Product development	Process Development	Quality Control (QC)	Process Operation	Regulatory	Medical marketing	Investment management
Large Originator								
Startup originator								
CMO								
CRO								
BizDev or VC								
IP or Patent attorney								
	slow	competitive	tedious	neurotic	repetitive	buarecrautic	hyper competitive	miracle

MANUFACTURING STAGES

- Stocks, banks and standards
  - Freezers and procedures
- API = Active Pharmaceutical Ingredient
  - Method of synthesis
  - Method of control
  - Method of storage and transportation
- DP = Drug Product = FDF
  - Method of production (formulation)
  - Method of control
  - Method of storage and transportation
- Packaging
  - Method of production
  - Method of control
  - Method of storage and transportation
- QC & Stability

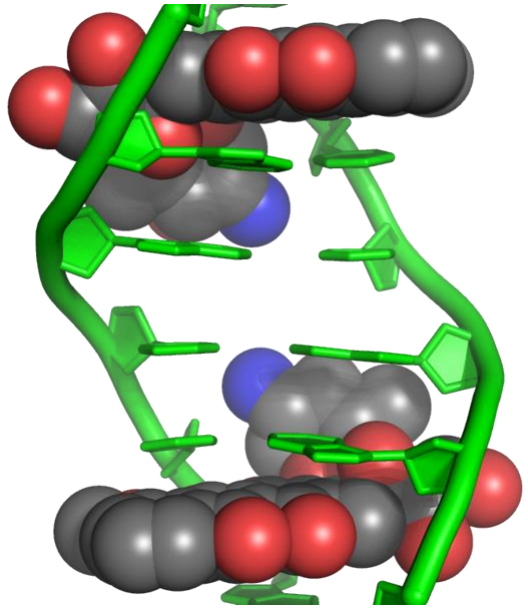


QC IS HUGE AND IMPORTANT SEPARATE WORLD

- Process
  - Process development and validation
  - Pilot batch release
  - Commercial production
- QC
  - Development and validation
  - Pilot batch release
  - Reporting and archiving
- QA
  - Policy
  - SOPs
  - Reporting

QC is key to GMP and ~ 40% of your potential industrial job

- Developing and Mastering existing analytical techniques under GLP
  - Nobody else can do it, only you
- Providing scientific diligence to everything you and your organization do
  - Input control
    - biological activity
    - Phys-chem characterization
  - Output control
  - In process controls
  - Batch release controls
  - Stability control
  - **Orthogonal controls (QBD)**

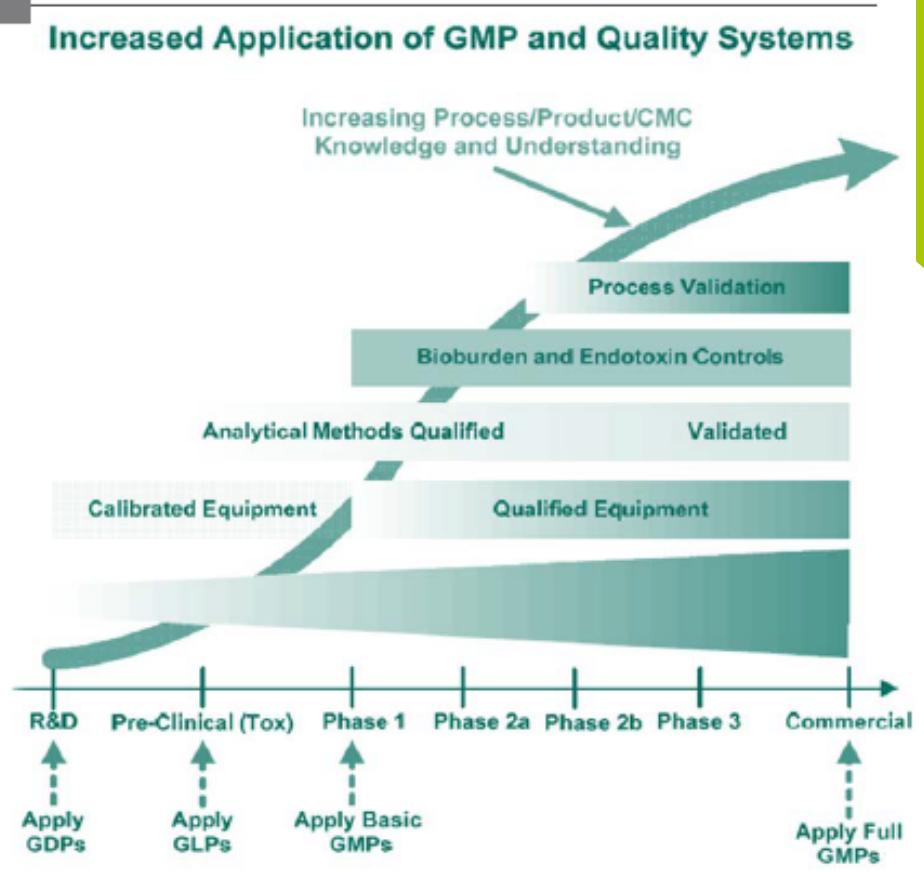


QUALITY LIFE-CYCLE MANAGMENT

QUALITY INTEGRATION THROUGHOUT THE PRODUCT LIFE-CYCLE

Quality LCM Expertise

- QMS is core infrastructure regardless of product life-cycle phase
- Application of GMP depends on product life-cycle phase
- Ensures the early, integrated analysis of product Quality from the planning and design phases through testing and manufacture to proactively address quality issues before they are manifest in prototype or fielded products



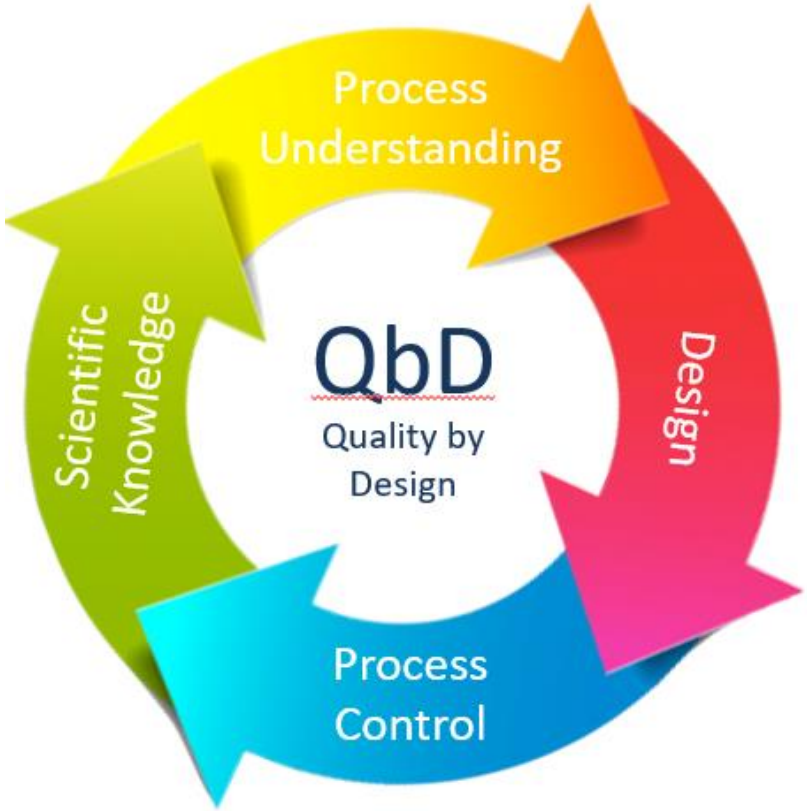
QUALITY ESSENTIALS

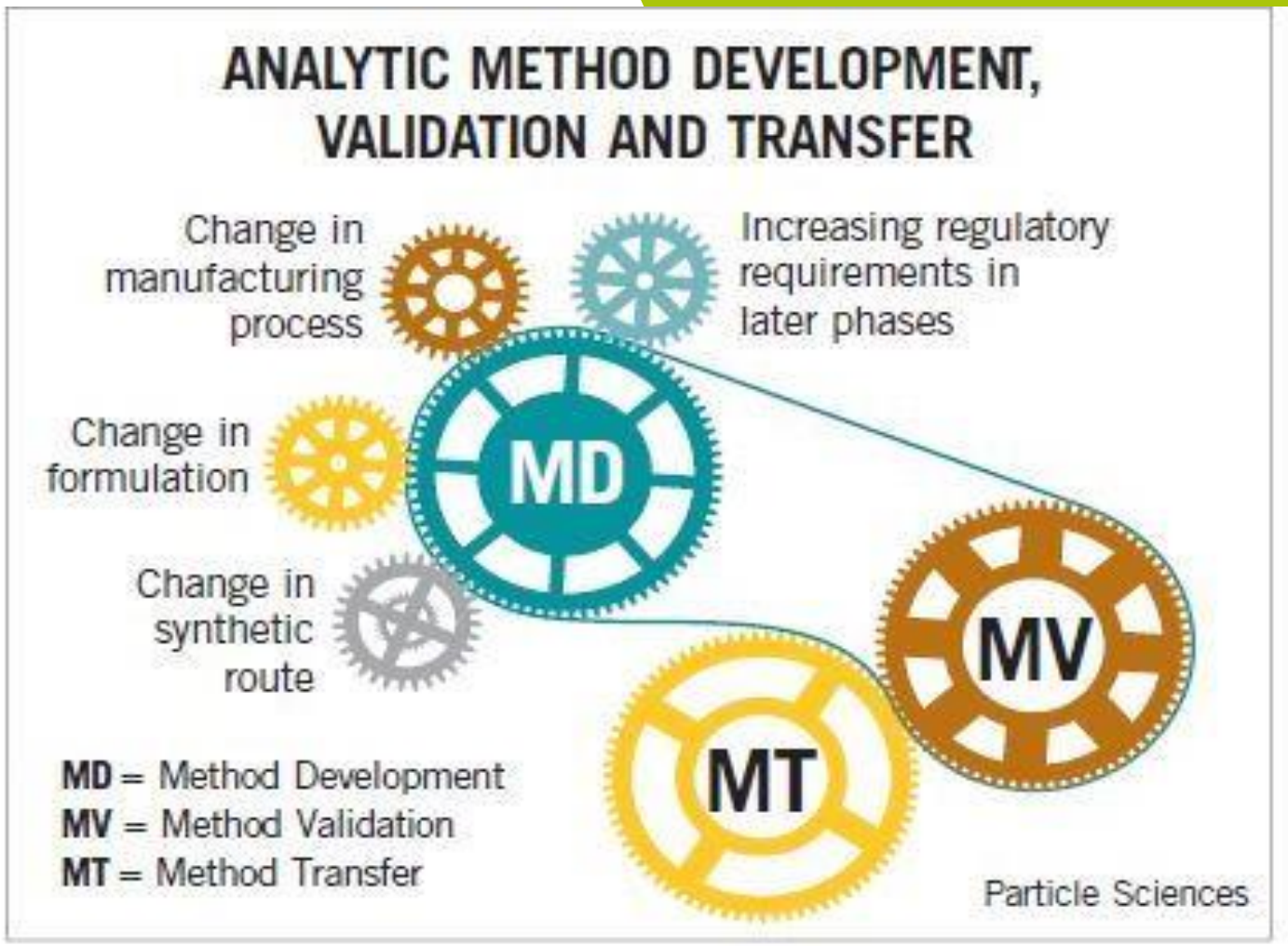
REDUCING TIME TO MARKET AND ENSURING COMPLIANCE

Specialized Skill Sets

Quality Systems	QC Laboratory	Manufacturing Quality	Supplier Quality
• Regulatory Inspections • Document Control • Management and Annual review • Change Control • Investigation/ CAPA	• Equipment qualification • Method development • Method validation and transfer • Stability • Product testing	• Facility & utility qualification • Equipment qualification • Facility motoring • Process validation • Product Release	• Vendor Qualification • Material Qualification • Sterilization

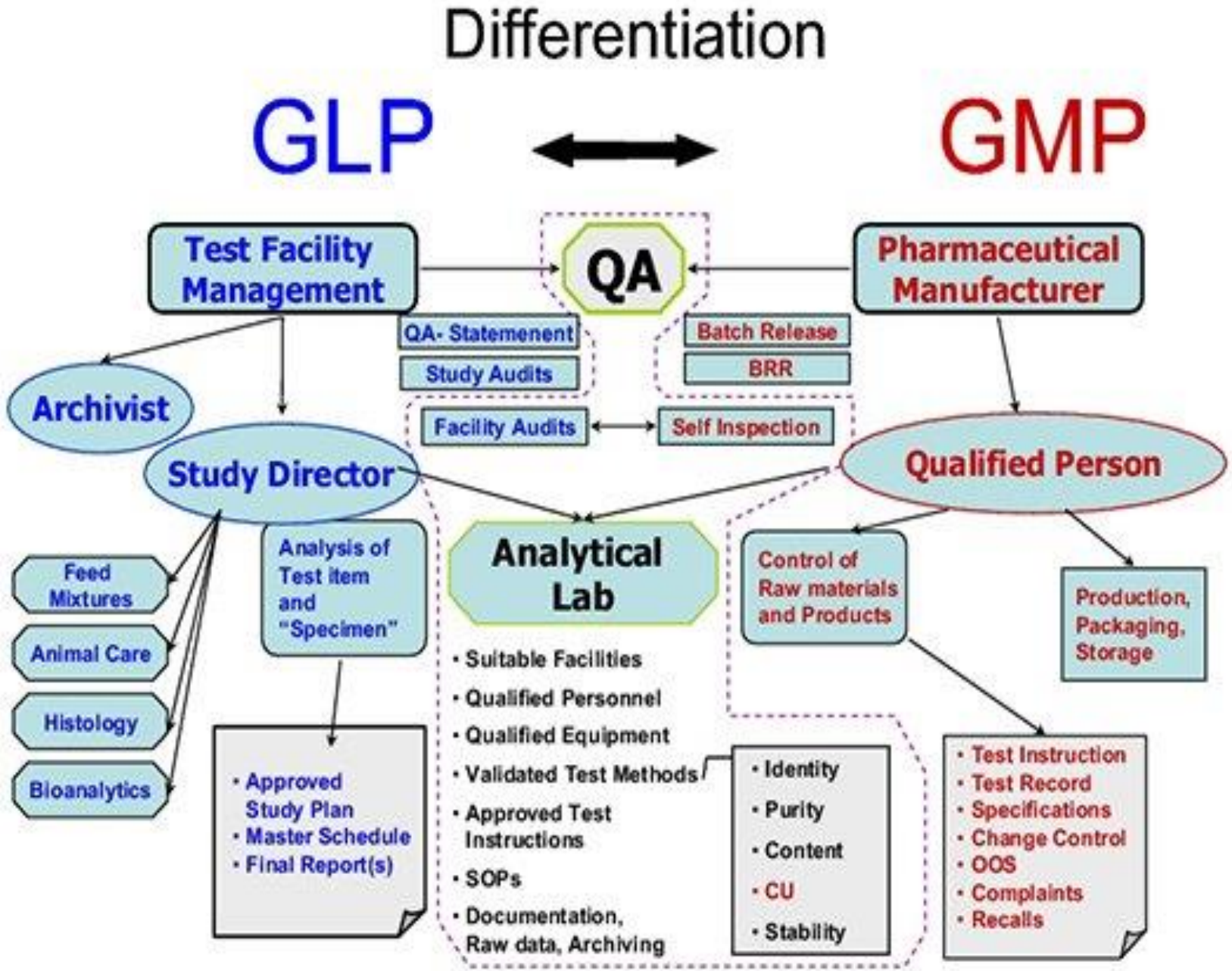
QBD = rocket Science in your backyard





GMP & GLP make sense and add value
PDCA = science

- **Minimize deviations**
  - Highly protected equipment
    - Even from sabotage
  - QBD assurance
- **Control everything**
  - journals
- **Record everything**
  - Batch records
  - Archives
- **Standardize everything**
  - SOPs
- **BEFORE YOU AND YOUR FRIENDS CONSUME THAT TABLET**

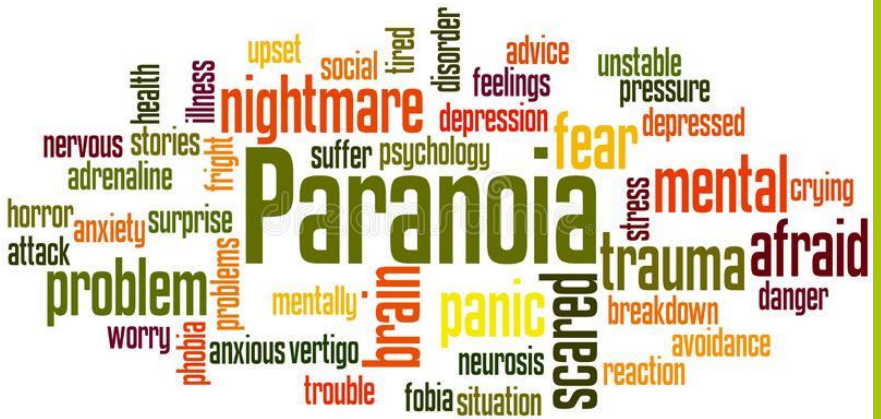

Differentiation
GLP
GMP
Test Facility Management
QA
Pharmaceutical Manufacturer
QA- Statemenent
Study Audits
Facility Audits
Batch Release
BRR
Self Inspection
Archivist
Study Director
Qualified Person
Analysis of Test item and "Specimen"
Analytical Lab
Control of Raw materials and Products
Production, Packaging, Storage
Feed Mixtures
Animal Care
Histology
Bioanalytics
• Approved Study Plan
• Master Schedule
• Final Report(s)
• Suitable Facilities
• Qualified Personnel
• Qualified Equipment
• Validated Test Methods
• Approved Test Instructions
• SOPs
• Documentation, Raw data, Archiving
• Identity
• Purity
• Content
• CU
• Stability
• Test Instruction
• Test Record
• Specifications
• Change Control
• OOS
• Complaints
• Recalls

Your potential roles in manufacturing

- Project scientist
  - Design lab production process for CMO
  - Design QC protocol
  - Audit CMO
- CMO scientist
  - Scale-up production protocol
  - GMP QC protocol
  - Production management
- QC scientist
  - Mastery of techniques
  - Scientific diligence
    - *StartUps vs Corps = Adventure vs Stability*

PRODUCT AND QC PRECLIN PARANOIA

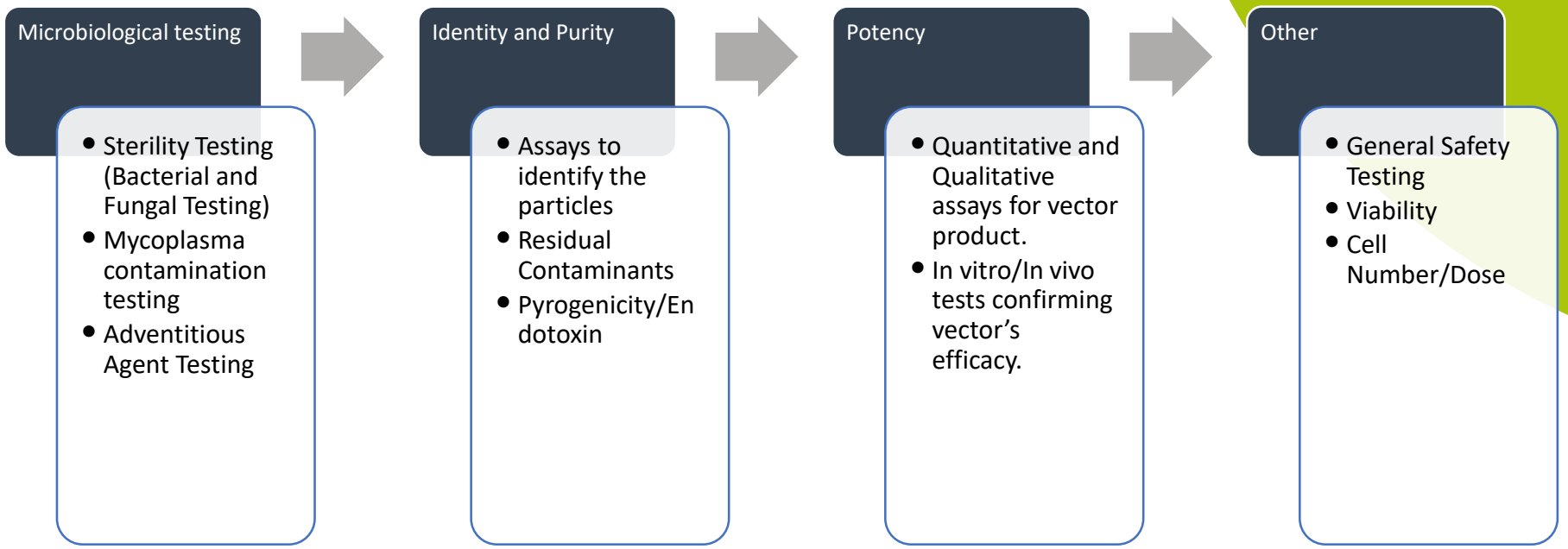
- **PRODUCT ENTERING THE GLP PRECLIN IS YOUR FINAL PRODUCT**
  - If you change the product later, the regulator will reasonably send you for another GLP study
    - Shocking discovery for many scientists
- **QC IS YOUR ONLY PROTECTION FROM MANAGEMENT FAILURE**
  - Storage mistakes
  - Logistics mistakes
  - Third party mistakes
    - How you protect your time and reputation and money?
      - Only by the standardized QC passport
- **STABILITY IS PAIN BUT IT CAN NOT BE BYPASSED**
  - Are you sure your preparation may reach SPB?



Batch Release QC Protocol & Passport Common sense

- Does your product has proper chemical composition?
  - How you prove it quickly and inexpensively?
    - Spectroscopy
    - HPLC
  - Quantify it
- Does your product retains proper biological activity?
  - How you prove it quickly and inexpensively?
  - Quantify it
- Microbiological safety
  - Plating and culturing
- Is your product stable for prescribed period of time?
  - What is the standard technique of stability testing for your product class?

Product Testing – Q&C assessment



Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) 2018

HOMEWORK

- **MANUF/DELIVERY BLOCK DIAGRAM**
  - schematic journeys
    - Materials, products, devices, patient
- **MANUF/DELIVERY CORE TECHNOLOGY/EQUIPMENT**
  - **3 key assets and technologies** needed to deliver your innovation
    - picture, ballpark price and manufacturer
    - do not forget a concept of freezer to store your cell lines !
- **QC batch release protocol / Device validation protocol**
  - very formal for **the 3rd party outsourcing**
    - detailed enough to fill 1 slide

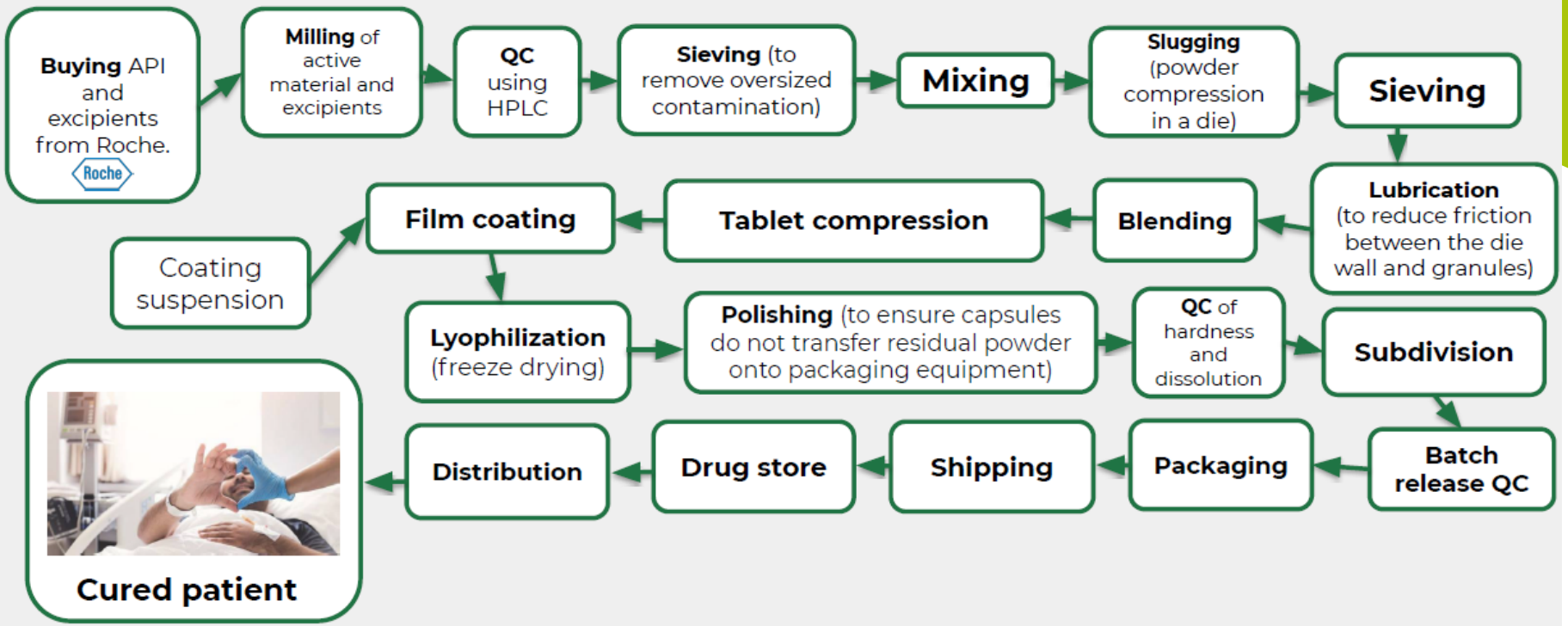
PRESENTATION #5

- **SLIDE 1: Your final drug product or medical device description**
- **SLIDE 2: MANUF/DELIVERY BLOCK DIAGRAM**
  - schematic journeys
    - Product, device, patient
- **SLIDE 3: MANUF/DELIVERY CORE TECHNOLOGY/EQUIPMENT**
  - **3 key assets and technologies** needed to deliver your innovation
- **SLIDE 4: QC batch release protocol / Device validation protocol**
  - very formal for the 3rd party outsourcing

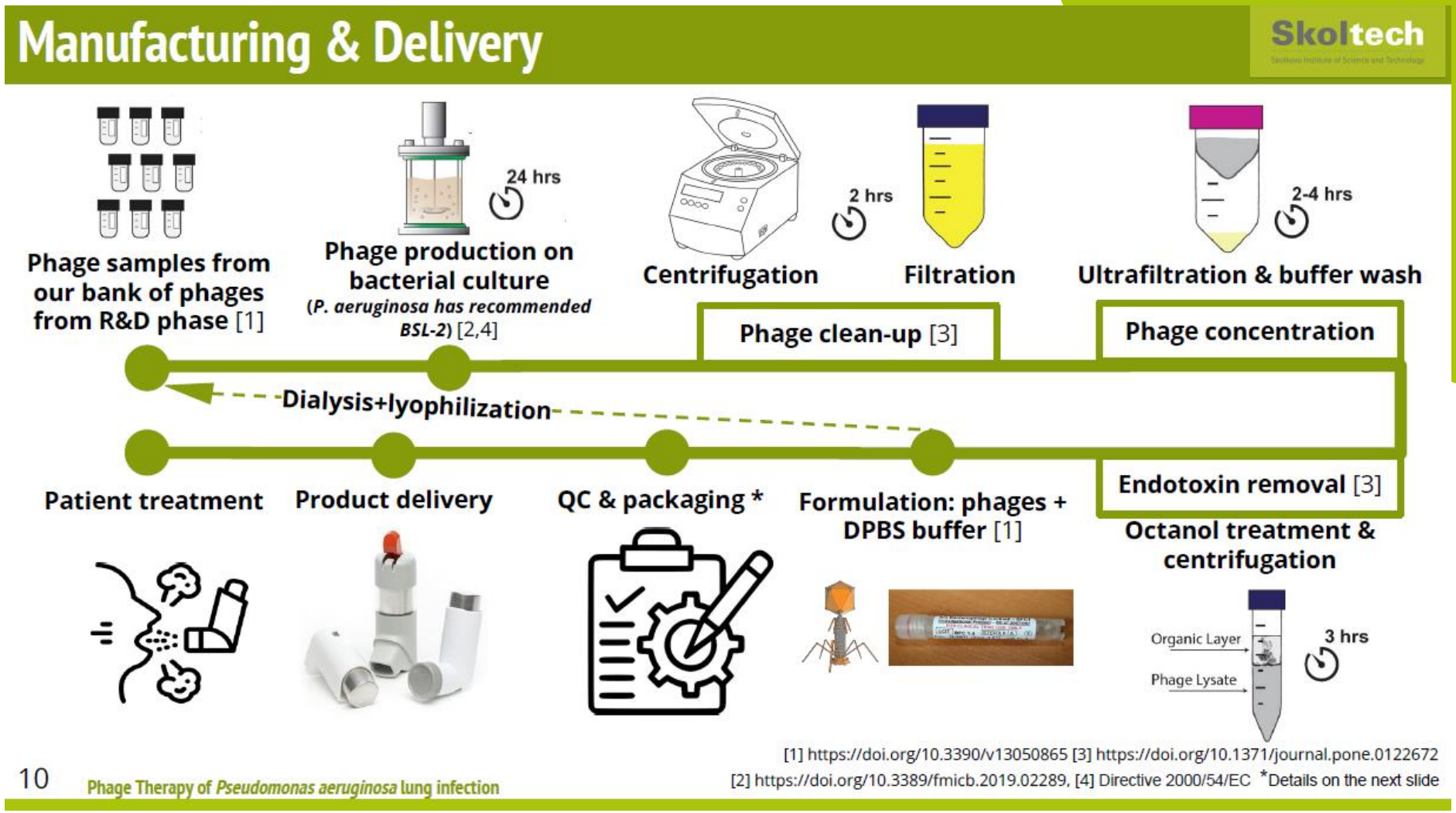
KIND OF BORING, BUT A LOT TO DISCUSS

MANUF&DELIVERY BLOCK DIAGRAM

Release form: Film-coated tablets 200 mg.6 tablets per blister aluminum / PVC-aluminum. 2 or 6 blisters, together with instructions for use, are placed in a cardboard box

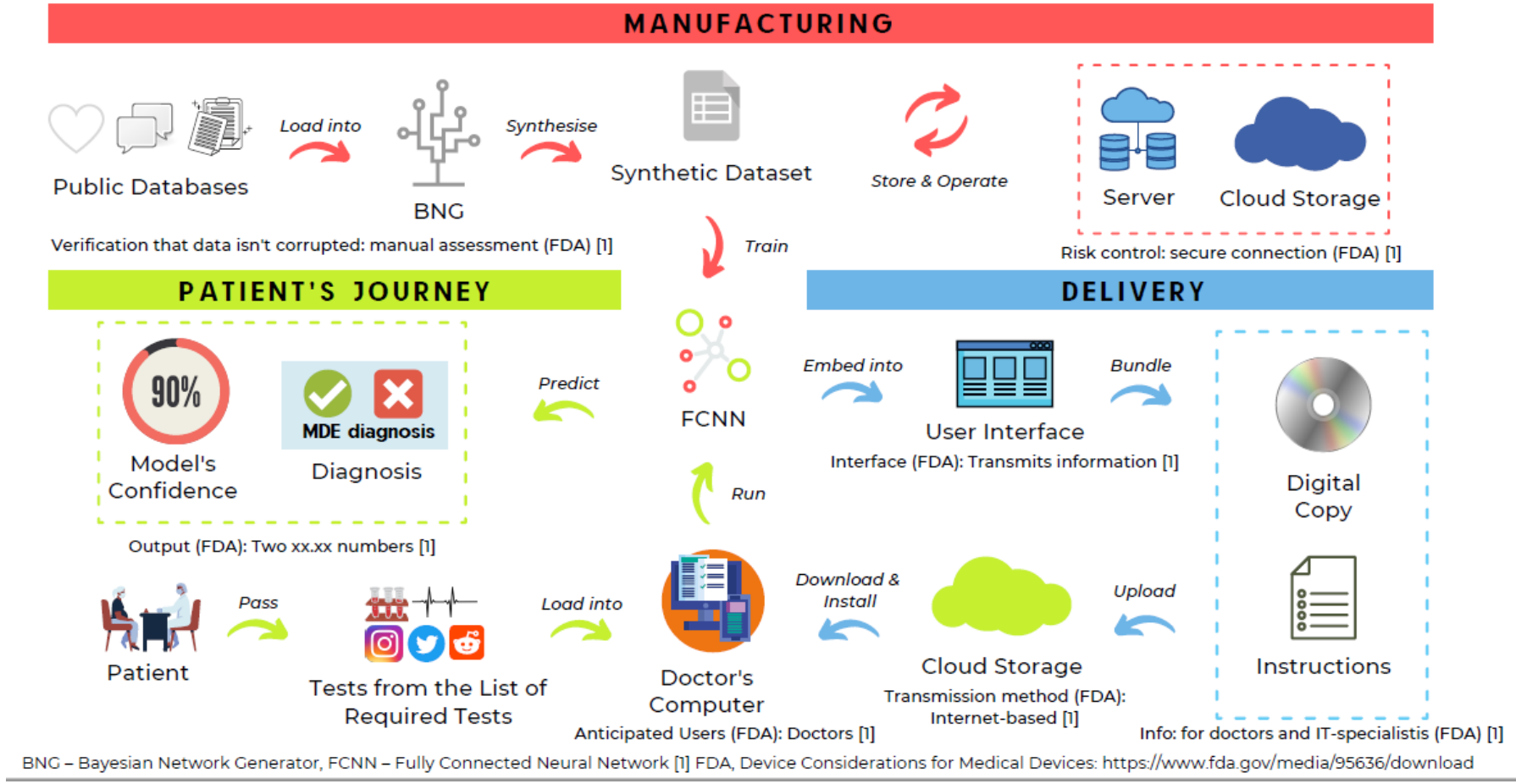


NICE, BUT KIND OF EMPTY



PRACTICAL FOR SW MED DEV

DELIVERY



SCIENTIFIC, NOT FORMAL

QC Batch Release

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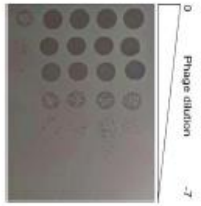
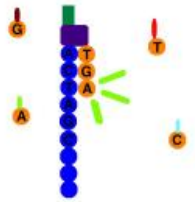
Phages quality → **Quality of drug stability** → **Quality of drug purity** → **Quality of inhaler**

Efficacy of plating (EOP)
A simple and reliable way to determine the viability and specificity of phages.



Genome sequencing using illumina dye
Detection of mutations in order to control the emergence of new strains and variants

Using a special buffer DPBS*.
Preliminary testing by the **EOP** method **during the year** and the provision of a **guarantee**.

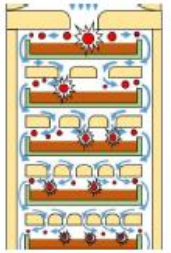


The product must be free from microbiological contamination of the culture with which the phage was produced and other contamination.

Under FDA guidance:
(21 CFR 610.13) FDA

Aerodynamic Particle Size Distribution
Particle size determination is important for the drug to enter the smallest lung cavities.

Metered-dose inhaler (10 ml)
Under FDA guidance:
Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations (FDA)



11

Phage Therapy of *Pseudomonas aeruginosa* lung infection

*doi: 10.3390/v13050865

PRACTICAL FOR MED DEV

DEVICE VALIDATION PROTOCOL

User Validation

1. Two-factor authorization;
2. Version control - update software if available;
3. User's hardware settings validation;
4. Log user's activity.

Fig.1 User has successfully authenticated

Performance Validation

1. CI/CD methodology;
2. Wide list of numerical tests to control quantitative behaviour of the algorithm after system reload;
3. Track statistics to identify outliers (95% confidence interval) - look through during the week.

Fig.2 Algorithm shows ROC-AUC >=0.81 [1]

Tech-side Validation

1. Every time before the workday:
   a. Get CT scan from template object and compare the result to reference to check the CT scanner parameters;
   b. Send the fixed set of CT scans to the service and compare the response time and analysis to the reference
2. During the workday:
   a. Continuous connection tests;
   b. Continuous workload monitoring;
   c. Study format check;
   d. Limited access and rights for users.

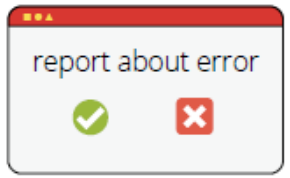
Fig.3 Rare case when the AWS server is down to RKN actions

[1] Acceptable threshold defined by the NPCMR

QC & FEEDBACK PROTOCOL

1 SOFTWARE PERFORMANCE CONTROL

INSTALLATION QUALIFICATION



- possibility to send feedback form for bugs report
- survey form for suggestions

"...determine that the users are capable of correctly using the device ..." [1]

OPERATION QUALIFICATION

- conduct QC on validation dataset before testing the patient

"...verify and validate that when data is corrupted it can be detected and appropriately managed..." [1]

Validation Dataset

Load into

Uni-MDED

Incorrect work

Error report

Correct work

Correct work

Real patients

2 FEEDBACK CONTROL – REVALIDATION

PERFORMANCE QUALIFICATION

- patients' medical history 1 year after the diagnostic study

VALIDATION SUMMARY REPORT

- anonymous data collected from polyclinics via the feedback form
- each form is filled by the therapist for a fixed payment or extension of access to the licence

REVALIDATION DECISION

- the Uni-MDED System is periodically updated with the obtained data

:...implement a fault-tolerant design and verify its performance..." [1]

[1] FDA, Device Considerations for Medical Devices: https://www.fda.gov/media/95636/download

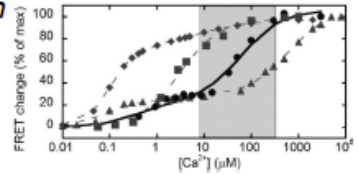
TO GOOD TO BE TRUE

Development of autologous anti-tumor B-cell biomedical cell treatment for lung adenocarcinoma patients. Team #7

QC Batch Release based on (21 CFR 610) FDA

potency

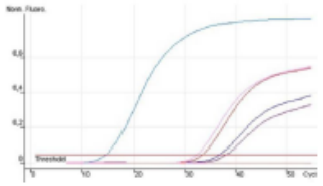
Surrogate cytotoxicity markers[2]:
B-cells activation stages tracking:
- Early: *Calcium flux* + *phosphirization*
Method: calcium dyes and image cytometry



- Intermediate: *cytokine production*
Method:
  - cytokine production assays: ASF testing for IFN-γ, IL-4, IL-6, TNFα via ELISpot assays[5]
  - effector molecule release assays: ELISA for TRAIL/Apo2L ligand[4]
- Late: *B-cells proliferation*
Method: membrane-associated fluorescent dye CFSE by flow cytometry [7]

purity

Methods:
- LAL endotoxin detection system (Endosafe®), acceptable result is <5EU/kg
- separate qPCRs with primers specific to IGHs, IGKs (B-cells) and TCRs (T-cells)

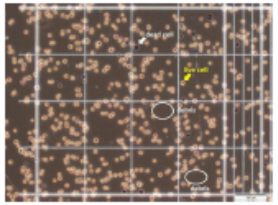


sterility

Methods:
- USP sterility test with cGMP testing facilities
- BacT/ALERT® for aerobic, anaerobic, fungal cultures

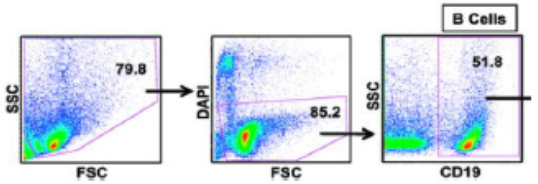
viability/cell count

Method:
Cellometer AO/PI or Manual Trypan Blue
Cell count acceptable result: $0.1 - 2 \times 10^{11}$ cells; *viability* acceptable result: >70% viable cells



identity

Methods:
- Flow cytometry for CD19+, accepted result is >90% of the corresponding cells
- qPCR with B-cell specific primers



1 (21 CFR 610) FDA https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=610
2 Ex vivo analysis of T-cell function doi: 10.1016/j.coi.2005.05.002
3 Regulatory perspective on in vitro potency assays for human T cells used in anti-tumor immunotherapy. doi: 10.1016/j.jcyt.2018.01.011
4 The B-Side of Cancer Immunity: The Underrated Tune. doi: 10.1016/j.jcyt.2018.11.004
5 Cytokine-producing B lymphocytes – key regulators of immunity. doi: 10.1016/j.coi.2008.03.003

thx.

Skoltech