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ATMPs from Academia to Industry
Getting It Right First Time (GIRFT)

Prof. Mark Lowdell
Professor of Cell & Tissue Therapy, UCL
Director of Centre for Cell Gene & Tissue Therapeutics, Royal Free Hospital
CSO INmuneBio Inc
London, UK

1

Disclaimer and declaration

- **Professor Lowdell is a founder & shareholder of:**
  - Achilles Therapeutics Ltd.
  - Autolomous Ltd. - Director
  - INmuneBio Inc. - Chief Scientific Officer & Director
  - INmune Ventures Inc. - Director
  - Novamune Ltd. - Director
- **Professor Lowdell is a consultant to:**
  - Advent Bio Services Ltd.
  - Autolus Ltd.
  - Avectas Ltd.
  - NWBio Therapeutics Inc.
  - Quell Therapeutics Ltd.
  - ViroCell Biologics Ltd.
- The opinions presented today are those of Professor Lowdell and not necessarily those of UCL, Royal Free London NHS FT or any of the companies listed above

2

Advanced Therapy Medicinal Products (ATMP)

Gene therapies

Somatic cell therapies

Tissue-engineered products

3

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Advanced Therapy Medicinal Products (ATMP)

- **ATMP development 2021**
  - >90% of ATMPs are developed by investigators
  - >60% of ATMP clinical trials are led by investigators
  - Remainder are:
    - Academic spin-out
    - Academic spin-off to pharma (e.g., CAR-T)
  - Biopharma / pharma successful ATIMPs will only become successful ATMPs if they are:
    - Cost effective
    - Deliverable at scale
    - Easily technically transferred

ATMP development

- **>90% of ATMPs are investigator developed**
- **Investigator aims**
  - Treat HIS / HER own patients - "clinical condition blindness"
    - Is this the right clinical use of the ATMP?
    - If it fails in this application, will it be tested in another?
  - Publish a high impact paper
  - File some IP?
  - Change clinical practice??

4

ATMP development

- **>90% of ATMPs are investigator developed**
- **Make the ATMP in-house to treat 10 patients**
- **Drug development?**
  - Even consider how to make it for 1000 patients?
  - Understand issues of tech transfer?
  - Understand product definition?
  - Understand the large-scale supply chain - Strimvelis!

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This is the fastest moving field in drug discovery

There are hundreds of companies working in the ATMP field

5

What are the problems?

Drug definition

"Process defines the product"?

6

What are the problems?

Drug definition

- **Process**
  - Reliability
    - How often does it fail?
    - What is "failure"?
  - Reproducibility
    - How variable is the output when it doesn't fail?
- **Product**
  - Identity
  - Quantity
  - Purity
  - Sterility
  - Potency

Assays?

- Understand
- Define
- Qualify

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What are the problems?

Process development

- How far, how soon?
- How long to be ready for each phase?

What is the minimum degree of process needed?

What are the problems?

Trial Design

- Who / when to treat?
- Product formulation
  - Dose/kg
  - Dose/m²

  Doesn't make much sense as the product is likely to proliferate *in vivo*
  - Fixed dose
  - Max volume?

What are the problems?

Product cost

- Is it affordable now or can it be affordable at scale - effect of formulation

Product packaging and supply chain

- Many products are still packaged in research-grade cryovials
- Packaging that can be commercialised is more suitable, such as cryogenic bags or AT crystal vials

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What are the problems?

Phil Vanek, General Manager Cell Therapy Technologies GE Healthcare

"The process today is not 2017 technology, it's 2010 technology," he adds. "That's fine for dealing with academic centres that handle five to 10 patients a year, but we have to figure out a process for tens of thousands."

"It would be a mistake to automate totally today, because first we have to streamline the current process."

Automation comes with expensive consumables which add a fixed cost to your product

7

What are the problems?

Phil Vanek, General Manager Cell Therapy Technologies GE Healthcare

"The process today is not 2017 technology, it's 2010 technology," he adds. "That's fine for dealing with academic centres that handle five to 10 patients a year, but we have to figure out a process for tens of thousands."

"It would be a mistake to automate totally today, because first we have to streamline the current process."

The time from phase I / II to approval is often too fast to make necessary changes!

EU MA since Regulation (EC) 2007 / 1394 n=12

ChondroCelect	Voluntary withdrawal 2016 Cartilage biopsy digestion, expansion, 1m cells/cm^2
MACI	Approved 2013 , suspended 2014 (manufacturing discontinued) Autologous chrondocytes, a cellular porcine matrix
Provenge	Approved 2013, withdrawn 2015
Glybera	Approved 2012, 1 patient treated - $1m cost! Voluntary withdrawal 2017
Imylgic	2015
Holoclar	2015 irradiated 3T3, autologous epithelial cells, fibrin NICE to approve £80,000 per tx
Strimvelis	2016 - GSK sold to Orchard Tx
Zalmoxis	2016 (conditional MA), GM T cells for haloidentical HSCT
Spherox	**2017**
Kymriah	**2018**
Yescarta	**2018**
Alofisel	**2018**

8

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Kymriah	
Yescarta	
Alofisel	2018

Were the drugs that were withdrawn or sold on ready for the market when taken?

EU MA since Regulation (EC) 2007 / 1394 n=12

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Of the newer drugs, are the Costs of Goods (CoG) sustainable?

EU MA since Regulation (EC) 2007 / 1394 n=12

We need to worry about the cost of goods early in the drug development pathway

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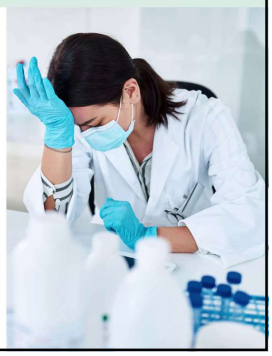
Real-world challenges in commercial drug development

9

Transfer from academia to biotech creates new challenges

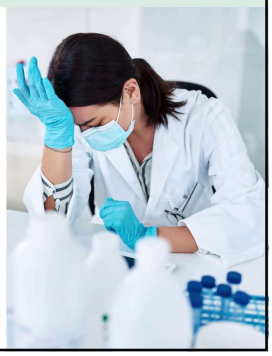
- **Investor pressure - "get clinical trial data"**
  - There is often investment in a clinical trial even if the product is poorly designed and poorly produced
    - There is even a 'trial a similar product' mentality
  - There is often a weak rationale for the clinical indication
    - Accessing patients is challenging for biotech companies



Real-world challenges in commercial drug development

Transfer from academia to biotech creates new challenges

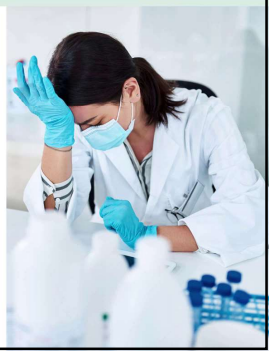
- **Investor pressure - "get clinical trial data"**
  - Patients in phase I are rarely the target patients for the licensed medicine; over expectation of efficacy
  - It is a challenge to get investment in the product / process development
    - If the "Process IS Product", then process development (PD) may change the product
    - Why invest in PD for 1000 doses per year if phase II hasn't finished?



Real-world challenges in commercial drug development

Transfer from academia to biotech creates new challenges

- **Biotech companies are rarely run by drug developers**
  - Competing demands between R&D, clin ops, manufacturing and investors



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If you can find money for PD?

Requirements for a successful PD

Define the product

The product should be defined, not the process

Qualify the assays

- Assay reproducibility
- How will you qualify new batches of reagents used ?
- Produce robust assays

10

If you can find money for PD?

Requirements for a successful PD

Engineer the process

- Closable and scalable
  Cost:Benefit analysis for automation
- Ensure steps for in-process QC
- Source and validate multiple suppliers
- Start gathering stability data during development
- Optimise data to support cold supply chain
- Validate the process
  eBMRs and eQC/QP release procedure
- Develop assays and qualify them

If you can find money for PD?

Requirements for a successful PD

Design the product packaging EARLY, in consultation with end users

- *e.g.*, CORDStrom in MISSION Epidermolysis Bullosa (EB)
  The product packaging designed was rejected by the end users and had to be redesigned

Work out the final fill-finish for the scale likely to be needed

- Prepare the Board of Directors (BoD) for investment in bespoke development if required

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GIRFT: Mesenchymal Stromal Cells (MSC)

- **MSC production at CDMO**
  - Adherent cell culture system
  - Cost of Goods (CoG) ~$40/million
  - Single donor MSCs

11

GIRFT: Mesenchymal Stromal Cells (MSC)

- **MSC Production at UCL**
  - Adherent cell culture system, with a perfusion media
  - Xpansion® PALL
  - Incubation required

incubator

GIRFT: Mesenchymal Stromal Cells (MSC)

- **MSC Production at UCL**
  - Adherent cell culture system, with a perfusion media
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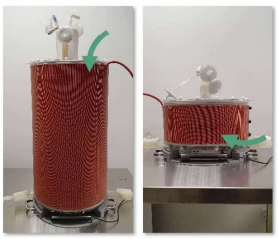
  - Incubation required
  - Thermal jackets
    - Improved temperature control
    - Improved use of lab space



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GIRFT: Mesenchymal Stromal Cells (MSC)

MSC Production at UCL

- Adherent cell culture system, with a perfusion media
- Xpansion® PALL
- Incubation required
- Thermal jackets
  - Improved temperature control
  - Improved use of lab space
- CoG ~$12/million
- 10 pooled donors

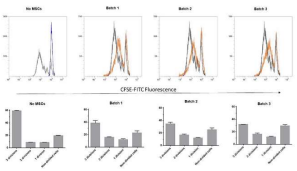
Packaging
AT crystal vials
Cryobags

Shipping
Dry ice in a Crēdo Cube™
Use a thawing device

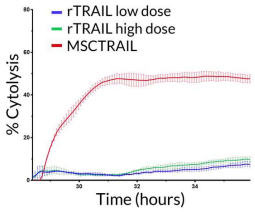
GIRFT: Mesenchymal Stromal Cells (MSC)

MSC Production at UCL

CORDStrom suppresses activated T cell proliferation in vitro



MSC-Trail kills cancer cells resistant to rTRAIL



GIRFT: Mesenchymal Stromal Cells (MSC)

Define the process

Scalable method of manufacture

Downstream packaging

Shipping

Develop and qualify assays

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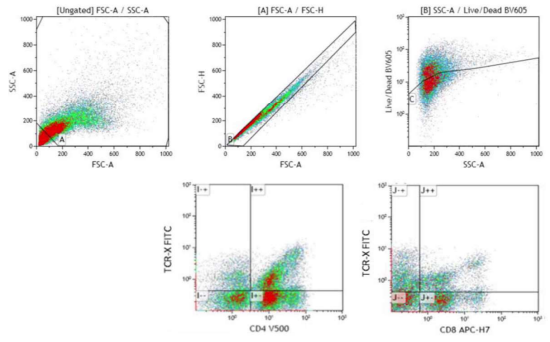
Defining the product: Challenges of FCM

QC - British Pharmacopoeia Working Group

Identity / safety / number / "viability"



12

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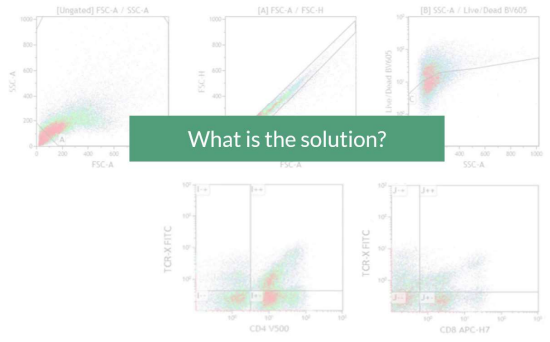

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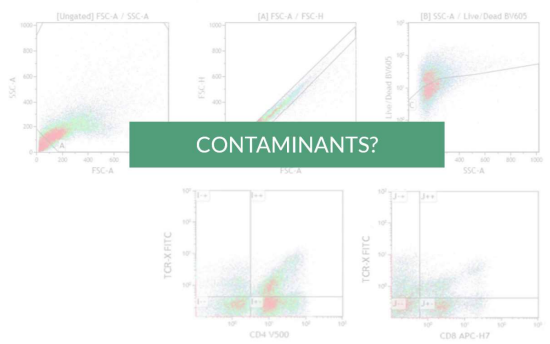

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Defining the product: BLA failures

QC Potency

Potency assay must reflect putative mechanism of action of the drug

October 6, 2020 07:04 AM EDT | Cell/Gene Tx

Iovance shares hammered on TIL therapy filing delay — although analysts aren't as bothered

Amber Tong
Senior Editor

"Iovance won't be able to file for its first-ever approval by the end of this year after all. At issue is the potency assays Iovance is using to define what would be the first-ever tumor-infiltrating lymphocyte (TIL) therapy. Regulators want to have more data on the current assays, or potentially see different assays in the BLA, the biotech suggested."

13

Defining the product: BLA failures

QC Potency

Potency assay must reflect putative mechanism of action of the drug

FDA U.S. FOOD & DRUG ADMINISTRATION

ODAC Briefing Document | BLA 125706 Remestemcel-L: CMC

FDA Briefing Document

"While it is not established how the specific *in vitro* assays discussed above relate to the *in vivo* activity of remestemcel-L, it is possible that the quality attributes used by the Applicant and other sponsors of MSC-based clinical trials are not capable of detecting biological heterogeneity arising from variability related to allogeneic donor-specific differences and duration in culture."

Novel data from flow cytometric analysis

Flow cytometry analysis of MSC phenotype at DP

	Xpansion bioreactor (%)	T175 control flask (%)
CD73	99.7	100
CD90	99.7	99.9
CD105	99.7	99.9
CD45 / CD20 / CD34 / CD14 / HLA-DR	0.3	0.6

MSC-TRAIL expression post-transduction

Passage	PD	tD	Viability (%)	TRAIL expression (%)	TRAIL molecules per cell
P1	4	N/A	98.5	86.3	20986
P2	6	25.3	83.5	86.1	12805
P3	8	27.5	91.2	90.8	14456
P4	8	19.1	88	90.6	13700
P5	6	22.2	97.3	93.0	11475
P6	4	30.3	95.6	92.5	11657

14

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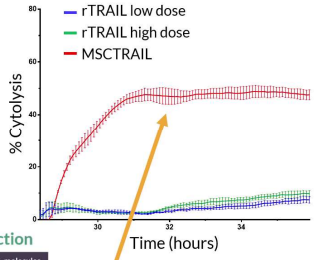
Novel data from flow cytometric analysis

From passage 2, the degree of expression of TRAIL is stable

This data can be passed on to the regulator

MSCTRAIL potency



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What is unique about ATMPs?

- Most current commercial ATMPs are autologous or patient-specific allogeneic
  - The starting material requires patient or donor participation in the manufacturing process
  - The procurement standards differ globally
  - When does "GMP" start?

Hospital?

Manufacturing site?

15

What is unique about ATMPs?

Determined by the product and where you manufacture

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What is unique about ATMPs?

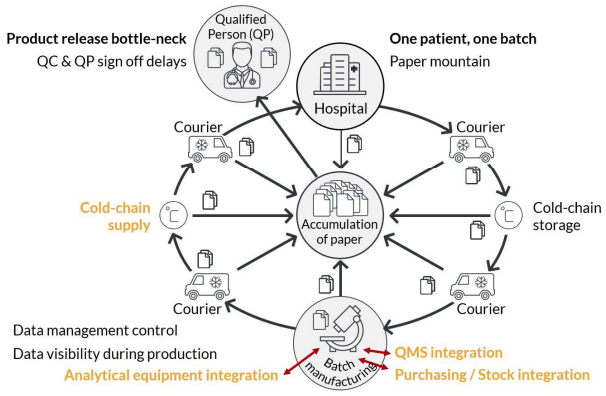
- Most current commercial ATMPs are autologous or patient-specific allogeneic
  - The starting material requires patient or donor participation in the manufacturing process
  - The procurement standards differ globally
  - When does "GMP" start?

Hospital?

Manufacturing site?

  - How do you define the drug product (DP)?

What is unique about ATMPs?



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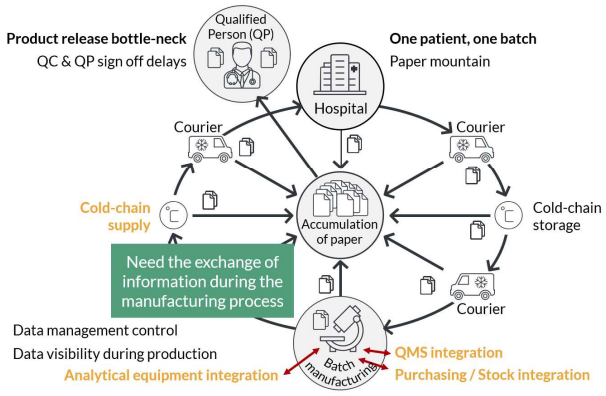

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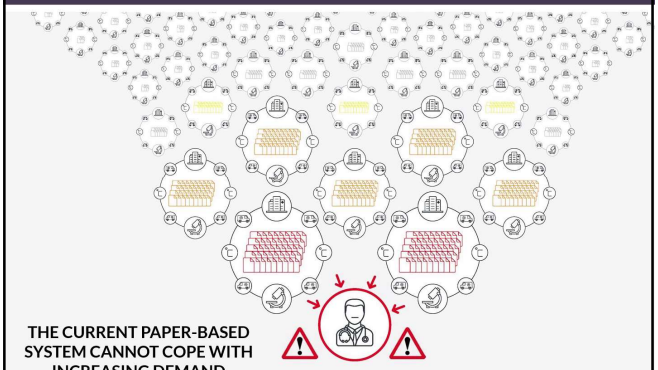
Scale-out of manufacturing is the primary challenge

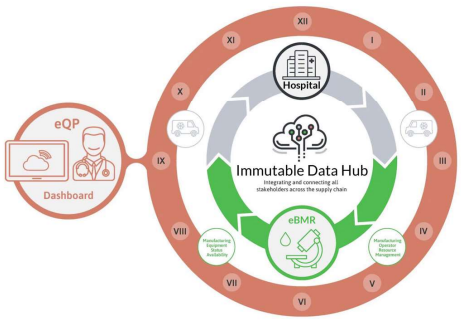


THE CURRENT PAPER-BASED SYSTEM CANNOT COPE WITH INCREASING DEMAND

16

Scale-out of manufacturing is the primary challenge

autolomous autoloMATE



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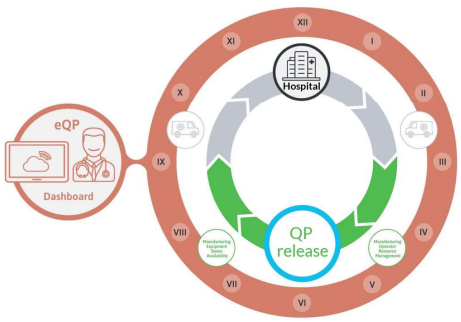

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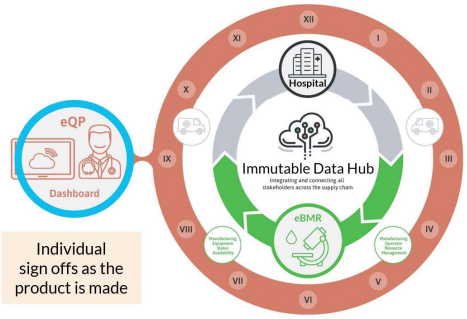


Individual sign offs as the product is made

For further information, see tab of external links

Scale-out of manufacturing is the primary challenge

autolomous autoloMATE

- Release by exception is allowed

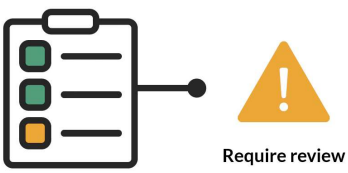
Passed

For further information, see tab of external links

Scale-out of manufacturing is the primary challenge

autolomous autoloMATE

- Release by exception is allowed



Require review

For further information, see tab of external links

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Scale-out of manufacturing is the primary challenge

autolomous autoloMATE

- Release by exception is allowed
- Aids the clinician

For further information, see tab of external links

Scale-out of manufacturing is the primary challenge

autolomous autoloMATE

Autolomous provides a reliable and time efficient supply chain solution

It allows the data to be edited, audited, and used for continuous process improvement

For further information, see tab of external links

Final element of TPP: Is it affordable?

- **Have I chosen the most valuable indication?**
- **What is the CoG for the efficacious dose in my patient population?**
  - Is dose weight dependent?
  - Mesoblast for Steroid-Refractory acute Graft-versus-Host Disease (SRaGvHD)

Phase III trial in adults and paediatrics - different cost benefit analysis

MSC of SRaGvHD

Typical dose = $2x10^6$/kg x 8 doses

100kg Adult = 1600 million

40kg Child = 640 million

Open market cost of MSC = £200/106 Rooster Bio and Alofisel

Likely real cost of MSC = £80/106 (pooled allo donor, so not Remestemcel)

Adult treatment course = £128,000

Paediatric treatment course = £51,200

17

Kebriaei P., *et al., Biol Blood Marrow Transplant.* 2020; 26: 835-844

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Final element of TPP: Is it affordable?

- **What is the CoG for the efficacious dose in my patient population?**
  - Mesoblast for Steroid-Refractory acute Graft-versus-Host Disease (SRaGvHD)

    Phase III trial in adults and paediatrics - different cost benefit analysis

	Durable Complete Response, n (%) [95% CI]		Overall Response, n (%) [95% CI]	
Characteristic	Remestemcel-L	Placebo	Remestemcel-L	Placebo
Multiorgan	20/73 (27.4)	11/43 (25.6)	40/73 (54.8)	17/43 (39.5)
	[17.6-39.1]	[13.5-41.2]	[42.7-66.5]	[25.0-55.6]
Age				
<18	9/14 (64.3)	6/13 (46.2)	9/14 (64.3)	3/13 (23.1)
	[35.1-87.2]	[19.2-74.9]	[35.1-87.2]	[5.0-53.8]
≥18	51/149 (34.2)	20/68 (29.4)	86/149 (57.7)	41/68 (60.3)
	[26.7-42.4]	[19.0-41.7]	[49.4-65.8]	[47.7-72.0]

Kebriaei P., *et al., Biol Blood Marrow Transplant.* 2020; 26: 835-844

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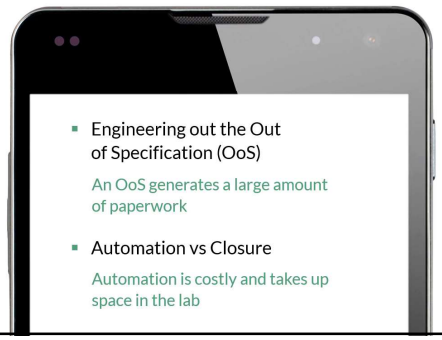
    Phase III trial in adults and paediatrics -different cost benefit analysis
- What is the effect of dose-by-weight on product COG?
- **Where are the economies of scale?**

18

Final element of TPP: Is it affordable?

- **Where are the economies of scale?**



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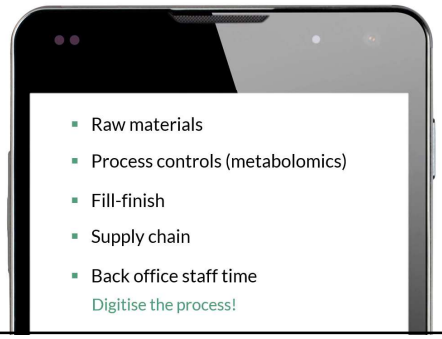
Final element of TPP: Is it affordable?

- Where are the economies of scale?



Current and near-future challenges

Product definition	Too few standards Too little understanding of "cell QC assays" Evolving regulatory perspective
CMC	Too many immature products in late-stage development
Transport and LOGISITICS	
SCALE 1 BATCH = 1 PATIENT	QC pressures QP pressures Storage!

19

Current and near-future challenges

Product definition	Too few standards Too little understanding of "cell QC assays" Evolving regulatory perspective
CMC	Too many immature products in late-stage development
Transport and LOGISITICS	

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Current and near-future challenges

DIGITISE

SCALE
1 BATCH = 1 PATIENT

- QC pressures
- QP pressures
- Storage!

Summary

- Plan for success
- Don't assume your first patient population is the best
- Think about product formulation at scale from the start
  - Dose/kg is not advised
- Gather QC data early - even from pre-clinical to provide support for assay qualification and product definition
- Keep developing QC assays

20

Summary

- Find a potency assay which reflects MOA - test as early as possible
  - This is NOT an efficacy assay
- Before phase I, do an honest appraisal of the likely cost of the licensed drug and decide whether it is right to proceed
- Draft a Target Product Profile (TPP) for each phase of development and sketch out a development pathway

Prof. Mark Lowdell – University College London, UK