Enhanced formulation decision-making in early phase clinical trials for parenteral products

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Quotient services and solutions

Translational Pharmaceutics®

Formulation Development

Clinical Trial Manufacturing

Clinical Pharmacology

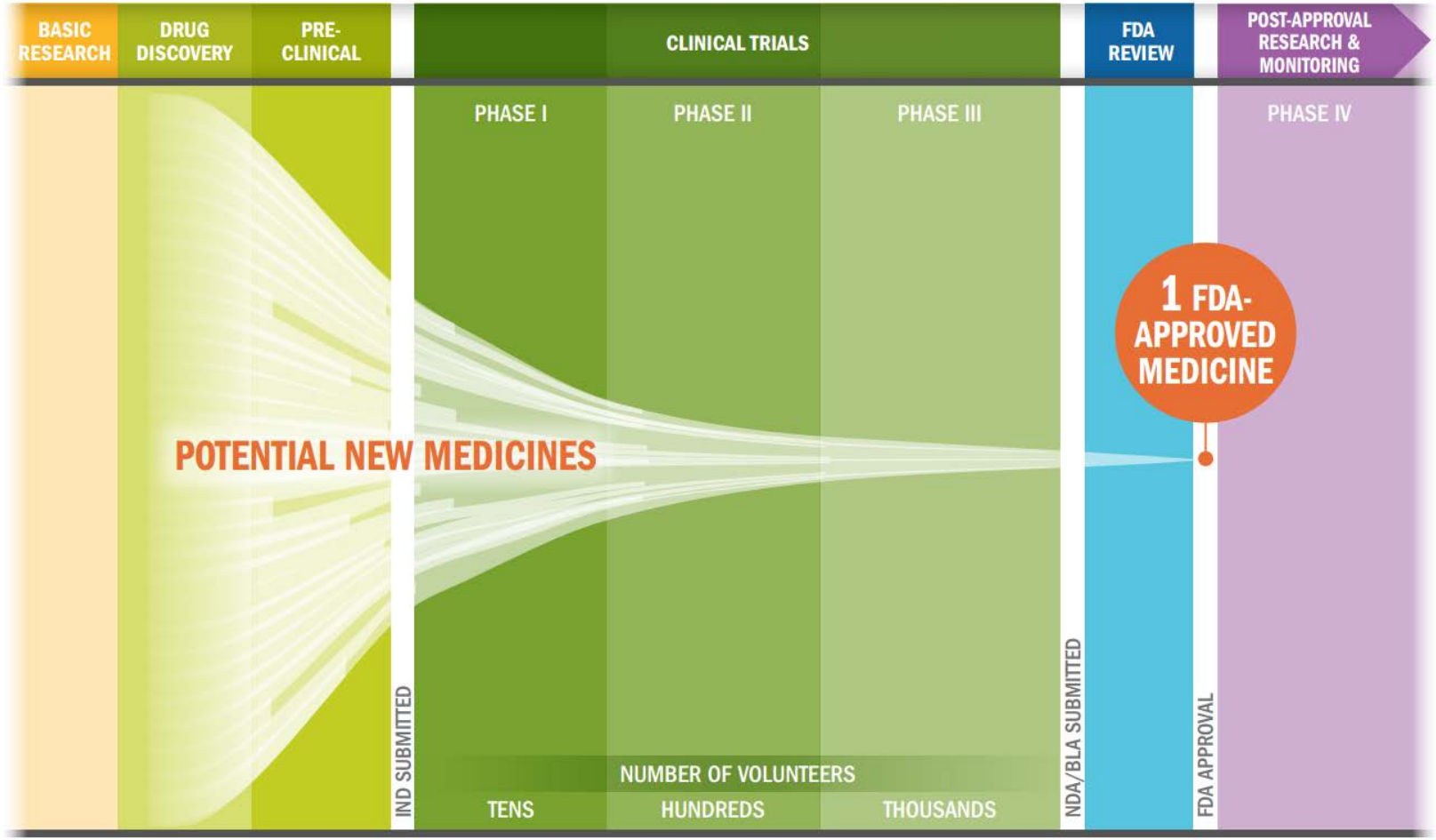
Commercial Manufacturing

Translational Pharmaceutics® | Formulation Development | Clinical Trial Manufacturing | Clinical Pharmacology | Commercial Manufacturing

Presentation overview

- Opportunity to improve R&D outcomes
- Translational Pharmaceutics
- Sterile product manufacture using Translational Pharmaceutics
- Applications in clinical trials

Improving the pharmaceutical R&D process



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

Graphic source: http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf

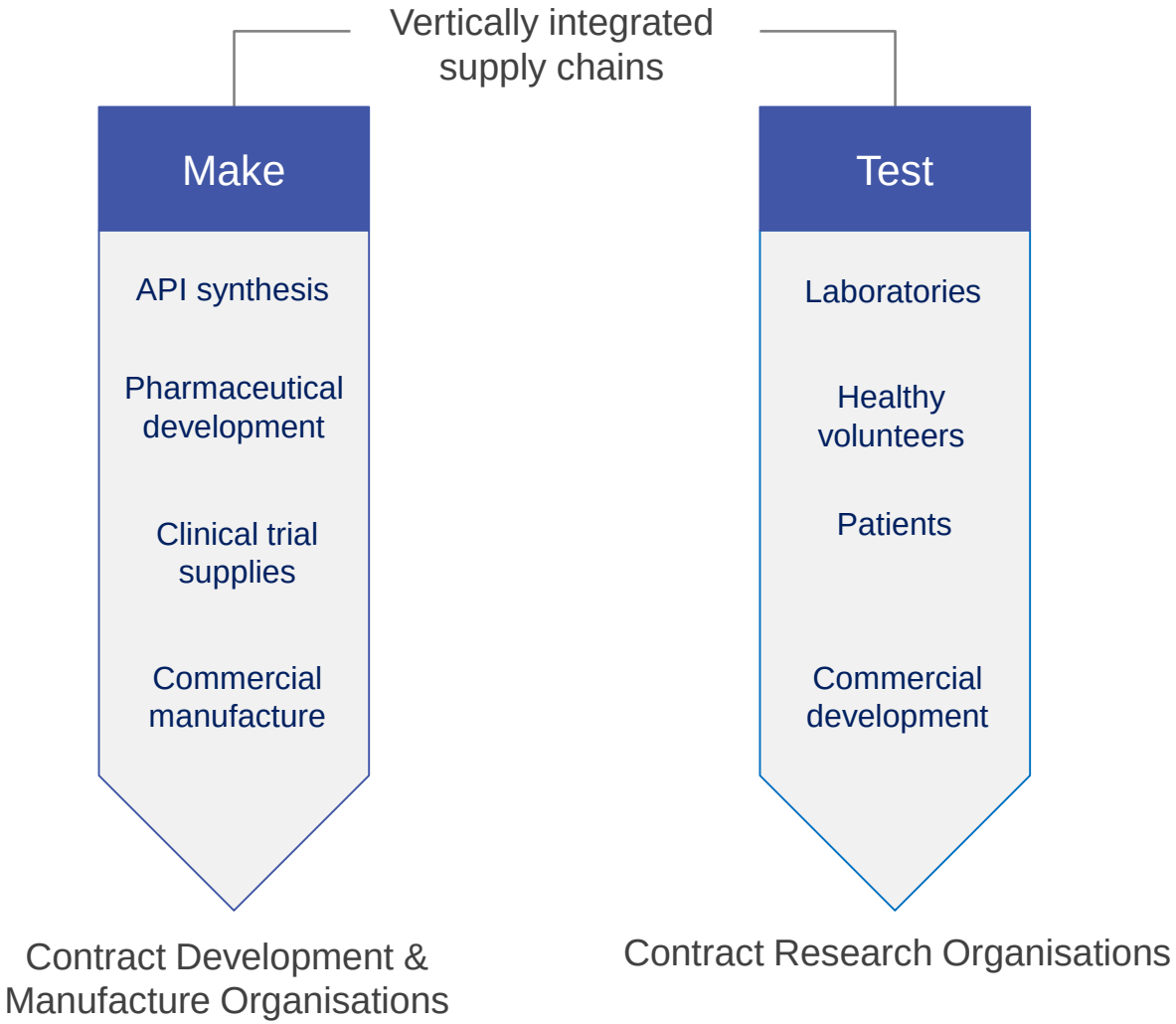
Improvement areas

- Slow and costly
- Uncertain outcomes
- High numbers of human volunteers
- New products with marginal therapeutic advances

Drug delivery challenges impacting R&D

- Challenging biopharmaceutics properties of both small and large molecules
- New formulation / device technologies slow to emerge
- *In vitro*, *in silico*, animal models often not predictive of human performance

Industry configured in silos



Drivers for change in drug development

"There is a disconnect between the investment we're making in discovering treatments and the result in practical treatments that are reaching patients.

We think that there are scientific approaches we could be taking that would help us learn more about drugs in a shorter time and for less cost."

Scott Gottleib, FDA Commissioner, 2017

Translational Pharmaceutics

How do I innovate my drug development?

Translational Pharmaceutics

All dosage forms
Oral, Inhaled, Topical, Sterile
High potency
Poor solubility
Modified release
Phase I–III CTM
Packaging/labelling
Global distribution
Commercial M/F (oral)

Make

API synthesis

Pharmaceutical development

Clinical trial supplies

Commercial manufacture

Horizontal integration

Translational Pharmaceutics

Drug Product Optimization

First In Human

Test

Laboratories

Healthy volunteers

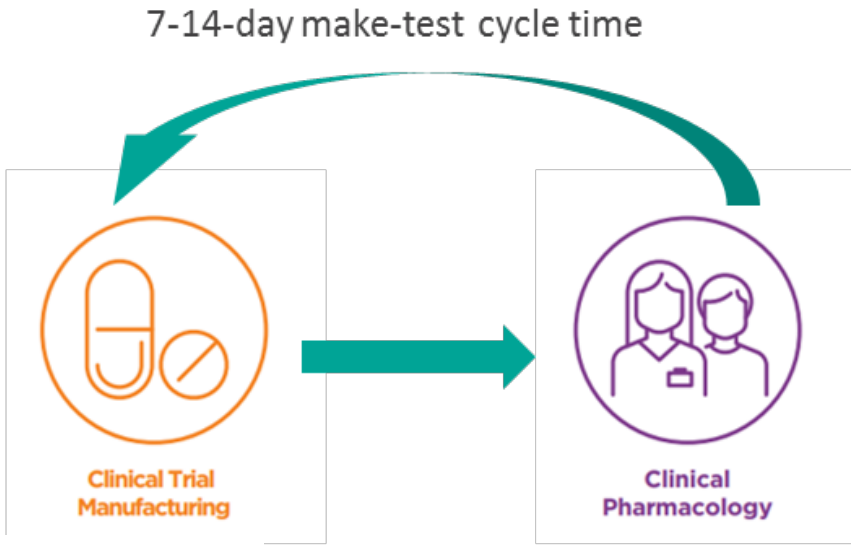
Patients

Commercial development

First-in-human
Drug-drug interaction
Food effect & bioavailability
Biosimilar & bioequivalence
Age, Gender, Japanese
QT/QTc & cardiac safety
Human ADME/^{14}C
Regulatory Affairs
Data sciences
PK & biomarkers

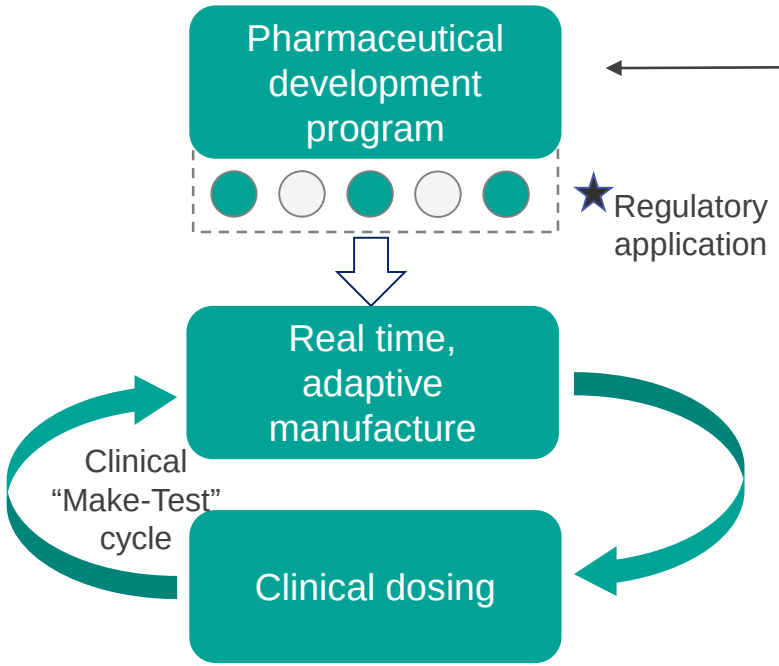
Real-time adaptive manufacturing, iterative clinical testing

- Fit-for-Phase drug product strategy:
  - Batch size typically 25-250 unit doses
  - Shelf-life typically 7 days
- Full GMP manufacture
- Emerging clinical data informs manufacture instructions every 7-14 days
- Technologies and processes scaleable for downstream development

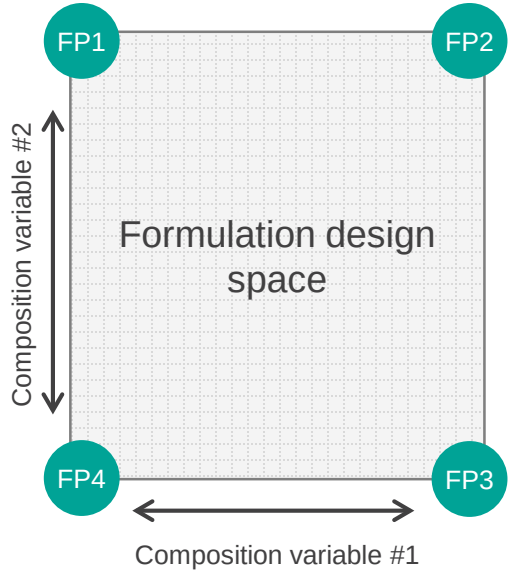


Applications of Translational Pharmaceutics

- ✓ Oral liquids
- ✓ Tablets
- ✓ Capsules
- ✓ Multi-particulates
- ✓ Spray drying
- ✓ Coating
- ✓ Particle size reduction
- ✓ **Lipids**
- ✓ **Parenterals**
- ✓ **Non-oral delivery**



Pre-approved design space can provide within-trial formulation flexibility



CMC strategy for sterile product

Introduction

- A GMP-compliant approach to parenteral product manufacture for rapid clinical assessment.
- Not a compounding approach
- >125 studies completed dosing to date
- Used for a range of formulation and study types
  - Intravenous (iv) and subcutaneous (sc) administration
  - Unlabelled, ^{13}C and ^{14}C-API formulations
  - IVMicrodose, IVmicrotracer and ADME studies
  - Early Phase studies assessing safety & tolerability / PK / Proof-Of-Concept
- Proven and acceptable strategy with MHRA
  - Position supported via numerous CTA approvals and GMP audit history
  - Strong emphasis on environmental and process controls
  - Minimal QC testing – products can be dosed within hours of manufacture

Formulation approaches

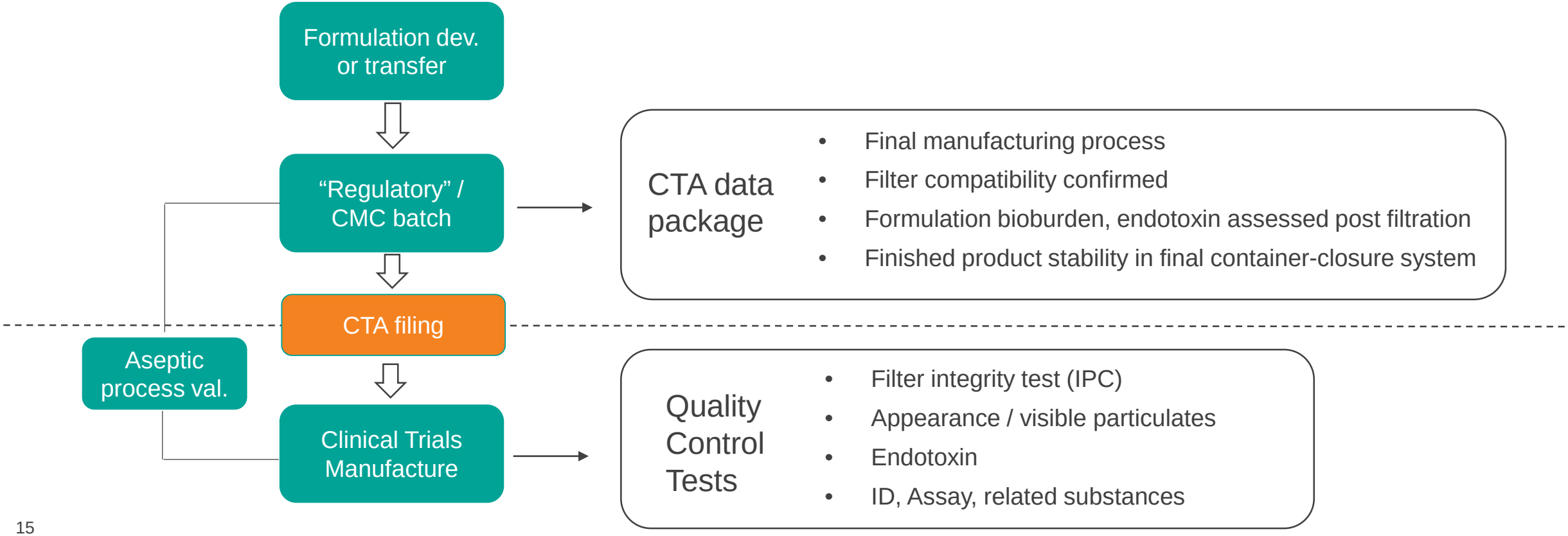
- Formulation development or tech transfer scope
  - Achieve target solubility
  - Screen pH adjustment, co-solvent, complexes as needed
  - Aseptic double filtration process
  - Filter selection
  - Develop analytical methods
  - Establish short-term bulk stability

Product examples:

- Typical batch size = 25 units
- Final container
  - 1 - 60mL syringes
  - 15mL vials
  - 250mL – 2L infusion bags
- Shelf-life targets
  - Syringes: 8 hrs
  - Vials: 7 days
  - Infusion bags: 24 hrs

Parenteral quality control

- Risk assessment undertaken by Quotient Qualified Person's
- Risk assessment covers, raw materials, product contact components, manufacturing process, environment and personnel. Scale, shelf-life and handling are important risk-factors



Case Study – New delivery route

Case study 1 - Delivery route switch for peptide

- Background
  - Peptide molecule had shown POC in early clinical trials with IV formulation
  - Multiple-indications under consideration with some requiring patient self-administration

- Program goals
  - Transition from IV to sub-cutaneous formulation
  - Evaluate safety & tolerability of sub-cutaneous administration
  - Determine viability of achieving target exposure via new route

Stealth BIOTHERAPEUTICS | Leading Mitochondrial Medicine

Using real-time sterile manufacturing to enable a new route of administration

Deborah Gouveia
Vice President, Program and Alliance Management, Stealth

Stealth BioTherapeutics is an innovative biopharmaceutical company based in Massachusetts, USA, focused on developing targeted therapies for diseases linked by a common aetiology of mitochondrial dysfunction. There are more than 270 inherited orphan mitochondrial diseases that are characterized by known genetic defects. Recently, however, research has shown that mitochondrial dysfunction is associated with conditions including heart failure, kidney disease, age-related macular degeneration, cardiovascular and metabolic diseases, neurodegeneration and some musculoskeletal disorders.

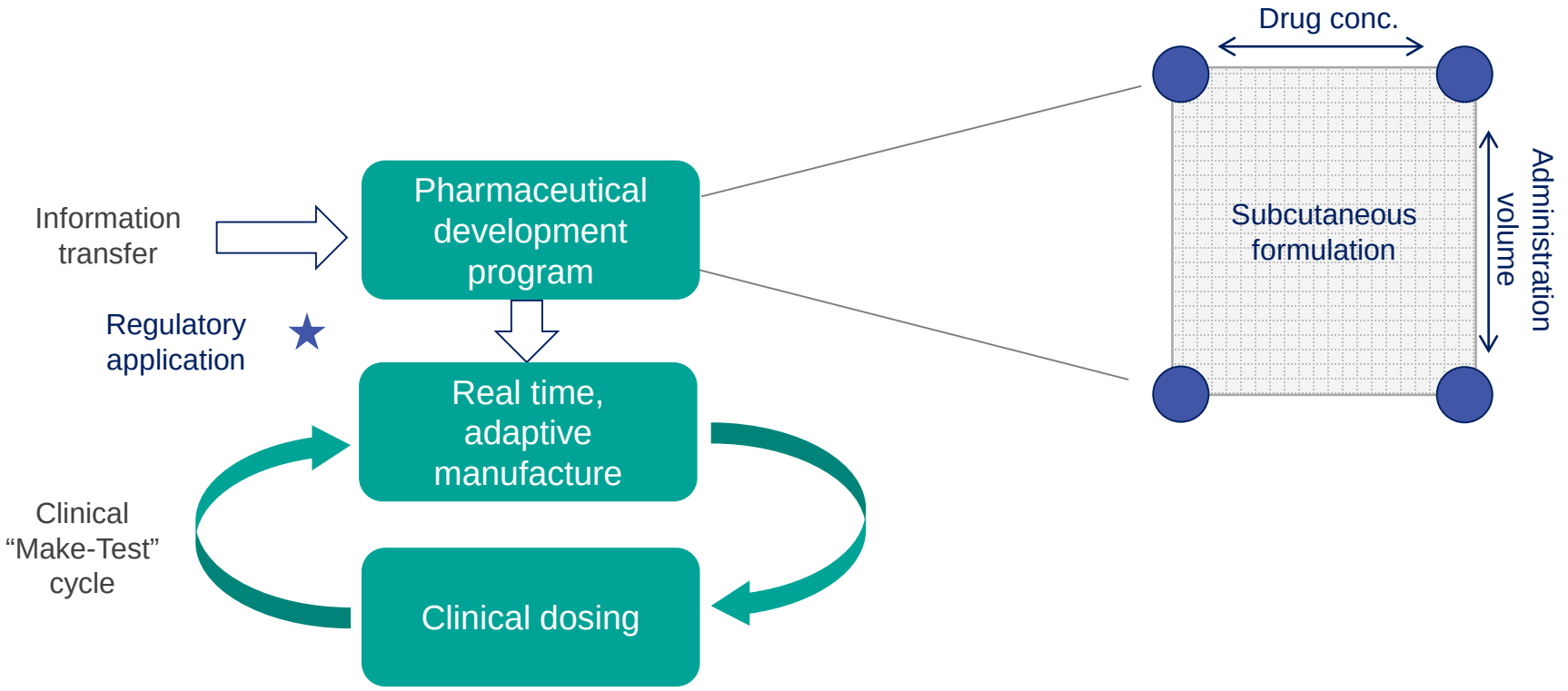
The challenges of a traditional outsourcing model

To begin with, Stealth looked at CRO partners in the US to help to reformulate the drug target, as Deborah Gouveia, Vice President, Program and Alliance Management at Stealth, explained: *"We approached four US CROs and the only options they offered were very cumbersome. They relied on manufacturing many lots of material to allow for flexible dosing in the clinic, and a delay of several weeks – if not months – to get the data evaluated and amend the protocol between doses. Using this approach, it would take several months –probably more than a year – to*

"We had (clinical) data within weeks... reducing the overall timeline by half, if not more."

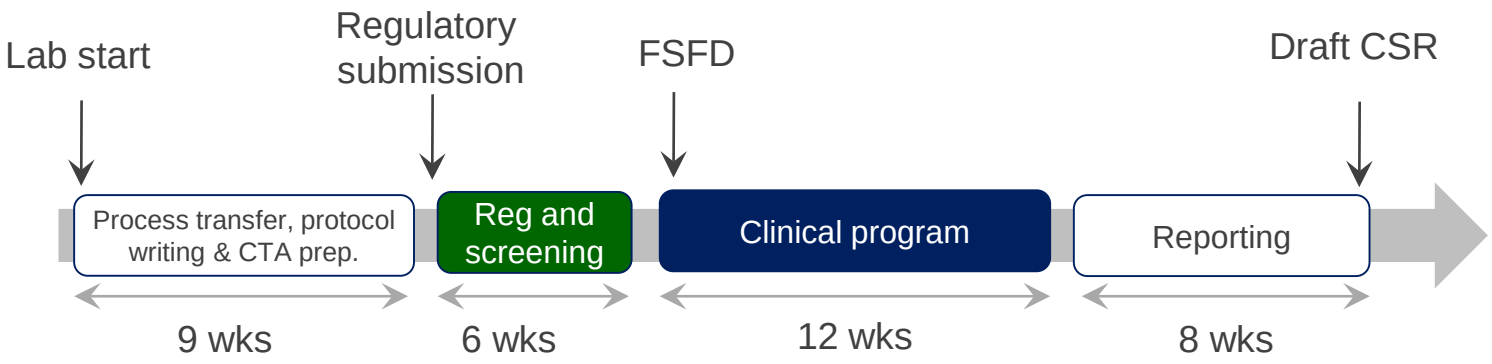
Case study 1 – program design

- Formulation adjustments / data generation for on-site GMP sterile manufacture
- Evaluate effect of conc. and volume of administration on PK and local side-effects



Case study 1 – outcomes

- Six formulation / dose combinations administered to healthy volunteers
- Interim formulation-selection decisions driven by emerging data
- Formulation selected that met the target exposure and reduced pain on injection



- Reduced development timelines by >6 months
- API consumption reduced by >85%
- Simplified supply chain

Programs to optimize parenteral formulations

Integrated studies to optimize parenterals

More complex parenteral products and programs can benefit from an integrated Translational Pharmaceutics approach:

- Adjusting formulation parameters to optimize PK performance,

  e.g. Long-Acting Injections
- Selecting device parameters,

  e.g. Auto-injectors

Factors such as high delivered dose, novel excipients, novel devices mean that multi-functional input into the design of the clinical study and regulatory strategy is critical

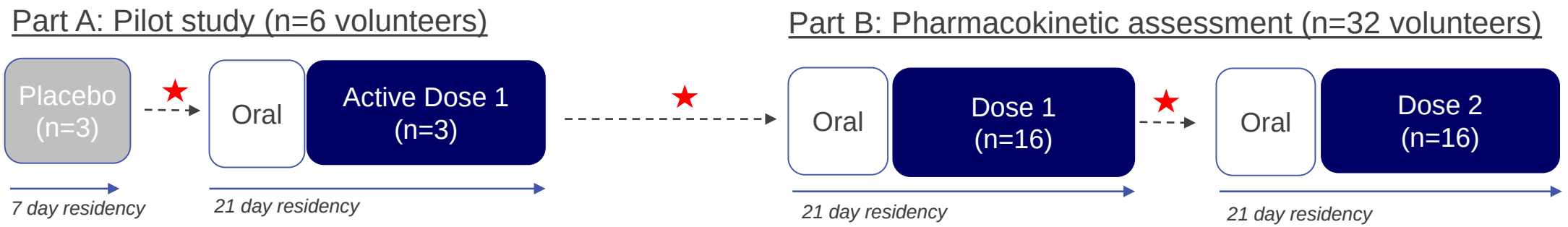
Case study 2 - Depot injection PK study

- Background
  - One-month depot injection developed by client using novel drug-delivery system
  - Human proof-of-concept clinical trial planned using an approved molecule

- Program goals
  - Assess safety and tolerability of depot injection
  - Assess pharmacokinetics of depot injection, including comparison of site of injection

- Strategy
  - Multi-part study design required to establish safety and tolerability of placebo injection before administration of active injection
  - Dosing in healthy volunteers planned with design measures taken to minimize safety risks due to dose dumping and tolerance to active

Case study 2 – Program design and outcomes



Specific design features

- Single-site placebo injection in Part A, included assessment of rubbing inj. site (n=1 subject)
- Active depot injection preceded by oral dosing to establish tolerability for each volunteer
- In Part B, two doses and two inj. sites assessed in larger cohorts (n=8 PK data sets for each injection site)

Outcome

- In vivo data generated to support decision on formulation scale-up for a pivotal bioequivalence study

Case study 3 - Long-Acting Injection proof-of-concept

- Background
  - Early phase injectable molecule has demonstrated POC with immediate-release injection
  - Long-acting injection (LAI) may produce sustained pharmacodynamics response
  - Multiple LAI prototypes screened in animal model – no clear lead identified

- Program goals
  - Assess safety and tolerability of LAI (both excipient matrix and active)
  - Establish PK-PD relationship for LAI product

- Strategy
  - Multi-part study design required to establish safety and tolerability of placebo injection before administration of active injection
  - Dose escalation design required due to limited availability of human data

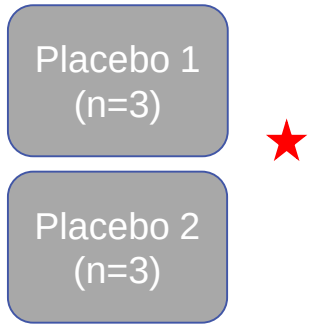
Case study 3 - Program design

CMC data package

- Two placebo formula's
- Two active formulations with freedom to adjust drug concentration in fixed volume injection

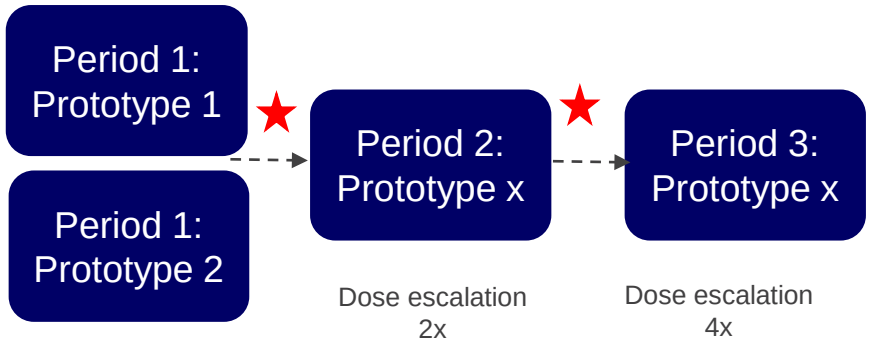
Clinical study

Part A: Placebo safety



Part B: Formulation / dose selection

★ Interim decision



Small cohort sizes for Part A

Two placebos can be dosed in parallel

Risk of placebo Adverse Events judged to be low

Study Period 1 allows selection of lead injection formula for Periods 2 and 3

Placebo-controlled study (n=8 volunteers: 6 Active / 2 Placebo)

Volunteers resident for 4 days for PK and biomarker sampling

Case studies - Summary

- A streamlined CMC approach for parenteral product can support rapid clinical assessment
- Design of the CMC data package and clinical protocol must occur hand-in-hand, allowing design flexibility to be built-in
- Clinical design prioritizes safety risk management (factors are both drug and delivery system)
- Regulatory submission included CMC / safety package for novel excipients

Summary

- Pharma industry is under pressure to develop better products more rapidly
- Translational Pharmaceutics can unlock opportunities across different molecules, drug delivery routes and delivery technologies:
  - Study flexibility
  - Timeline savings
  - Conserve drug substance / drug product
  - Simple supply chain
- Translational Pharmaceutics is a proven approach to understanding the developability of products faster and more cost-effectively

Assess. Adapt. Accelerate.