A Systems-Based Approach to Digital Design and Operation in the Formulation of Pharmaceuticals

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1 Britest Limited, 2 Process Systems Enterprise Limited

Britest

Britest is a highly successful not-for-profit SME. Since its founding in 2001, the application of Britest tools has generated many €millions of productivity gains, driving enhanced business sustainability and competitiveness.

Britest's **expert technical facilitators** use a suite of proprietary tools to help organisations **define, structure, and translate knowledge into process understanding**.

This promotes **effective communication** of the underlying science across disciplines and functions, **enabling knowledge transfer** and allowing organisations to derive tangible **business value**.

The ADDoPT Project

Advanced Digital Design of Pharmaceutical Therapeutics

ADDoPT

A £20.4m UK Government-Industry-Academia collaboration

Part-funded under the Advanced Manufacturing Supply Chain Initiative (AMSCI*)

*A BEIS initiative delivered by Finance Birmingham and Birmingham City Council

Department for Business, Energy & Industrial Strategy

finance birmingham

Birmingham City Council

Instigated by the Medicines Manufacturing Industry Partnership (MMIP)

abpi Bringing medicines to life

BIA UK BioIndustry Association

"This project has the potential to propel the UK to the forefront of medicinal product design and manufacture"
ABPI & BIA

ADDOPT

Project Consortium

Pharma Primes:

AstraZeneca

Bristol-Myers Squibb

gsk GlaxoSmithKline

Pfizer

SMEs:

PSE

PERCEPTIVE ENGINEERING LTD

Britest

Research:

UNIVERSITY OF CAMBRIDGE

UNIVERSITY OF LEEDS

University of Strathclyde Glasgow

The Cambridge Crystallographic Data Centre

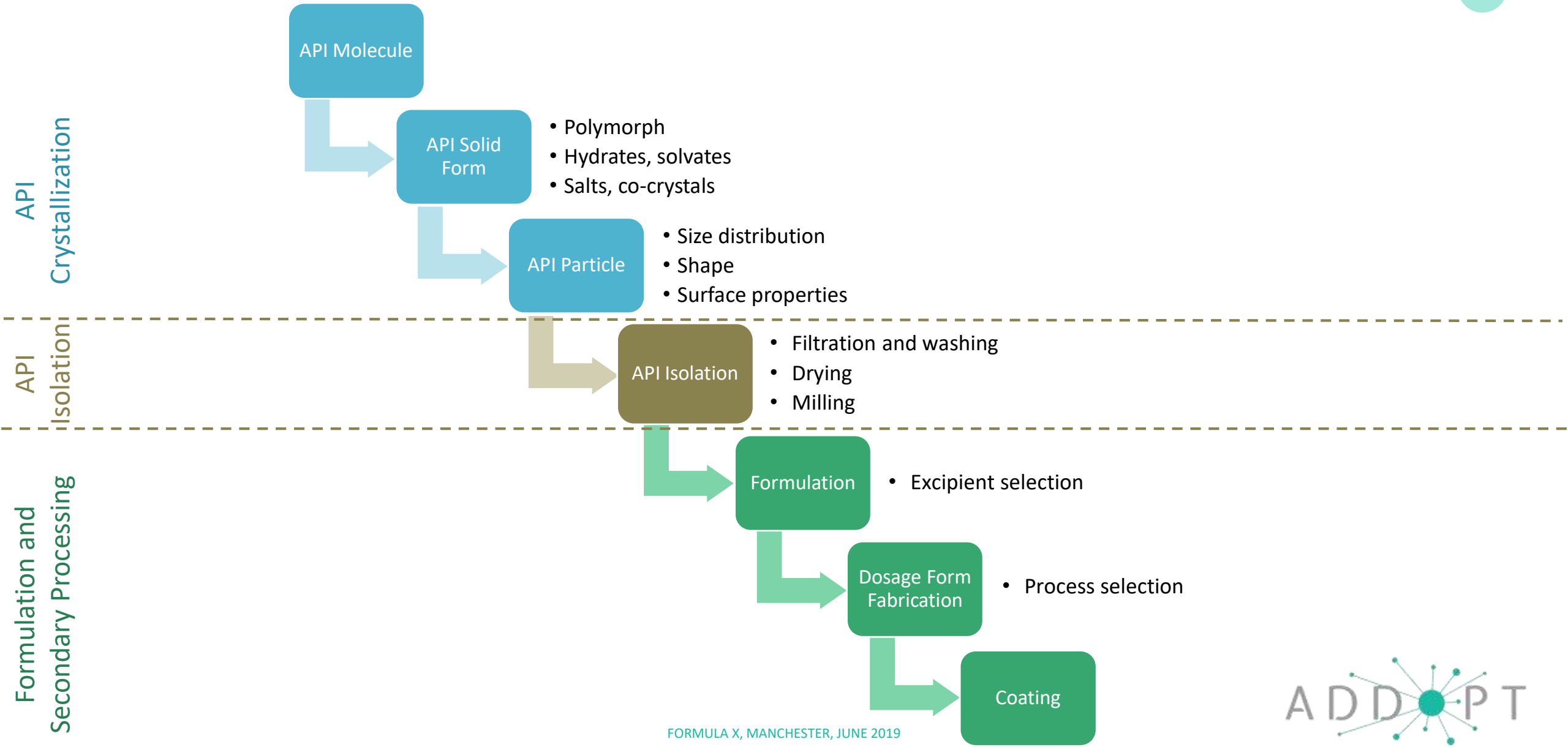
Hartree Centre
Science & Technology Facilities Council

ADDOPT

Solid Oral Dose Tablets

Solid oral dose tablets are formulations of:	Excipients are present for:	Material properties and process selection interact to determine:
• The Active Pharmaceutical Ingredient (API) • Excipients • Coating	• Function – e.g. disintegrants • Processing – e.g. lubricants	• Performance • Stability • Manufacturability

From Molecule to Dosage Form



Secondary Processing

Secondary Processing Options	Selection Criteria	Manufacturing Classification System[1]
• Direct Compression • Dry Granulation • Wet Granulation	• Powder flow • Segregation • Compressibility • API sensitivities	• Secondary process selection based on API particle characteristics and dosage level

1. M Leane, K Pitt, G Reynolds, A Proposal for a Drug Product Manufacturing Classification System (MCS) for Oral Solid Dosage Forms, Pharmaceutical Development and Technology, August 2014

Advantages of a Digital Design Approach

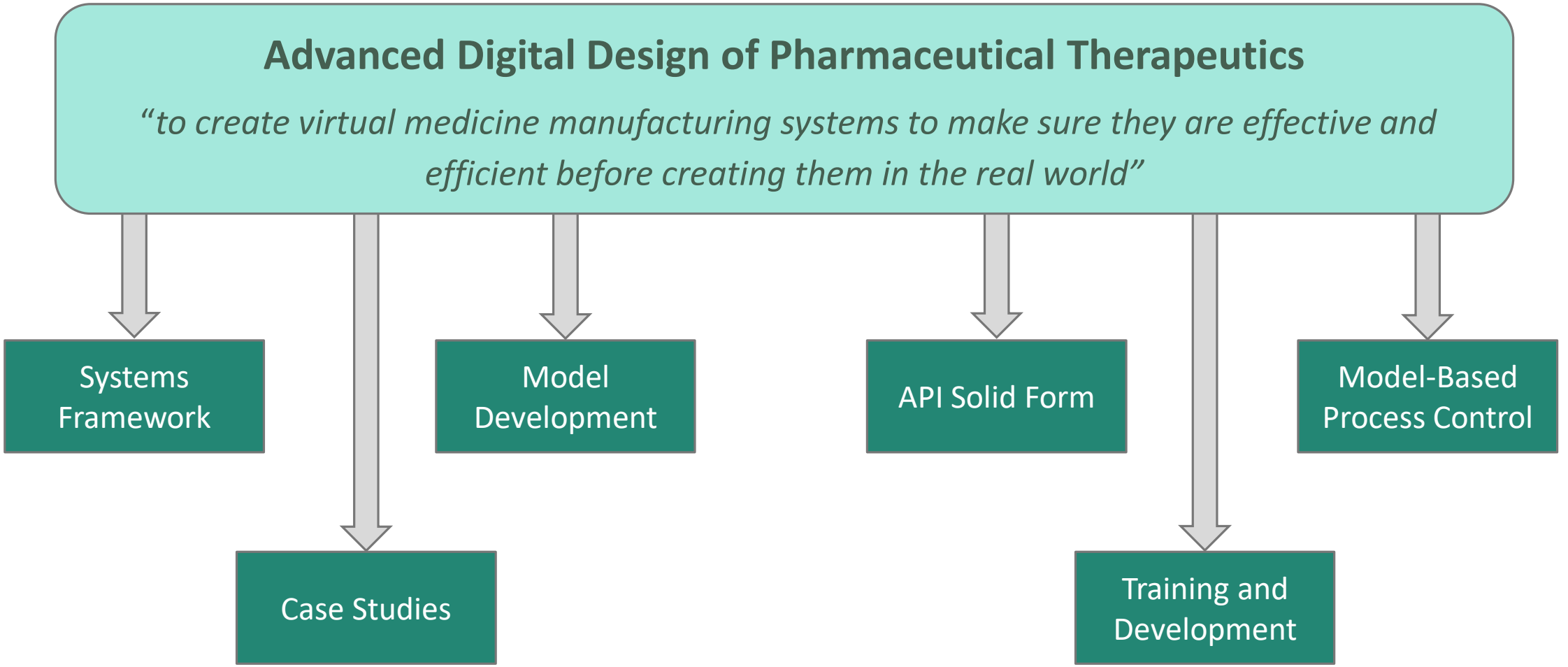
A "Digital Twin" of a product or process is created. Experiments are used to parameterise and validate the model.

Qualitative systems models can be used to help develop and test the assumptions of the quantitative model, and in the selection of parameters to explore in "virtual DoEs"

Conducting virtual DoEs allows:

- Exploration of a wide range of material attributes and process parameters
- Identification of which parameters are critical to performance
- Assessment and optimisation of the robustness of performance with respect to variability in raw materials, physiology etc.
- Reduction in development time, costs and use of scarce materials

Scope of the ADDoPT Project



Development of the Digital Design Information Flow

Need for a Digital Design Information Flow

There is a need for an overall framework that:

- Allows users to understand the current state of models and their data requirements, and identifies potential future developments
- Combines the information flows from individual aspects of modelling and experimentation into an integrated structure
- Maps the digital design opportunities to the current product and process development workflows
- Links to training materials required to support the approach

Data Gathering

Pharma Companies

- What information is required to move from the API molecule to the dosage form manufacturing process?
- What is the current experimental workflow?
- Which steps are challenging in terms of data collection or reliability?
- What is the current use of models?

Academic Partners, CCDC, STFC

Existing and emerging models:

- Behaviour of molecules, particles, mixtures
- Impacts on relevant unit operations

SME Partners (PSE, PEL)

Use of mechanistic models in:

- Digital design
- Process optimisation and control

Information Flow Requirements and Structure

Requirements for the Digital Design Information Flow:

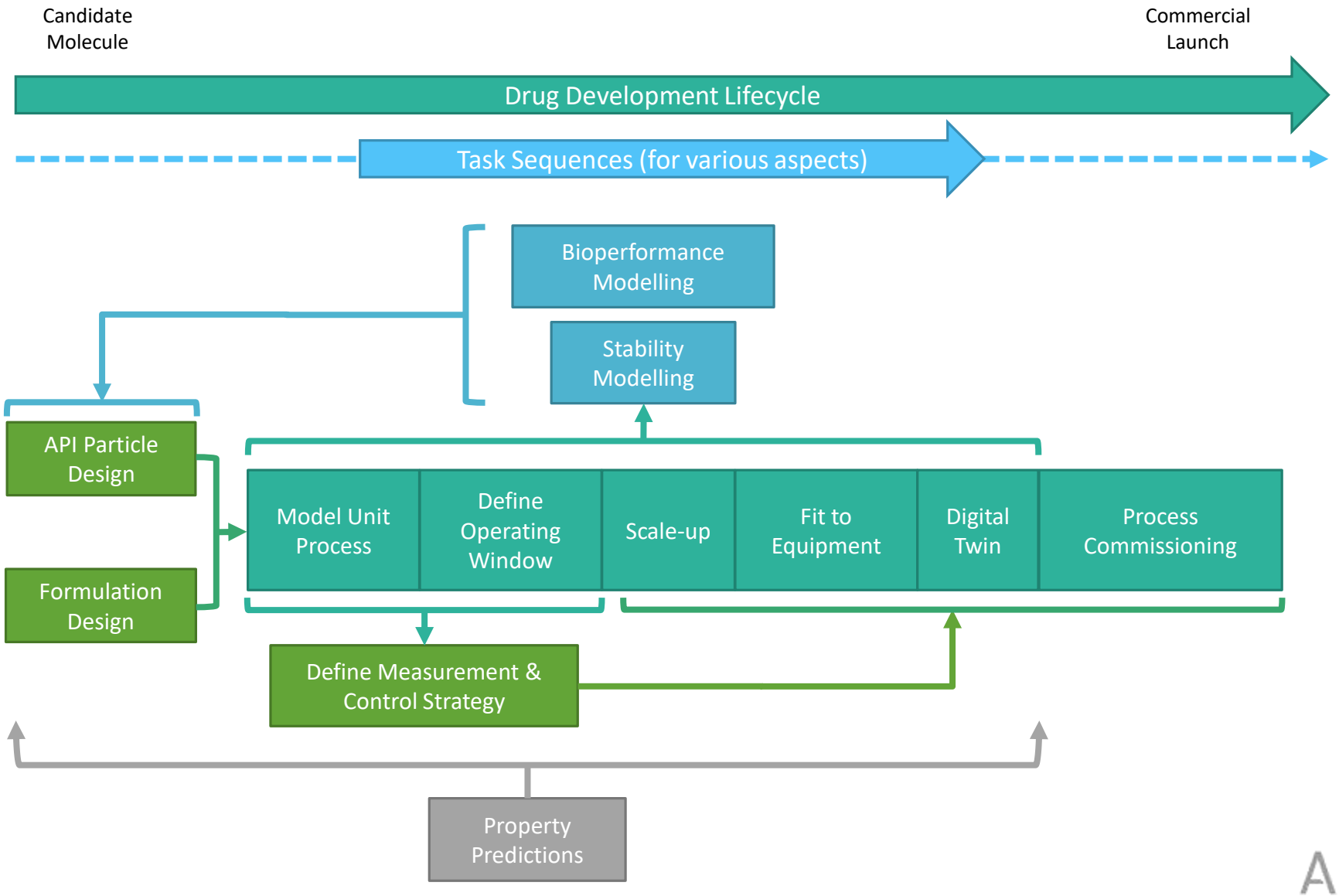
- Start at a high-level and provide layers of information to enable access to increasing levels of detail as required
- Enable the user to select their own navigation path
- Link to external sources of information, including training materials
- Capable of being web-hosted, meaning no new software requirements for the users

Implemented in:

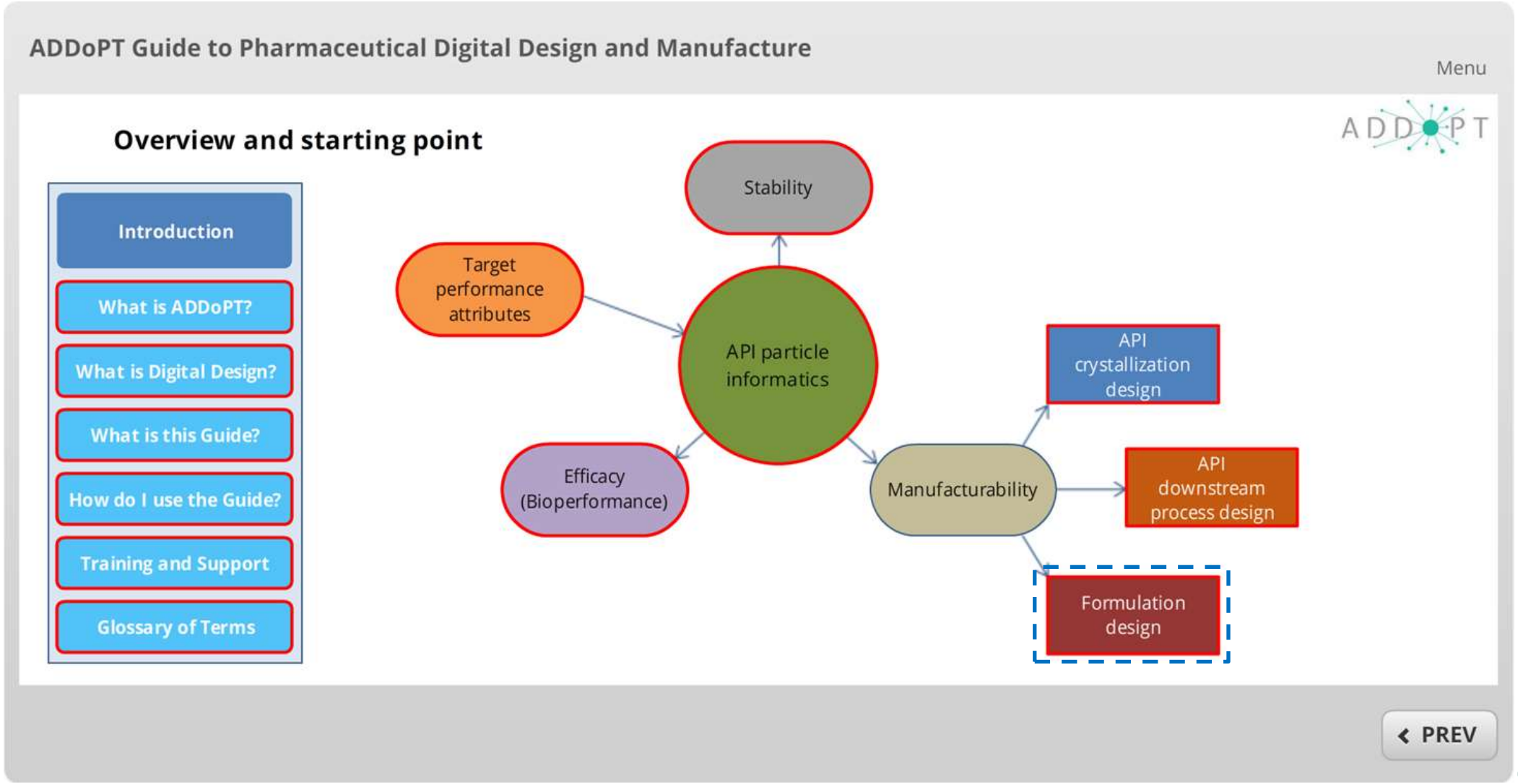
(a) Articulate Storyline (for main navigation), with links out to

(b) SharpCloud (for models, providers and training packages)

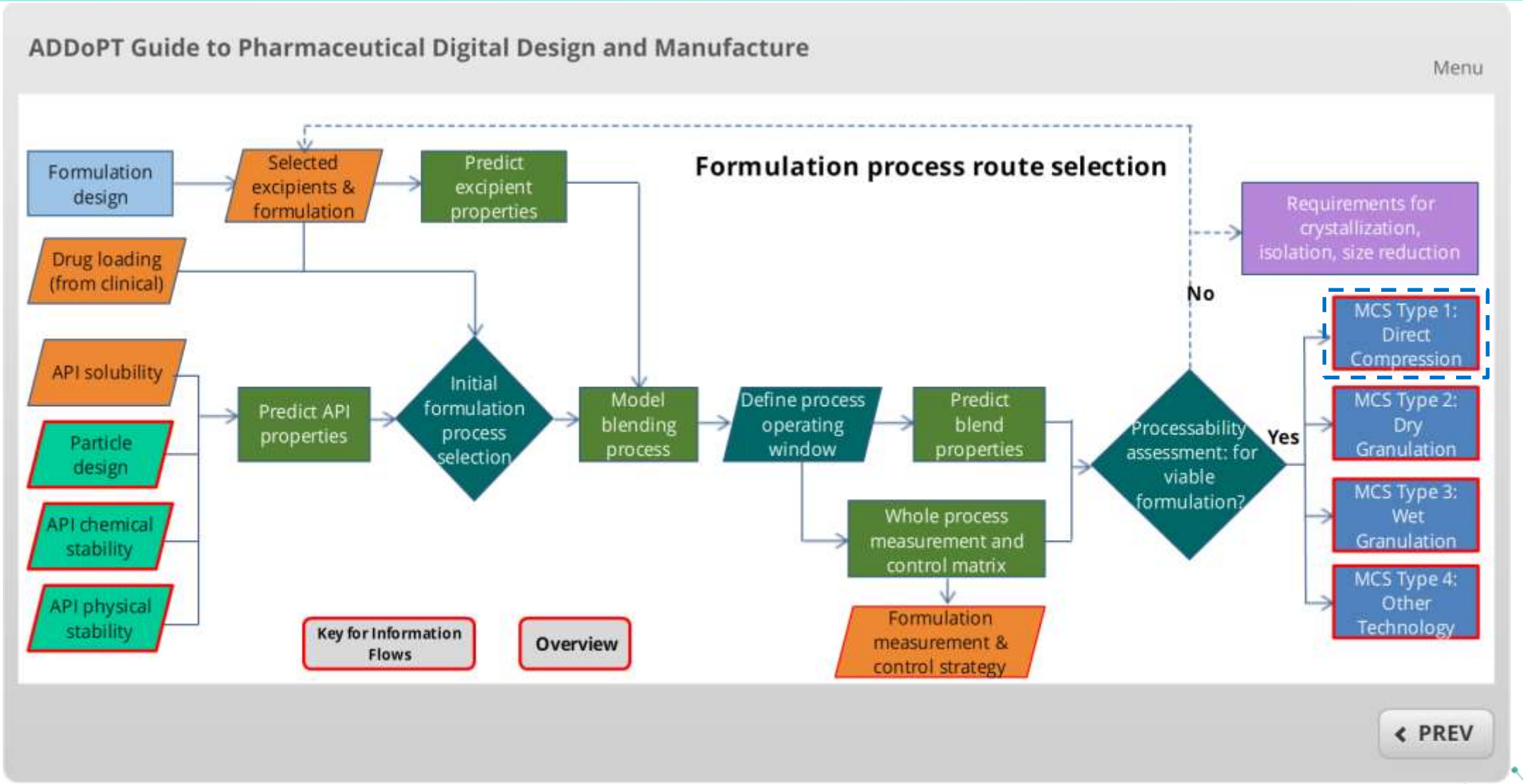
Overview of a Potential Integrated Workflow



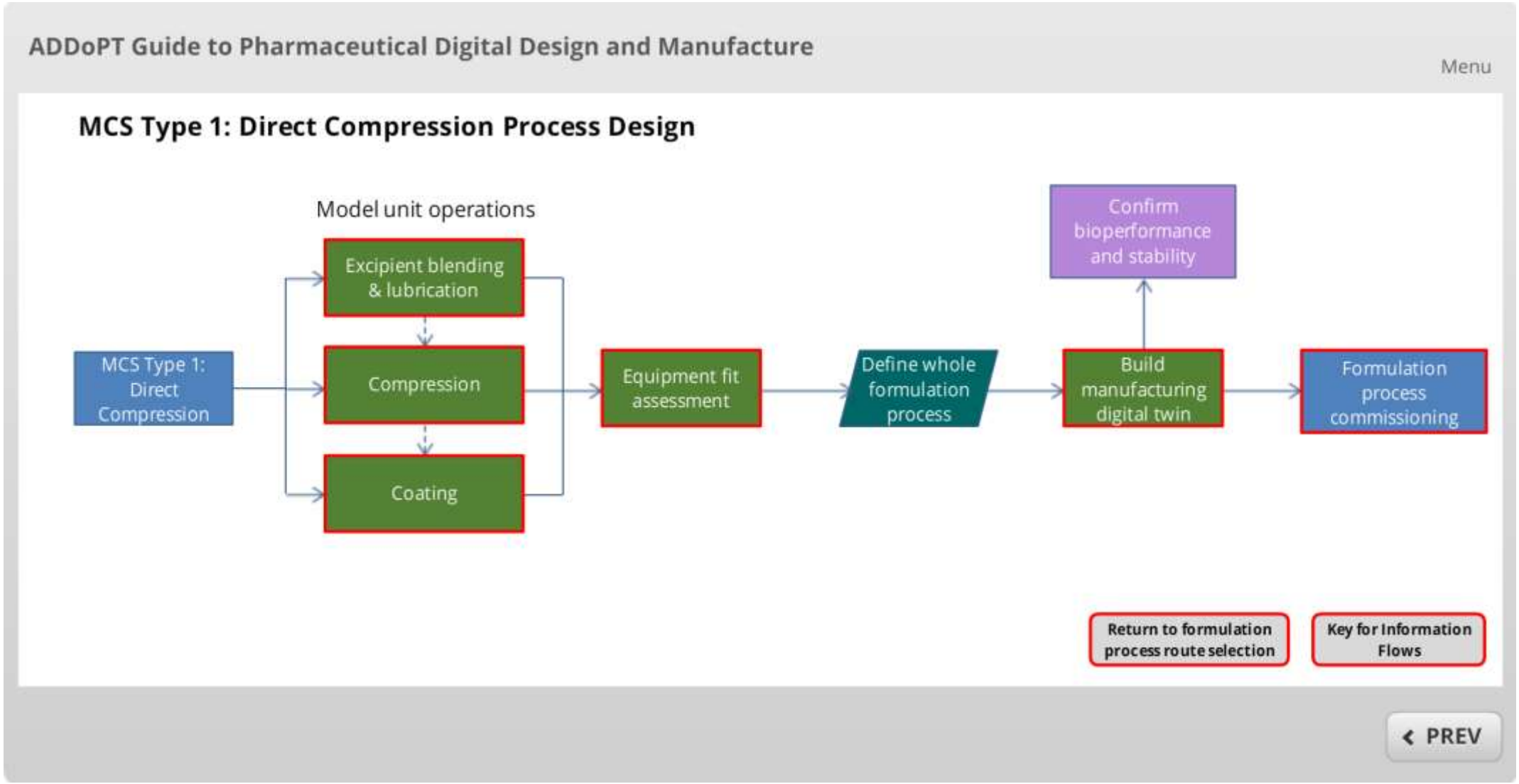
Digital Design Guide Overview



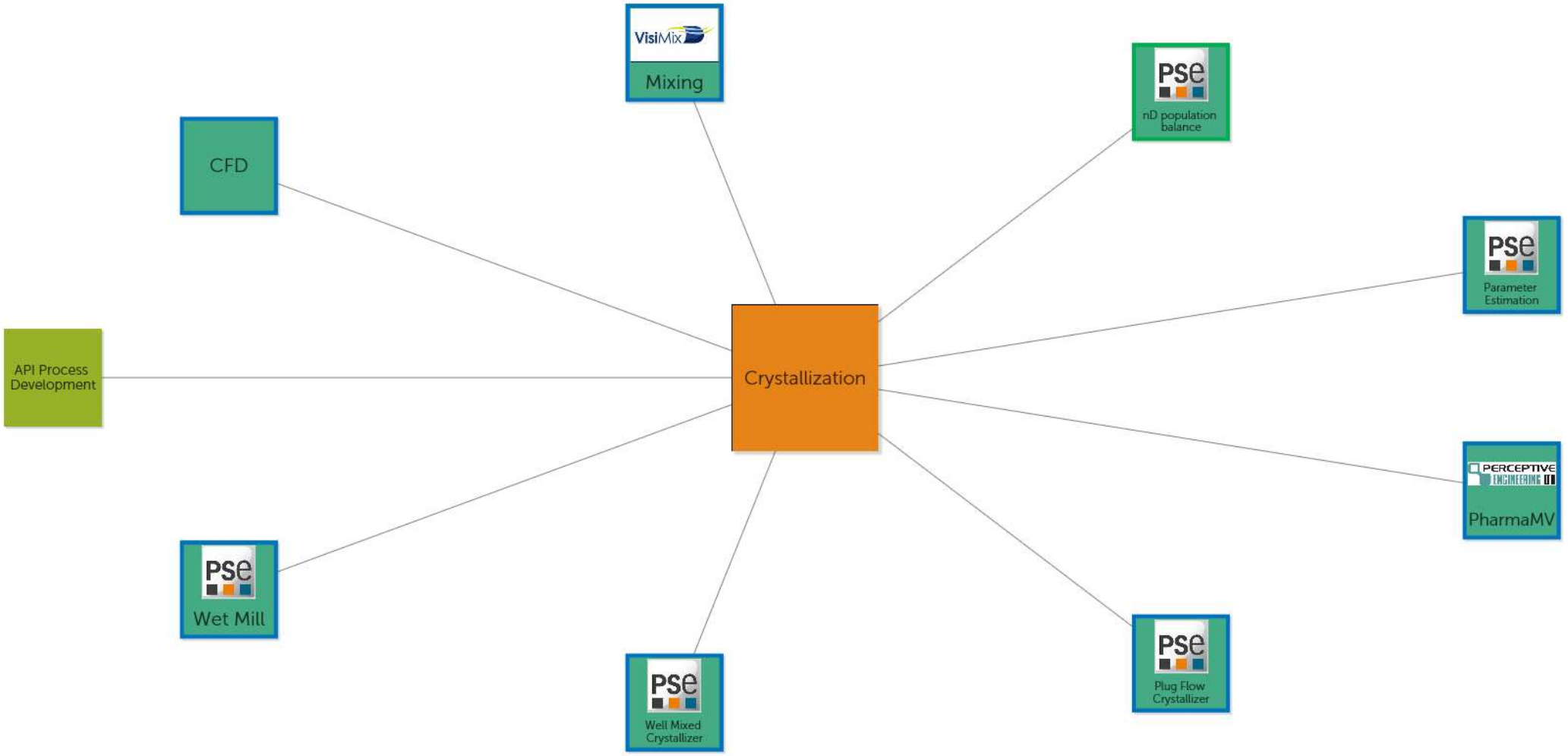
Formulation Process Route Selection



Direct Compression Information Flow



SharpCloud Display of Crystallization Models



Summary

1. Digital Design approaches offer a number of advantages in drug product design and manufacture
2. The ADDoPT project has led to the development of new quantitative models for property predictions and manufacturing processes
3. Britest has worked with the consortium partners to integrate these modelling approaches into an overall interactive information flow
4. The information flow maps digital design opportunities to development workflows, and links to supporting training materials
5. Specific information flows have been developed for pharma partners
6. The approach could be extended to other sectors