Catalent

Leads to Development
non-clinical development solutions

CLARA
CANCÉROPÔLE LYON AUVERGNE RHÔNE - ALPES

Webinar

How to Accelerate Early Drug Development in Oncology for Small Molecules and Biologics

2:00 pm	**Welcome Note**
2:05 pm	Arnaud Bathelier (CP), Julien Massiot (L2D) and Mylène Honorat (CLARA)
2:05 pm 2:25 pm	**Formulation Development to Efficiently Complete Preclinical Studies and Transition to First-in-Human Studies** Stephen Tindal (CP)
2:35 pm 2:55 pm	**Navigating Through the Regulatory Challenges of Early -Stage Drug Development (NCE and biologics)** Julien Massiot (L2D)
3:05 pm 3:25 pm	**Challenges and Opportunities in Biopharmaceuticals Development** Christelle Dagoneau (CP)

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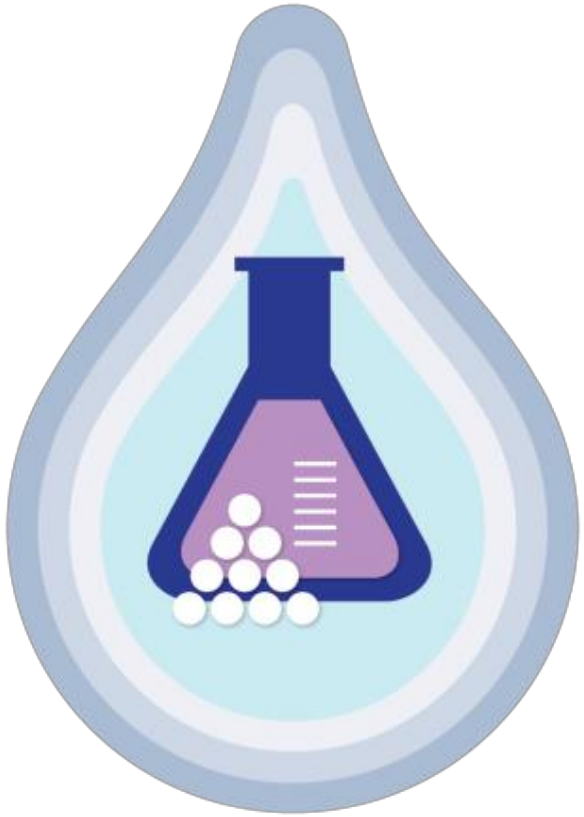


Formulation Development to Efficiently Complete Preclinical Studies and Transition to First-in-Human Studies (Small molecules)

STEPHEN TINDAL
DIRECTOR, SCIENCE & TECHNOLOGY

DEVELOPMENT DELIVERY SUPPLY

more products. better treatments. reliably supplied.™

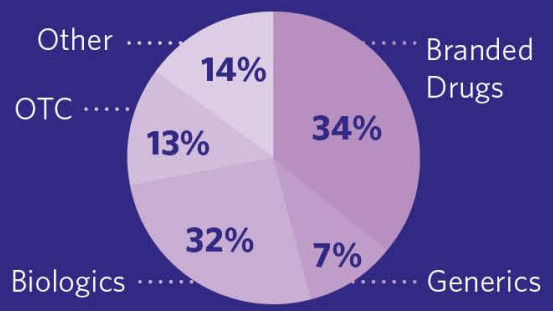
About Catalent

1,100+
ACTIVE DEVELOPMENT PROGRAMS

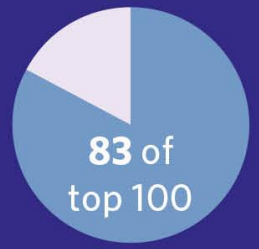
25+
R&D TEAMS WITH OVER 1,400 SCIENTISTS

ASSISTED NEARLY 50%
OF FDA APPROVALS IN LAST 10 YEARS

70+
BILLION DOSES



PRODUCT TYPE



PHARMACEUTICALS

GENERICS

BIOTECHS

WE SERVE

BIOLOGICS

35+
COMMERCIALLY APPROVED PRODUCTS

600+ ANTIBODIES
80+ RECOMBINANT PROTEINS DEVELOPED

EXPERIENCE WITH 60+
CELL & GENE THERAPY PROGRAMS

CLINICAL SUPPLY

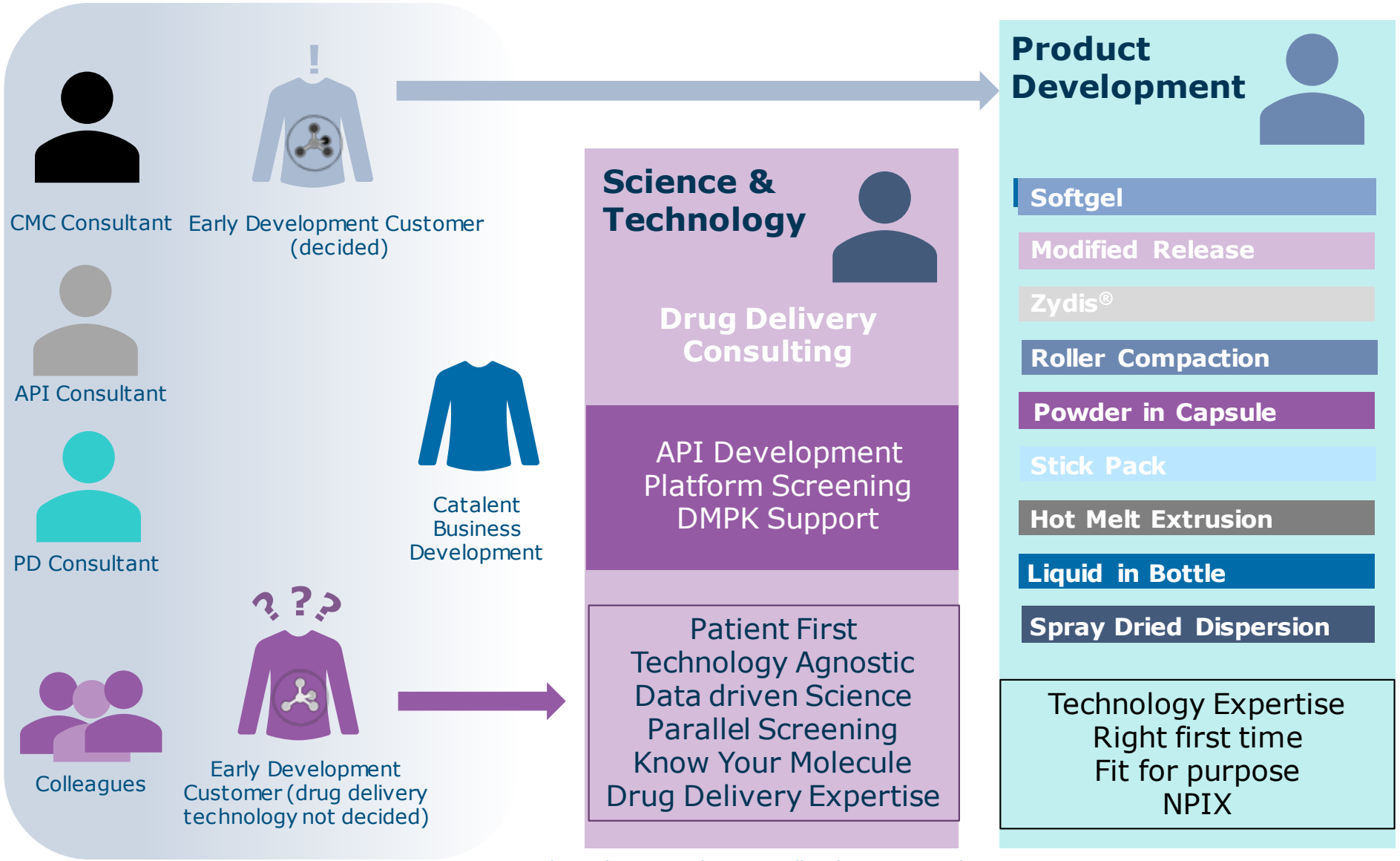
320,000+
PATIENT KITS ASSEMBLED ACROSS **1,200+** DIFFERENT PROTOCOLS EACH YEAR

150,000+
SHIPMENTS EVERY YEAR

Catalent's Recent Focus on Early Development

- **Broad range of projects**
- **Catalent acquisition of the OptiForm® preformulation team, Pharmatek and Juniper Pharma Services**
  - **Form centers of excellence for early development.**
- **Catalent's Early Development sites are focused on the small customer – fast and flexible with Project Management oversight to help maintain visibility and ensure cross site teamwork.**
- **Management and scientific review processes monitor capacity constraints and roadblocks.**

About Catalent Science & Technology



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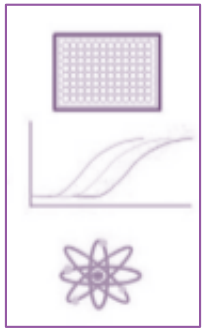
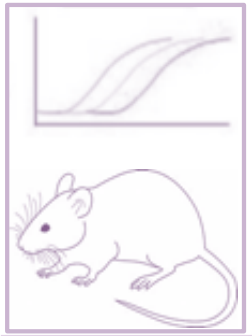
Recognizing Early Development Stages

Disease Targeting		API Development				Dosage Form Development		
Identify Target	**Target Validation**	**Identify Actives**	**Confirm Hits**	**Identify Chemical Lead**	**Select Optimized Chemical Lead**	**Select Development Candidate**	**Develop Drug Product**	**Human Proof of Concept (Ph1)**
Establish disease biology	Find molecule targets that treats disease process	Develop and Screen library of candidates with HTS assay	Confirm hits with second assay	Preliminary tox and drugability assessment	Test PK and confirm acceptable toxicity	Formulate to address PK issues, Confirm safety margin,	Preliminary drug product development	Human efficacy, Dose response, Maximum tolerated dose
								
# Entities Time	**!! 2 years**	**1000s**	**100s 2-3 years**	**10s**	**1-3 2-4 years**	**1 1-3 years**	**1 ½-1 year**	**1 ½-1 year**

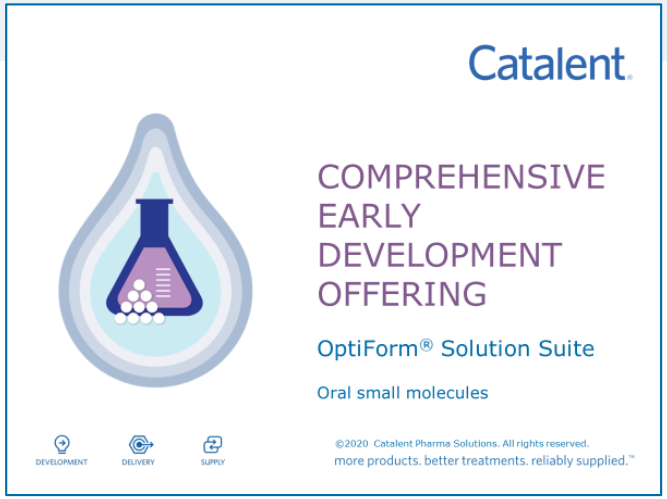
When can Catalent help?

When to Engage Catalent

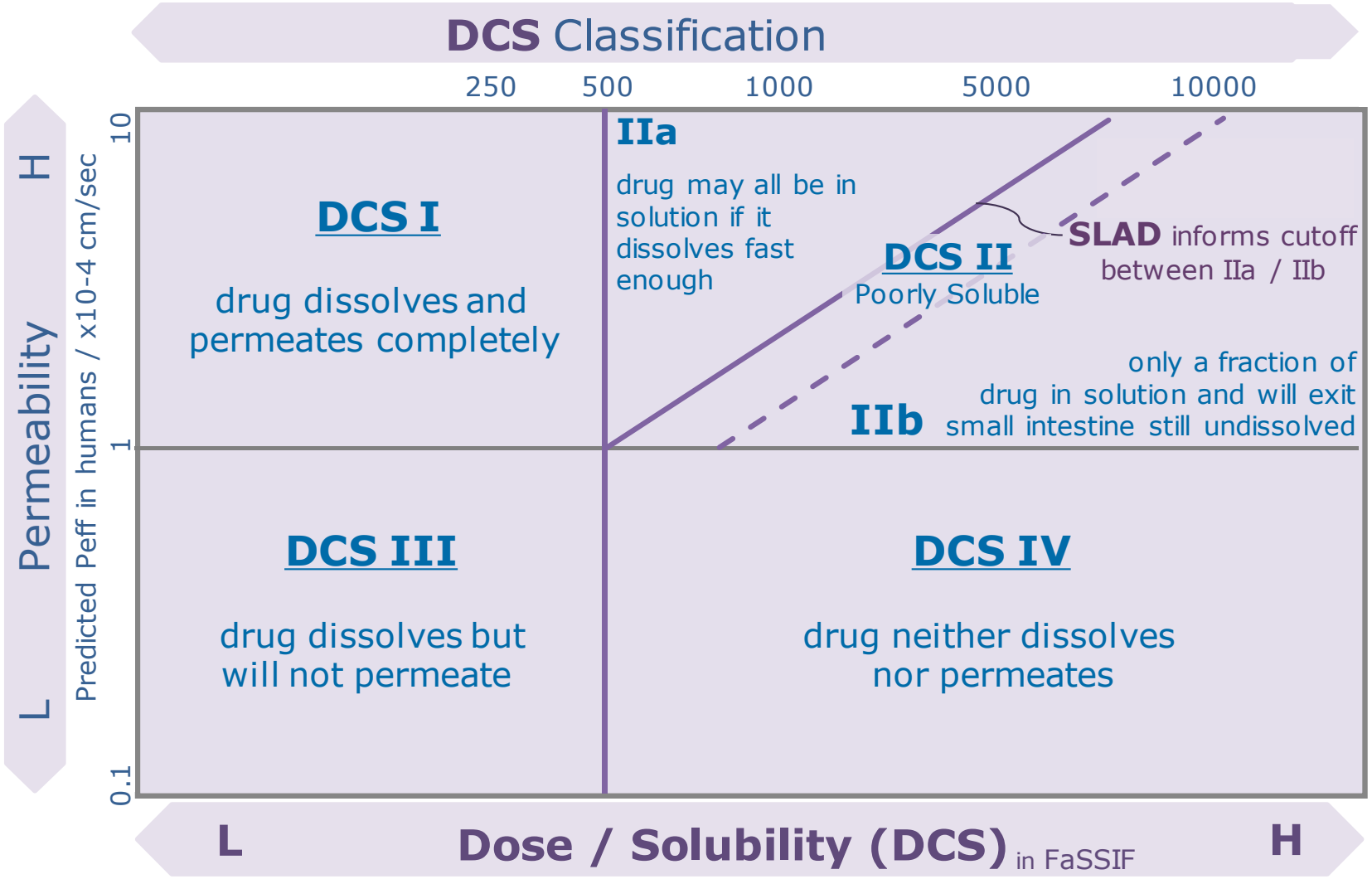
Disease Targeting		API Development				Dosage Form Development		
Identify Target	**Target Validation**	**Identify Actives**	**Confirm Hits**	**Identify Chemical Lead**	**Select Optimized Chemical Lead**	**Select Development Candidate**	**Develop Drug Product**	**Human Proof of Concept (Ph1)**
Establish disease biology	Find molecule targets that treats disease process	Develop and Screen library of candidates with HTS assay	Confirm hits with second assay	Preliminary tox and drugability assessment	Test PK and confirm acceptable toxicity 	Formulate to address PK issues, Confirm safety margin,	Preliminary drug product development	Human efficacy, Dose response, Maximum tolerated dose

No Catalent Offering

- Not looking to help with disease targeting
- Do not manufacture APIs
  - Morrisville can convert g quantities from free form to salt and vice versa
  - Morrisville can advise on crystallization
- No HTS assays, cell lines or vivarium
- Collaboration with third parties to provide cell line and Vivarium services.



Dose Form Selection Model:
Developability Classification System (DCS)



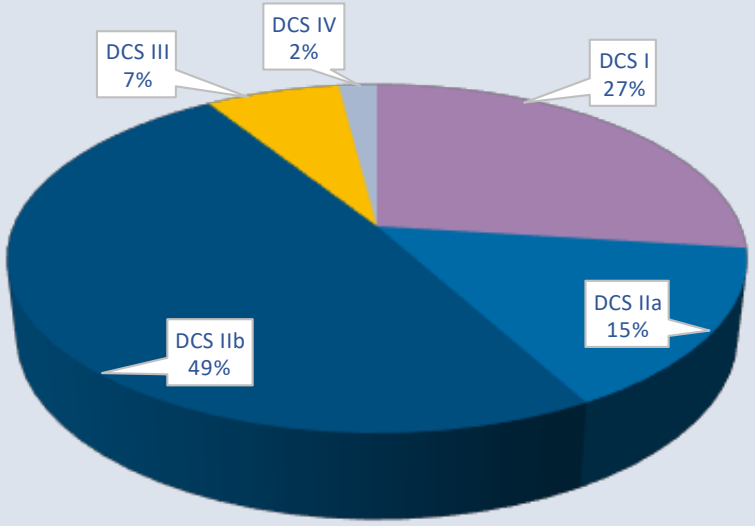
*DCS: Developability Classification System

Source: Butler, J. *The optimal use of biorelevant media & simple modeling for the prediction of in-vivo oral behaviour* (http://www.apsgb.co.uk/Events/PastEvents/20110609/James%20Butler.pdf)

The Solubility Problem and Dose Escalation

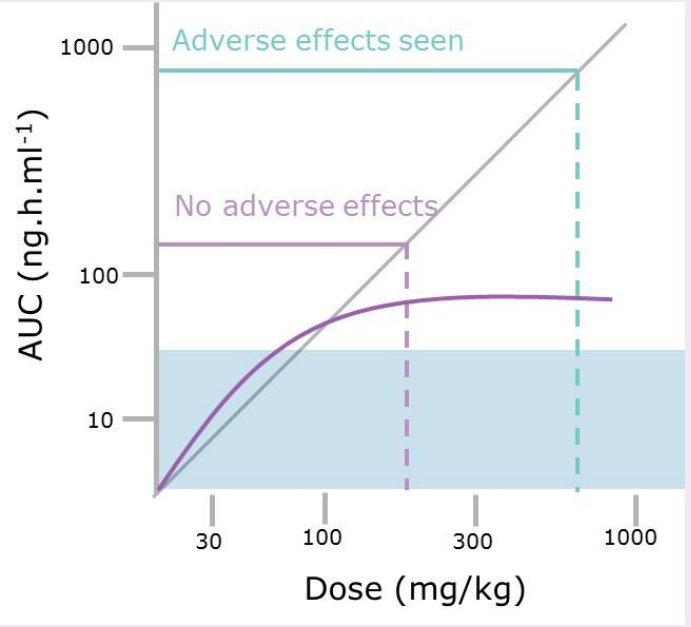
Less than 30% of NMEs in active clinical development are readily bioavailable

Solubility of 178 GSK Pipeline Products (2001 – 2010)



Bayliss et al., 2016. Quality guidelines for oral drug candidates: dose, solubility and lipophilicity. Drug Disc Today, 21(10), 1719-1727

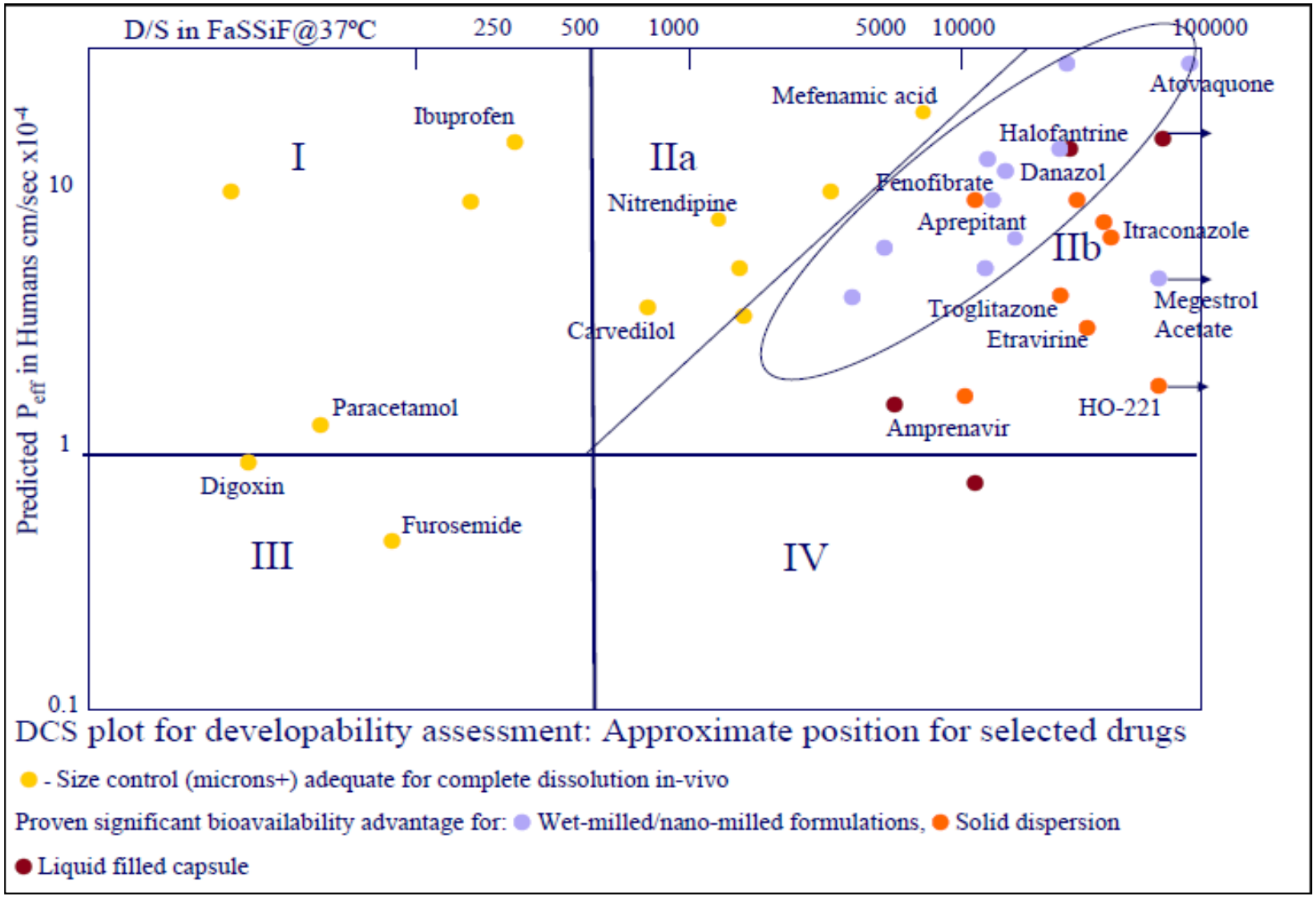
… BUT when dosed at escalated levels these "bioavailable" NME may not be sufficiently absorbed



Pointeaux T et al. , Drug Development and Delivery, 2011, 11(8):60-66

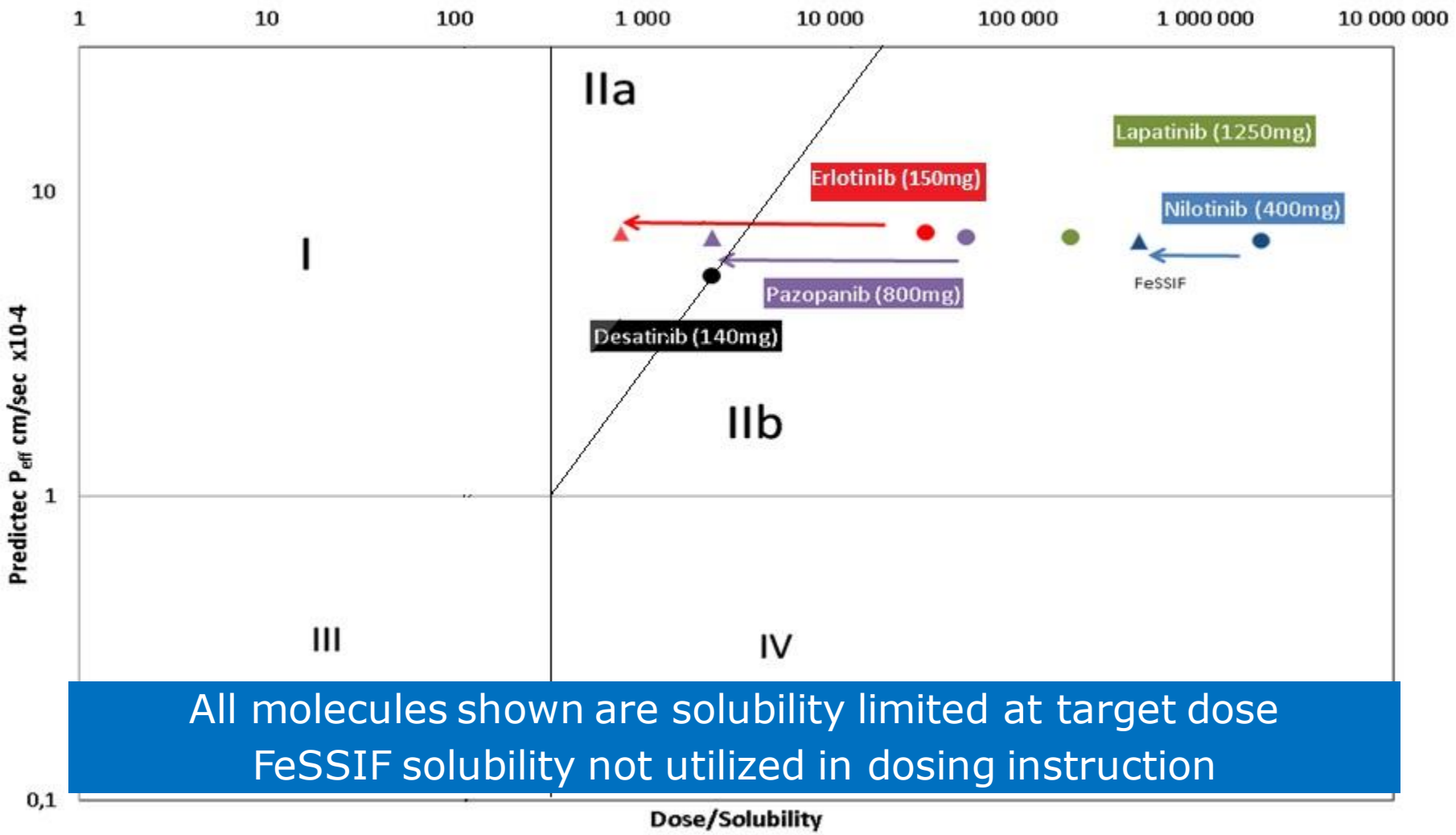
Traditional "Powder in Bottle" is Unlikely to Achieve Targeted Efficacy for Most New Oral Dose Molecules

Solubility: Many Compounds in Quadrant II!



J. Butler 2013 Phys Chem Forum

Oncology Compounds in class IIb Often with Food Effect



All molecules shown are solubility limited at target dose
FeSSIF solubility not utilized in dosing instruction

Key Takeaways on These Products

80+ % Poorly Soluble Drugs

Food Effect

Most exhibit a positive food effect (AUC and Cmax)

Variability in Absorption

Safety: a number of these products have Black Box Warnings (Efficacy…exposure)

Majority are labeled to be taken fasted

Potential for poor patient compliance

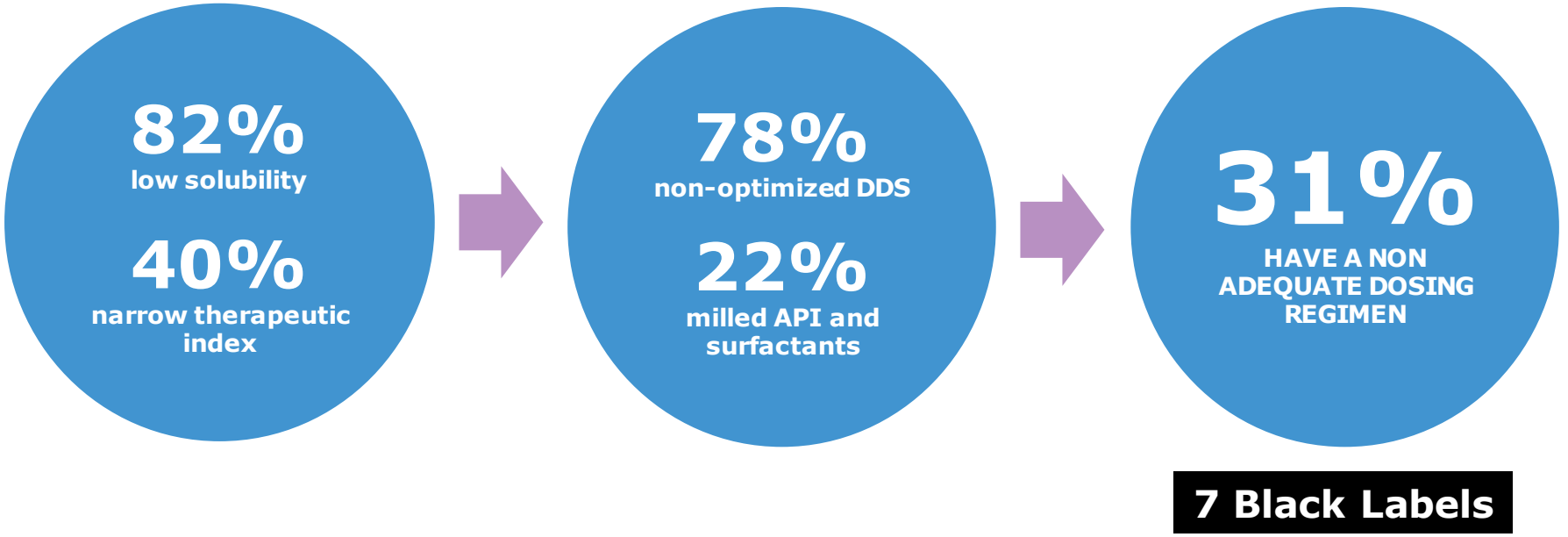
- 1-2 hours before and after meals

Some are labelled simply based on administration during clinical trials

- Without regard to food

Labelled to take on empty stomach even though a clinically significant (PK) effect does not exist

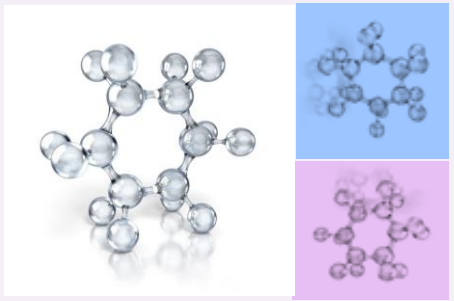
Marketed Protein Kinase Inhibitors Overview
Formulation to Differentiate PKIs under Development



SIMILAR PROPERTIES	SIMILAR FORMULATION RECIPES	SUBOPTIMAL OUTCOMES

Catalent Pharma Solutions data analysis from 29 marketed PKIs, August 2015

Know Your Molecule(s) (OptiForm® API)



Physicochemical Properties

Solubility, chemical stability, pKa, density, permeability…

Molecular Descriptors

Solid Form Properties

Salts…

Polymorphism

Dissolution rate
Solvates

Particle size
Morphology

Hygroscopicity

Melting point

Formulation & Shelf Life

- Flowability
- Excipient/Molecule interactions
- Physical and chemical stability
- Formulation strategy
- Mitigate impurities

ADME Properties

Clearance

Fraction absorbed

Rate of absorption
Volume of distribution
Metabolism
Transporters…

Pharmacology & Toxicology

- On-Target binding
- Off-Target binding
- Toxicity

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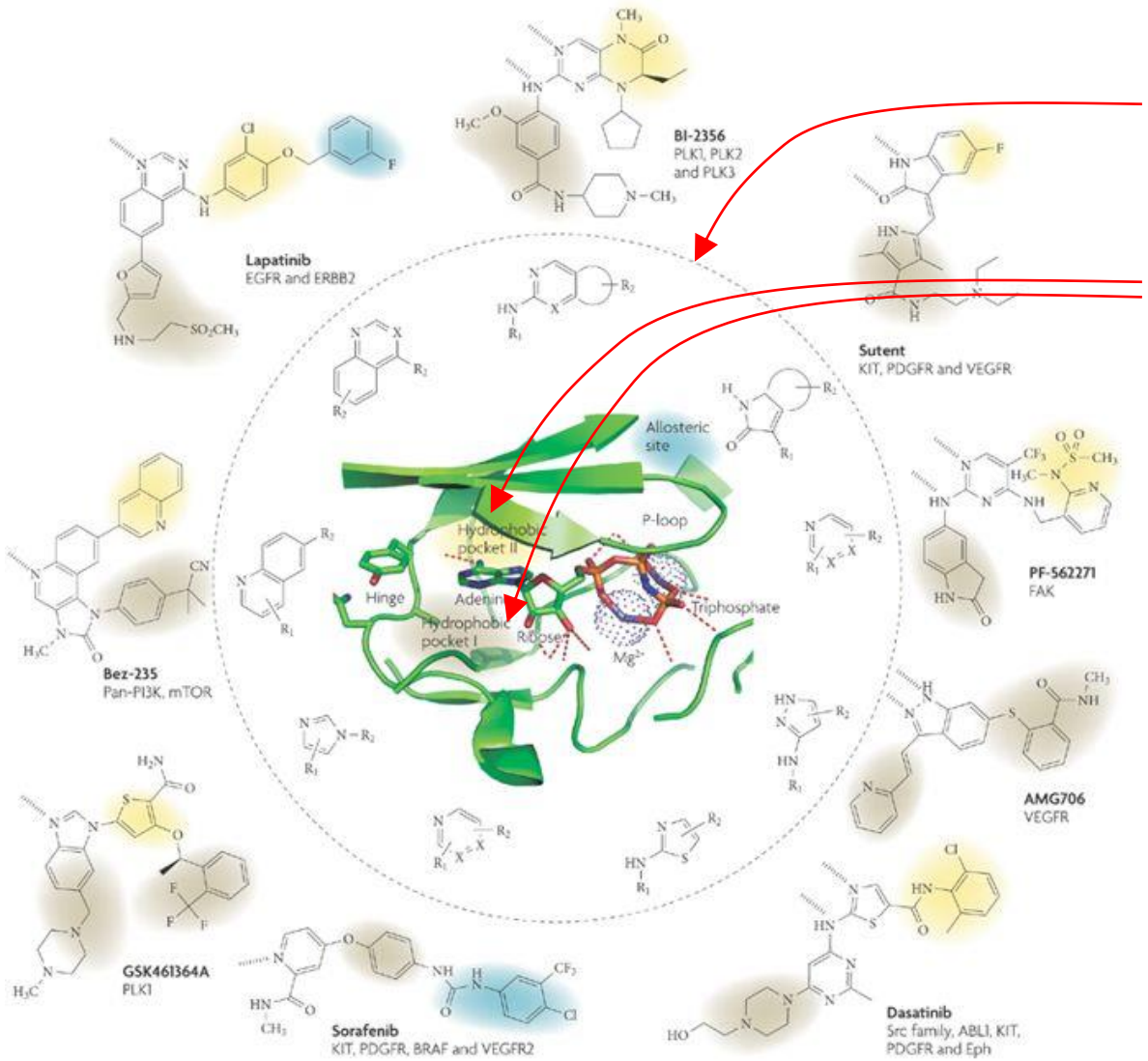
Protein Kinase Inhibitors - Issues with the target



Growth signalling transmitter AKT1 complexed with ATP binding site

Shading shows 2 hydrophobic pockets crucial for activity. Hydrophilic linker also required for H bonding

Target leads to development of molecules with similar structures and **hydrophobic** tendency

As a class, prone to **strong positive food effect**

Zhang, J., Yang, P. & Gray, N. Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer* **9,** 28–39 (2009). https://doi.org/10.1038/nrc2559

Nature Reviews | Cancer

Nilotinib – black box warning – avoid food with dose

WARNING: QT PROLONGATION AND SUDDEN DEATHS

See full prescribing information for complete boxed warning.

- **Tasigna prolongs the QT interval. Prior to Tasigna administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies (5.2). Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments (5.2, 5.3, 5.7, 5.15).**
- **Sudden deaths have been reported in patients receiving nilotinib (5.3). Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome (4, 5.2).**
- **Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors (5.8).**
- **Avoid food 2 hours before and 1 hour after taking the dose (5.9).**

Sub optimal molecules may need phase IV studies and risk of short life

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Unresolved Dosing Issue with Regard to GI Tolerability

The proposed dosing regimen for ceritinib with regard to food is 750 mg daily on an empty stomach at least 2 hours before or 2 hours after food. At the recommended dose under fasted conditions, the majority of patients experienced gastrointestinal (GI) adverse reactions including diarrhea (86%), nausea (80%), vomiting (60%), and abdominal pain (54%). The absolute bioavailability of ceritinib has not been studied but is expected to be low. The food effect study showed that a high-fat, high-calorie meal increased ceritinib AUC by 73% and C_{max} by 41%; a low-fat meal increased ceritinib AUC by 58% and C_{max} by 43% as compared to fasted conditions. Administration of ceritinib at 750 mg with food may improve GI tolerability and compliance, but

Post-marketing requirements under 505(o) are listed below. The rationale for these PMRs are described in Section 5 of this Summary Review

- Conduct a clinical trial to evaluate the systemic exposure and safety of 450 mg Zykadia (ceritinib) taken with a meal and 600 mg Zykadia (ceritinib) taken with a light meal as compared with that of 750 mg Zykadia (ceritinib) taken in the fasted state in metastatic ALK-positive NSCLC patients.

Center for Drug Evaluation and Research. Summary Review. Application Number: 205755Orig1s000.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000SumR.pdf

Center for Drug Evaluation and Research. Cross Discipline Team Leader Review Application number: 205755Orig1s000.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000CrossR.pdf

Summarizing the challenge with PKI

- **High permeability to reach intracellular target**
- **More hydrophobic to bind to hydrophobic target – with resulting low aqueous solubility / high log P**
- **High doses to maintain target saturation and to help overcome poor aqueous solubility**
- **Black box warnings to avoid taking with food**
- **Tendency for other off target toxicities reducing patient compliance and making them vulnerable to replacement**

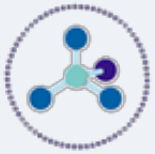
Those challenges translate into opportunities to

- **Reduce toxicity**
- **Greatly enhance bioavailability**
- **Eliminate revenue risks associated with relabeling, if drug is initially labeled under conditions that result in suboptimal bioavailability**

What Would an Ideal Target Product Profile for Orally Delivered Cancer Drugs Look Like?

Simple Dosing Regimen	*High patient adherence* *Without regard to food* *Infrequent dosing… once daily*
Wide Therapeutic Window	*Minimal side effects* *No Black Box Warnings*
Less Variability	*Intra- and inter-patient* *Consistent absorption*
No Drug Interactions	*Reduced transporter and metabolic effects* *Target specific mechanism of action* *Reduced lipophilicity*

Catalent's Early Development Services – How We Can Help

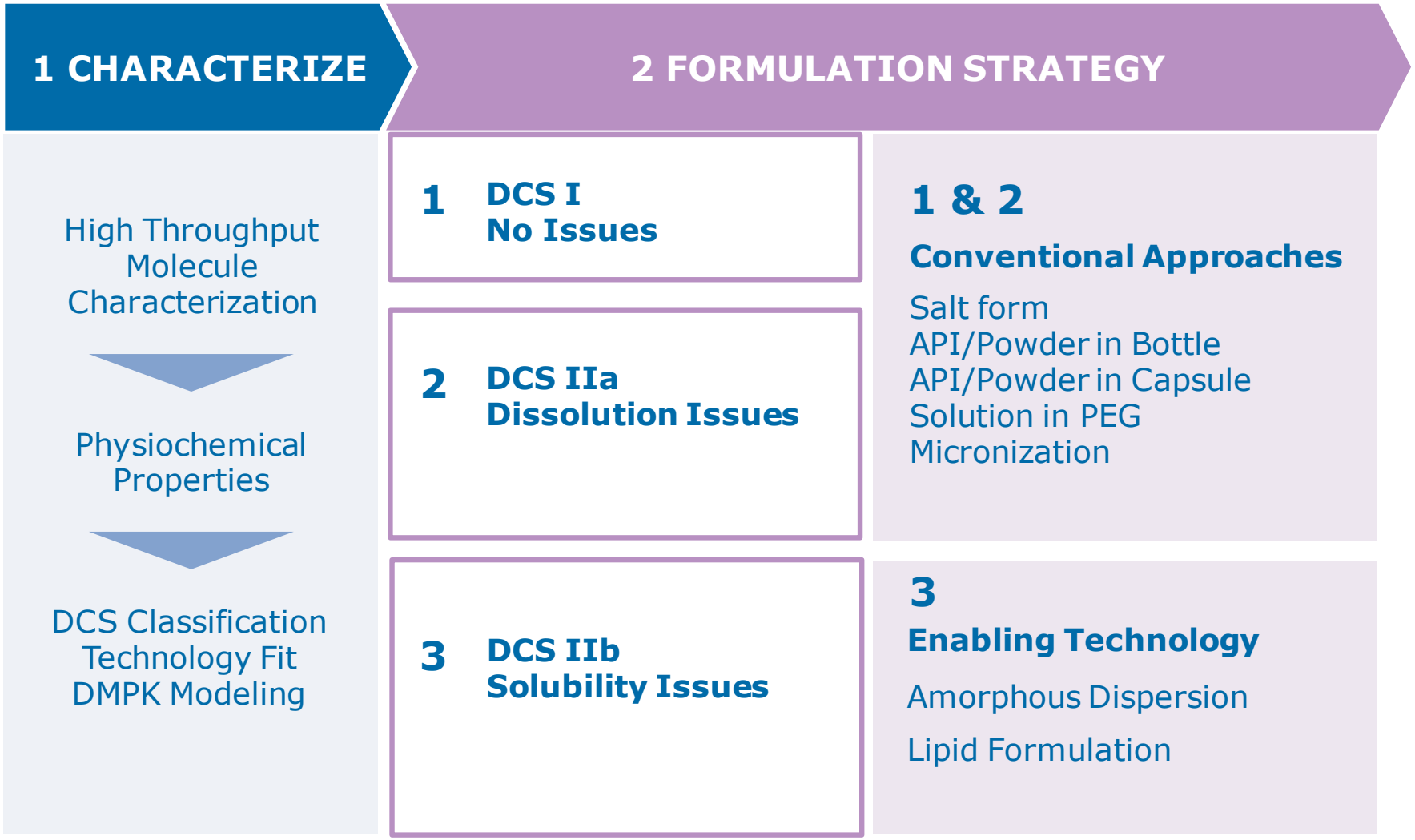
Candidate selection	Pre-formulation	Technology Selection	GLP Studies	Phase 1
				
Molecule Screening (first oral dose to animal) **Injectable Development** **DMPK Modeling** (S, Peff, efflux, transporters, metabolism, half life, estimate DCS)	**Solid State Selection** (salts & polymorphs) **Molecule Characterization** (verify sample) **Technology fit evaluation** (confirm DCS)	**Rapid Parallel Screen** **Enabling:** • **Lipid Formulation** • **Solid Dispersion** **Conventional:** • **PIC / BIC** • **Particle Size Reduction** Test PK 	**Dosage Form Development** **Maximize Exposure while Maintaining Safety** **Analytical Development**	**Phase 1 Dose Forms** *Enabled Formulations & First-in-Human Strategies* **GMP** **Release & Stability** **Clinical Supply Services**

DMPK Model refinement

DELIVERABLES

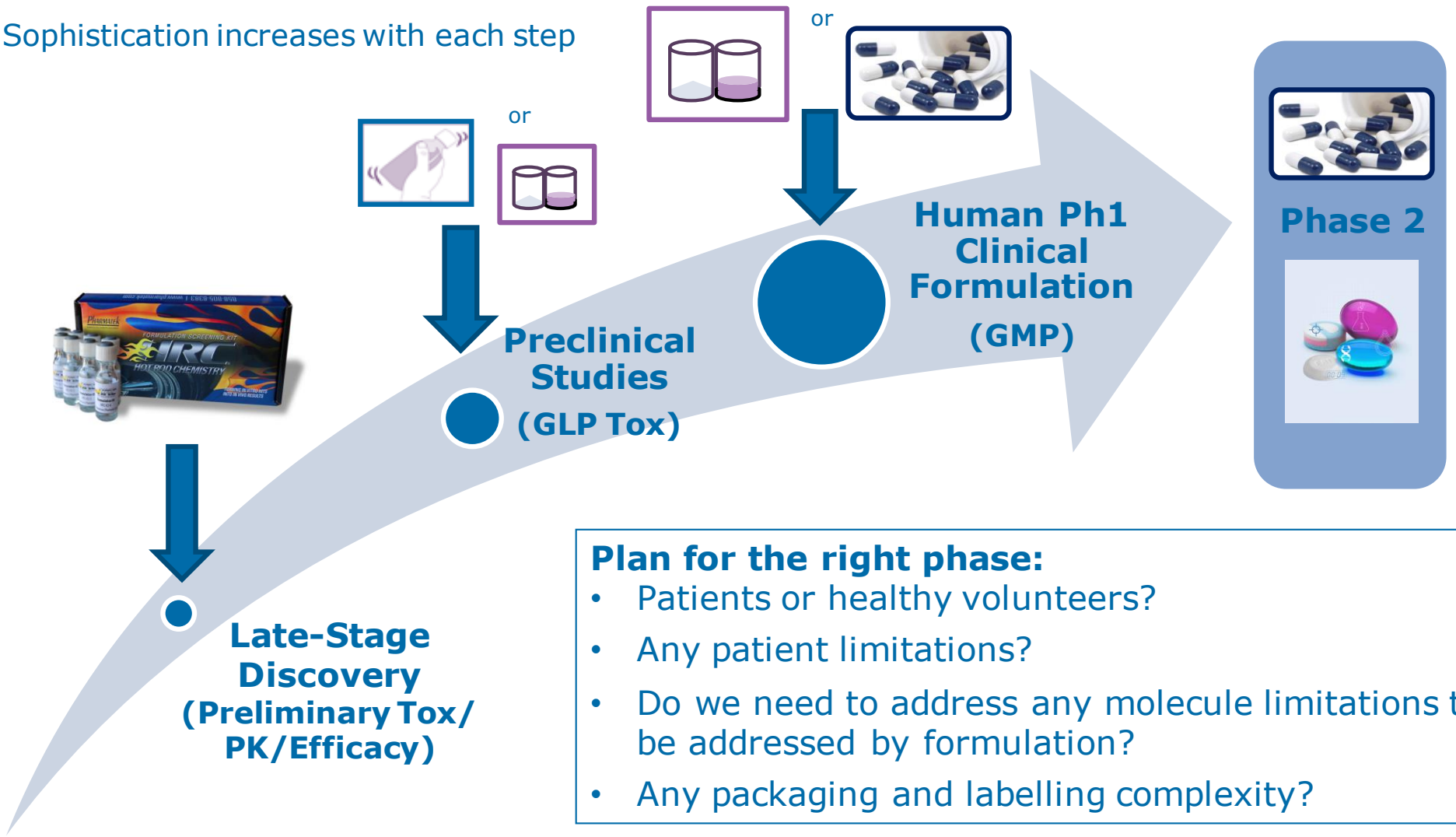
Right Candidate	Right API Form	Right Technology	Right GLP Tox Formulation	Right Dosage Form

Catalent's Data-driven Approach Helps You Determine The **Most Successful Formulation Strategy**



Evolution of Formulation

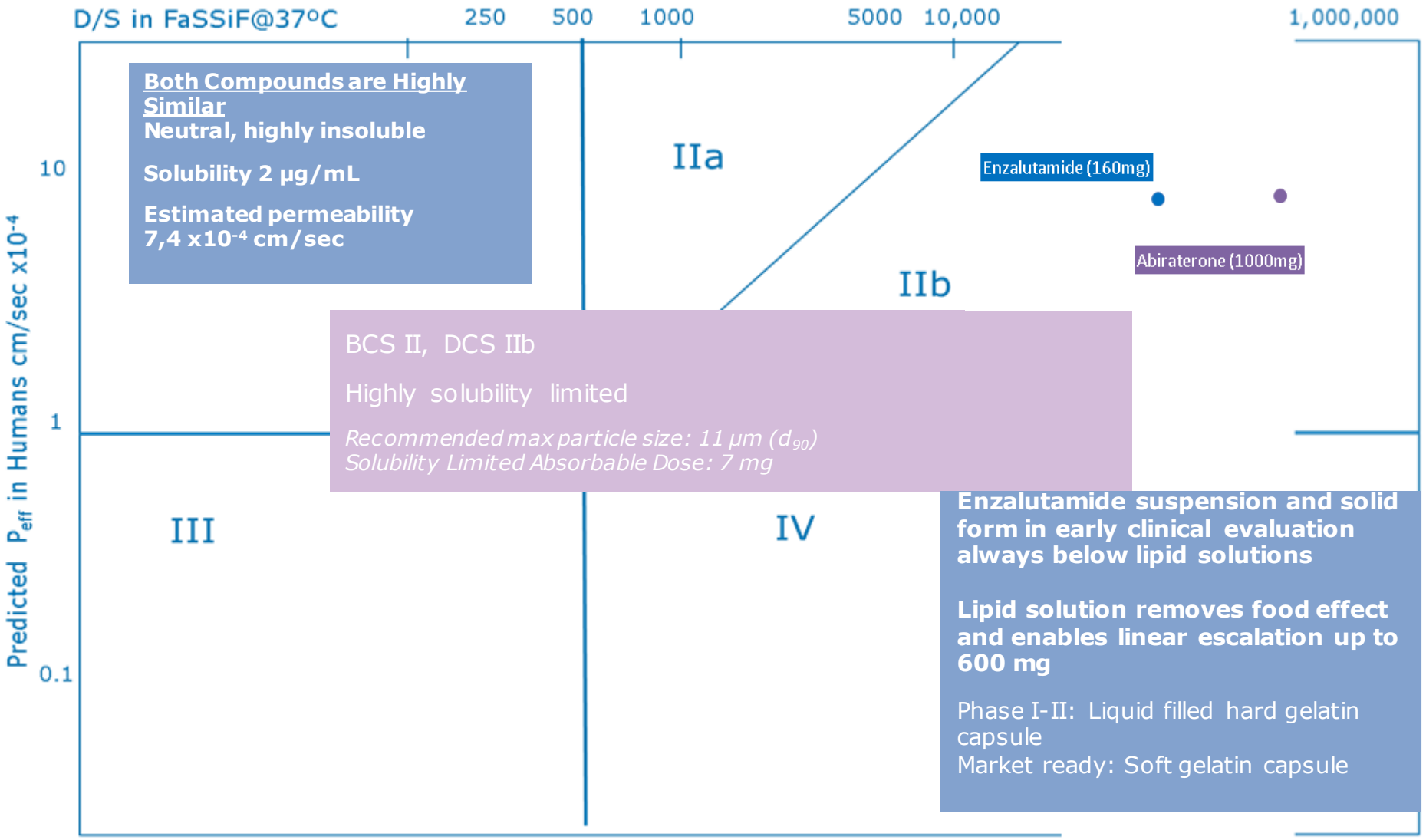
Sophistication increases with each step



Plan for the right phase:

- Patients or healthy volunteers?
- Any patient limitations?
- Do we need to address any molecule limitations that could not be addressed by formulation?
- Any packaging and labelling complexity?

Take Abiraterone vs Enzalutamide as an example…is good enough, good enough?



Zytiga® vs Xtandi® as an example…is good enough, good enough?

Abiraterone acetate DCSIIa formulation

API in Tablet Formulation (Lipid in softgel to phase 3)

- Indication: Treatment of patients with metastatic castration-resistant prostate cancer (CRPC) in combination with prednisone
- Dosage: 1,000 mg (4 X 250 mg) once daily
- Product Administration Directions: Must be taken on an empty stomach (no food at least 2 hours before and 1 hour after consumption)
- Food Effects: Approximately 17-fold and 10-fold higher, Cmax and AUC respectively, when a single dose of abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting

Enzalutamide DCSIIb formulation

Lipid in Softgel & Spray Dried Dispersions

- Indication: Treatment of patients with metastatic castration-resistant prostate cancer (CRPC)
- Dosage: 160 mg (4 X 40 mg) once daily
- Product Administration Directions: Can be taken with or without food
- Food Effects: A high-fat meal did not alter AUC to enzalutamide or N-desmethyl enzalutamide

Important Points to Take Home Today

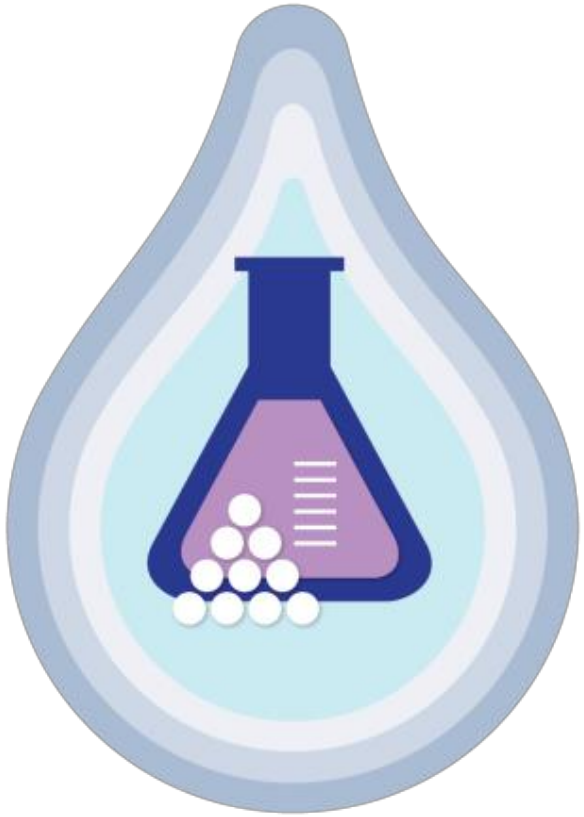
1) **Many of today's oral cancer compounds fall into DCS IIb and conventional solid dose forms may not provide optimal bioavailability, i.e. poor absorption, marked food effect and significant variability**

2) **DCS is a valuable tool for aiding in the selection of suitable formulation strategies early in the development of these compounds**

3) **For DCS IIb cancer compounds, often an enabling formulation technology which allows pre-absorption drug solubility is required to assure enhanced bioavailability**

4) **OptiForm® Solution Suite is a platform offered by Catalent incorporating 2 and 3 above which can be executed in 12 weeks or less**

Catalent®



Thank You – Questions?

STEPHEN TINDAL
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CANCÉROPÔLE LYON AUVERGNE RHÔNE - ALPES

Webinar

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3:05 pm 3:25 pm	**Challenges and Opportunities in Biopharmaceuticals Development** Christelle Dagoneau (CP)

Leads to Development
non-clinical development solutions

Navigating through the regulatory challenges of early-stage drug development

Julien Massiot
Project Manager
jmassiot@leadstodevelopment.com

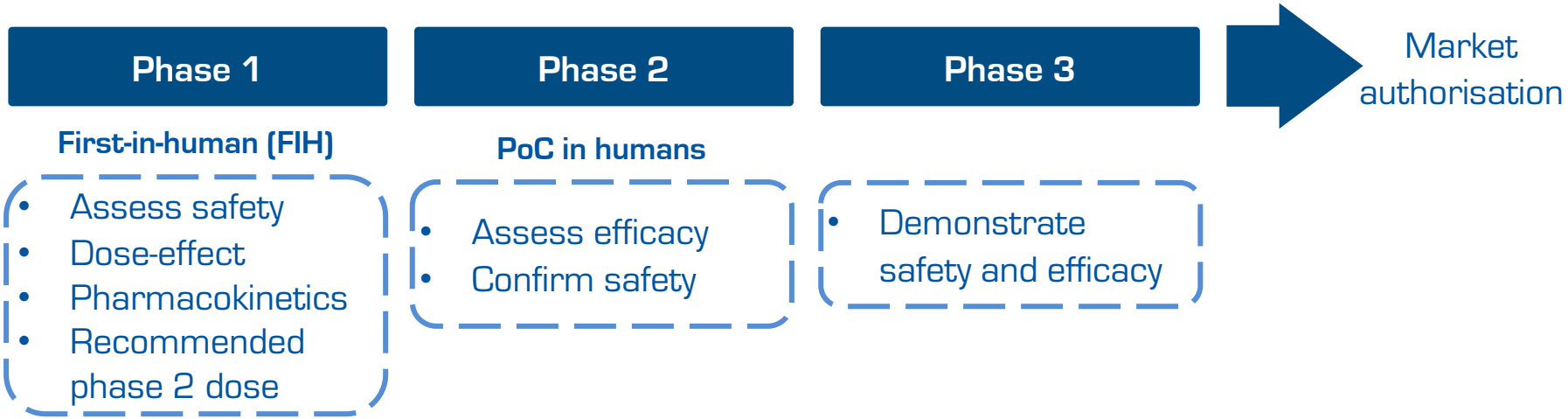
22nd April 2020

Master Class
How to accelerate early drug development in oncology for small molecules and biologics

THE MAIN OBJECTIVES

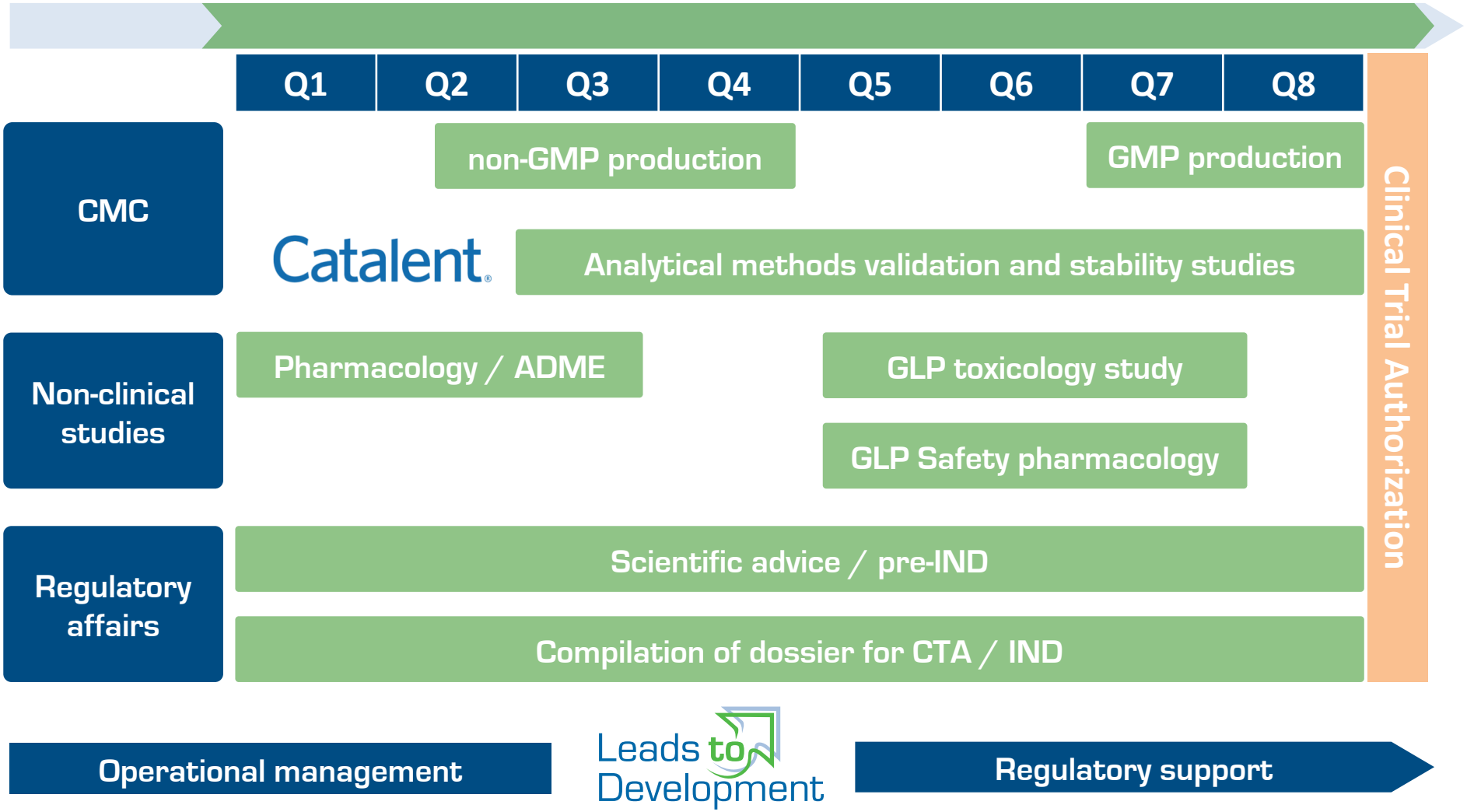
- New drug development:
  - To provide new options to treat unmet medical needs
  - Cure more patients or improve their quality of life

- Stepwise process, learning curve towards establishing the benefit-risk ratio



- Clinical use and development has to be supported by non-clinical development, including preclinical data to support proposed FIH clinical trial

CMC & NON-CLINICAL DEVELOPMENT



MANUFACTURING

Identify your drug substance

- Drug substance (DS) : active pharmaceutical ingredient (API)
- Also referred to as active substance

Formulation and filling

Drug product

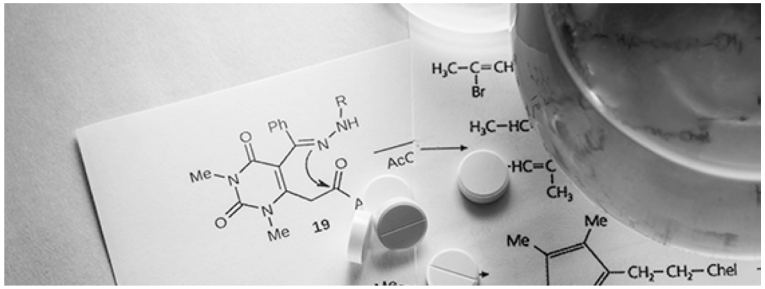
- Drug product (DP): finished dosage form comprised of the appropriate quantity of DS, possibly in association with one or more inactive ingredients (excipients)
- Also referred to as finished product (E.U.)

Small scale process establishment

NON-GMP PRODUCTION

Objectives:
- **Demonstrate that a sufficient quantity & quality of DS and DP can be produced**
- **Generate material required for non-clinical activities**

- Process transfer to GMP-compliant CMO
  - Optimisation & scale-up
- Non-GMP batch can be used for:
  - Formulation development
  - Toxicology studies
  - Analytical methods development
  - Stability studies
  - Reference standard



- This also allows tentative specifications to be defined for GMP production

Required documentation (recommended)

- Manufacturing process development & formulation development reports
- Non-GMP manufacturing reports (or batch documentation) & certificate of testing

GMP PRODUCTION

Objective:
Generate clinical trial material

- GMP production of DS
- GMP production of bulk DP
- GMP Fill & finish
- Enough GMP-compliant material should be generated for:
  - Whole clinical study
  - Quality control
  - Stability studies
  - Retain samples

Regulatory and documentation requirements

- Batch records
- Certificates of analysis (CoA)
- GMP certification of the batches
- QP release of IMP

ANALYTICAL METHODS VALIDATION

Objective:
Develop & validate methods as appropriate to confirm the quality of the DS & DP, at release and during stability studies

- Description, general features
- Identity
- Content
- Purity, quantification of impurities and/or degradation products
- Potency (for biologics only)
- ...

Regulatory requirements

- Analytical methods validation protocols and reports
- Stability-indicating methods

STABILITY STUDIES

Leads to Development

Objectives (for both DS & DP):

- **Determine main product degradation pathway(s)**
- **Determine the optimal storage conditions**
- **Support shelf-life claim under selected storage conditions**
- **Confirm that the product remains within specifications during its period of use**

- Different types of studies:
  - Stress testing (heat, pH, humidity, oxidants, …), to identify the main degradation pathways
  - Long-term conditions, to establish a shelf-life for the product in normal storage conditions
  - Accelerated conditions, to observe the behaviour outside the normal conditions

Regulatory requirements, documentation required

- Stability protocols and reports
- Data analysis, including trending when applicable

PHARMACOLOGY – PK ADME

Pharmacology: Define mechanism of action and evaluate efficacy

- *In vitro* & *in vivo* PoC
  - Relevant models; appropriate controls; dose-ranging
- Specificity & selectivity

ADME: Absorption, distribution, metabolism and excretion

- Metabolism
- Pharmacokinetics
  - Bioanalytical methods development
  - Dose-ranging, treatment schedule relationship

→ PK-PD relationships

Documentation requirements

- Study reports of all key studies and/or publications in peer-reviewed journals
- Bioanalytical method(s) validation protocol(s) and report(s)

TOXICOLOGY - GLP

Objectives:

- **Identify & characterise the potential toxicities associated with treatment and reversibility of effects**
- **Help determine the starting dose for the FIH study**

- Program design is based on intended clinical use of the product, particularly FIH study protocol
- Main studies:
  - Usually two relevant species, 1 rodent & 1 non-rodent
  - Typically, repeated-administration, dose ranging studies
  - Toxicokinetic (TK) assessments should normally be included (first & last administration)
  - Include a recovery group to confirm reversibility of any toxicities
- Additional studies may be required

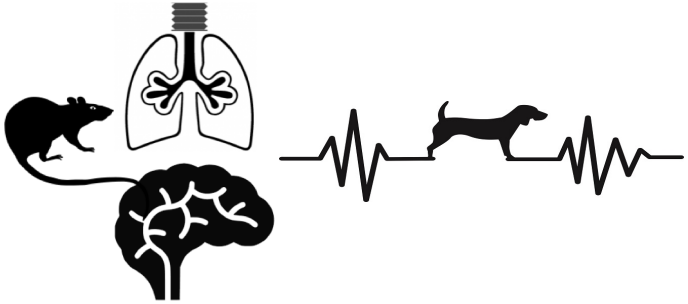
Regulatory requirements

- Rationale for toxicology species selection & administration schedule
- Study plans and study reports, including a GLP statement

SAFETY PHARMACOLOGY - GLP

Objective:
Reveal any functional effects of the new DS on organ systems, particularly cardiovascular, respiratory & nervous systems

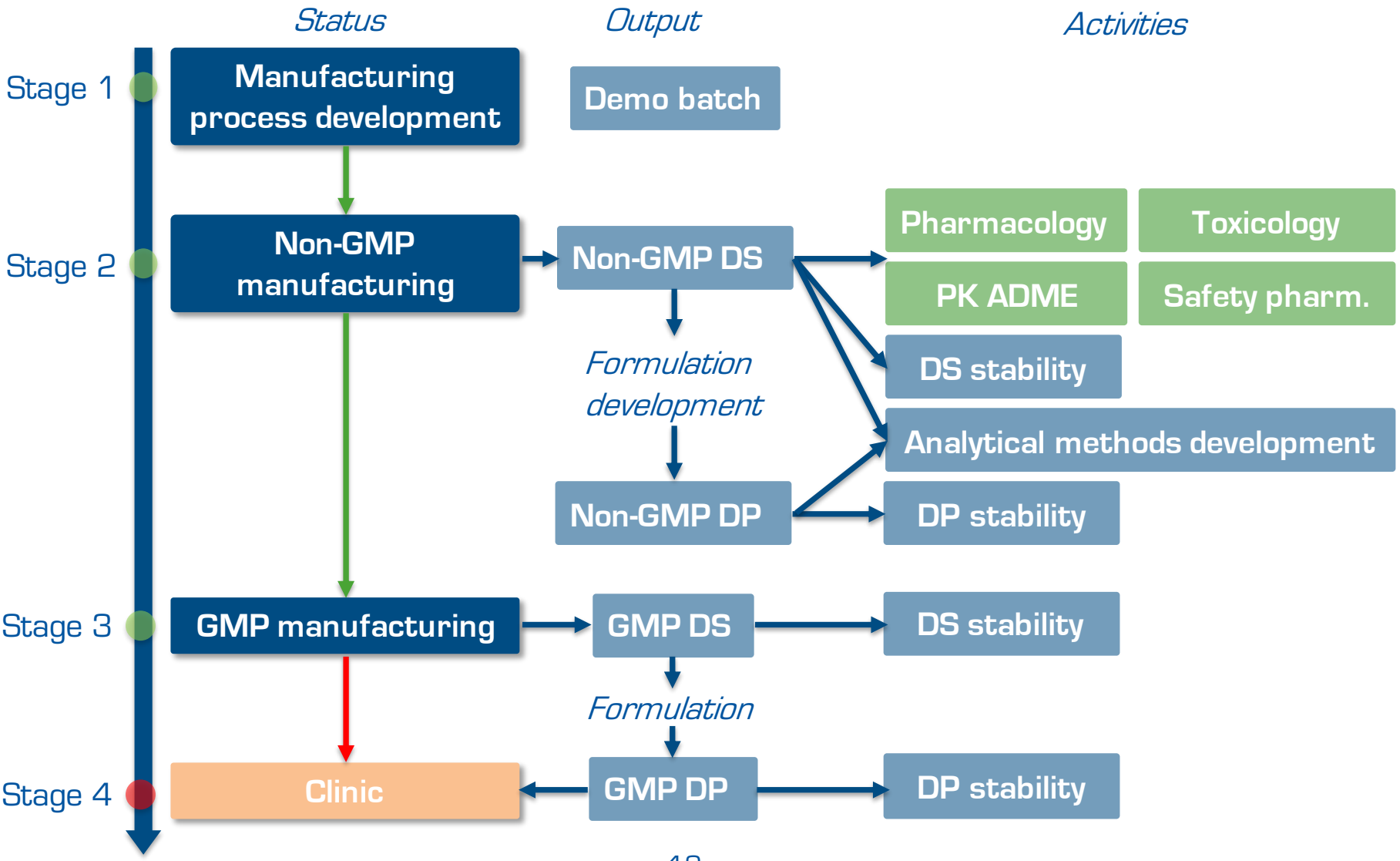
- Safety pharmacology endpoints included within the scope of the main toxicology studies
  - Respiratory function often assessed in rodents
  - Cardiovascular function normally assessed in non-rodents
  - CNS function assessed in rodents
- May not be required for certain products



Regulatory requirements

- Study plans and study reports, including a GLP statement

SUMMARY - GLOBAL STRATEGY



SCIENTIFIC ADVICE MEETINGS

Objective:
Obtain regulatory advice specifically related to your drug development

- Request a scientific advice meeting
- Generate a detailed briefing document covering:
  - Description of the drug product, its mode of action & efficacy
  - Completed and planned production tasks (CMC)
  - Completed and planned toxicology studies
  - A clinical trial protocol synopsis
  - List of questions & the company's position related to each question
- A short presentation should be provided to the Authority prior to the meeting
- Minutes are usually generated by the sponsor & commented/finalised by the authority
- Scientific advice is non-binding
- Possible in the US as well (*e.g.* pre-IND meeting), but the process is slightly different

CLINICAL TRIAL AUTHORIZATION

EU	US
Clinical trial application (CTA)	**Investigational new drug application (IND)**
Clinical trial protocol	Clinical trial protocol
Patient information leaflet (PIL)	Patient information Leaflet (PIL)
Informed consent form (ICF)	Informed consent form (ICF)
Investigator's brochure (IB)	Investigator's brochure (IB)
Investigational medicinal product dossier (IMPD) - Quality (CMC)	IND dossier (5 modules) 1) Administrative 2) Summaries 3) Quality (CMC) 4) Non-clinical study reports 5) Clinical study reports

TAKE HOME MESSAGE

Leads to Development

What makes up a high quality clinical trial application?

- A tailored, regulatory-compliant, well planned and executed development plan
  - There is probably not one guideline that describes how to develop YOUR drug
- Respond to the authorities' expectations:
  - Drug safety
  - Drug quality
- Remember that guidelines are guidelines & should only be followed if there is a scientific rationale to do so
- Request scientific advice & take advice into account
- Experience counts:
  - In your drug/pathology,
  - In regulatory requirements,
  - In designing and delivering adequate development plans,
  - In the generation of the CTA/IND
- **It is a team effort!**

Leads to Development

non-clinical development solutions

Thank you for your attention!
Any question?

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non-clinical development solutions

CLARA
CANCÉROPÔLE LYON AUVERGNE RHÔNE - ALPES

Webinar

How to Accelerate Early Drug Development in Oncology for Small Molecules and Biologics

2:00 pm	**Welcome Note**
2:05 pm	Arnaud Bathelier (CP), Julien Massiot (L2D) and Mylène Honorat (CLARA)
2:05 pm 2:25 pm	**Formulation Development to Efficiently Complete Preclinical Studies and Transition to First-in-Human Studies** Stephen Tindal (CP)
2:35 pm 2:55 pm	**Navigating Through the Regulatory Challenges of Early -Stage Drug Development (NCE and biologics)** Julien Massiot (L2D)
3:05 pm 3:25 pm	**Challenges and Opportunities in Biopharmaceuticals Development** Christelle Dagoneau (CP)

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Current CMC Strategies for Recombinant mAb & Protein Candidates

CHRISTELLE DAGONEAU, PHD
SENIOR ACCOUNT DIRECTOR,
BIOLOGICS & BIOSIMILARS, DRUG SUBSTANCE

DEVELOPMENT DELIVERY SUPPLY

more products. better treatments. reliably supplied.™

Agenda

1. **Catalent Biologics Overview**
2. The Pathway to Phase I
3. The Cell Line Development: A Critical Step
4. Selection Criteria for Partnering with a CDMO
5. Benefits of Integrated Approach
6. Timeline & Budget Considerations

Your Large Molecule Has So Much Potential
Our Passion for Biologics Can Help You Achieve It

Across our biologics offerings, we have the passion to help you accelerate, simplify and de-risk your project from development and biomanufacturing, to fill/finish, analytical, clinical supply and commercial launch

Biologics | Biosimilars | Cell & Gene Therapies | Oncolytic Viruses | Advanced Vaccines

Catalent Biologics
Smart Technologies. Tailored Solutions. Better Treatments.

OneBio® Integrated Suite
A single solution from cell line development through supply to reduce timelines and complexity

GPEx® and GPEx® Boost Technology
Proven development of high-performance, highly stable production cell lines

Development & Biomanufacturing
Leveraging advanced technology and proven expertise in drug substance

Drug Product Manufacturing
Trusted clinical and commercial fill/finish and packaging of vials, syringes and cartridges

Biologics Analytical Services
Broad range of solutions from pre-clinical through post-approval release and stability

SMARTag® Bioconjugation Technology
Site-specific conjugation enabling improved homogeneity, manufacturability and tolerability

Cell & Gene Therapy
Industry-leading expertise in adeno-associated virus (AAV), autologous and allogeneic cell therapies

Discover the Power of Integration

Trusted

20+ years experience in Biologics services

600+ antibodies and **80+** recombinant proteins developed

120+ clinical trials utilizing GPEx® cell lines

13 approved products using GPEx® technology

Proven

Partnerships with **41** of Top 50 Biopharma/Biotech

9 clinical supply facilities

50+ audited depots on **6** continents

99%+ on-time delivery for clinical supply

Committed

$2.5 Billion+ invested

30+ years experiences providing analytical services

35+ commercially approved products

3,000+ employees

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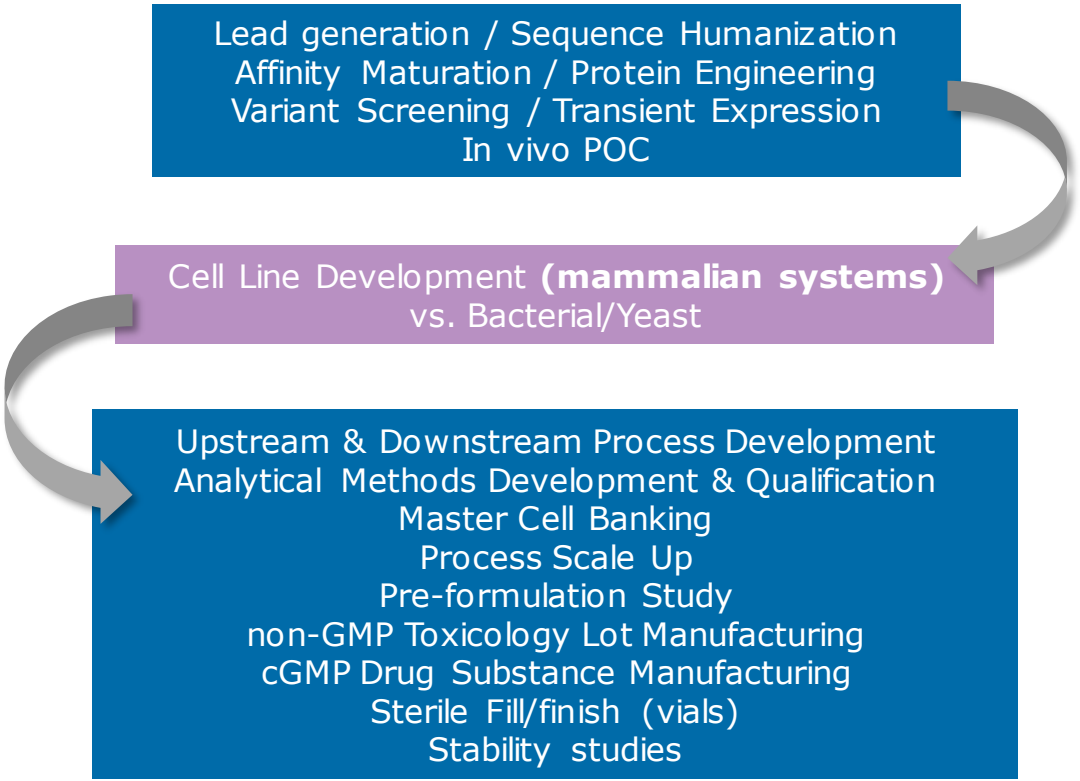
The Pathway to Phase I



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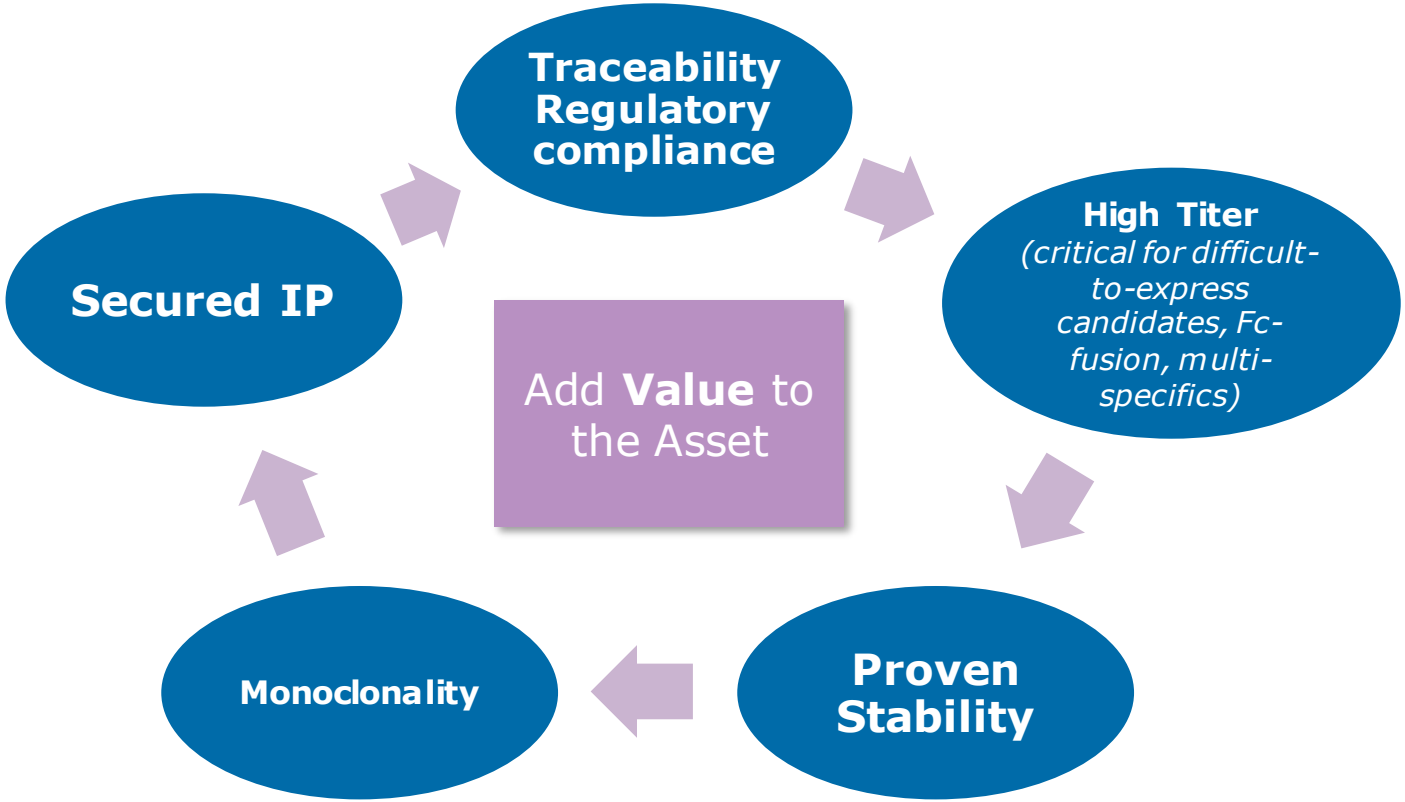
The Best Cell Line: Key Features



Cell Line Development : The Fundamentals

- Technology platform will drive **titer** and **stability**
- Some technologies can help modulate ratios of protein expression for non-standard format like bi-specific / multi-specific mAb (antibody assembly)
- Host cell lines may impact protein **glycosylation patterns / functionality** but also **titer**
  - mAbs will require use of proven CHO / mammalian cell lines
  - Human proteins may need to be expressed in human type of cells: HEK293, CAP cells, PER-C6, etc.
- Use of expression platforms may lead to difference in protein purification scheme / aggregation profile
  - Fab case study : CHO >> E.coli / Yeast

Why using a high-performance cell line development platform is critical?

Because the cell line is the KEY component of the CMC package & will eventually drive commercial Cost of Goods.

Proprietary Platform Business Model: Myths & Reality

- **Typical business model:**
  - Fee-for-service component for development
  - One or multiple payments linked to development milestones
  - Royalty component or fixed fee at BLA/market authorization
- **Milestone payments can usually be waived or reduced when the CDMO develops the cell line AND supports Phase I manufacturing**

Why track records/performance of cell line development platform should drive selection over financial terms:

- Biotechs only pay for the development steps (=fee for service)
- PhI/II milestone payments are ususally low
- PhIII / BLA / royalty payments will be supported by the Pharma partner
- Royalty component **ARE NOT** an issue for product licensing IF technology is supporting lower COGs (and can also be converted into a fixed fee)

Impact of Titer on Phase I DS Batch Price

Illustrative Example

1. Rec. protein (difficult-to-express candidate)

Titer	Bioreactor size (SUB)	Price (inc. consumables)	Difference
700 mg/L	1000L	2M$	(800k€)
2.1 g/L	250L	1,2M$	

2. mAb

Titer	Bioreactor size (SUB)	Price (inc. consumables)	Difference
1,6 g/L	3x1000L	5,7M$	(2,7M€)
4,2 g/L (after PD)	1000L	3M$	

- Productivity and recovery will impact the bioreactor size
- Financial impact is reduced for PhI trial but will increase with larger API needs

Impact of Titer on Commercial COGs

Commercial Needs per Year	Process Yield		
	1,5 gr/L	2,6 gr/L	4,5 gr/L
90 Kg (cardio-vascular indication)	60,000L required volume **72M$ Drug Substance manufacturing**	34,000L required volume **44M$**	20,000L required volume **24M$**
25 Kg (orphan indication or very low dose indication)	16,600L required volume **24M$**	7140L required volume **10,6M$**	5555L required volume **8,7M$**

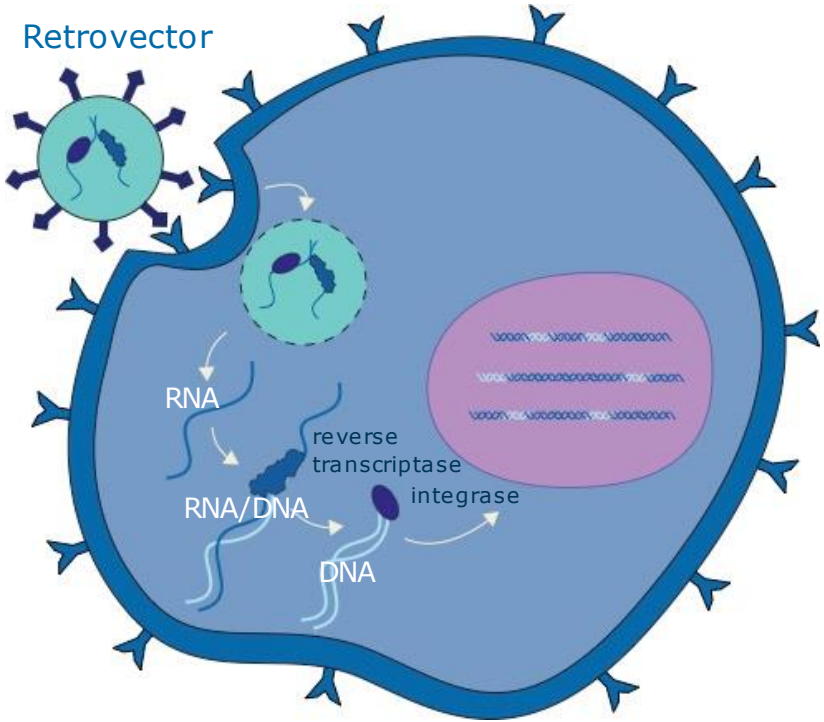
- Ensuring optimal COGS becomes crucial for large market - oncology drugs or chronic indications requiring large or repeat dose or for biosimilar products.
- Immediate ROI when using a high-performance cell line platform:
  - **Manufacturing COGs reduction >> Licensing fees**

Cell Line Development Step: Key Learning

Use of a high-performance cell line development platform is an investment for a biotech candidate.

Return on investment can be made early with reduced process development, lowering manufacturing scale.

Example of Proven & High Performance Cell Lines
Catalent GPEx® Technology



GPEx® technology targets insertion of gene into multiple transcriptionally active sites

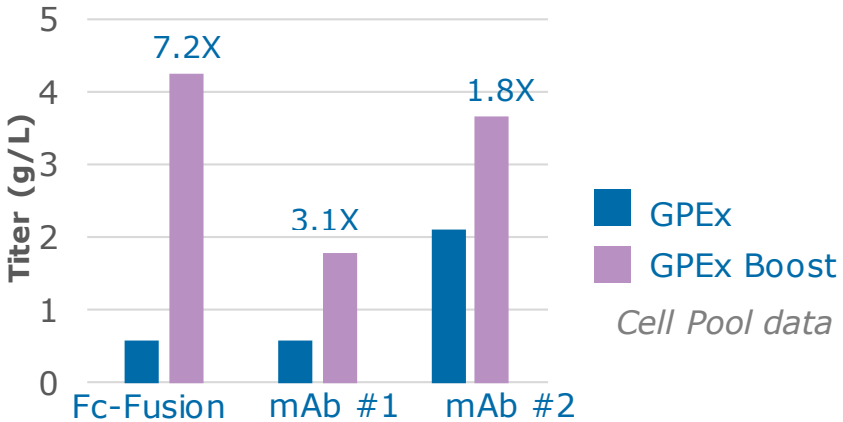
- No antibiotic selection
- No gene amplification using toxic compounds
- No need to test genetic stability
- Titers up to 7 g/L+ in fed-batch
- 680 R&D programs
- 120+ clinical trials utilizing GPEx® cell lines
- 13 commercially approved products using GPEx® technology

Next Generation: **GPEx® Boost** Technology

The Next Generation

Combines GPEx® technology with Glutamine Synthase knockout CHO cell line

Additional culture optimization to further improve the platform

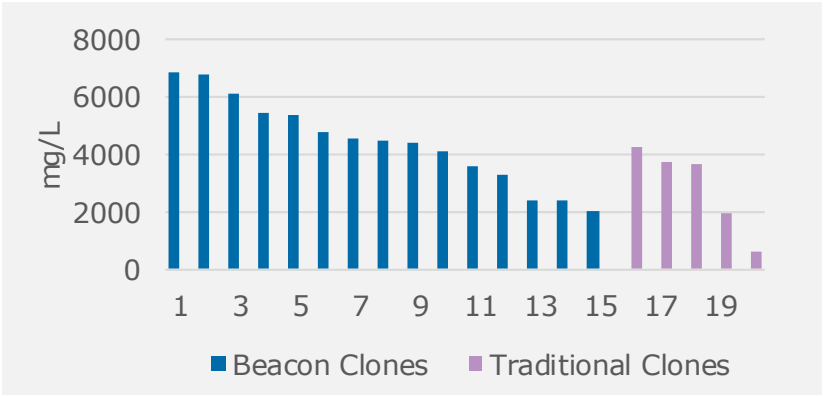


Synergy between two technologies results in significantly better cell lines

Beyond Cell Line Platform: Combining Cutting Edge Technologies to Isolate the Top Clones

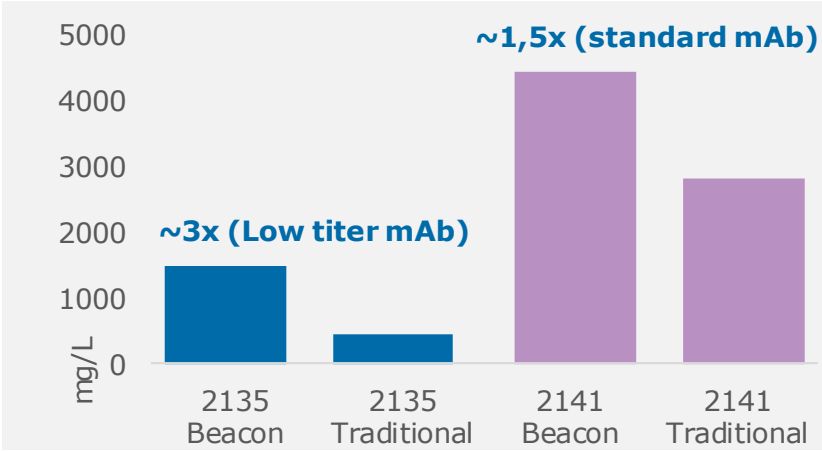
Beacon® Platform

Automated system that can be used for clonal selection of antibody or Fc fusion producing cell lines



ambr® Systems

Mini bioreactor system for process development and process characterization



Combination of GPEx®, Beacon® and ambr® technology: > **2½ month time savings & improved titer.**

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Key Points to Evaluate When Speaking with CDMOs

- Flexible manufacturing scale: 50-2000L is a minimum range for PhI/II programs
- Discuss single-use v. stainless steel bioreactors and which would best fit your program
- Minimum # of manufacturing suites provides flexibility
- Ensure CDMO facility allows easy transfer from R&D to PD to manufacturing - harmonized equipment from PD small-scale to cGMP large-scale
- On-site analytics is mandatory for IPC and release testing
- Integration of capabilities help optimize timelines
- Communication channels & Project Management should be a selection criteria
- **Go visit the CDMO site, speak with the technical team – cultural fit is extremely important as the CDMO should be a real partner to bring the candidate into PhI**

Select a C**D**MO with relevant Development expertise and track records.

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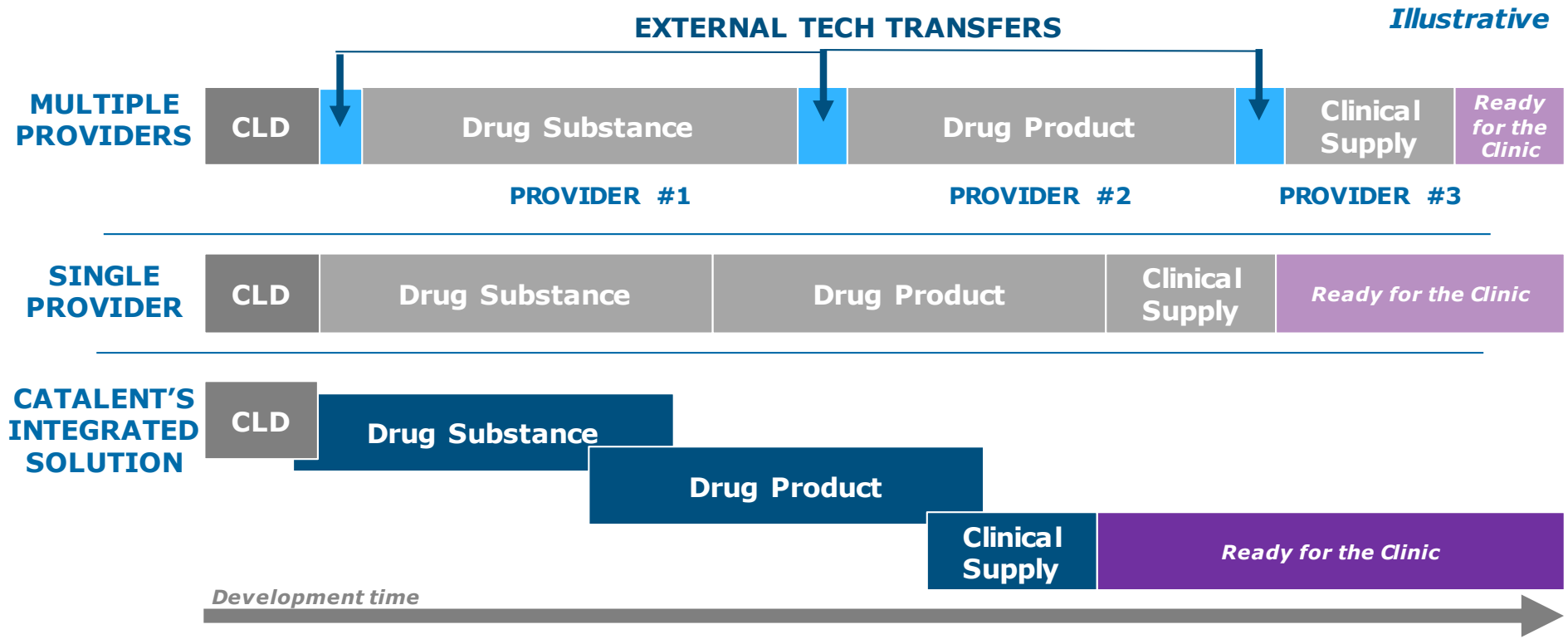
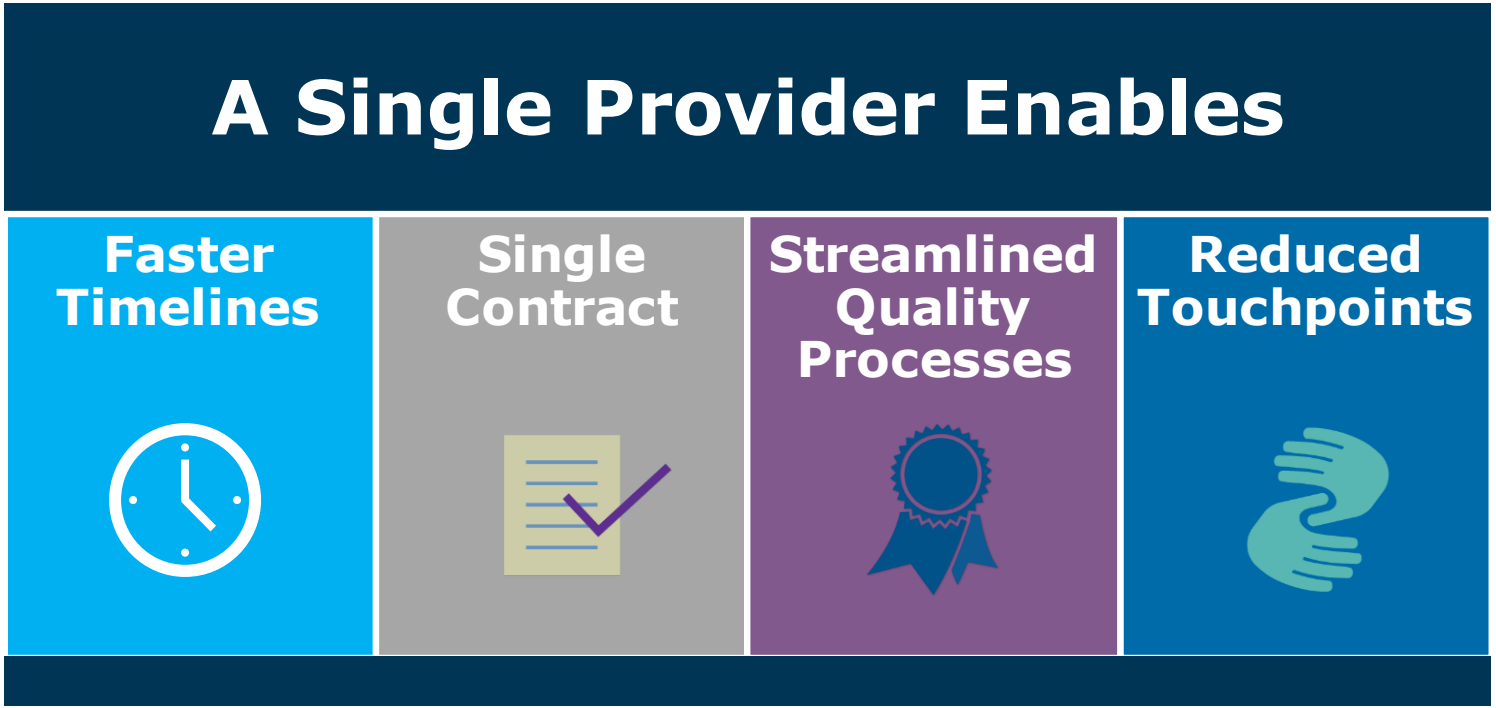
Objective is to Avoid Time Lost on Path to Clinic Due to Handoffs and Contracting with Multiple Providers



Burn rate estimated at $250k/week using total annual operating costs of small biotech companies *(sourced from comparable pre-revenue public companies)*

What's Behind Integrated Development, Manufacturing and Clinical Supply?



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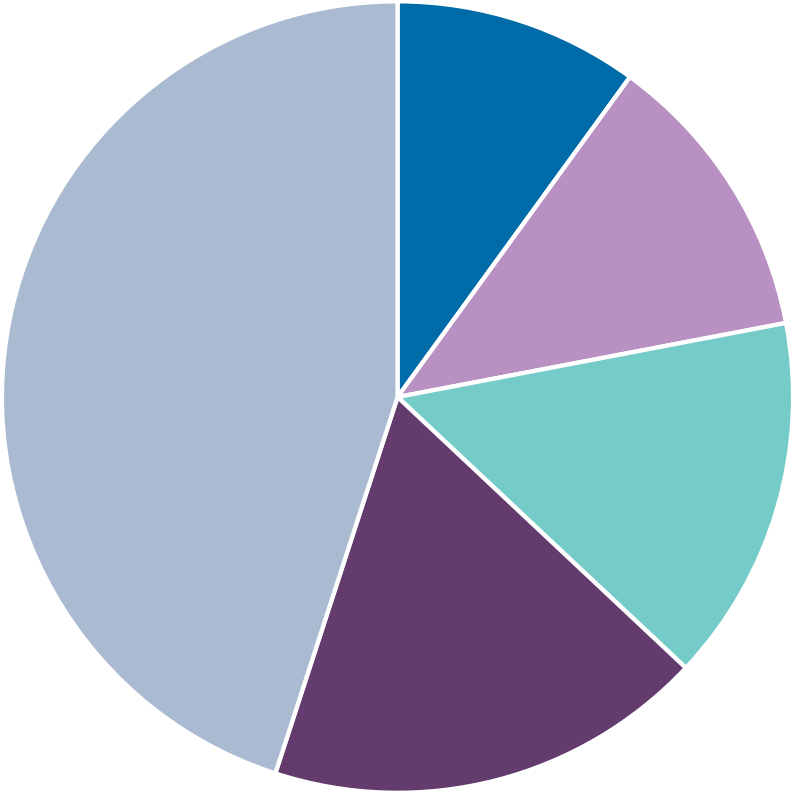
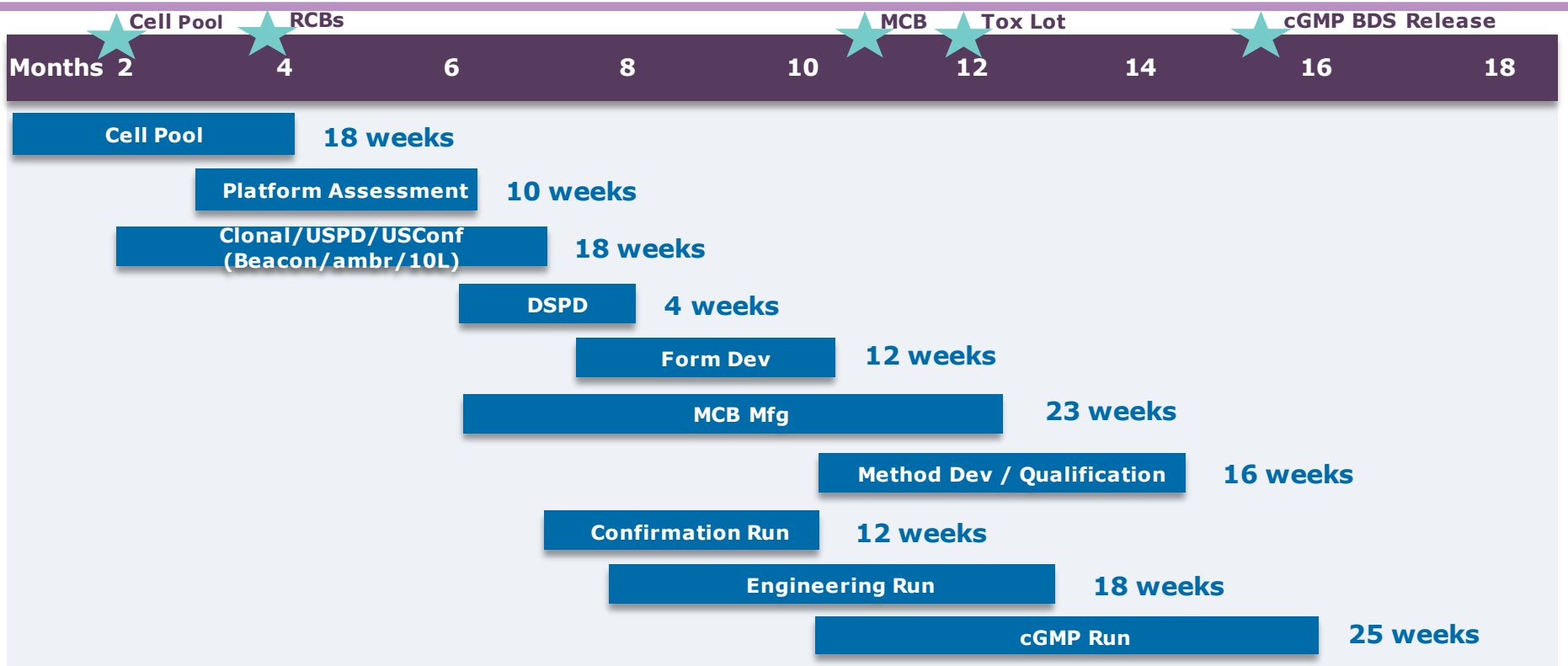
Total Program Investment



Total Budget: 5-6M$

- Cell Line Development
- Process Development
- Analytical / Formulation
- non-GMP Manufacturing
- GMP Manufacturing DS / DP

Standard Timeline from Cell Line to DS Manufacturing



Longer timelines apply for Fc-fusion, rec protein, multi-specific mAbs

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ambr is a registered trademark of The Automation Parnership (Cambridge) Limited

Be Aware

- In the current competitive CDMO environment, some attractive but unrealistic timelines (9-12 months to GMP….) are advertised.
- Currently marketed condensed timelines rely on platform approach and do not provide room for customization / process optimization / scale-up phase.
- Experienced Biotechs will know that building a robust CMC plan takes time, especially for non-standard biological candidates.

Accelerating the timeline ALWAYS introduces a notion of risk.

Don’t be overly optimistic with budget & timeline expectations

- A biologic program can always bring “surprises”
- Board/VCs don’t like deviations, their expectations must be managed at the start of the program with

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Thank You! – Questions?

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Webinar

How to Accelerate Early Drug Development in Oncology for Small Molecules and Biologics

Thank you for
your particpation

Stay safe…