Catalent BIOLOGICS

Biologics Analytical Methods:

TRENDS AND STRATEGIES TO ACCELERATE DEVELOPMENT

Wai Lam Ling, Ph.D., VP Scientific Advisory, Catalent

DEVELOPMENT DELIVERY SUPPLY

more products. better treatments. reliably supplied.™

TODAY'S AGENDA

1. **Introduction**
2. Analytical Testing Landscape
3. Common Challenges
4. Catalent's Stepwise Approach
5. Conclusion and Questions

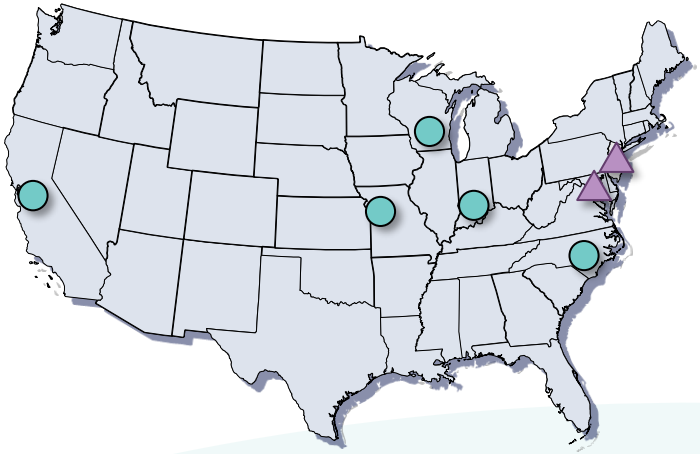
WE ENABLE OUR PARTNERS TO DEVELOP & SUPPLY BETTER TREATMENTS FOR THEIR PATIENTS BY KEEPING PATIENTS FIRST

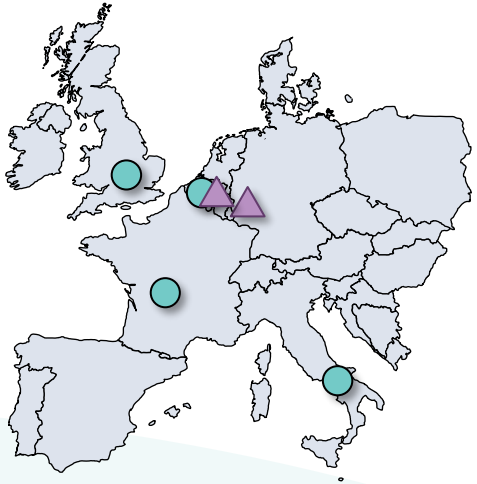
At the core of Catalent's mission is developing and supplying products to **ENHANCE & IMPROVE THE LIVES OF YOUR PATIENTS**

We are dedicated to using our passion, expertise, and advanced technologies in partnering with you to design better treatments that deliver for **PATIENTS FIRST**

With our responsibility for supplying thousands of products to patients worldwide, we share your view that when patients come first, **EVERY OUTCOME MATTERS**!

Our Biologics Network: Benefit From Our Strategic Locations





- **EMERYVILLE, CA**
  SMARTag® Technology
- **KANSAS CITY, MO**
  Analytical Development
- **MADISON, WI**
  GPEx® Cell Line Development
  Technology
  Process Development
  Drug Substance Manufacturing
  Analytical Development
  Formulation Development
  mRNA *in vitro* Transcription
- **BLOOMINGTON, IN**
  Process Development
  Analytical Development
  Formulation Development
  Drug Substance Manufacturing
  Fill/Finish
  Lyophilization
  Vials, Prefilled Syringes, Cartridges
  Device Assembly & Packaging
- ▲ **BALTIMORE, MD**
  Gene Therapy
- ▲ **PRINCETON, NJ**
  Cell Therapy
- **MORRISVILLE/RTP, NC**
  Analytical Development
  Formulation Development
- **OXFORD, UK**
  Coming soon
- **LIMOGES, FRANCE**
  Process Development
  Formulation Development
  Fill/Finish
  Vials, Prefilled Syringes, Cartridges
  Packaging
- **ANAGNI, ITALY**
  Fill/Finish
  Vials, Prefilled Syringes
  Packaging
- **BRUSSELS, BELGIUM**
  Process Development
  Analytical
  Fill/Finish
  Prefilled Syringe
  Device Assembly & Packaging
- ▲ **GOSSELIES, BELGIUM**
  Cell Therapy
  Plasmid DNA
- ▲ **DUSSELDORF, GERMANY**
  Cell Therapy (iPSC)

● Biologics ▲ Cell & Gene Therapy

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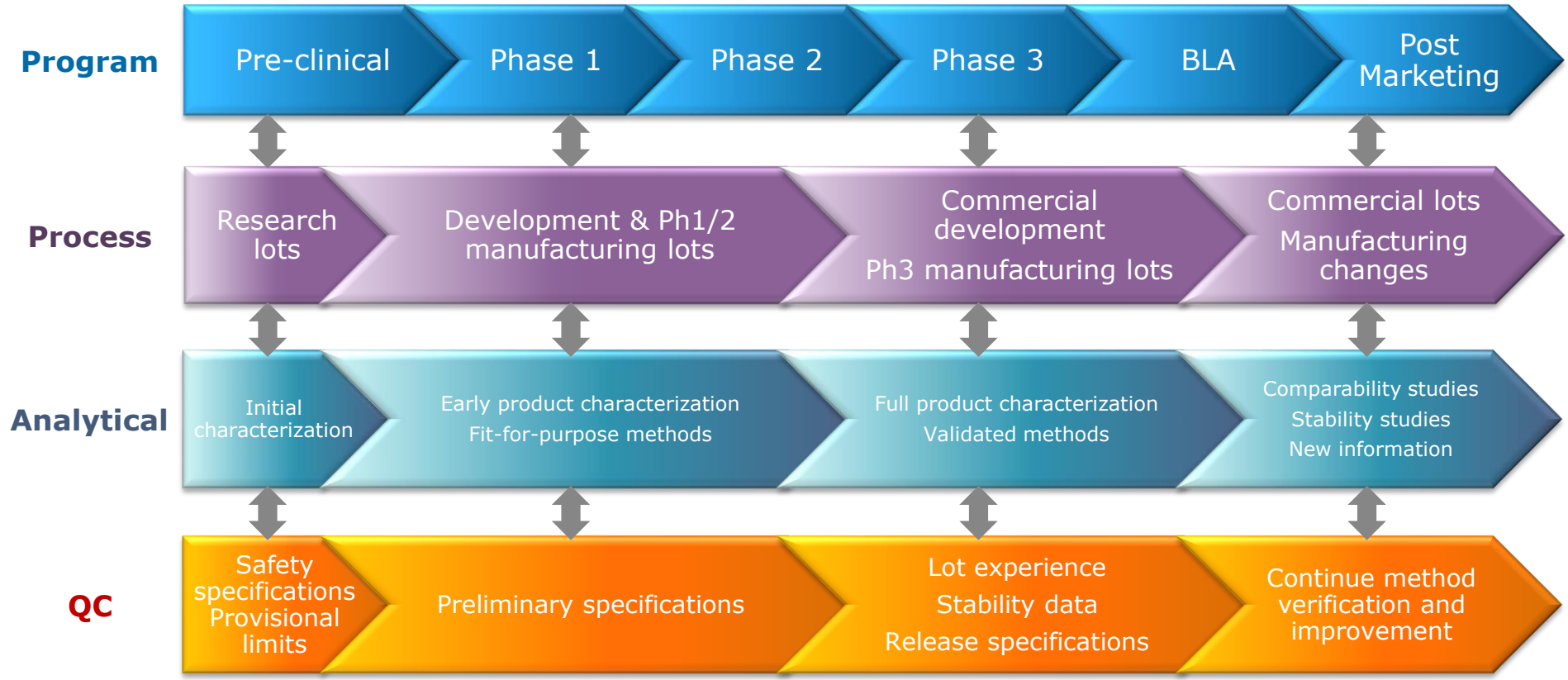
The Growing Biologics Market Has Led to a Corresponding Growth in the Biological Testing Needs

Biologics are medicinal products derived from various natural sources and are either extracted or produced by genetic engineering techniques or other technologies.

Biologics show a remarkable intrinsic variability and complexity, that makes the characterization more cumbersome than that of small molecules.

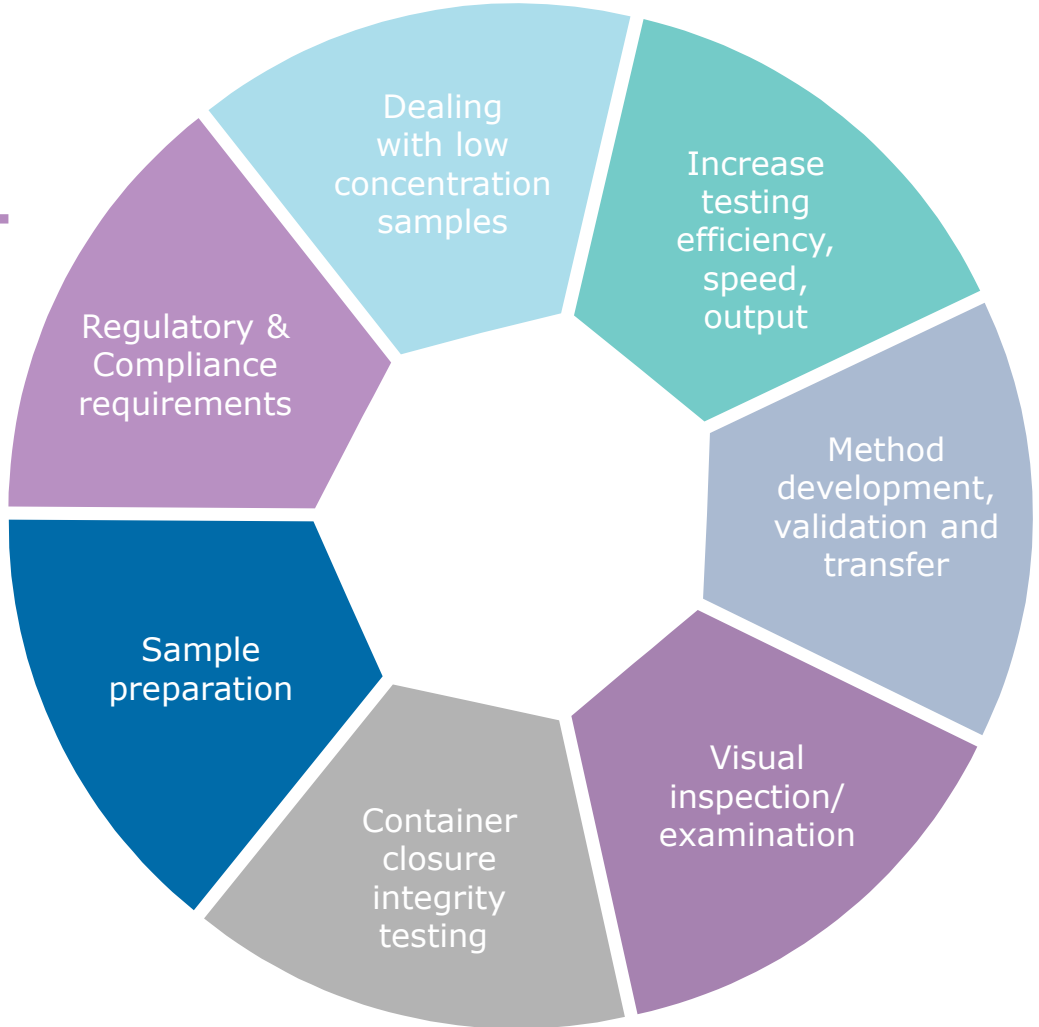
mRNAs | Antibodies | Recombinants | Fc-fusions | Bispecifics

Alignment of Product Quality into CMC Framework



Industry Trends: Analytical Challenges

- Surge of emerging modalities
- Evolving advancement & new technology in instrumentation
- Evolving regulatory requirements
- Increased volume of data
- Data integrity
- Scientists expertise/training
- Technical issues



Current Changes in Industry Trends

Greater demand for integrated/turnkey analytical solutions to meet short timeline, reduce development cycle & complex analytical characterization services

Pharma will innovate and prosper further by using the right tools

Digital Transformation

Artificial Intelligence

Big Data & Analytics

Flexible Production

How Companies are Addressing the Industry Trends?

- Increasing outsourcing
- Strategic partnership
- Technological advancements
- New operational techniques

Faster time-to-market and improved cost-efficiency are the primary reasons for the popularity of outsourced manufacturing services.

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Common Challenges
Method Development, Validation & Transfer

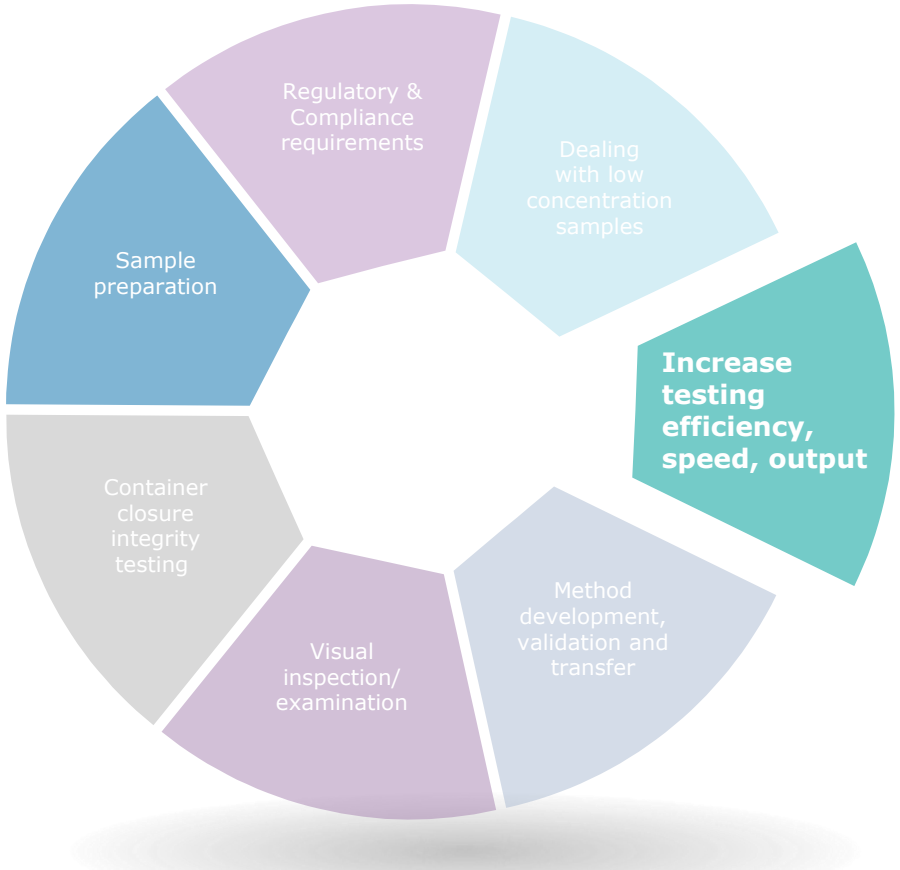
Specific challenge

- Phase appropriateness
- Stability-indicating
- Challenges with newer modalities (e.g., viral vectors/LNPs)
- Suitability for in process control testing

Examples on how to overcome

- Understanding of phase appropriate needs
- Assure work is informed by knowledge of molecule structure function, biochemistry and degradation mechanisms
- Apply technical, functional, and industry knowledge to design and evaluate methods via DoE/QbD

Common Challenges
Increase Testing Efficiency, Speed, Output



Specific challenge

- Implementation of new technologies
- Automation
- Rapid testing methods

Examples on how to overcome

- NTIx due diligence
- Continuous improvement
- Regulatory assessment
- Using statistical knowledge to guide decisions and/or impact of specifications

Method Related Challenges
Container Closure Integrity (CCI) Testing

Specific challenge

- Method development
- Need to test for biologics undergoing deep cold storage/shipment
- Increased scrutiny of regulators on CCI
- Drive towards a coherent CCI strategy across the product life cycle
- Development of surrogate and standard samples

Examples on how to overcome

- Interpretation of regulatory requirements
- Establish working groups on the topic to end up with company best practices
- Orthogonal methods for investigational purposes

Method Related Challenges
Visual Inspection/Examination

Specific challenge

- Ability to detect product-specific defect typical of biologics (e.g., agglomerates)
- Adaptability of multiple container format in automated visual inspection machine
- Regulatory definitions for lyo product defects

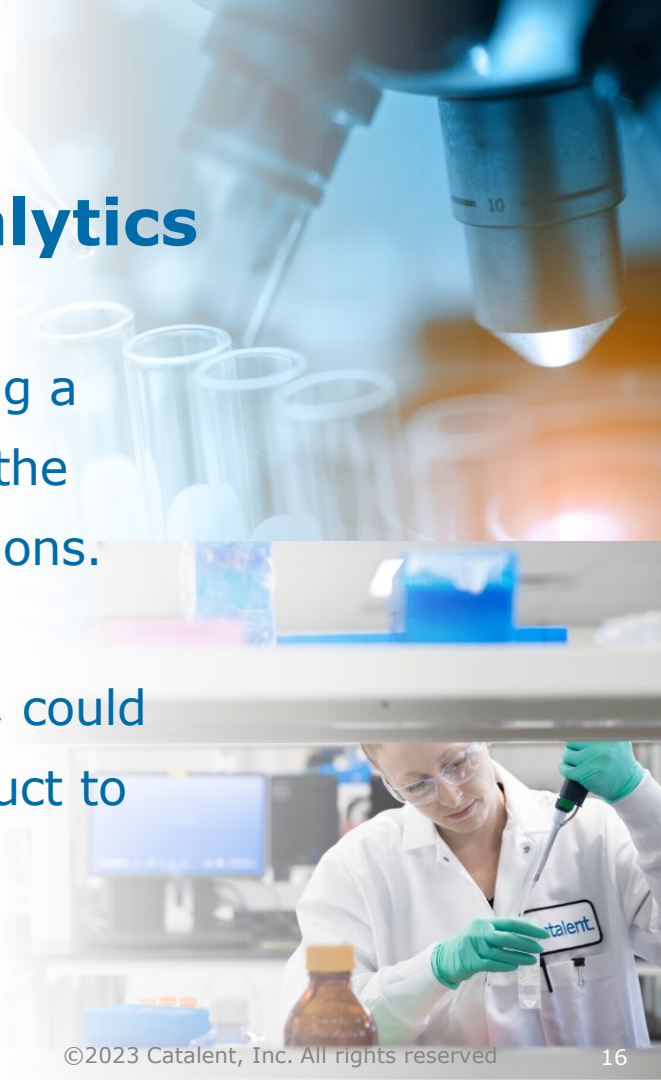
Examples on how to overcome

- Understand the product properties/characteristics to develop inspection criteria and defects kit
- Training of operators and/or appropriate program for automated inspection equipment

The Importance of Speed in Analytics

The success of the analytics depends on acquiring a good understanding of the theory that supports the method development and asking the right questions.

Any delays in developing or executing a method, could result in a delay in developing or supplying product to patients to enhance & improve their lives.



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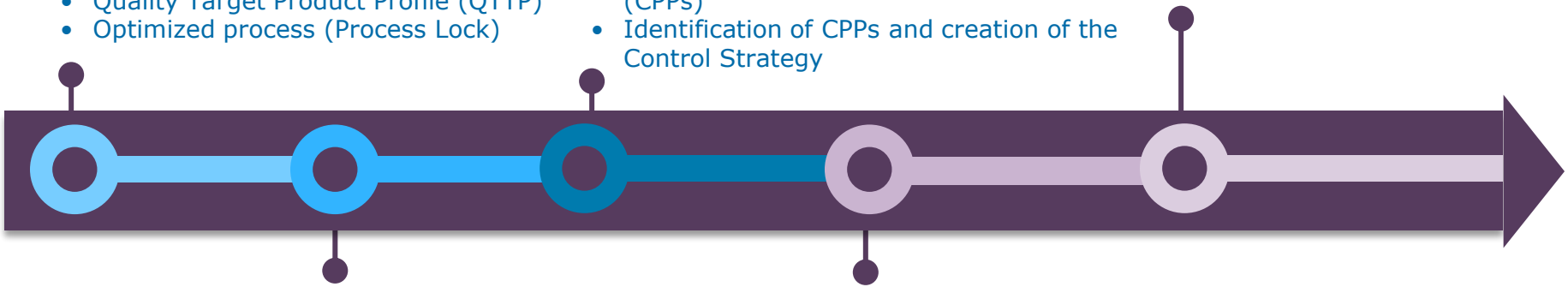
Bioanalytics Pathway Aligns with Program Development Lifecycle

Early-Stage Development (Ph 1&2)
- Initial process using platform technologies
- Quality Target Product Profile (QTTP)
- Optimized process (Process Lock)

Process Characterization Studies
- Determine scope of studies to evaluate potential Critical Process Parameters (CPPs)
- Identification of CPPs and creation of the Control Strategy

Commercial Manufacturing and Lifecycle Management



Risk Assessments (RA) or FMEAs
- Data mining (early-stage batches)
- Detailed assessment of Product Quality Attribute, Process Parameter and Raw Material RAs

Process Performance Qualification (PPQ) Campaign & Regulatory Filings

Catalent Biologics' process validation philosophy is based on the FDA's Guidance for Industry
Process Validation General Principles and Practices (2011) and the *Quality Risk Management ICH-Q9 Guidelines*

Product Lifecycle Milestones

Pharmaceutical Development

- Drug substance development
- Formulation development (including container/closure system)
- Manufacture of investigational products
- Delivery system development (where relevant)
- Manufacturing process development and scale-up
- Analytical method development

Technology Transfer

- New product transfers during development through manufacturing
- Transfers within or between manufacturing and testing sites for marketed products

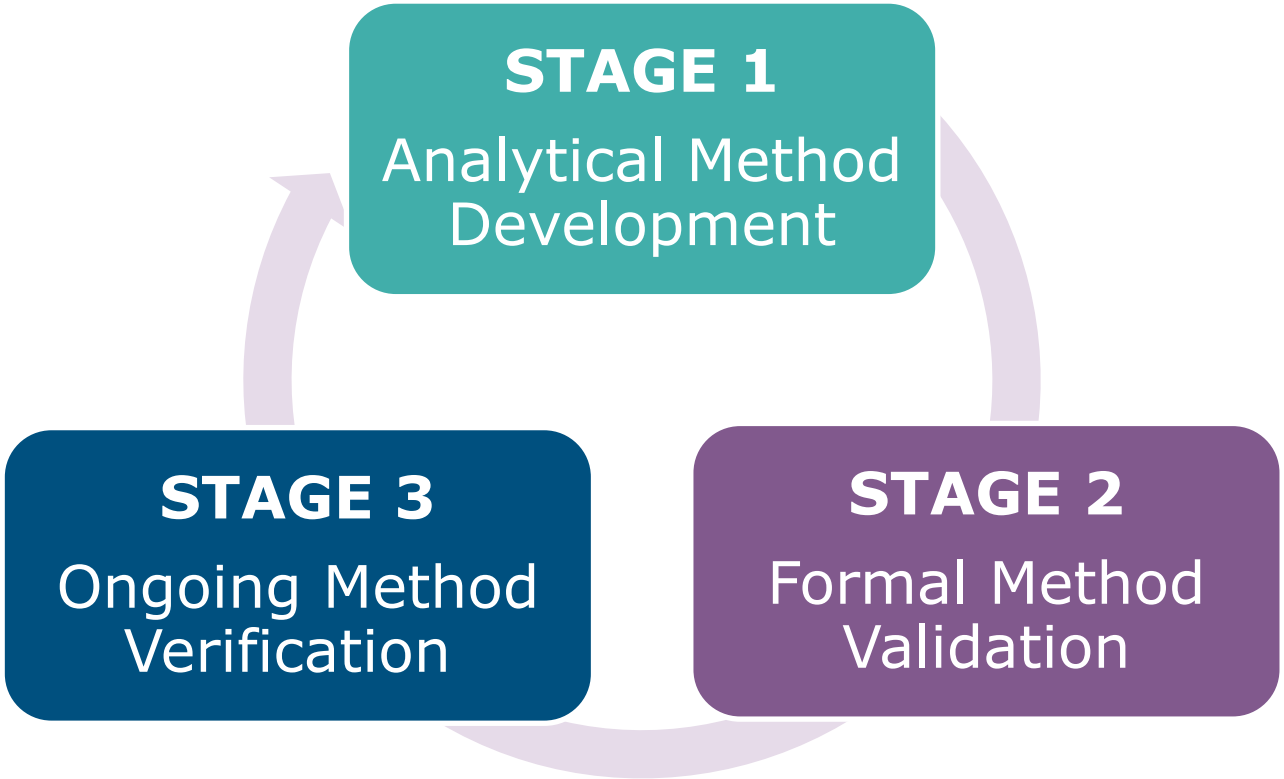
Commercial Manufacturing

- Acquisition and control of materials
- Provision of facilities, utilities, and equipment
- Production (including packaging and labeling)
- Quality control and assurance
- Release
- Storage
- Distribution (excluding wholesaler activities)

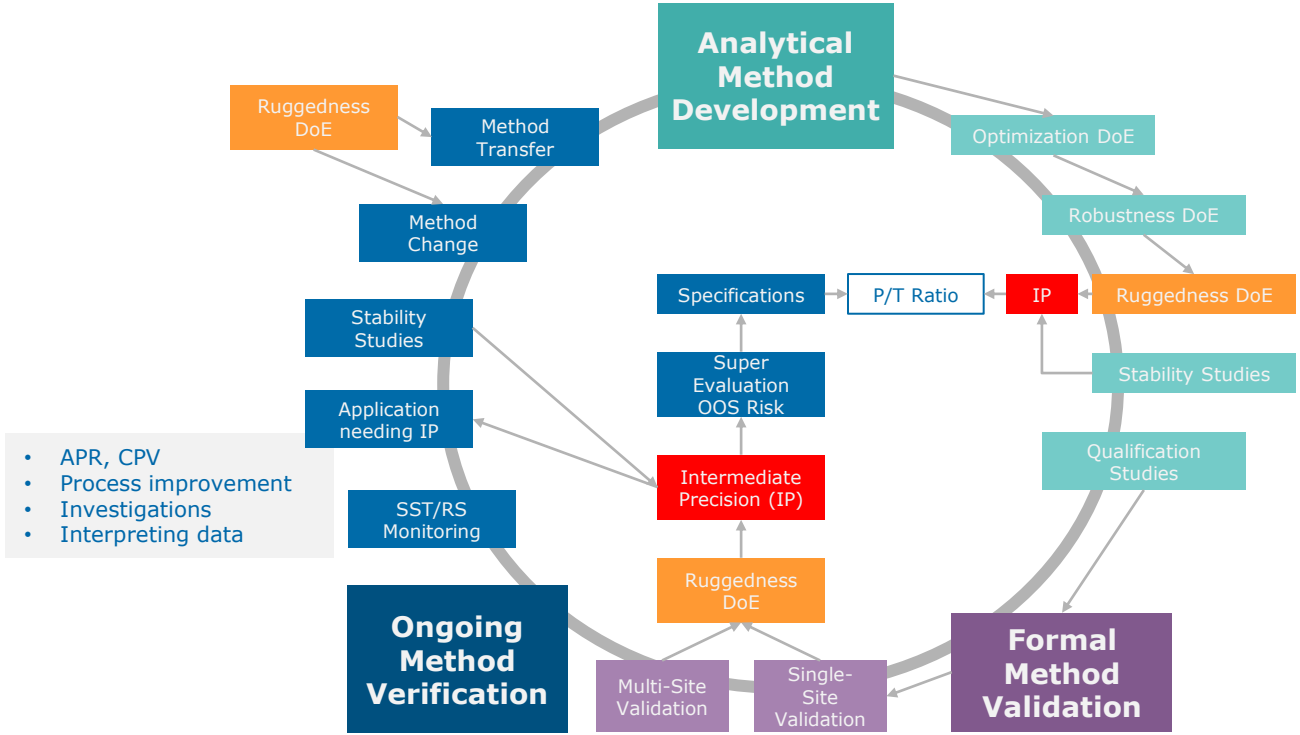
Product Discontinuation

- Retention of documentation
- Sample retention
- Continued product assessment and reporting

The Three Stages

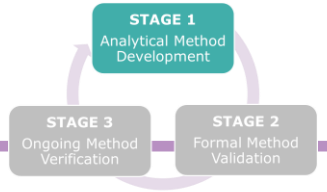


Catalent's Analytical Method Life-Cycle Model



At any time that data are being utilized to take decisions, understanding the measurement variability is important to properly interpret data and direct effective actions.

Stage 1
Analytical Method Development



Product/Process Development

Analytical Development

Pre-clinical

Tox Studies

Phase 1

Phase 2

Phase 3

PPQ

Commercial

GOALS

Short Term

Efficiently meeting the immediate needs of internal customers and clients with minimal amounts of resources

Long Term

Major Milestone

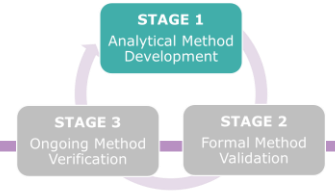
Pass formal validation

Best Practice

To provide an analytical method that is fit for purpose, optimized, robust, rugged, cost effective, precise, and accurate with monitoring strategy for enabling such activities as effective batch disposition, specification, setting/evaluation along with supporting investigations and process improvement.

The ongoing development of an analytical method should align with the current clinical phase of product/process development.

Focus Areas During Development



Early Phase

- Ensure potency
- Understand the impurity and degradation product profile
- Help understand key drug characteristics
- Indicate stability and begin to measure the impact of key manufacturing parameters

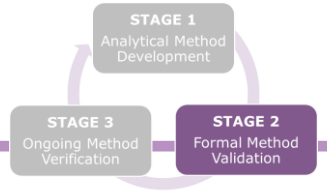
Focus on specificity, accuracy or linearity, and appropriate elements of Intermediate Precision

Late Phase

- Ensure robust, cost effective, transferable, accurate, and precision for specification setting
- Provide stability assessment, and approval of final marketed products
- Prepare for formal validation
- Support phase process development

Mimic formal validation with tighter criteria; heavy focus on estimating IP reliably through ruggedness studies or stability analysis

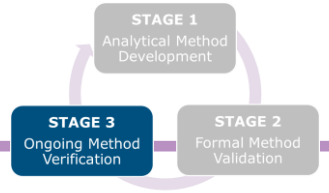
Stage 2
Formal Method Validation ICH Q2(R1)



Type of Analytical Procedure Characteristics	Identification	Testing for Impurities Quantitat.	 Limit	Assay • Dissolution[4] • Content/potency
› Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
› Interm. Precision	-	+[1]	-	+[1]
› Specificity[2]	+	+	+	+
› Detection Limit	-	-[3]	+	-
› Quantitation Limit	-	+	-	-
› Linearity	-	+	-	+
› Range	-	+	-	+

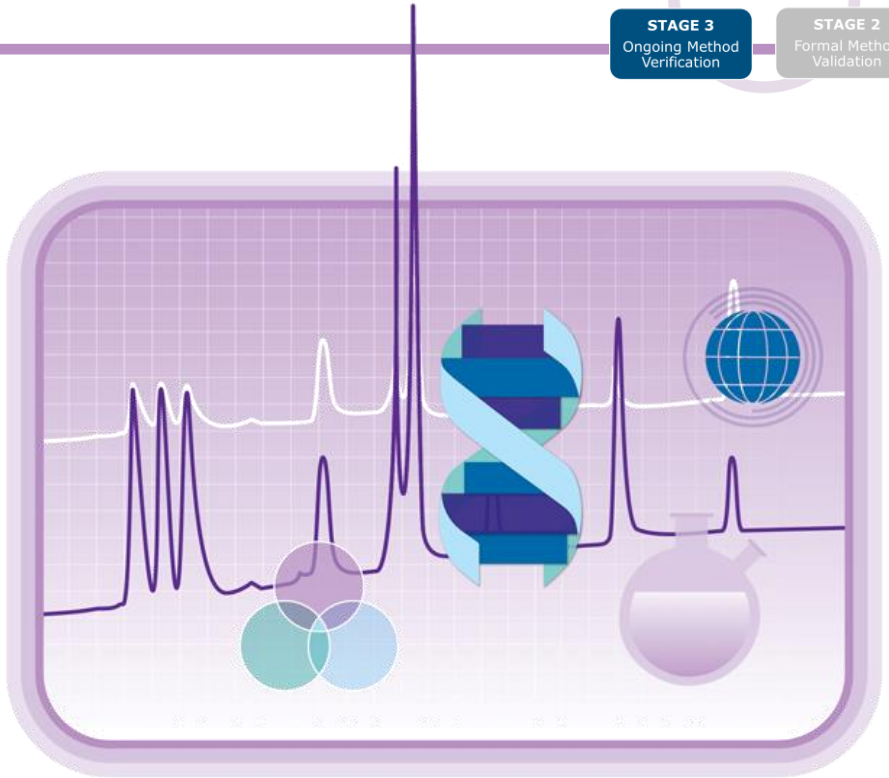
- signifies that this characteristic is not normally evaluated
+ signifies that this characteristic is normally evaluated
1. in cases where reproducibility has been performed, intermediate precision in not needed
2. lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s)
3. may be needed in some cases
4. measurement only

Stage 3
Ongoing Monitoring



The primary purposes in stage 3 of the analytical method lifecycle are:

1. Ongoing monitoring of the method using risk-based approaches
2. Improvement of the method where required



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Driving Reliable Solutions Across a Global Community of Scientists

With the help of our experienced scientific team and range of capabilities, our goal is to serve as your strategic partner to support all your biologics analytical development and testing needs.

1,500 Scientists | 30+ Years Experience | 26 Laboratories | 10 Countries

Conclusion

- The goal of method development is more than just qualification/validation
- A tailored, well planned & executed development is key
- Meet authorities' expectations
- Apply a scientific rationale and make data driven decisions
- Build a strong analytical package with fit for purpose methods
- Leverage the knowledge of the network because experience counts

A well-structured product life-cycle management leads to increased success, increased efficiency, and better-quality therapeutics for patients.

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Thank you

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more products. better treatments. reliably supplied.™

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Questions

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Catalent®
BIOLOGICS

Analytical Capabilities

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more products. better treatments. reliably supplied.™

Integrated & Stand-Alone Capabilities | Single Source for a Range of Biologics Analytical Services

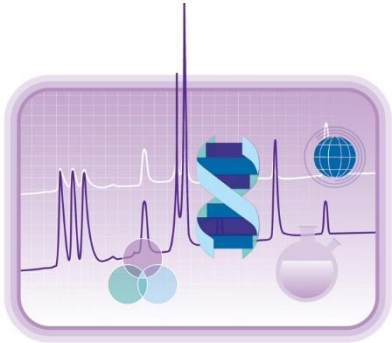
For **Integrated** or **Stand-Alone** Projects

GMP, GLP & characterization studies for:

- Drug substance, drug product or intermediates
- New Biologic Entities (NBEs) & biosimilars/biobetters

Wide variety of sample types:

- Monoclonal, polyclonal & bispecific antibodies
- Bioconjugates
- Oligonucleotides
- Recombinant proteins
- Fusion proteins
- Pegylated peptides
- Gene and cell therapies
- Aptamers
- Vaccines
- Oligosaccharides
- Cell-based bioassays for small & large molecules



70,000+ ft^3 of Stability Chambers

Thousands of Analytical Methods

Biologics Analytical | Comprehensive Capabilities for All Stages of Development

Support for:

- Method development, optimization, validation and transfer
- Stability testing
- In-process testing
- Release testing
- Biosimilarity
- Formulation & preformulation
- Extractables & leachables
- Reference standards
- Many more…

Renowned expertise in **bioassay** & **binding assay**

Kansas City, MO

Opened	1992, large molecule analytical testing
What's New	Adding 2 new labs (3,500 & 3,000 sq. ft. each) by Q1 2023, adding ~50 positions
Total Area	15,000+ sq. ft. Biologics Analytical Labs

PRODUCT FOCUS

- Biologics including proteins, mRNA, cell & gene therapies, biosimilars
- Drug substance, drug product and intermediates

ANALYTICAL CAPABILITIES

- Release testing of clinical and commercial material; stability testing and storage
- Full product characterization; analytical reference standard qualification and characterization
- Extractables and leachables; ad hoc sample analyses

SITE OFFERINGS

- Method management: development, optimization, transfer, verification
- Phase specific method validations per ICH guidelines
- Manufacturing and formulation development support

STRENGTHS

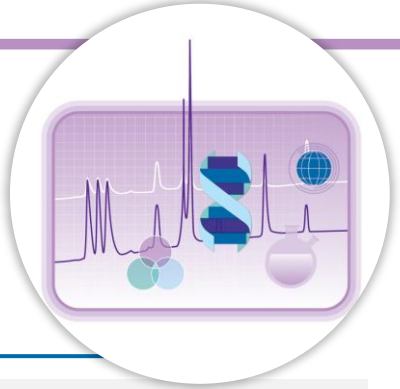
- BLI/SPR, AUC, FACS
- Polysorbates
- Antibody-drug conjugates

Kansas City's Comprehensive Biologics Analytical Experience

- Support of **Innovator** and **Biosimilar** programs
- Characterization and GMP support for a full spectrum of biologics including **drug substance** and **drug products** and **intermediates**
- Capabilities include various **orthogonal analytical** techniques required for characterization and testing of Biologics
- Experience with biologics in various project phases **since 1992** from **pre-IND to NDA/BLA/MAA approval to commercial release**
- Support for the **US and outside markets** in characterization and GMP activities
- All activities performed in **cGMP laboratories** by **analysts trained in cGMP** regulations
- >150 clients supported since 1999 (entry into Contract business)

Durham, North Carolina

Coming Soon	New site, July 2023
Transition Plan	Current RTP Biologics Analytical team to relocate, adding 200+ over time
Total Area	80,000+ sq. ft.



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SITE OFFERINGS

- Method management: development, optimization, transfer, feasibility, verification, pre-validation
- Phase specific method validations per ICH guidelines
- Good laboratory & manufacturing practices (GLP & GMP)

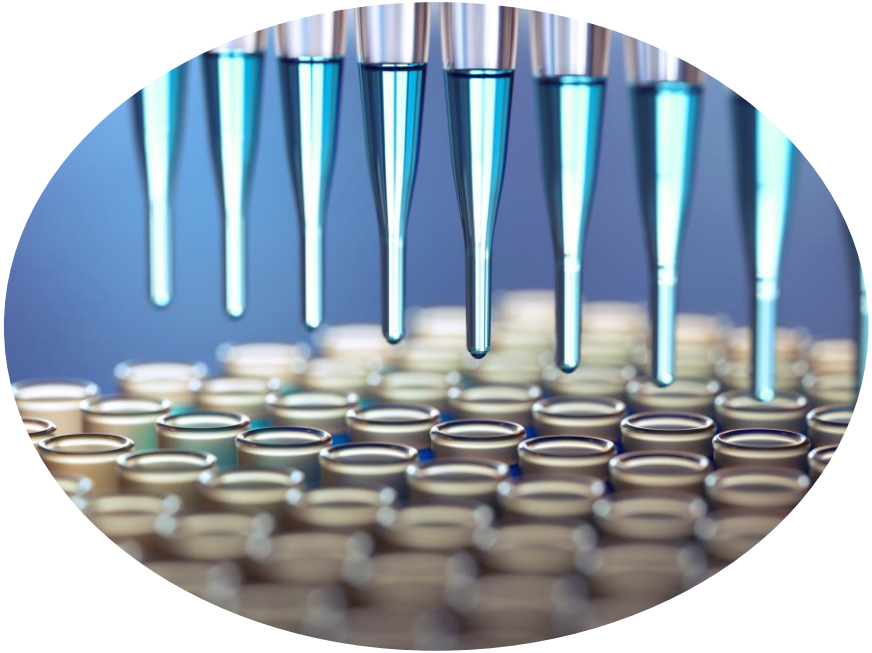
STRENGTHS

- Binding & potency, structure, identity & purity
- Bioassay automation
- Supports emerging modalities including mRNA, cell and gene therapies

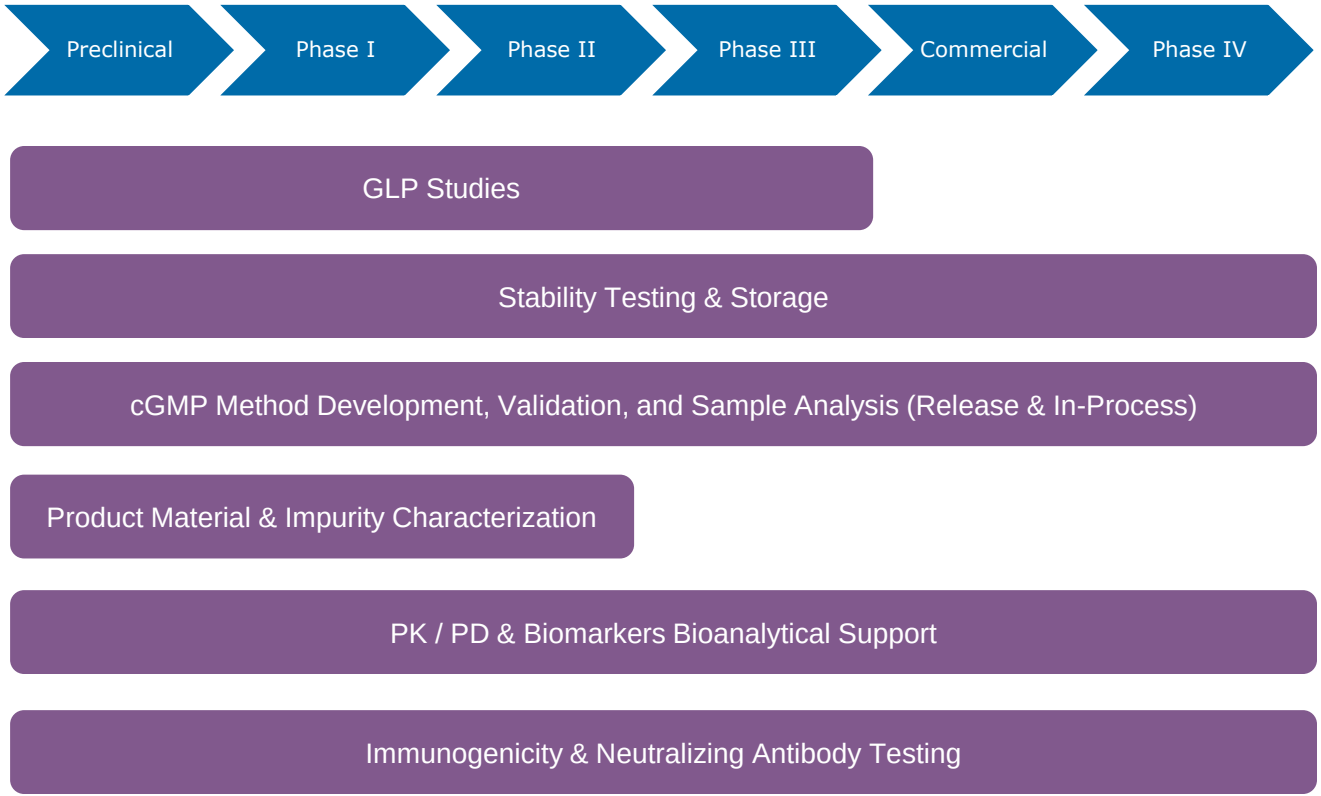
New Durham Facility Coming Online in July 2023

State-of-the-Art Laboratory

- 80,000 square foot facility
- Spacious, custom designed laboratory space
- Dedicated to biologics analytical with latest technology, instrumentation and automation
- Dedicated one way pass PCR suite
- 4x current capacity
- Flexibility for resources including dedicated FTEs and lab space

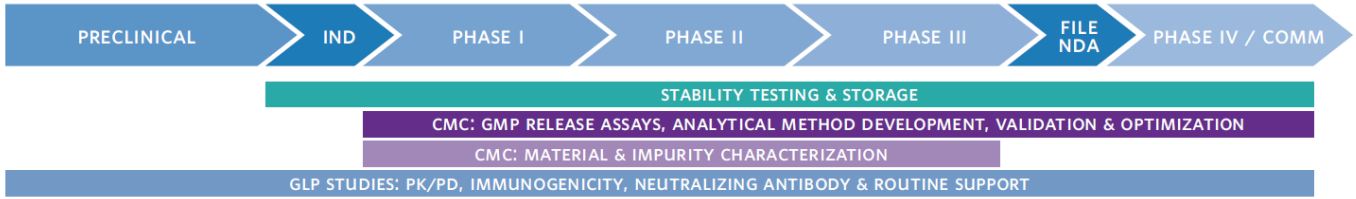


Durham’s Integrated Solutions Across All Phases



BIOLOGICS ANALYTICAL SERVICES

Catalent BIOLOGICS



STABILITY STORAGE CAPABILITIES

Over 70,000 ft^3 of mapped/qualified chambers
Temperature range: -80C to 60C
Humidity range: 25% to 90% RH
Redundancy in power, water & air systems
ICH photostability option 2
WHO, ASEAN, ICH and customizable chambers
Thermal cycle & freeze/thaw exposures
In-use studies
Dedicated stability coordinators

CMC ANALYTICAL CAPABILITIES (GMP & NON-GMP)

RELATIVE POTENCY BIOASSAY
Bioassay automation (robotics)
Proliferation/cytotoxicity assays
Reporter gene assays
mRNA transcription assays
CRE-luciferase assessment
NF-KB luciferase assessment
Surrogate assays for effector antibody potency (ADCC and ADCP)
Receptor activation (phosphorylation) assays
Coagulation assays
Flow cytometry
Master and working analytical cell banks
- Generate, characterize and/or store
- Continuous culture analytical banks
- Thaw-and-Go analytical banks

BINDING POTENCY ASSAYS
Binding assay automation (robotics)
ELISAs (96 & 384-well formats)
- Colorimetric
- Fluorescent/luminescent
- Electrochemiluminescence (ECL) (MSD)

Radioassays
- Radioligand binding assays
- Radioligand uptake assays

kD-determining binding assays

IMPURITY ASSAYS
Host cell residual DNA content
Host cell protein (generic & specific)
Residual protein A, L, G
Residual insulin
Residual glucagon
Biolayer interferometry (BLI; Octet)

MOLECULAR BIOLOGY
PCR/qPCR/ddPCR
- TaqMan & SYBR green
- qPCR virus detection

Mycoplasma determination
Magnetic bead extraction (automated)
Agarose gel analyses
- RNA/DNA ID & integrity testing
- Restriction digest DNA ID testing

PHYSICAL & COMPENDIAL TESTING (USP, EP, JP)
Extinction coefficient determination
Protein concentration by UV/Vis
Appearance testing (USP/EP)
Color & clarity (USP/EP)
pH (USP/EP)
Reconstitution time
Fill volume
Functional testing (PFS, auto-injector, cartridge)
Osmolarity
Refractive index
Specific gravity
Water content by Karl Fischer titration:
- Volumetric
- Coulometric

Sub-visible particle analysis:
- HIAC
- MFI
- Microscopy
- Dynamic Light Scattering (DLS)

Trace metals:
- ICP-OES
- ICP-MS
- AA

Particle size determination

ELECTRO-SEPARATION ANALYSES
Capillary electrophoresis
- CE-SDS/CZE/CGE incl. LIF detectors
- Capillary IEF (Protein Simple iCE3)
- Lab chip
- Maurice

Slab gel electrophoresis
- Reducing & non-reducing SDS-PAGE
- Western blot (Gel & WES/JESS)
- IEF gels

CHROMATOGRAPHY
UPLC/HPLC with the following detection: UV/FLR/ELSD/CAD/RI/MALS/MS, supporting: IEX, HIC, HILIC, reverse phase, SEC
- Disulfide bonding with free Cys analysis
- Glycosylation (N- and O-linked)
- Oxidation
- Payload-linkers, DAR, free drug for ADCs
- Sequence variants
- Amino acid composition analysis
- Carbohydrate analysis (released glycans, monosaccharides, sialic acid)
- Polysorbates (PS20, PS80, poloxamer)
- Anti-foam
- Triton

MASS SPECTROMETRY (MS)
UPLC/HPLC/NanoLC with Single Quad, Triple Quad, MS types
- Disulfide bonding
- Glycosylation (N- and O-linked)
- Carbohydrate analysis (released glycans, monosaccharides, sialic acid)
- Chemical & post-translational modifications (LC/UV/MS/MS-based peptide mapping)
- Process impurities, clearance & degradant ID
- Intact, reduced, PNGase F-treated average mass (MW) determination
- Sequencing (N-terminal, oligonucleotides)
- Extractables & leachables
- Top down, middle down, bottom up
- Structural elucidation
- HCP ID via UHPLC-MS/MS

GC-MS with headspace & FID
- Residual solvents & impurities

EXTENDED CHARACTERIZATION
Analytical ultracentrifugation
- Sedimentation velocity/equilibrium
- Absorbance or interference optical detection

Differential scanning calorimetry (DSC)
Light scattering (MALS, DLS)
FTIR

MICROBIOLOGY
Identification of microorganisms
Sterility qualification & testing
Endotoxin detection
Microbial limits & enumeration testing
Bioburden
Antimicrobial & disinfection testing

GLP CAPABILITIES

Cell-based bioassays & ELISAs
Immunogenicity
- Anti-Drug Antibodies (ADA)
- Neutralizing antibodies
- Reporter gene

Drug metabolism
- PK/PD & biomarkers
- Bioanalytical

Catalent®
BIOLOGICS

discover more.

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more products. better treatments. reliably supplied.™