ASTM INTERNATIONAL
Helping our world work better

Technical Committee E55

Manufacture of Pharmaceutical and Biopharmaceutical Products

www.astm.org

What is ASTM International?

ASTM International

- 118 year-old international not-for-profit organization that develops consensus standards – including test methods
- Participation open to all - 32,000 technical experts from across the globe

ASTM's Objectives

- Promote public health and safety
- Contribute to the reliability of materials, products, systems and services
- Facilitate national, regional, and international commerce

ASTM Standards

- Known for high technical quality
- Over 12,500 ASTM standards for more than 100 industry sectors
- Over 5,000 ASTM standards used in regulation or adopted as national standards around the world in at least 75 countries

6,788
ASTM standards have been adopted, used as a reference, or used as the basis of national standards outside the USA

Role of Standards in Global Regulatory Frameworks

Legal basis for the use of Standards

- Standards are voluntary until referenced in regulation or contracts

USA

- Use of Standards described by FDA

Other regions

- ASTM International Standards are cited in many laws and regulations around the world
- To date, E55 Pharmaceutical Standards have not been cited in regulation

What are the characteristics of Standards Development Organizations (SDOs)?

- SDOs differ in organization and processes used to develop Standards
- ASTM International is a voluntary consensus standards organization
- "A voluntary consensus standards body is defined by the following attributes:

  (i) Openness; (ii) Balance of interest; (iii) Due process; (vi) An appeals process; (v) Consensus"

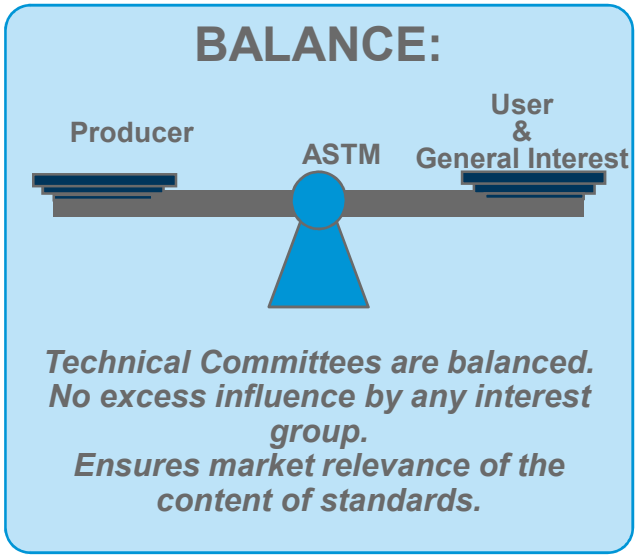
How ASTM Works

ASTM provides Infrastructure and Tools:

- Templates and meetings support
- Online balloting and online collaboration areas
- Administrative support, ASTM managers and editors
- Promotional support

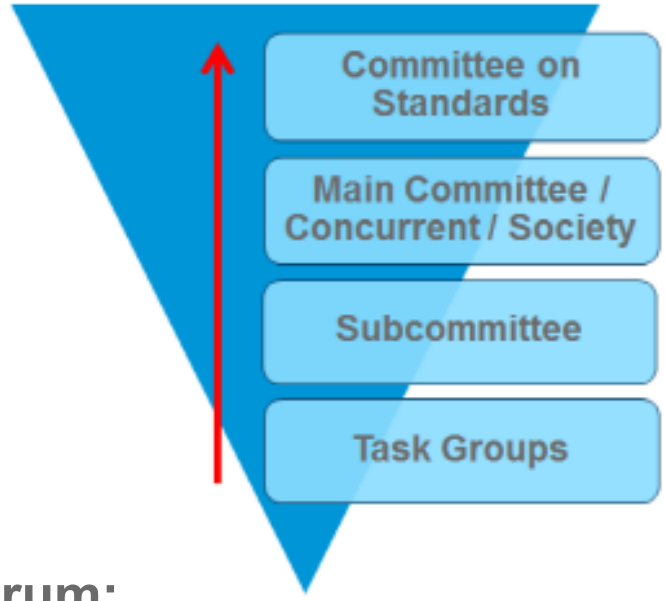
Industry comes Together:

- Experts, individuals, organizations, academia, regulators, trade associations, consultants and consumers
  - Exchange expertise and knowledge
  - Participating in a transparent process – open to anyone, anywhere
- ASTM Staff does not write standards, remains neutral



Snapshot: Standards Development Process

ASTM Process at a Glance



COS – 30 day ballot, Review Due Process, Appeals

Main – 30 day ballot, 60% return, 90% approval

Sub – 30 day ballot, 60% return, 2/3 approval

TG – no official ballot, bulk of work completed here, unofficial voting sometimes takes place

**see detailed workflow for more specifics*

Open Forum:

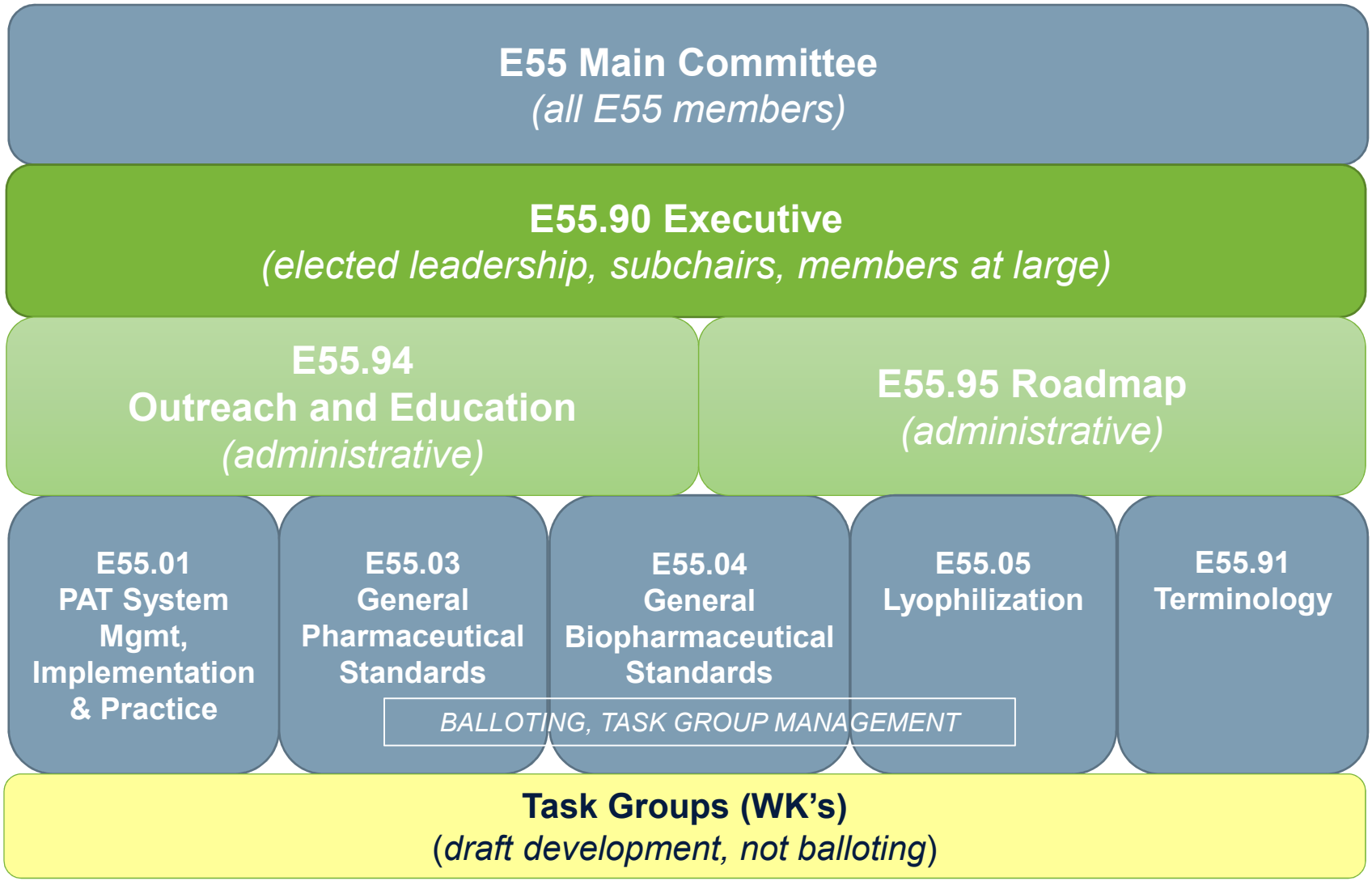
- Direct stakeholder involvement
- Every member has equal say - *1 vote per interest (organization)**
- Consensus-based procedures
- Private and public sector Cooperation
- Balance of Interests – ensures market relevance

E55 Scope and History

Scope: development of standardized nomenclature and definitions of terms, recommended practices, guides, test methods, specifications, and performance standards for the manufacture of pharmaceutical and biopharmaceutical products.

- Formed in 2003 under previous title “Pharmaceutical Application of Process Analytical Technology”
    - Improve efficiency, process control, safety, and ultimately, product quality and public health
- In 2006, E55 expanded to address all aspects of pharma, changing to current title “Manufacture of Pharmaceutical Products”
- In 2015, E55 again expanded to meet industry’s needs to the title of “Manufacture of Pharmaceutical and Biopharmaceutical Products”

Organization and Subcommittees



E55 Membership

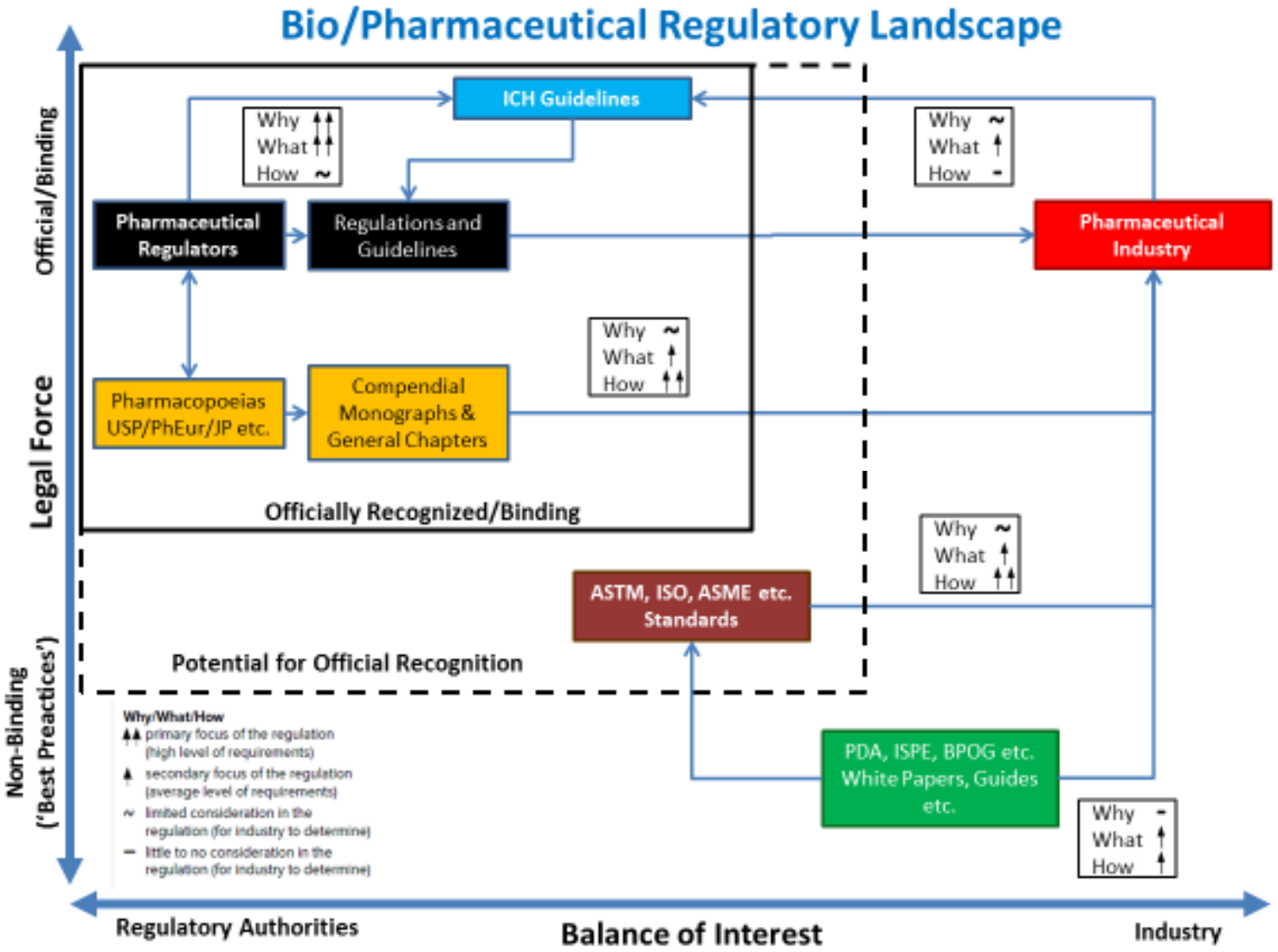
Diverse stakeholders

- 180 members representing
  - Industry: pharma, biopharma, suppliers
  - Government
  - Academia
  - Standards Development Organizations
  - General interest

International Membership including

- Australia, Belgium, Canada, Denmark, Finland, Germany, Ireland, Italy, Japan, Korea, Mexico, Mongolia, Nepal, Netherlands, Portugal, Sweden, Switzerland, Singapore, United Kingdom & United States

Regulatory Landscape



Thank you!

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Standards for Single-Use Support Emerging Technologies

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The pipeline is rich in new modalities

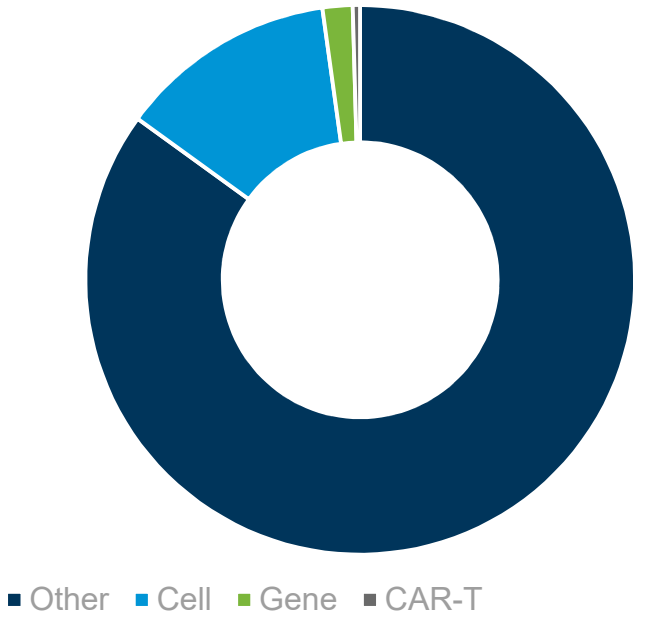
NIH U.S. National Library of Medicine

ClinicalTrials.gov

264,846 research studies in 50 states and 203 countries

- 8608 cell therapies
- 1149 gene therapies
- 201 CAR-T cell programs

Numbers are for studies recruiting; active, not recruiting; and enrolling



Industry recognizes the need for harmonization, co-opetition

Process Technologies	Single-use standards
	Continuous processing standards and guidance
	Reduce/eliminate changeover between products
	'Ball room' design and declassified facility
	Global regulatory harmonization
	Viral validation strategy
	Parallel processing of multiple products
	Cross-use of consumables among products

From Biophorum Biomanufacturing Technology Roadmap

Abbvie, Asahi Kasei Bioprocess, AstraZeneca, Bayer, Biogen, CRB, Emerson, Fujifilm Diosynth, GCON, GE Healthcare, GSK, ImmunoGen, Janssen, Kaiser Optical, Lonza, Merck, NNE, Novasep, Pall, Pfizer, Roche, Sanofi, SSB, Shire, Takeda, TF, UCB

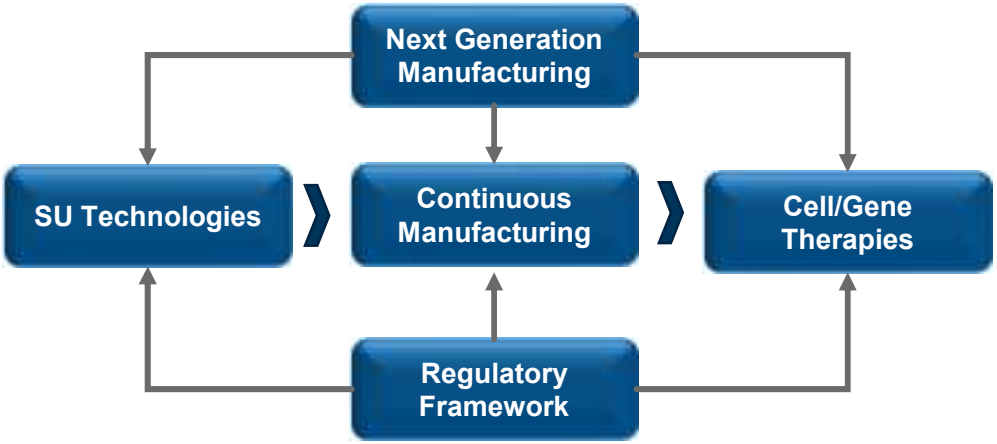
Market pressures require manufacturing innovation

Continuous, batch or hybrid manufacture

Single/multi-product - rapid changeover

Highly automated – innovative technology, robots, sampling, control

What has this to do with single-use?



- Provides a better assurance of sterility
- Reduces cross contamination

  - Meet or exceed current performance
  - Reduce or delay capital investment

Leverage professional societies to develop best practices

ASTM E3051-16 is an overarching standard

Based on PDA TR 66
Science and risk based approach
Critical aspects, functional performance
Materials selection and design
Supplier qualification and technical diligence
Subject matter expert requirements
Testing and handling procedures
Qualification and verification
Technical support and change control
Transportation receipt and deployment
Alternate source, interchangeability

Standard Guide for
Specification, Design, Verification, and Application of
Single-Use Systems in Pharmaceutical and
Biopharmaceutical Manufacturing

Multiple standards in development

Multiple standards are in development

WK43975 New Practice for determining and **characterizing bioprocess extractables** from materials used in single-use applications

WK43741 New Practice for **Testing Integrity** of Single-Use Systems at Vendors Manufacturing Facilities

WK43742 New Practice for Characterizing **Particulate burden** from Single-Use Systems for End-user Impact Assessment

WK48084 New Practice for Determining and **Characterizing Leachables** released from Materials used in Single-use Systems under bioprocess operating conditions

*WK47355 New Practice for **Controlling Integrity** of Single-Use Systems during Biopharmaceutical manufacturing process at End-user factory*

*WK47356 New Practice for Characterizing **Particulates Burden** from Single-Use Systems at Vendor Factory*

WK47357 New Practice for Application of Single-use System in Pharmaceutical and Biopharmaceutical manufacturing

*WK48956 New Practice for **Biocompatibility** of Single-use System at End-user Factory*

*WK48957 New Practice for **Purity, Biocompatibility and Toxicity** of Raw Materials used in the manufacturing of Single-use System*

There are six different types of ASTM standard

Specification – item and all its properties

Test method(s) – way or ways of measuring a property

Practice – how to conduct a procedure, without including a value for the result

Guide – how to choose the right approach for various conditions

Classification – an arrangement of information (e.g. types of filters) that doesn't specify a course of action

Terminology – defines an item, symbol, abbreviation or acronym

WK 43975 New Practice for Determining and Characterizing BioProcess Extractables from Components, Subassemblies, and Assemblies Used in Single-Use Applications: Part 1-Preparation of Extractables Test Solutions

Lead: Jim Bray

Scope: defines the standard method to create extraction samples from single-use bioprocess systems using model bioprocess extraction solutions. This practice covers only the preparation of extractables test solutions. Analysis of these extractables test solution is covered in a separate practice (WK43975 Part 2: Analysis of Extractables Test Solutions, in development).

Status: currently on hold

Challenges: Alignment with USP

Time line: ??

*WK 48956 New Practice for **Biocompatibility** of Single-use System at End-user Factory*

Lead: Greg Bremer, Sartorius Stedim Biotech

Scope:

- Assess impact of materials on cell growth
- Best Practice for selecting adequately sensitive cell lines
- Guidance for representative testing and controls: surface areas, irradiation of parts, controls
- Supplemental to current USP (87 and 88) and ISO 10933 tests

Status:

- Kick off today: call for volunteers to join team
- Ready to work through draft with work group

Time line:

- Assemble team by May 31
- Draft ready for vote Q3 2018

WK 54630 Extraction of Particulate Contamination from Single Use Components

Lead: Klaus Wormuth, Sartorius Stedim Biotech

Scope:

- Set overall parameter space of allowable procedures for **extraction of particulates** from single-use components and assemblies
- Will not address particulate measurement methods
- Applicable to both sub-visible (“USP 788”) and visible particulate analysis
- Will be a “standard practice” rather than “test method”

Suppliers involved: Sartorius, Millipore, Pall, Meissner, Saint Gobain, Dow Corning, GE

End users involved: Merck, Novartis, Johnson&Johnson, Amgen, Consultants

Status: active

Challenges:

- Method validation: which is best approach and how to validate an extraction method
- Applicability to a broad range (size/complexity) of single-use components and assemblies

Time line:

- Currently still discussing overall scope regarding method validation approach(s)
- First draft ready for first vote by Q4 2018?

WK 43742 New Practice for Characterizing Particulate burden from Single-Use Systems for End-user Impact Assessment

Lead: Patrick Evrard, Pall

Scope: all product path components (fluid or powders) of pharmaceutical and biopharmaceutical Single-Use manufacturing systems used for parenteral applications that have the potential to affect product quality and patient safety.

Not intended to be used by suppliers of SUS

Status: currently on hold

Challenges:

Time line:

Overview: WKs on Integrity Testing of SUS

Standard practices for Integrity Assurance incl. physical test methods:

WK43741 Practice for Testing Integrity of SUS at Manufacturing Facilities

WK55036 Controlling Integrity of SUS during biopharmaceutical manufacturing processes at End-user factory

Standards for probabilistic MIT test methods:

WK51753 Performing Microbial Ingress Test in Liquid Immersion for SUS applications

WK51754 Microbial Ingress Test in Aerosolization for SUS applications

*All WKs currently under the lead of **S**ingle-**U**se **T**echnology **A**ssessment **P**rogram (SUTAP)*

WK43741 Practice for Testing Integrity of SUS at Manufacturing Facilities

Lead: Alain Pralong (SUTAP) -> Marc Hogreve (Sartorius Stedim Biotech)

Scope:

- Describe a risk- & science based approach for integrity assurance of SUSs during the development, validation and manufacturing life cycle
- Sterility assurance & product loss (operator & environmental safety)
- Correlation between physical & microbial testing
- Will be a “standard practice” rather than “test method specification” with focus on physical testing
- A document in conjunction with WK55036 (from end-user point of view)

Status: on-hold

Challenges:

- Find a balanced risk-based approach in alignment with USP <1207>

Time line:

- April 2018: Transfer the document back into ASTM collaboration area, pull the team together & re-start WK
- Draft to be ready for bulleting Q4|2018

WK55036 Controlling Integrity of SUS during biopharmaceutical manufacturing processes at End-user factory

Lead: Alain Pralong (SUTAP) -> tbd (in discussion between end-users in the BPSA IT task force)

Scope:

- Describe a risk- & science based approach for integrity assurance of SUSs during use at end-user site
- Sterility assurance & product loss (operator & environmental safety)
- Correlation between physical & microbial testing
- Will be a “standard practice” rather than “test method specification” with focus on physical testing
- A document in conjunction with WK43741 (from supplier point of view)

Status: on-hold

Challenges:

- Find a balanced risk-based approach in alignment with USP <1207>

Time line:

- April 2018: Identify lead, transfer the document back into ASTM collaboration area and setup team
- Draft to be ready for bulleting Q4|2018?

WK51753 Performing Microbial Ingress Test in Liquid Immersion for SUS applications

Lead: Alain Pralong (SUTAP) ?

Scope (draft):

- Leak characterization and identification of MALL under use-cases using liquid immersion MIT
- Test method specification with focus on challenges coming with SUS testing
- Correlation between physical & microbial testing
- A document linked to WK43741 & WK55036

Status: planned

Challenges:

- Define a test method that can be reasonably applied on a statistical meaningful amount of samples to reduce as far as possible the uncertainty of the probabilistic nature

Time line:

- May 2018: Evaluate the need* and re-start or cancel the WK

** USP<1207> requests to identify the MALL under use-case conditions. Because the aerosol challenge test seems to be more representative compared to immersion, the need for this WK needs to be evaluated and finally agreed*

WK51754 Microbial Ingress Test in Aerosolization for SUS applications

Lead: Alain Pralong (SUTAP) ? -> Carole Langlois (Sartorius Stedim Biotech)

Scope (draft):

- Leak characterization and identification of MALL under use-cases using aerosolization MIT
- Test method specification with focus on challenges coming with SUS testing
- Correlation between physical & microbial testing
- A document linked to WK43741 & WK55036

Status: planned

Challenges:

- Define a test method that can be reasonably applied on a statistical meaningful amount of samples to reduce as far as possible the uncertainty of the probabilistic nature

Time line:

- May 2018: Setup team and detail scope, start writing
- Draft to be ready for bulleting Q2|2019

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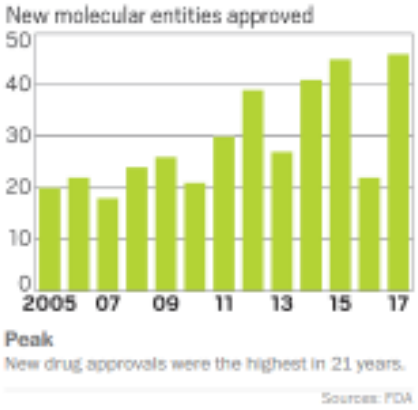
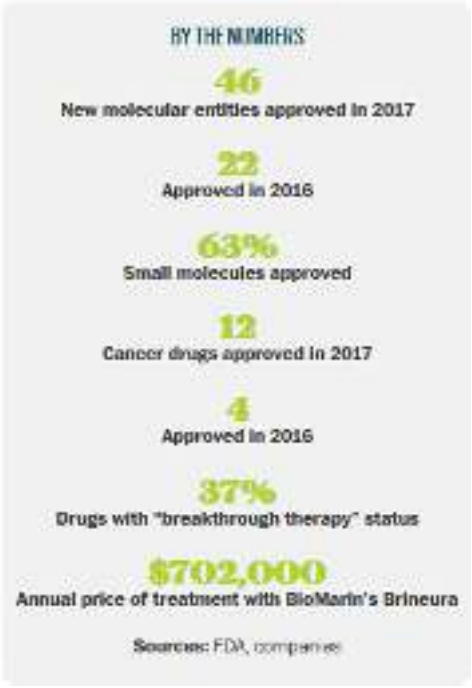
Additional slides?

2017 – a banner year for new drugs!





Plus

Two CAR T-cell therapies
One gene therapy
Four CM approvals

C&EN, Jan 22 2018

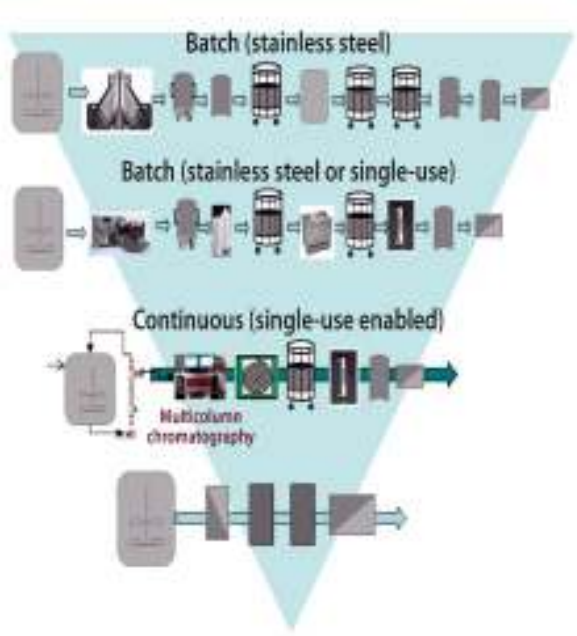
Growth attracts competition, supports innovation; increases variety

Materials of construction and designs continue to evolve
Designs may be functionally comparable but are seldom interchangeable
Limited standardization
Demand is hard to predict, especially for new products
Lead times are never short enough
Disruption can result from diverse events
New players enter the field – Amazon, Google, Apple

Change is constant, positive – embrace it, manage it

Continuous biomanufacture - a very different beastie

- Seed train
- Continuous perfusion cell culture
- Periodic Cycling Capture Chromatography
- Virus Inactivation in plug-flow reactor
- Periodic Cycling Polishing Chromatography 1
- Periodic Cycling Polishing Chromatography 2
- Periodic Switching Virus Filtration
- Single Pass TFF Concentration & Formulation



Continuous manufacturing – synthetics

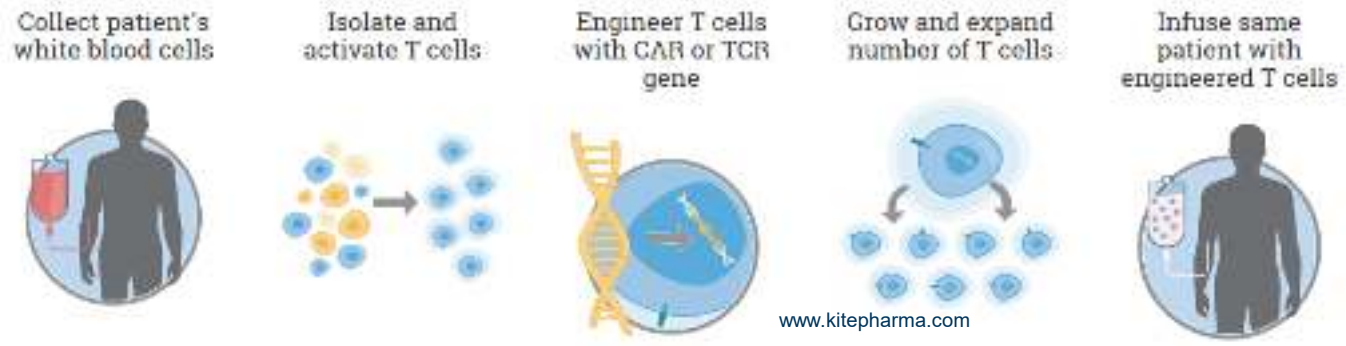
Tableting, dry powders
Fully connected, integrated system
Extensive use of PAT, automation
Multiple components, complicated to break down and clean

BioCM is about liquid handling – in plastic

Scale-down from traditional
Sterility is a major issue
Leaks are a concern
Biocompatibility
System integration and complexity

http://www.cbinet.com/sites/default/files/compendiums/pc17413/Kaiser_Klaus_pres.pdf

Cell and gene therapies are even more different

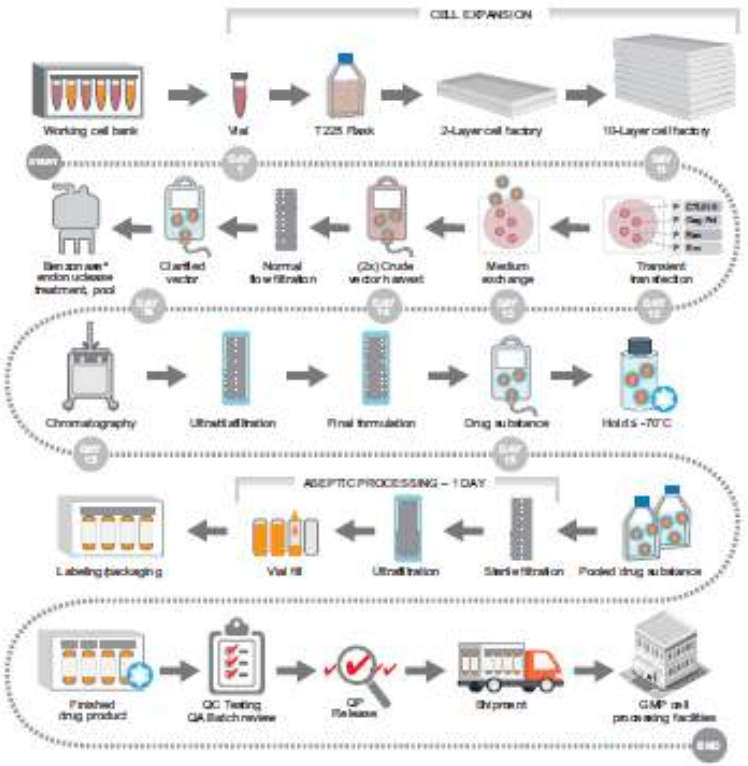


www.kitepharma.com

www.cartcellscience.com

Complex Issues need to be addressed

Proximity to the patient
Centralized vs decentralized manufacture
Maintaining sterility
Variability, patient history
Pace of cell therapies
Analytical methods, products are cells
Adventitious agent testing
Standards for storage
Leachables studies on cell therapies
Measure of potency
Cell banking
Data management
…and so on….



Lentiviral Vector Manufacture (Oxford BioMedica Ltd)
Molecular Therapy: Methods & Clinical Development 4 (2017) 92 - 101

Perceived challenges of single-use

Leaks
- Introduced during manufacture, shipping and handling
- Need for integrity testing methods

Compatibility with biologics
- Extractables, leachables, particulates

Suppliers and interchangeability of components
- Connectors from different suppliers
- Supply chain and change notification, supplier CoA's, supplier criticality

Packaging
- System integrity at the supplier and in the manufacturing environment – maintenance of sterility

Lack of guidance on the use

Disposal

Patricia Hughes CDER October 2016
https://myastm.astm.org/KEY_DOCUMENTS/PDF_FILES/e550000wrksh16.pdf

You are far more reliant on supplier quality systems

BPOG BEST PRACTICES – USER REQUIREMENTS

Uncertainty #1: User Requirement Specifications

- Inconsistent Expectations
  - ✓ Technical knowledge gaps
  - ✓ Site to site
  - ✓ Supplier to supplier
  - ✓ Various forms and formats
  - ✓ Slow response time from Suppliers
  - ✓ Lack clear expectations on what is acceptable
  - ✓ Numerous requests for documents/data in various forms
- Supplier's Frustration
  - ✓ Different formats for similar requests from different users
  - ✓ Lack clarity of what is acceptable and in what form
  - ✓ Additional requests throughout the process from different SMEs

W. Ding, BPOG Five Year Technology Road Map and How to Unleash the Full Benefits of Disposables, CBI SUS Conference, December 2017, San Diego, CA

BPOG BEST PRACTICES – EXTRACTABLES & LEACHABLES

Uncertainty #2: E&L

- "Fear" effect with the use of disposables in cGMP manufacturing environment
  - ✓ Need to understand E&L RISK
  - ✓ Lack standard testing protocol
  - ✓ Demonstrate acceptable E&L RISK (Cumulative)
  - ✓ Enormous volume of E&L assessments & studies

- Regulatory Uncertainties
  - ✓ Reviewers vs. Inspectors
  - ✓ Question your RA model
  - ✓ 483s and warning letters
    - Request for E&L data/assessments
    - Refusal to file
    - Request specific studies (design)

W. Ding, BPOG Five Year Technology Road Map and How to Unleash the Full Benefits of Disposables, CBI SUS Conference, December 2017, San Diego, CA

BPOG BEST PRACTICES – CHANGE NOTIFICATION

Uncertainty #3: Supplier Change Notification (SCN)

Time	Data	Process	Risk
• Too short to qualify by end-user	• Often does not meet end-users specifications	• Lack of single point of contact (SPOC)	• Imprecise understanding of intended application
• No end-user input prior to implementation	• Inconsistent expectations from end-users	• Inadequate handover package	• Resistance to continuous improvement
• Inventory Management	• Do we buy this part ?	• Over or under estimation of change requirements	• High volume of changes simultaneously
• Time and resource spent on minor or out of scope changes		• No feedback to supplier	• Unclear of misaligned understanding of risk
		• Unclear how changes will impact end-users	• Risk to lost of in-process and bulk materials due to failures/investigations
		• Lack of standardization for addressing customer specific designs	

Lack of Mutual Understanding

W. Ding, BPOG Five Year Technology Road Map and How to Unleash the Full Benefits of Disposables, CBI SUS Conference, December 2017, San Diego, CA

If you still need convincing….

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Industry/Regulator Communication is Linchpin in Addressing Cell/Gene Therapy CMC Challenges, Experts on Both Sides Are Affirming

Jan 22nd, 2018

Please Log in to print the full article

Industry and agency experts engaged with advanced therapies are stressing that the communication process between them is critical in clearing the CMC pathway for development of the products and that this communication needs to happen as early and as openly as possible to help sponsors navigate around the many pitfalls that lie along the journey.

As experience with cell and gene therapies (CGTs) grows, so does the recognition that the complexity of the CMC challenges involved, the difficulty in making clinical/quality connections and informed risk assessments, the lack of CGT-specific standards, and the severe consequences of missteps, make this industry/regulator communication process a linchpin in their development.

*WK 47355 New Practice for **Controlling Integrity** of Single-Use Systems during Biopharmaceutical manufacturing process at End-user factory*

Lead:

Scope:

Status: currently on hold

Challenges: Alignment with USP

Time line: ??

*WK 47356 New Practice for Characterizing **Particulates Burden** from Single-Use Systems at Vendor Factory*

Lead:

Scope:

Status: currently on hold

Challenges: Alignment with USP

Time line: ??

*WK 48957 New Practice for **Purity, Biocompatibility and Toxicity** of Raw Materials used in the manufacturing of Single-use System*

Lead:

Scope:

Status: currently on hold

Challenges: Alignment with USP

Time line: ??

WK 48084 New Practice for Determining and Characterizing Leachables Released from Materials Used in Single-Use Systems under Bioprocess Operating Conditions

Lead: Alain Pralong

Scope: all product contact materials of single-use systems used in pharmaceutical and biopharmaceutical manufacturing processes that have the potential to affect product quality and patient safety with regard to released leachables

.

Status: currently on hold

Challenges:

Time line: ??

CONTINUOUS MANUFACTURING IN BIOPHARMA

Workshop on Emerging Technologies in Biopharmaceutical Manufacturing

ART HEWIG

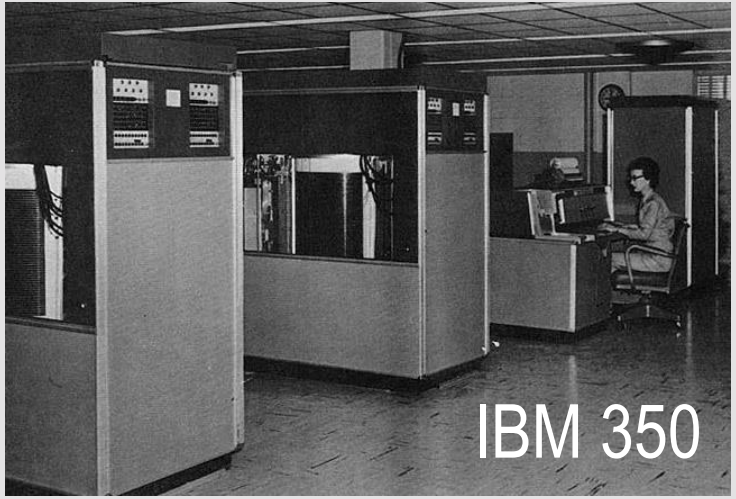
PROCESS DEVELOPMENT, AMGEN

ASTM , BOSTON, MA, APRIL 17TH 2018

AMGEN®

Pioneering science delivers vital medicines™

BIOMANUFACTURING CHANGE HAS BEEN EVOLUTIONARY IN COMPARISON TO OTHER INDUSTRIES

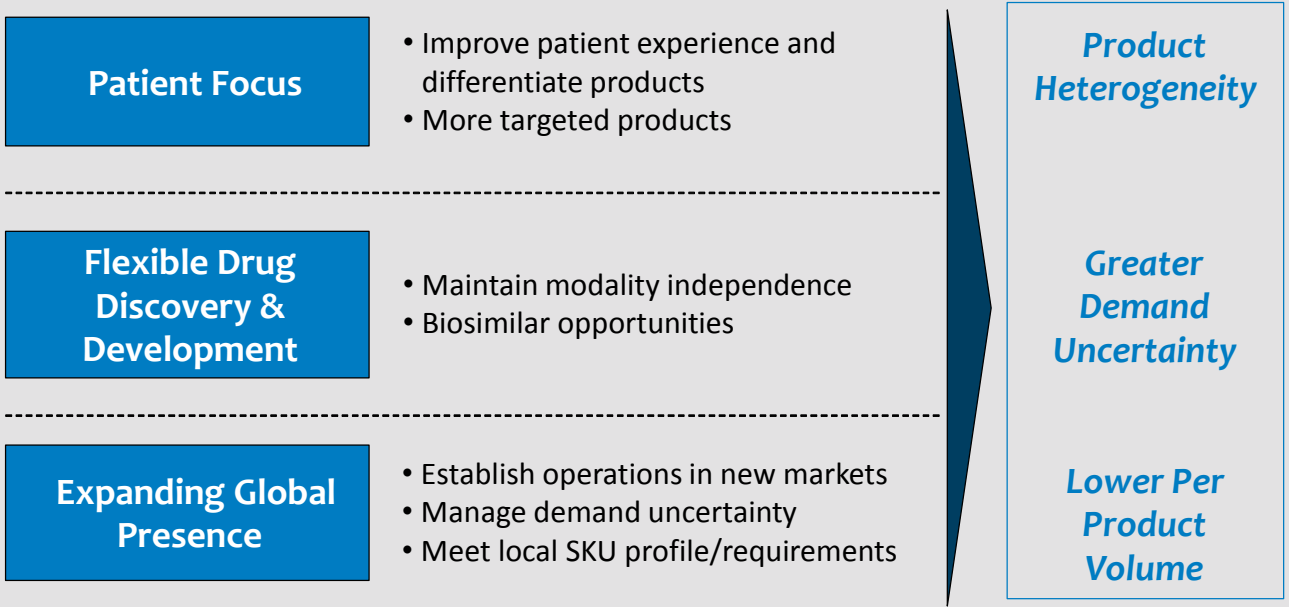


1956 (first disk drive)
3.75MB storage capacity
Weighed >1 Ton and was delivered in cargo airplanes

2017 (Largest solid state disk drive)
60TB storage capacity (can store >50,000 2-hour movies)
Weighs <1 kg and ships free Prime

A changing business landscape is requiring agility, flexibility, modularity, and dematerialization of biomanufacturing networks. Continuous manufacturing can help support this transformation.

THE CHANGING BIOPHARMACEUTICAL LANDSCAPE HAS COMPANIES RETHINKING HOW DRUGS SHOULD BE MANUFACTURED IN THE FUTURE



Balance use of *existing footprint* with addition of *new capabilities* to lower costs, and increase flexibility and speed

AMGEN

CONTINUOUS PROCESSING CAN HELP TO TRANSFORM THE CURRENT BIOMANUFACTURING PARADIGM

Reduction in CAPEX and Footprint

- Significant reduction in capital investment
- Miniaturization and intensification of process workflows
- Shift from fixed to variable cost structure

Flexible and Scalable Capacity

- Targeted investment based on market demand/product mix

Lean Tech Transfers

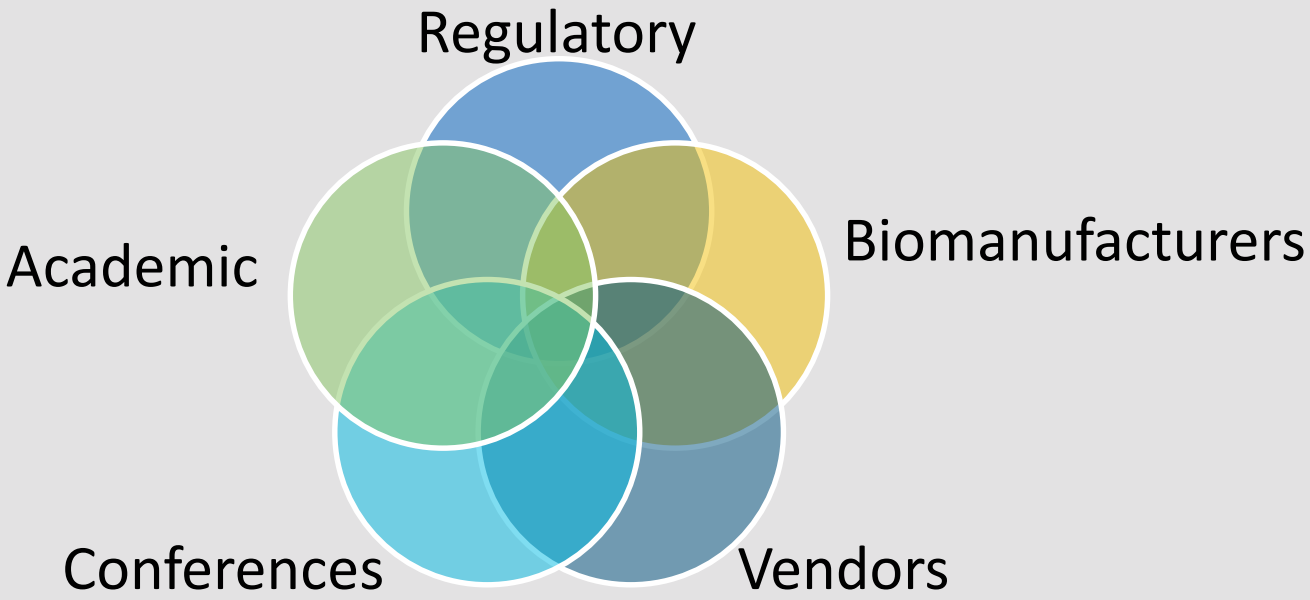
- Scale out in place of scale up
- Development and training at development site

Reduction in Facility Time to Deploy

- Significant reduction in time to build
- Use of modular facilities

AMGEN

OVER THE LAST 5 TO 10 YEARS THE INTEREST, EFFORT, AND FOCUS ON CONTINUOUS BIOPROCESSING HAS SIGNIFICANTLY INCREASED



HISTORICAL VIEW OF CONTINUOUS PROCESSING IN BIOMANUFACTURING (FIRST GENERATION CONTINUOUS)

Application of continuous processing to biomanufacturing is not 'new' to our industry

- Historically has been used for unstable molecules
  - Minimize residence time in bioreactor
  - Kogenate-FS (1993) first product approved using continuous process

- Typical application: continuous perfusion cell culture process followed by batch purification

Biopharmaceuticals produced by continuous perfusion manufacturing

Year Approved	Tradename	Generic Description	Type of Biomolecule	Indication	Company
1993	Kogenate-FS	Factor VIII	Blood factor	Haemophilia A	Bayer
1994	Cerezyme	b-glucocerebrosidase	Enzyme	Gaucher's disease	Genzyme
1997	Benefix	Factor IX	Blood factor	Haemophilia A	Pfizer
1997	ReoPro	Abciximab	Antibody	Percutaneous coronary intervention angioplasty	Janssen
1997	Gonal-f	Follicle-stimulating hormone	Blood factor	Infertility	Merck
1998	Remicade	Infliximab	Antibody	Autoimmune diseases	Janssen
1998	Simulect	Basiliximab	Antibody	Organ transplantation	Novartis
1999	NovoSeven	Factor VIIa	Blood factor	Haemophilia A	Novo Nordisk
2000	ReFacto	Factor VIII	Blood factor	Haemophilia A	Pfizer
2001	Campath/Lemtrada	Alemtuzumab	Antibody	Lymphoma and multiple sclerosis	Genzyme
2001	Xigris	Drotrecogin alfa	Blood factor	Sepsis	Eli Lilly
2002	Rebif	Interferon beta-1a	Blood factor	Multiple sclerosis	Merck
2003	Fabrazyme	Agalsidase beta	Enzyme	Fabry's disease	Genzyme
2003	Aldurazyme	Laronidase	Enzyme	Mucopolysaccharidosis I	Biomarin
2005	Naglazyme	Galsufase	Enzyme	Mucopolysaccharidosis VI	Biomarin
2006	Myozyme	Alglucosidase alfa	Enzyme	Pompe disease	Genzyme
2008	Xyntha	Factor VIII	Blood factor	Haemophilia A	Pfizer
2009	Simponi	Golimumab	Antibody	Autoimmune diseases	Janssen
2009	Stelara	Ustekinumab	Antibody	Psoriatic arthritis	Janssen
2010	VPRIV	Velaglucerase alfa	Enzyme	Gaucher's disease	Shire
2013	NovoEight	Factor VIII	Blood factor	Haemophilia A	Novo Nordisk
2014	Vimizim	Elosufase alfa	Enzyme	Morquio syndrome	Biomarin

Le et al., (2015) *CEP.* **Dec**, 132 - 37

Paradigms can be changed

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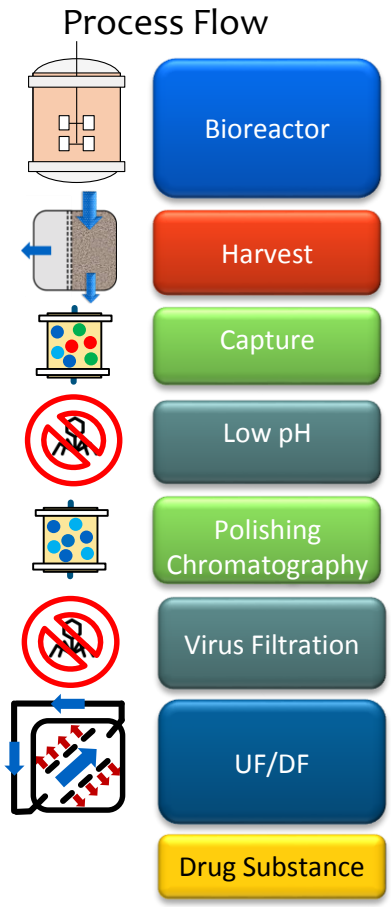
HIGH LEVEL COMPARISON OF BATCH AND CONTINUOUS PROCESS



Batch	Continuous
10 – 30 x 10^6 cells 10 – 15 days duration	30 – 130 x 10^6 cells * 30+ days duration
Cell removal (centrifugation, filtration, etc.)	Cell retention in bioreactor
Batch bind and elute	SMB, PCC, twin-column chromatography
Batch pH titration	Automated titration and/or low pH hold time set by residence time
Mix of batch bind and elute as well as flowthrough	Same options as with Capture, but also new ways of at looking at flowthrough
Batch filtration	Still an area for new ideas…
Batch UF/DF	Inline diafiltration

Process flow for Batch and Continuous are highly similar. The difference is in the operation and integration of the unit operations.

* Clinke et al., (2013) Biot. Progress. **Feb**, 754-767

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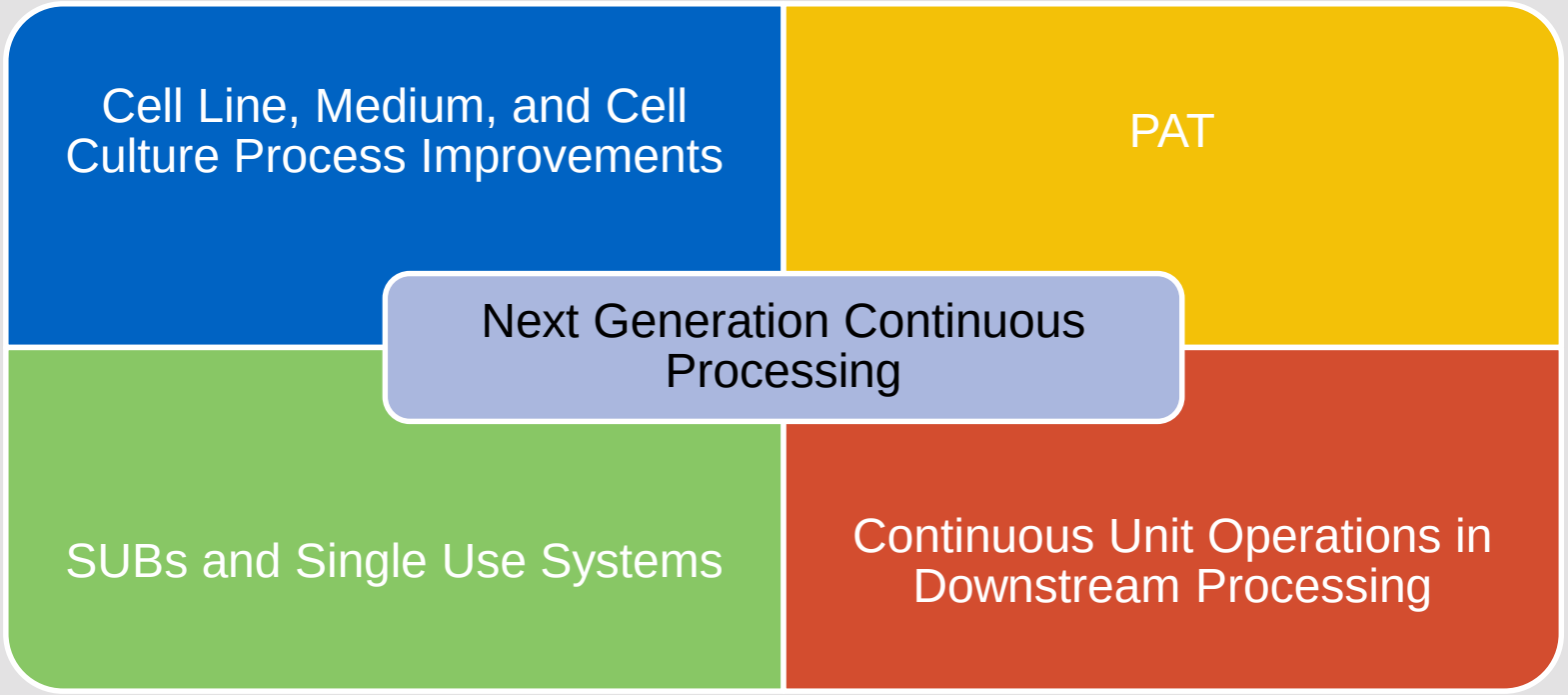
NEW TECHNOLOGIES ARE ENABLING NEXT GENERATION CONTINUOUS PROCESSING



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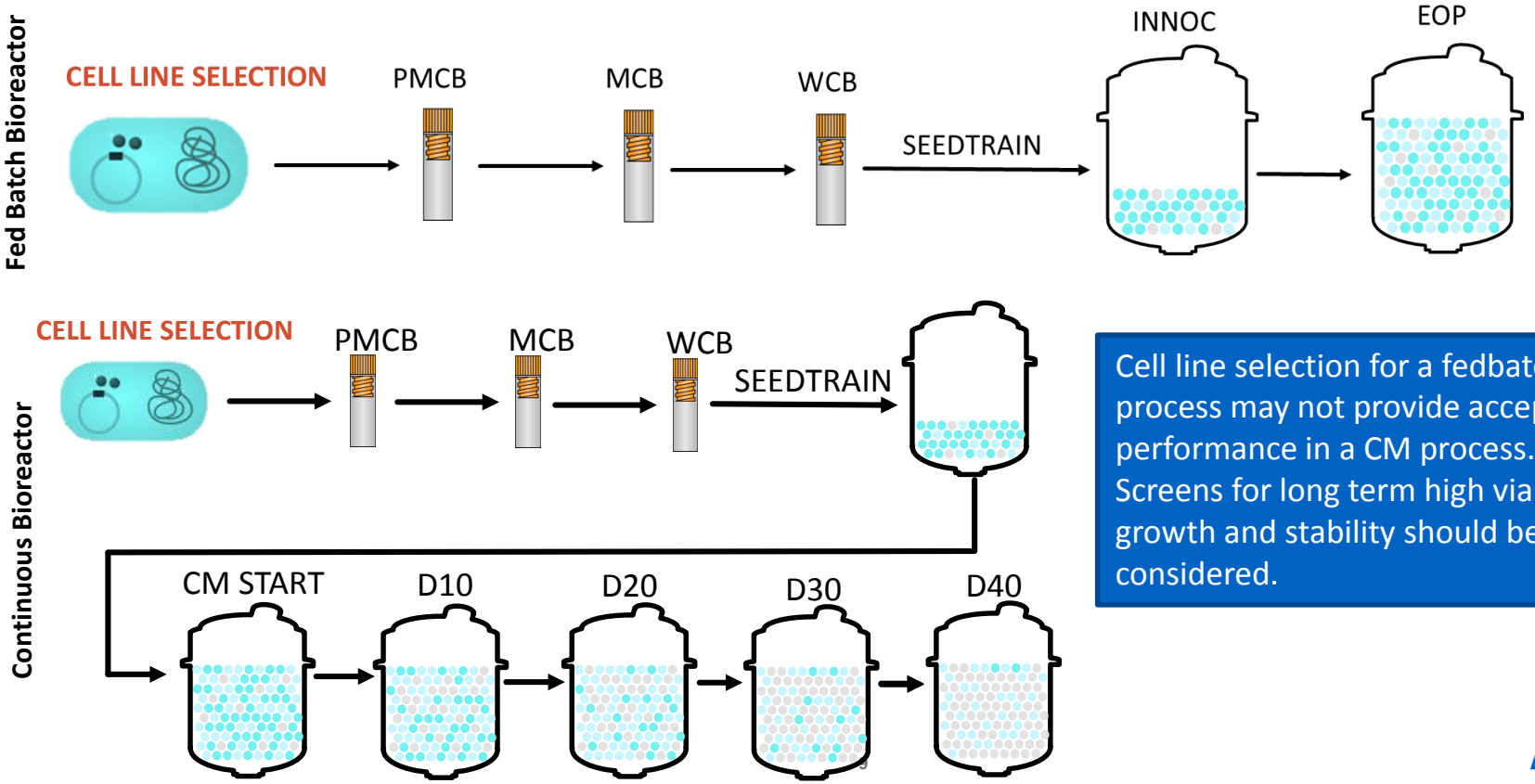
FUTURE MANUFACTURING PARADIGMS WILL REQUIRE CELL LINE STABILITY AT LONGER AGE



Cell line selection for a fedbatch process may not provide acceptable performance in a CM process. Screens for long term high viability growth and stability should be considered.

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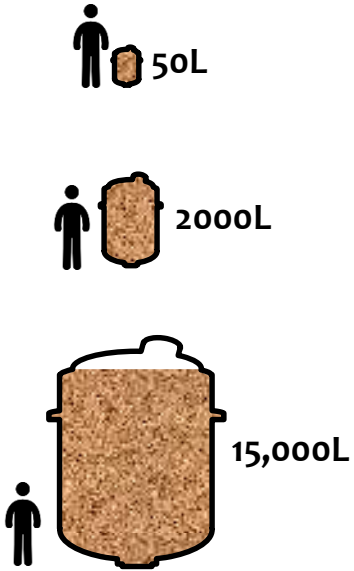
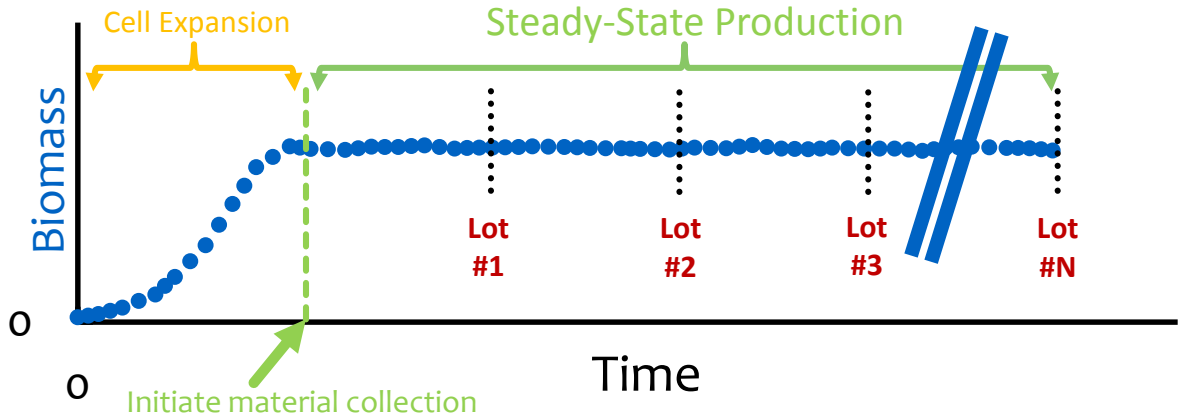
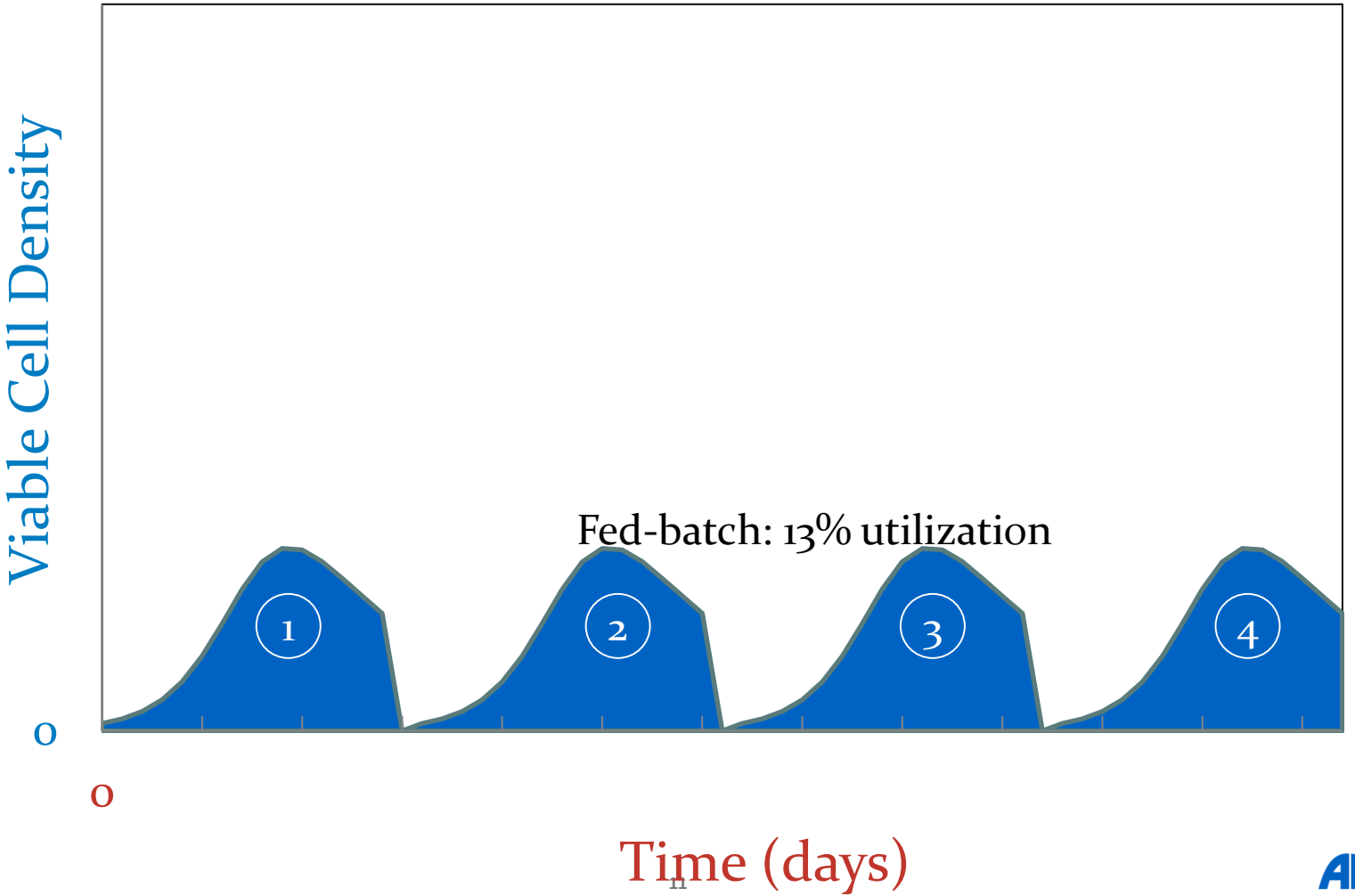
BIOREACTOR OPERATION AND LOT STRATEGY

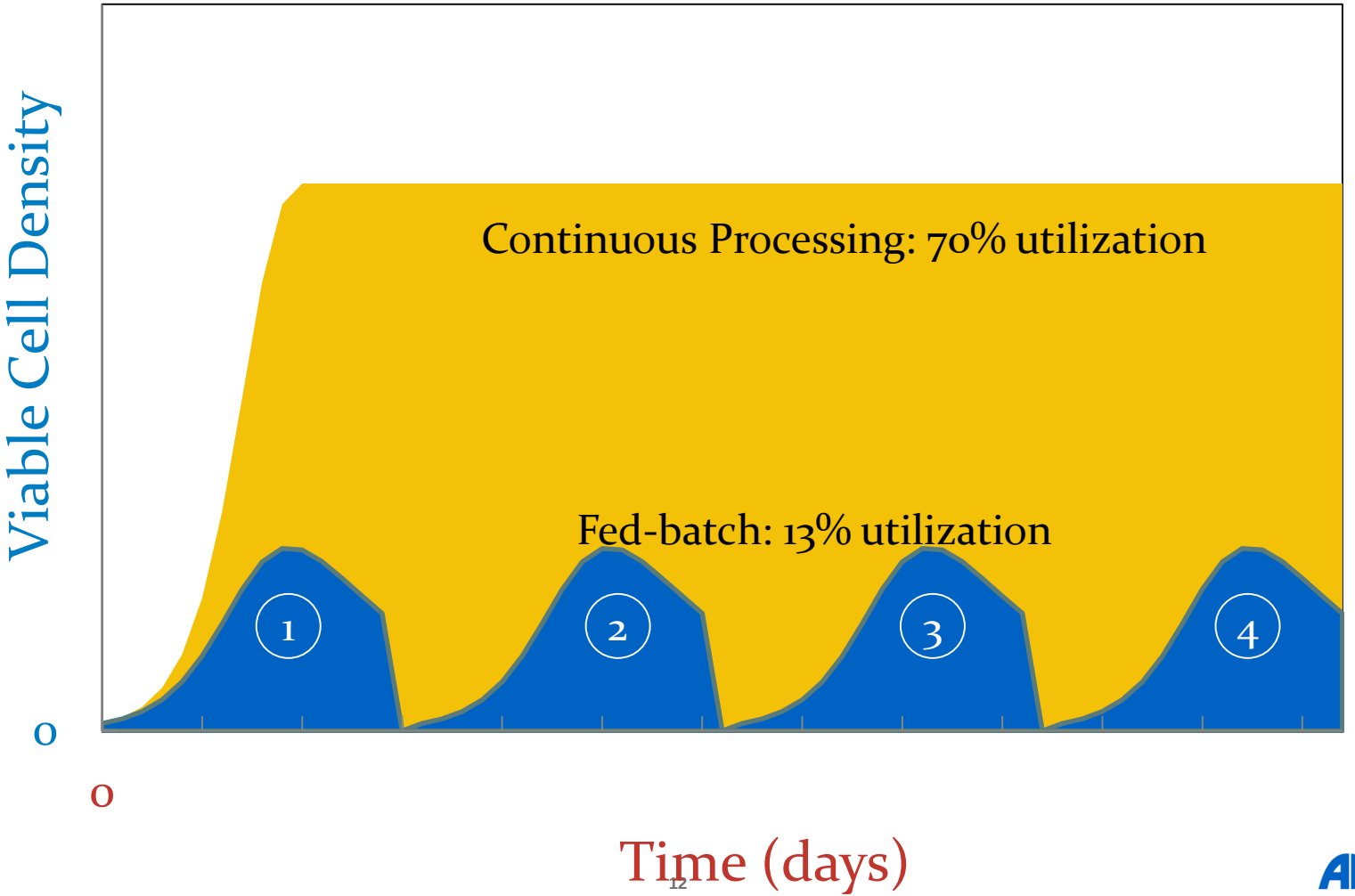


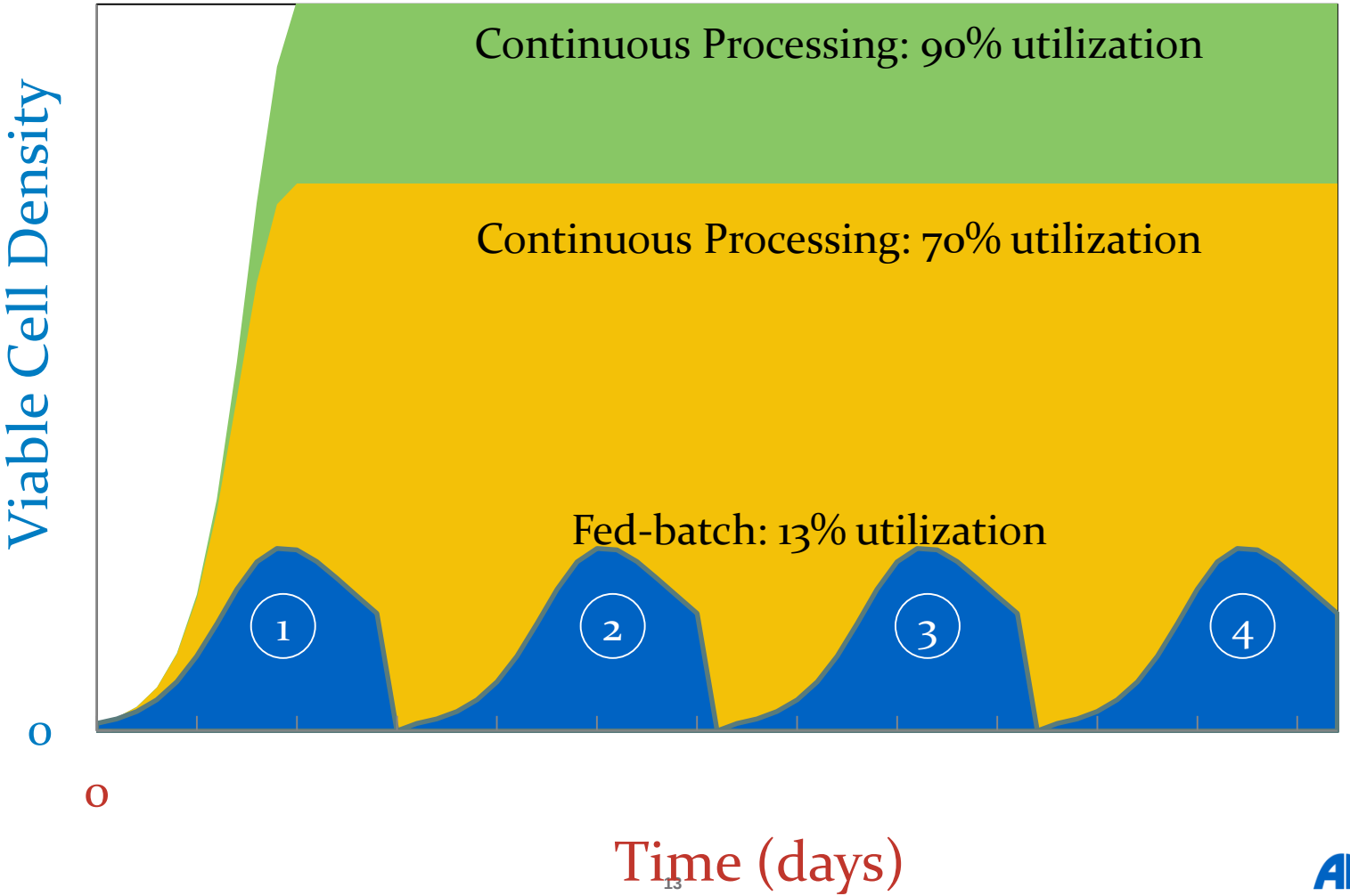
Key considerations for the Cell Culture process

- Supporting high cell densities for extended durations
- Cell separation at high cell densities
- Perfusion rates, media formulation, liquid handling
- Lot strategy




Viable Cell Density
0
0
Fed-batch: 13% utilization
1
2
3
4
Time (days)


Viable Cell Density
0
0
Continuous Processing: 70% utilization
Fed-batch: 13% utilization
1
2
3
4
Time (days)


Continuous Processing: 90% utilization
Continuous Processing: 70% utilization
Fed-batch: 13% utilization
1
2
3
4
Viable Cell Density
0
0
Time (days)

STEPPING ON THE ACCELERATOR: RIGHT SIZING THE BIOREACTOR MASS OUTPUT

There are at least three levers we can utilize in continuous manufacturing to ‘dial-in’ the needed mass outputs

- Bioreactor volume
- Viable cell density & Cell specific perfusion rate (VCD & CSPR)
- Run Duration

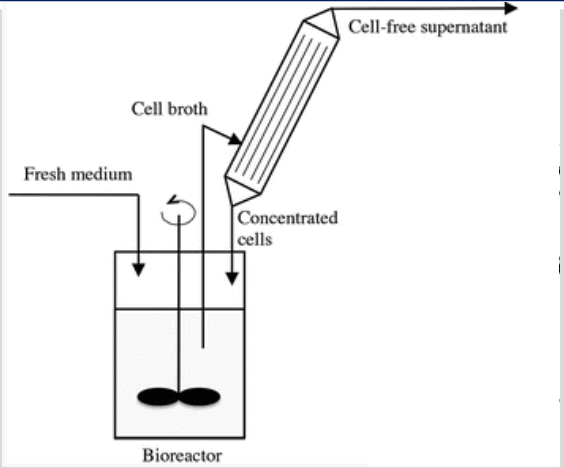
500 L
2 g/L/day
15 days

1,000 L
3 g/L/day
30 days

2,000 L
4 g/L/day
60 days

CELL RETENTION OPTIONS

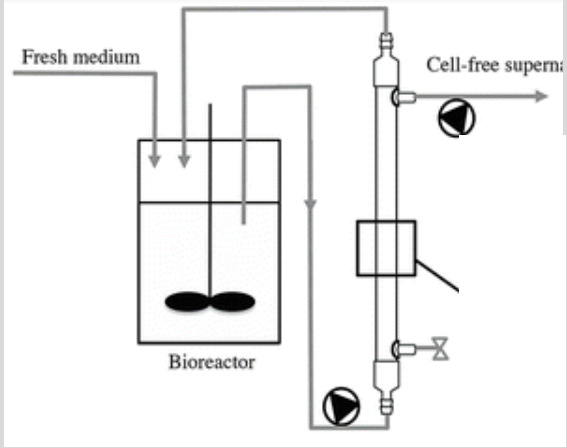
INCLINED SETTLER



Gravity Cell Separation

Proven technology, but limited capability at high cell densities

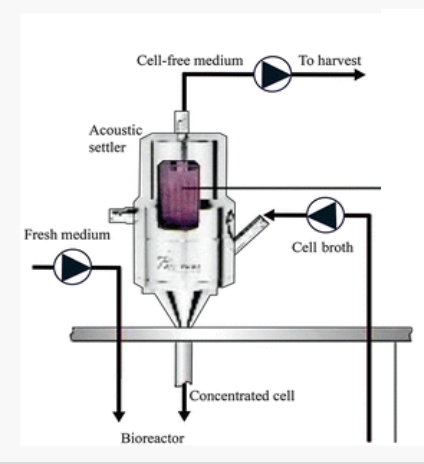
MICROFILTRATION



Filtration Based Cell Separation

TFF and ATF formats have increased in usage. Filter fouling at high cell densities continues to create challenges

ACOUSTIC SEPARATION

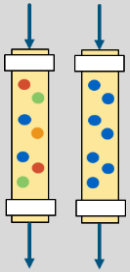
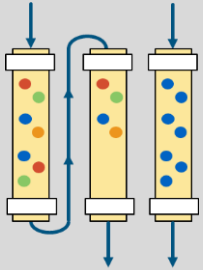


Gravity Cell Separation

Technology is progressing. Holds potential for improved process yields with efficient cell density control.

Chotteau V. (2015) Perfusion Processes. In: Al-Rubeai M. (eds) Animal Cell Culture. Cell Engineering, vol 9. Springer, Cham

CHROMATOGRAPHY

BATCH	TWIN COLUMN	PERIODIC COUNTERCURRENT CHROMATOGRAPHY (PCC)
		
Increasing complexity		
Serial / Sequential set of steps	Continuous Load Discontinuous Elution (Bind and Elute) Operation is similar to Batch	Continuous Load Discontinuous Elution (Bind and Elute) Allows for overloading 2 or more columns…

Numerous continuous options at play – PCC and twin column

- Column operation PCC and twin column
- Reliability and robustness in a GMP setting
- Single use flow paths
- Single use columns / membrane chromatography

Next generation chromatography: selectivity and productivity

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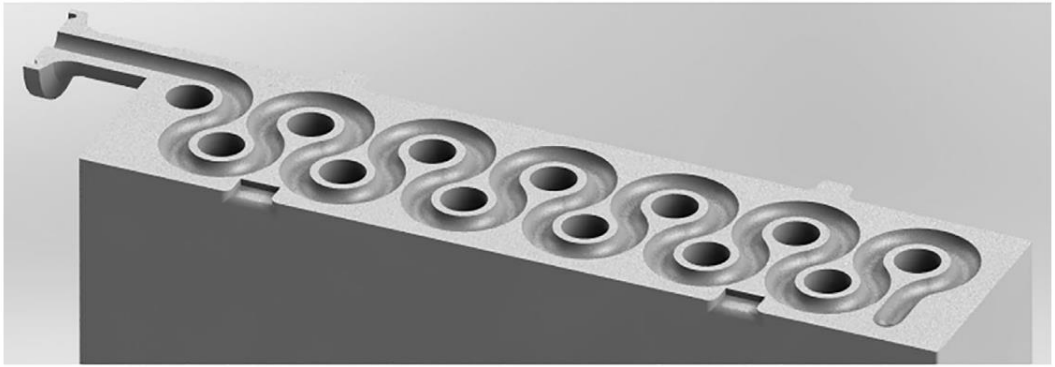
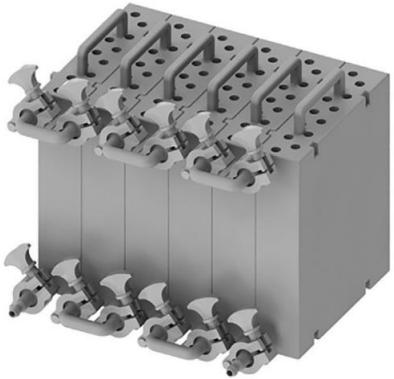
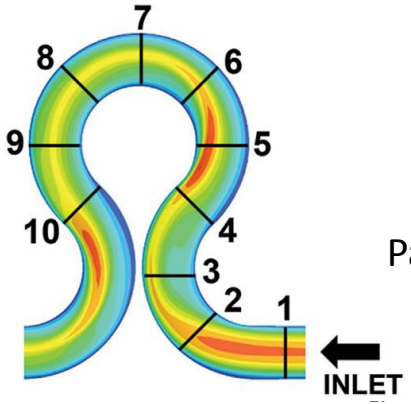
VIRAL INACTIVATION AND FILTRATION







- New approaches to viral inactivation:utilization of continuous flow reactors with defined residence times
- New ideas for continuous viral filtration are coming

Parker et al., (2017) Biot. And Bioeng. **115**, 606-616

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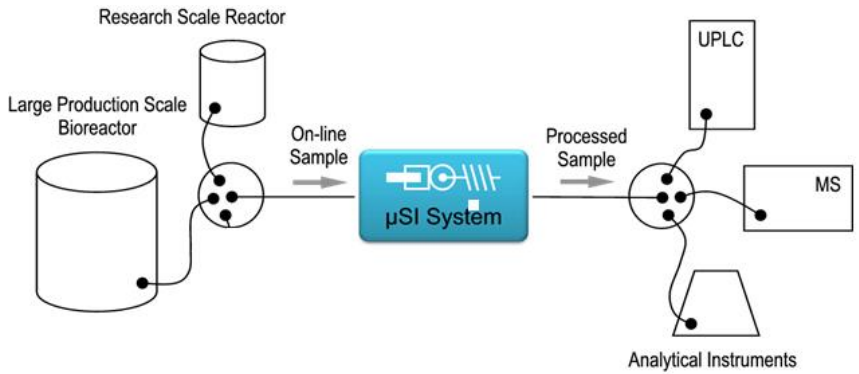
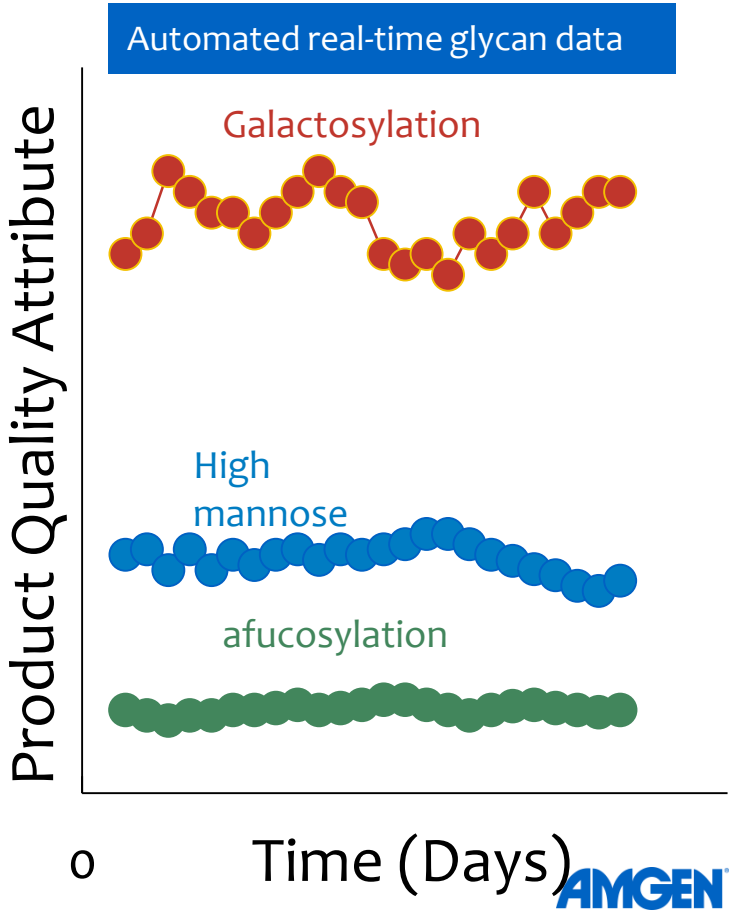
PAT FOR REAL-TIME PQA MONITORING, CONTROL, AND RTRT

- Product quality information is typically obtained weeks after completion of bioreactor runs. This delays evaluation of process impact on PQAs

- ☑ Real-time PQA data enables real-time process monitoring and/or control

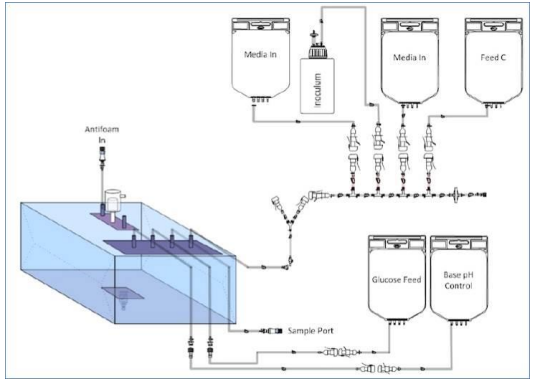




SINGLE-USE COMPONENTS ENABLE CONTINUOUS MANUFACTURING AND CREATE NEW CHALLENGES

Benefits:

- Elimination of cleaning and sterilization operations and validation
- Facility construction duration reduced
- Potential for closed processing in ballroom or CNC spaces
- Eliminates concern for product carryover in multiproduct equipment
- Reduced water use and chemical and wastewater discharge streams



Challenges:

- **Robustness**:
  - Caustic stable connectors and parts
  - Long duration processing results in leaks due to excessive wear
  - Low pressure limits restrict processing options
- **Leaks:** Product loss and compliance risk, particularly regarding ingress of bacteria
- **Particles and defects:** No standardized acceptance criteria
- **Single source**: Process developed with a specific vendor cannot be changed without significant work
- **High cost:** Downstream tubing sets may result in $10-15k per unit operation
- **Extractable/Leachables:** Potential for vendor standardization

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AUTOMATION AND EQUIPMENT COMMUNICATION IS CRITICAL TO ENABLE CONTINUOUS MANUFACTURING

Current State

- Many islands of automation
  - Manual operations result in excessive operator interaction driving the cost up significantly
  - Inadequate data acquisition, trending and analysis

OR

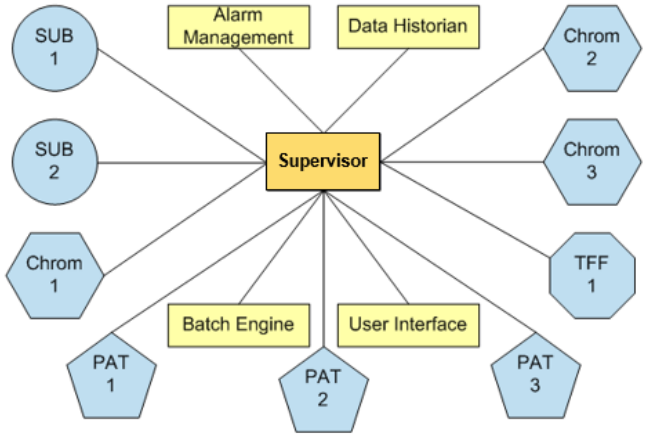
- Highly customized single-use skids
  - Expensive complex equipment
  - Long equipment and single-use assembly lead times
  - Intensive internal engineering resources

Ideal Future State:

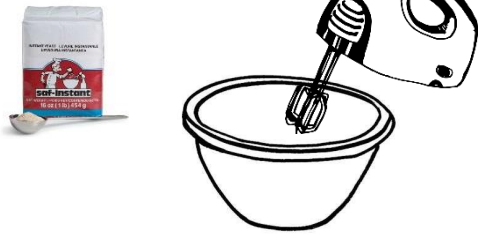
Ensure systems can communicate with each other

- Open architecture with client access to input/output level and equipment module level (standard interface)
- Ethernet IP for robust communication and data transfer capability (no OPC or Serial communication)

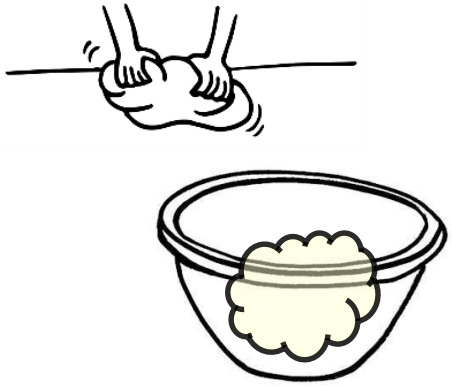
Best Case: Client specified control system with open vendor configuration



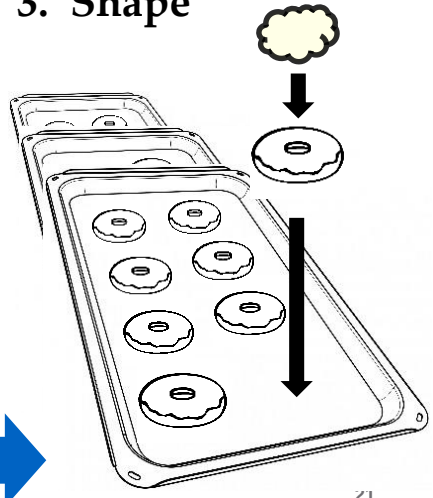
1. Batch Ingredients



2. Mix and Ferment

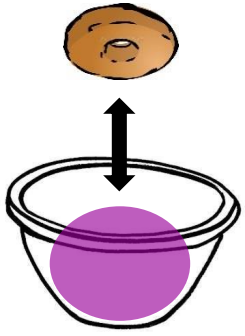


3. Shape



4. Fry

5. Glaze



Batch processing

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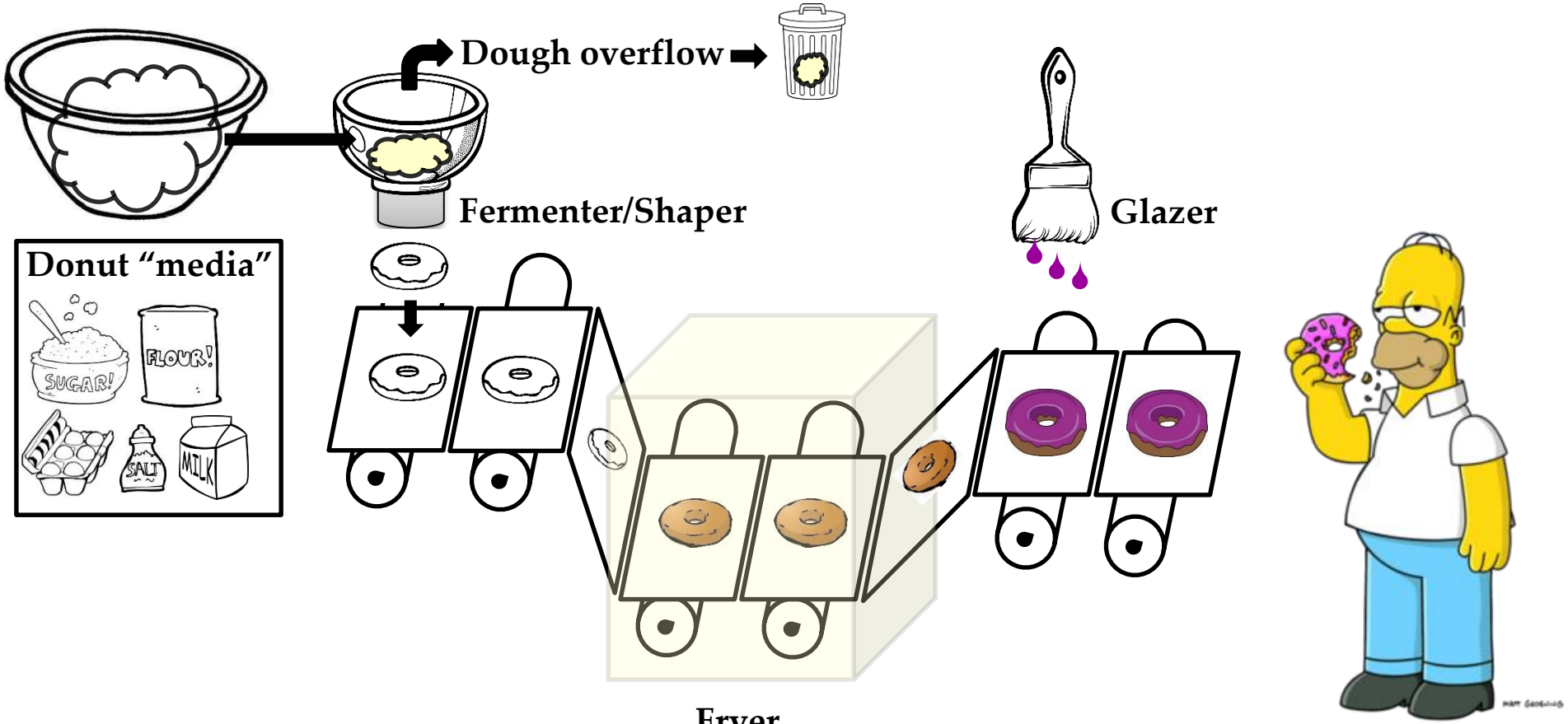

Dough overflow
Fermenter/Shaper
Glazer
Donut "media"
SUGAR!
FLOUR!
SALT
MILK
Fryer

THANK YOU

Regulatory Considerations for Continuous Manufacturing

ASTM Committee E55: Workshop on Emerging Technologies in Biopharmaceutical Manufacturing

Patricia F. Hughes, Ph.D.

Branch Chief

FDA/CDER/OPQ/OPF/DMA

April 17, 2018

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Outline

- Regulatory Framework for biomanufacturing
- Current state
  - Bulk drug substance
  - Sterile drug product
- New developments
- Regulatory perspectives
  - Product quality microbiology
- Conclusions

REGULATORY FRAMEWORK

Pharmaceutical CGMP for the 21st Century
A Risk Based Approach

- Initiative launched in 2002 to modernize FDA's regulation of pharmaceutical quality of drugs intended **to promote a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight**
  - Intended to encourage the adoption of modern and innovative manufacturing technologies
  - Overarching philosophy is:
    - ***Quality should be built into the product, and testing alone cannot be relied on to ensure product quality***

PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

- Guidance issued in 2004 defines Process Analytical Technology (PAT) as:
  - "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical and performance attributes of raw and in-process materials and processes".
- Overarching goal of PAT is ensuring product quality: "quality cannot be tested into products"

http://www.fda.gov/cvm/guidance/published.html

Need for new initiatives

- FDA has been confronted with drug shortages and product recalls in the US at unprecedented rates in recent years.
  - These problems reflect deficiencies in pharmaceutical quality and manufacturing (outdated manufacturing technologies, facilities and equipment).

Congressional Modernization Hearing

December, 12 2013

- Testimony cited need to "modernize manufacturing methods by taking advantage of advances in modern facility and process design, such as **replacing manually-intensive processes with automation, using closed systems, integrating process analytical technologies** into operations for better process control, and adopting continuous manufacturing platforms. These technologies would help achieve improved manufacturing reliability, increased robustness, and lowered costs."

Janet Woodcock, M.D., CDER Center Director

Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base

- In 2015 this draft Guidance was issued
  - to promote the modernization of manufacturing technologies which allow for more robust manufacturing process with fewer interruptions in production, fewer product failures and greater assurance for product meeting expected quality and clinical performance attributes.
- This guidance encourages companies to submit pre-submission questions and proposals to the FDA about the use of specific emerging technology to an Emerging Technology Team (ETT).

Adoption of new emerging technologies

- The biopharmaceutical industry is undergoing a paradigm shift in adopting new technologies in manufacturing.
- Examples:
  - Bulk drug substance:
    - Continuous biomanufacturing
    - Single-use systems
    - Process Analytical Technology
  - Sterile finished drug products:
    - Automation
    - Isolators and other barrier systems
    - Single-use-systems

Drivers for change

- Expanding global market for innovative biologics and biosimilars
  - Annual sales over $200 billion globally
- High cost of biopharmaceuticals
  - Unsustainable manufacturing costs
    - Complex products, complex processes, complex stainless steel based facilities required to meet product quality and microbial control standards for a continued supply of quality products to patients
      - Challenging scale-up and site transfers
        - » Inflexible, inefficient
      - Extensive regulatory oversight with long development time for new products
      - Shortages, recalls and other quality product issues due to manufacturing issues

2017 Biophamaceutical Trends: BioProcess Online; Warikoo,V. (2012)

A microbiologist's perspective of the

CURRENT STATE OF BIOMANUFACTURING

Susceptibility to Microbial Contamination

- Biotech processes and products are prone to microbial contamination.
  - Products are heat-labile and cannot be terminally sterilized.
  - Raw materials, personnel and the manufacturing environment are a source of bioburden, endotoxin and other adventitious agents.
  - Products, process intermediates and raw materials support microbial growth.
- Each QA investigation for an over action bioburden limit can cost up to 20,000 USD and a failed batch up to 1 million USD (Bioprocess International vol. 15 (7) p.50, 2017)

Traditional Biopharmaceutical Facilities

- Large complex costly facilities
  - Designed to minimize contamination and cross contamination
    - HVAC systems for filtered air, stringent area classifications and segregation of functions based on contamination and cross contamination risks
  - Large and complex WFI systems
    - For large scale operation with high quality water demands
  - Complex CIP and SIP support systems
    - Extensive stainless steel piping aqueous process transfers
  - Large foot print for equipment and storage
  - Extensive maintenance programs, subject to frequent breakdown and contamination
  - Environmental monitoring

Traditional Biopharmaceutical Equipment

- Complex stainless steel vessels/bioreactors/hold tanks with gaskets, O-rings, valves
  - Batch bioreactors typically 10-20K scale
- Fixed in place, not flexible
- Connected to extensive stainless steel piping
- Subject to extreme temperatures, harsh chemicals during CIP or SIP
- Susceptible to wear, tear, breakdown
  - microbial contamination

Traditional Biopharmaceutical Manufacturing

- Limited output at the cell culture phase
  - Large stainless steel bioreactors for low yielding cultures at low cell densities
  - Very expensive and inefficient process
  - Use of animal derived products, complex media, and high quality water (WFI)

Traditional purification process

- Batch process where by product is captured and purified via a large chromatography column.
  - Process supported by extensive validation activities.
    - Numerous hold steps after each column in stainless steel vessels that have undergone validated CIP/SIP cycles prior to use
    - Open operations (column packing and unpacking)
    - Microbial control is challenging
  - Process expansion is challenging (e.g., switching to larger columns is challenging).
  - Chromatography resin are typically underutilized because they are not loaded to their fullest capacity to avoid product breakthrough.

Traditional aseptic processing for sterile product

- High risk process:
  - Prone to microbial contamination and sterility breaches due to open operations and interventions.
  - Requires cleaning, sterilization and assembly of sterile components and equipment prior to aseptic filling in a clean room, RABS or isolator and during product changeover.
  - Operations are inflexible with long change overs and high operating costs.
  - Labor intensive activities.
  - Extensive regulatory oversight…….

Bulk drug substance

NEW DEVELOPMENTS

New development in biomanufacturing

- Use of single-use-systems (SUS)
  - Drug substance and drug product manufacturing
- Continuous biomanufacturing
  - Continuous perfusion systems with high cell densities, high yielding expression systems, prolonged manufacturing with disposable SUS
  - Simplification of harvesting steps
  - Continuous disposable multicolumn chromatography systems
- Use of PAT

Common uses of single use system in Biotech manufacturing

- Buffer/media preparation
  - Sterile bags and connectors
- Seed expansion
  - Disposable rocking sterile bag bioreactor, connectors and sensors (e.g., wave bags)
- Bioreactors for cell culture
  - Up to 2000 -3000 L scale
- Purification
  - Disposable chromatography columns
- Product holding
  - Sterile bags and connectors
- Sampling
  - Sterile bags with connectors for closed system sampling
- Single-use filtration systems/disposable fill systems
  - Sterile bags, filters, and connectors
  - Disposable depth filtration capsule systems
  - Disposable fill lines

Single-Use-Systems (SUS): Advantages

- Simplified facility design with extensive use of SUS:
  - Closed systems with less stringent area classification requirements
  - Reduced gowning – reduced human contribution to contamination
  - No requirements for clean-in-place and sterilize-in-place systems
  - Supplied gamma irradiated
    - Bags with in-line filters for closed system processing
    - Reduced hold time validation and microbial monitoring
  - Rapid change over
  - Multiproduct production
  - Easily replicated for installation in different facilities for tech transfers
- From a regulatory perspective facilities that have implemented the use of SUS have seen significant improvements in microbial control.
  - Fewer deviations and failures due to bioburden

Challenges of using SUS in biomanufacturing

- Compatibility with biologics
  - Extractables, leachables, particulates
- Leaks
  - Introduced during manufacturing, shipping, handling
- Suppliers and interchangeability of components
  - Connectors from different suppliers
  - Supply chain activities – change notification
- Packaging
  - System integrity; testing methods
- Lack of guidance on the use
- Disposal

Recent 483 observation from pre-license inspections: inappropriate connectors

- Equipment used for manufacturing *name* drug substance and *name* drug product is not adequate in that some of the parts do not match the equipment specifications. Specifically:
  - A leakage in the y-connector to the BDS filter assembly tool place on 2/24/2014 and was traced to a loose connection between 1/4" tubing and a 3/8" Y-connector (deviation report # 102882). The 1/4" tubing was used to fit the peristaltic pump. SOP-XXX-YYYY was updated (change control #101953) to replace the 1/4" tubing for a 5/16" tubing. However, the 5/6" tubing is not the right fit for the 3/8" Y-connector.

Issue:

Supplier limitations for spare parts; connectors from different suppliers are not interchangeable resulting in leaks during manufacturing; lack of integrity testing before use in manufacturing.

Continuous Manufacturing

- Konstantinov and Cooney (2014) in a White Paper on Continuous Bioprocessing described four examples of continuous manufacturing (three hybrid and one fully integrated):
  - Continuous upstream with batch downstream
    - Commonly used for complex and labile proteins
  - Batch upstream with continuous downstream
    - One or more downstream unit of operations are converted into a continuous operation
      - Examples: precipitation, flow-through purification, directly coupled chromatography columns without hold vessels
  - Continuous bioreactor and capture followed by batch downstream
    - Described by Warikoo *et al.* 2012
  - Fully Integrated continuous process
    - Not available at commercial scale yet

Continuous manufacturing: Past practice

- Continuous (perfusion) bioreactor operation has been used by some biopharmaceutical manufacturers for > 25 years.
  - Does not represent a new technology
  - Used to manufacturing high valued and labile proteins from low yielding expression systems
- Regulatory challenges:
  - Lengthy and complex
    - Maintenance of pure cultures in stainless steel bioreactors for very long times (e.g., 10-100 days)
    - Extensive holding and monitoring of process intermediates
      - Prone to equipment failures and microbial contamination
    - Difficult and expensive manufacturing site transfers
    - Vulnerability of medically necessary drugs from single sourced facilities
      - Vesivirus contamination at Genzyme in 2010

Continuous manufacturing: New process developments

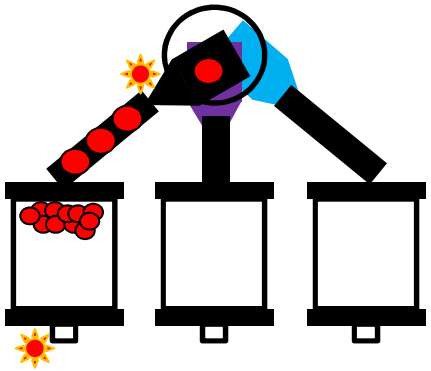
- Cell line development:
  - Cells capable of growing in chemically defined media (CDM) without animal derived materials to very high cell densities (50-60 x 10^6 cell/mL).
- Inoculum expansion:
  - Simplified with the use of SUS (disposable wave bags and bioreactors).
- Protein expression:
  - Use of single-use bioreactors up to the 2000-3000 L scale
  - High protein expression (10 g/L) as a result of very high cell densities and appropriate media (cell nutrition).
  - Use of disposable cell retention devices (e.g., Alternating Tangential Flow [ATF] in the perfusion cell culture system.
- Reduced microbial contamination rates due to the use of SUS in spite of the very long processing times and complex perfusion operations.

Continuous manufacturing: What is next?

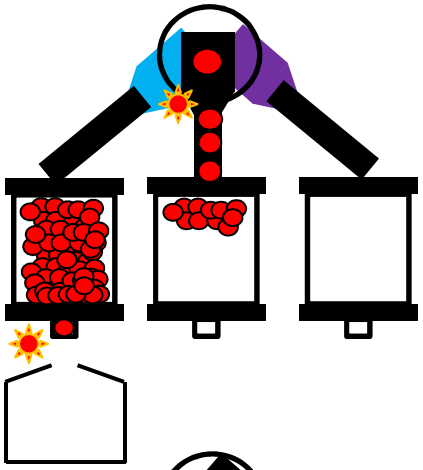
- Integration of both upstream and downstream operations:
  - Continuous processing from the bioreactor to purification
  - Continuous chromatography steps
- This approach is fully encouraged by the FDA:
  - Support provided in recent presentations by FDA personnel
    - FDA 2011. Advancing regulatory science at FDA – A strategic plan. August (http://www.fda.gov/regulatoryscience)
    - Godwin 2011. Continuous manufacturing, a regulatory perspective. Interphex, New York, March

Integrated continuous manufacturing

- Warikoo et al. in 2012 described an integrated continuous manufacturing process for both a monoclonal antibody and a therapeutic protein:
  - A capture column connected to a bioreactor
  - The harvest from the bioreactor through a cell retention device (e.g., ATF) is pumped into a 2 L disposable bag serving as a surge vessel
    - Centrifugation step is eliminated
  - The harvest passes through a 0.2 µm filter and is loaded onto a capture column
  - Continuous operation at the capture step using multiple columns operated in series



Load first capture column with harvest

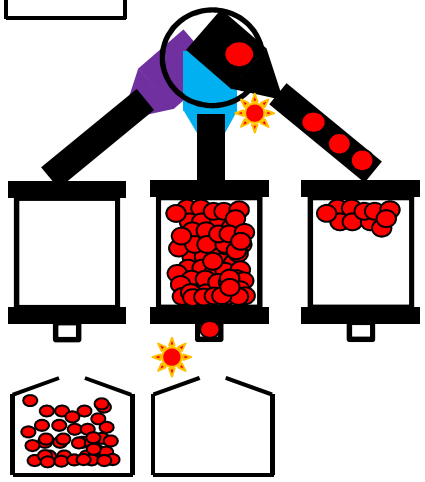


UV detector signal increases above threshold

Valve switch: Load second capture column with harvest

Elute first capture column with **elution buffer**

Collect eluate in vessel



UV detector signal increases above threshold

Valve switch: Load third capture column with harvest

Elute second capture column with **elution buffer**

Clean & equilibrate first column

Figure by: Scott Nichols, Ph.D.

Integrated continuous manufacturing: Benefits

- Improved process efficiency during purification:
  - More efficient utilization of chromatography resins
  - Decreased buffer usage
  - Reduced column sizes
  - Disposable columns
- Regulatory perspective
  - Use of closed system with improved microbial control
  - No hold times in vessels susceptible to microbial ingress and product contamination
  - No CIP or SIP validation
  - Reduced column cleaning sanitization and storage validation
  - Overall reduced microbial monitoring
    - Reduced sampling and testing

Use of PAT in continuous manufacturing

- Allows for a high degree of automation
  - Reduces human interactions for measurements and provides for greater process consistency.
  - Example (from Warikoo *et al.* 2012)
    - In-line measurement of product concentration with feedback control for column switching strategy using dynamic UV monitoring.
    - ΔUV absorbance between the feed inlet and column outlet
      - Increase in UV absorbance in the outlet above impurity baseline triggers the column flow from one column to a second column in the series.
- Microbial monitoring is still conducted off line.
  - Progress needs to made in this area

Sterile drug product

NEW DEVELOPMENTS

Improvements in the fill finish facilities

- Use of separation technologies:
  - E.g., closed gloveless isolator systems, isolators, closed RABS
- Automation:
  - E.g., automated loading and unloading of lyophilizers; use of robotics
- Integration:
  - Minimize or “design out” interventions and other risks -
    - Disposable flow path e.g., SUS assemblies for sterile filtration and filling
    - Replacement of stainless steel tanks with SUS for holding and streamlining the process
    - Rapid transfer ports; self-contained closed isolators;
  - Advanced Testing/Analytics

Operational integration in the fill finish facilities

- Many current processes involve multiple transfers of product to various stainless steel vessels and hold conditions in classified areas.
  - Each transfer and hold step is prone to contamination.
  - Requires sampling for bioburden and endotoxin to verify continued microbial control.
- New developments involve the use of gamma irradiated SUS systems and/or isolators. These are operated as closed systems should allow for better microbial control and a reduction in validation activities and in-process tests.
  - Replacement of CIP'ed and SIP'ed stainless steel vessels with sterilized gamma irradiated bags with in-line filters.
  - Reduction in supporting equipment validation and maintenance.
  - Elimination of microbial hold time validation requirements.

SUS for fill finish

- Gamma irradiated bags with and without mixer
  - Used in formulation, holding product
  - Closed systems
    - Microbial control
    - Extractable leachable studies and compatibility studies to support use
- Sterile assemblies for sterile filtration and aseptic filling
  - Components consisted of filling needles and needle cartridge, filling tube manifold to deliver the sterile drug product from the reservoir bag into the needles at the filling station
  - The SUS assemblies are gamma irradiated, triple wrapped, and for single use
  - Filling needle pumps are located on the outside of the isolator.

Single-use fill finish assemblies for sterile product

- Must meet requirements to ensure flow-path sterility and integrity.
  - Supporting sterilization validation summary data and information on the gamma irradiation process is assessed during the review of the BLA or supplement and is verified during an inspection
  - Integrity tests are also reviewed during the review of the BLA and on inspection

Sterilization

- Assemblies are exposed to gamma irradiation level of 25-40 kGy.
- The sterilization process follows the ANSI/AAMI/ISO process (ANSI/AAMI ST32, ISO 11137) for establishing the dose map of the product, developing the dose run and validating the irradiation run.
- Periodic dose audits

Sterilization validation

- Sterilization validation summary data and information should be in submitted in the BLA for approval.
- The BLA will be refuse-to file if the data and information are missing.
- The following is an example of an IR that was sent to the applicant:
  - "Provide gamma-sterilization validation data summaries for the sterile disposable single-use-bag/system performed per ANSI/AAMI/ISO 11137 at the gamma sterilization site. This information should include initial sterilization dose establishment report, dose mapping report, three recent quarterly dose audit reports. In addition, submit the COA for the sterile disposable bag/system."

SUS leak testing

- Integrity of the SUS fill finish assemblies must also be demonstrated to ensure that the sterile fluid path has not been breached during shipping handling and installation.
  - Leak testing is conducted using pressure decay methods.
    - E.g., Leak test based on ASTM F2095 and this information should be in the BLA
- An example of an information request sent to an applicant is as follows:
  - “You have submitted supplier’s leak testing data and method qualification information for the single use assembly. Implement a leak integrity test for the single use assembly prior to use for filling at the facility.”

Media fills for SUS

- On-going requirement:
  - Aseptic filling operations using SUS filling assemblies must be validated with three media fills.

Overall advantages of SUS in fill finish

- Single use technology in fill/finish using isolator filling technology:
  - Reduced risk of cross contamination.
    - Reduce risk of microbial contamination by limiting the number of valves and manifolds traditionally used for transport of media and buffers.
    - Reduction in the number of open operations and process transfers
  - Optimized the capacity of the filling line and improved efficiency by shortening time required for set-up and changeovers as well as minimize product loss.
    - Reduced complexity of installations, interventions within the isolator such as no CIP/SIP equipment installation; reduce capital investment, elimination of cleaning and sterilization; elimination of CIP/SIP maintenance costs; substantial energy costs for SIP;
    - Placement of peristaltic pump rack outside the isolators aseptic core in Grade D environment for ease of set up and maintenance.
  - Increased flexibility for multiproduct filling by ensuring application for high throughput plant and small scale products and /or clinical demands.

CONCLUSION

Approaches to Biologics Manufacturing

- Traditional Approaches:
  - Open processing
  - Aseptic connections
  - Large complex facilities
  - Stainless steel tanks, bioreactors
  - CIP/SIP systems
  - Manually intensive
  - Inefficient
  - Extensive monitoring
  - Extensive regulatory oversight
  - Vulnerable to manufacturing disruptions leading to shortages
- New Approaches:
  - Closed processing
  - Single use systems
  - Continuous manufacturing
  - Process intensification
  - Simple facilities
  - Separation (isolators, RABS, single use technologies)
  - Integration/automation (robotics)
  - Use of Advanced Analytics
  - Improved microbial control

New developments in biopharmaceuticals

- Continued need to develop and implement more flexible and cost effective manufacturing approaches while maintaining the high product quality standards.
  - Advances have been made in cell culture using chemically defined media with feeding regimes capable of sustaining high cell densities and allowing high protein yields.
    - Extensive use of single-use systems instead of stainless steel systems
    - Should provide for increased manufacturing flexibility, agility, efficiency and product quality
      - Should facilitate site transfers
      - Process simplification with reduced number of operations (elimination of centrifugation and hold steps)
    - Improved microbial control
      - Closed systems

New developments in biopharmaceuticals (cont.)

- Additional developments in downstream purification process are in the pipeline:
  - Introduction of multi-column and other continuous purification systems.
  - Fully integrated continuous manufacturing.
  - Purification needs further development for implementation.
- Increased adoption of restricted-access barrier systems (RABS) and isolator units for aseptic filling:
  - Use of single-use-system in fill-finish operations.
  - Use of more advanced closed, gloveless isolator systems.
  - Improved sterility assurance.

Conclusions

- Implementation of continuous manufacturing approaches in biologics should improve overall process control from a microbiology perspective and increase manufacturing efficiency, consistency and flexibility.
- From a product quality microbiology perspective, areas requiring further development and clarification include:
  - Reduction SUS vulnerability to leaks.
  - Development of fully integrated continuous manufacturing processes
    - Fully closed systems
  - Use of more advanced systems for aseptic filling
    - Fully closed systems
  - Development and implementation of more PAT for in-line testing and feedback-control.
    - Microbial testing

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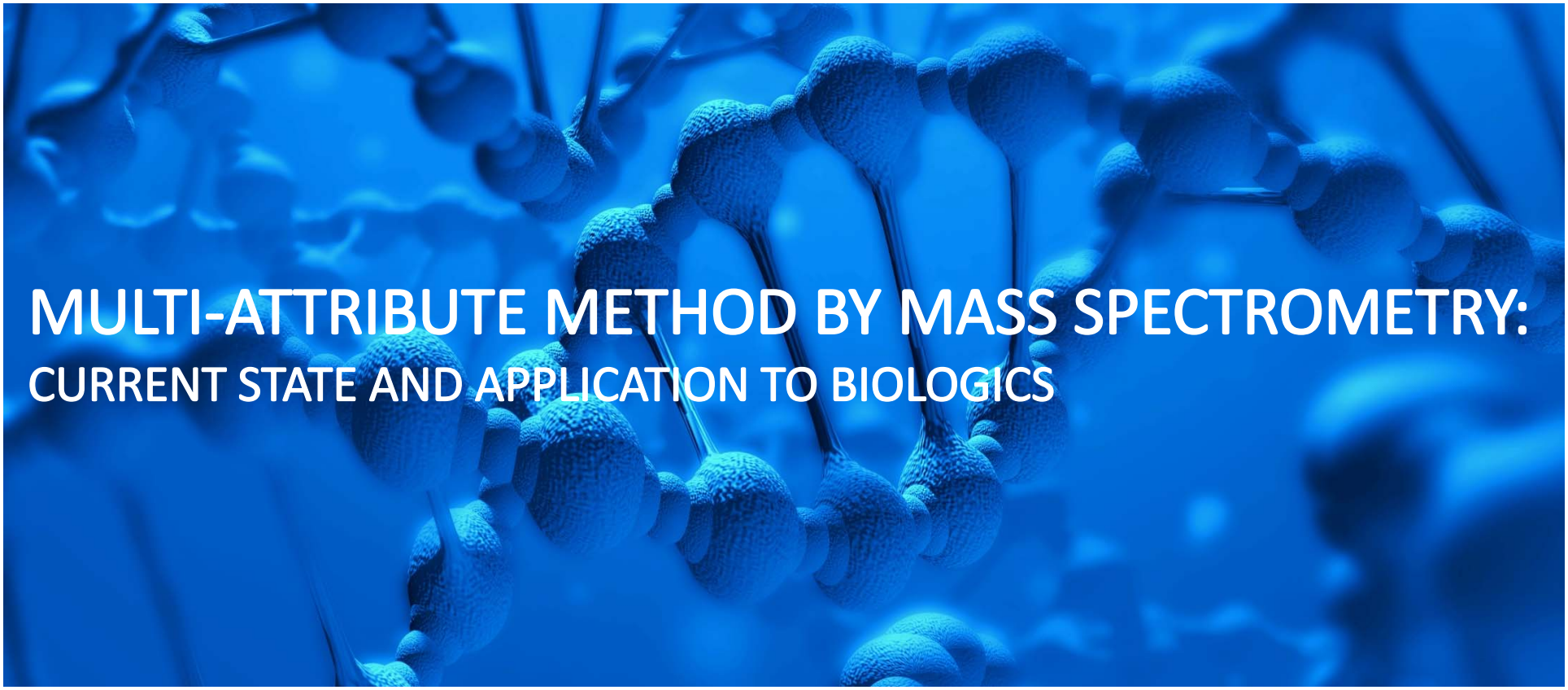
- Lynne Ensor, Ph.D., OPQ/OPF/DMA Division Director
- Reyes Candau-Chacon, Ph.D., OPQ/OPF/DMA/BIV


FDA
U.S. FOOD & DRUG
ADMINISTRATION



MULTI-ATTRIBUTE METHOD BY MASS SPECTROMETRY:
CURRENT STATE AND APPLICATION TO BIOLOGICS

JETTE WYPYCH, DIRECTOR IN ATTRIBUTE SCIENCES, PROCESS DEVELOPMENT

CAMBRIDGE MA, APRIL 17, 2018
ASTM MEETING

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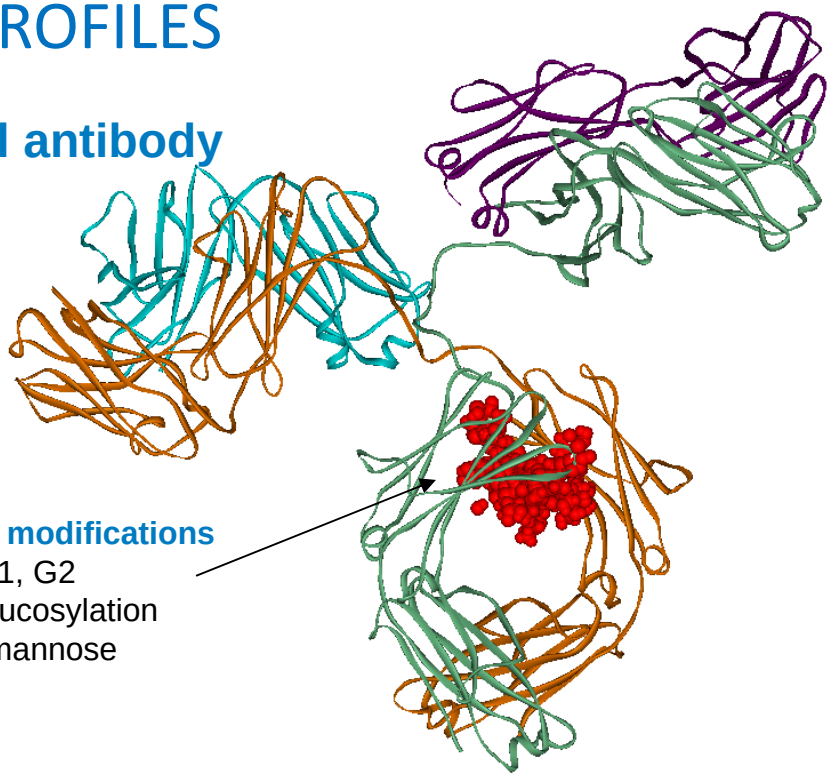
Pioneering science delivers vital medicines™

BIOLOGICAL PRODUCTS HAVE VERY COMPLEX STRUCTURES AND PRODUCT PROFILES

Monoclonal antibody



Glycan modifications
- G0, G1, G2
- Core fucosylation
- High mannose
- etc

Peptide modifications
- Deamidation
- Succinimide
- Oxidation
- Glycation
- C-terminal variants
  - HC- Lys
  - HC-ProAmide
- N-terminal variants
  - Pyro Glu
- Amino acid substitution
- Truncation
- Half molecules
- Disulfide isoforms

Peptide & glycan maps, mass spectrometry and other characterization methods provide orthogonal assessment of primary structure and product profile

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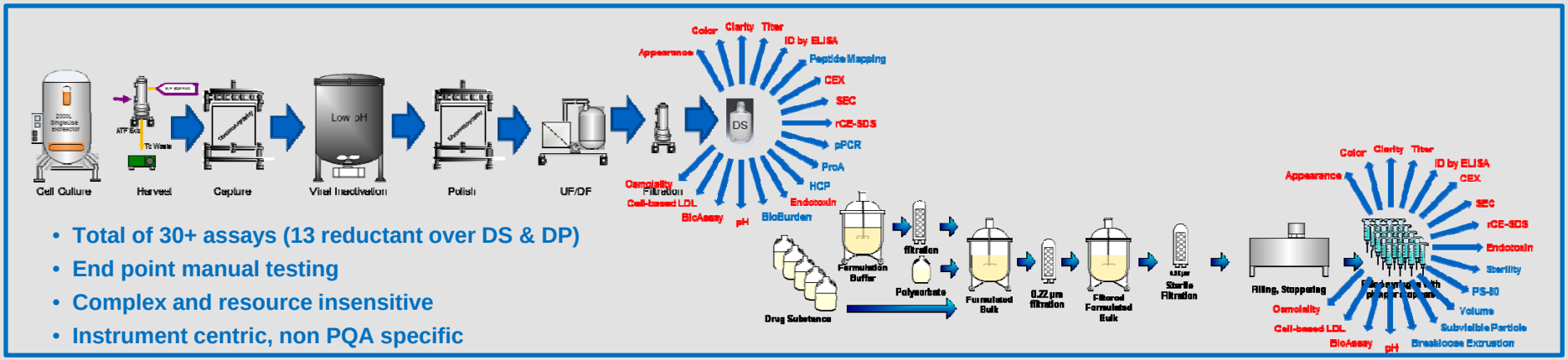
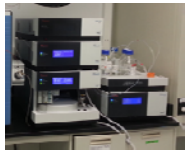
NUMEROUS TEST METHODS ARE OFTEN REQUIRED FOR DEVELOPMENT/PRODUCTION

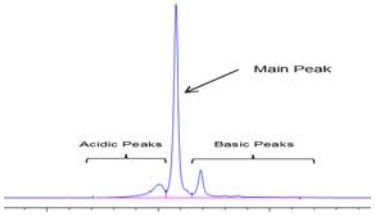


- Total of 30+ assays (13 reductant over DS & DP)
- End point manual testing
- Complex and resource insensitive
- Instrument centric, non PQA specific

CONVENTIONAL PURITY METHODS ARE LOW RESOLVING

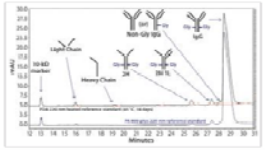
Chromatography based Methods:

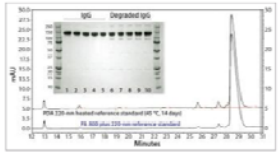




- **Size Exclusion: size based attributes**
- **Ion Exchange: charge attributes**
- **Hydrophobic Chromatography: oxidation and isomerization**
- **Reversed Phase Chromatography: product titer, product oxidized species and process related impurities**
- **Affinity Chromatography: product titer**
- **Peptide Mapping with UV detection: post translation modifications**
- **Glycan Analysis (HILIC, HPAEC or HPLC): oligosaccharide variants**

• *Electrophoretic based Methods*

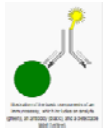




- **Gel Electrophoresis**
  - **Denatured state reduced or non-reduced: SDS-PAGE for size based attributes**
  - **Isoelectric focusing for charge based attributes**
- **Capillary Electrophoresis**
  - **Denatured state reduced or non-reduced: CE-SDS for size based attributes**
  - **cIEF for charge based attributes**

• *Immuno based Methods and qPCR*

Immuno



- Product ID
- Host cell protein analysis
- Impurities from processing with ligand chromatography
  - Protein A
  - Protein L
  - Lectin chromatography

qPCR

- DNA quantitation

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MASS SPECTROMETRY PROVIDES SPECIFICITY AND IS AN INVALUABLE TOOL FOR IDENTIFYING AND QUANTIFYING PRODUCT QUALITY ATTRIBUTES

J. Am. Soc. Mass Spectrom. (2017) 28:786–794
DOI: 10.1007/s13361-016-1531-9

FOCUS: 28th SANIBEL CONFERENCE, CHARACTERIZATION OF PROTEIN THERAPEUTICS BY MS: RESEARCH ARTICLE

A Retrospective Evaluation of the Use of Mass Spectrometry in FDA Biologics License Applications

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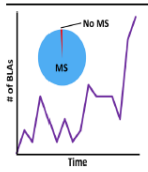

Abstract. The characterization sections of biologics license applications (BLAs) approved by the United States Food and Drug Administration (FDA) between 2000 and 2015 were investigated to examine the extent of the use of mass spectrometry. Mass spectrometry was found to be integral to the characterization of these biotherapeutics. Of the 80 electronically submitted monoclonal antibody and protein biotherapeutic BLAs included in this study, 79 were found to use mass spectrometric workflows for protein or impurity characterization. To further examine how MS is being used in successful BLAs, the applications were filtered based on the type and number of quality attributes characterized, the mass spectrometric workflows used (peptide mapping, intact mass analysis, and cleaved glycan analysis), the methods used to introduce the proteins into the gas phase (ESI, MALDI, or LC-ESI), and the specific types of instrumentation used. Analyses were conducted over a time course based on the FDA BLA approval to determine if any trends in utilization could be observed over time. Additionally, the different classes of protein-based biotherapeutics among the approved BLAs were clustered to determine if any trends could be attributed to the specific type of biotherapeutic.

Keywords: Mass spectrometry, Monoclonal antibodies, Protein therapeutics

Mass spectrometry technology is widely used in product characterization for regulatory filings

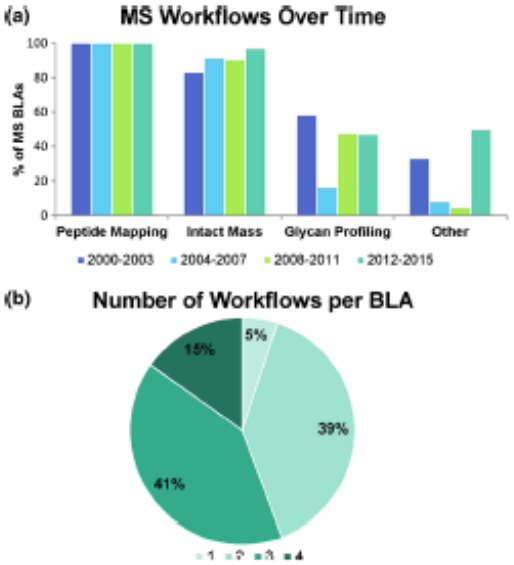

Figure 3. MS workflows. **(a)** MS workflows over time. Three major MS workflows were found within the analyzed BLAs: intact mass analysis, peptide mapping, and glycan profiling. Percentages are based on the total number of electronic BLAs that used MS. **(b)** Number of MS workflows per BLA. The total number of MS workflows used per BLA is shown, indicating that in 95% of the BLAs at least two workflows were used (i.e., intact mass was often used alongside peptide mapping)

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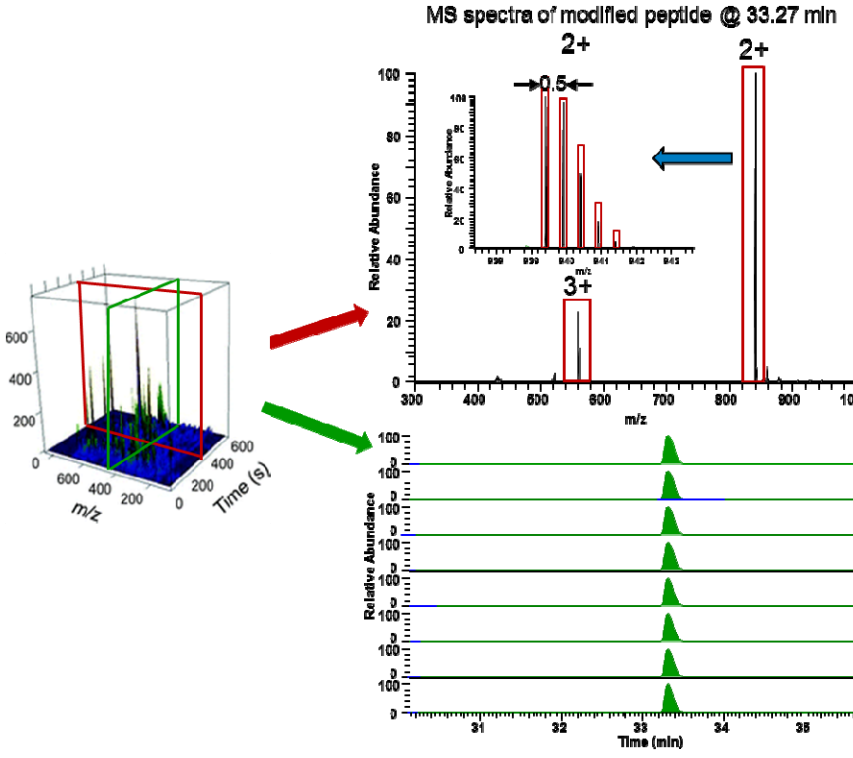
PRINCIPLES OF MASS SPECTROMETRY FOR MASS DETERMINATION AND RELATIVE QUANTITATION



Calculate the monoisotopic mass of peptides:

$$Monoisotopic\ Mass = (m/z - H^{+}) \times z$$

Calculate the peak area of modified peptide

Calculate the peak area of unmodified peptide

$$\%Mod = \frac{Peak\ Area_{Mod}}{Peak\ Area_{Mod} + Peak\ Area_{Unmod}}$$

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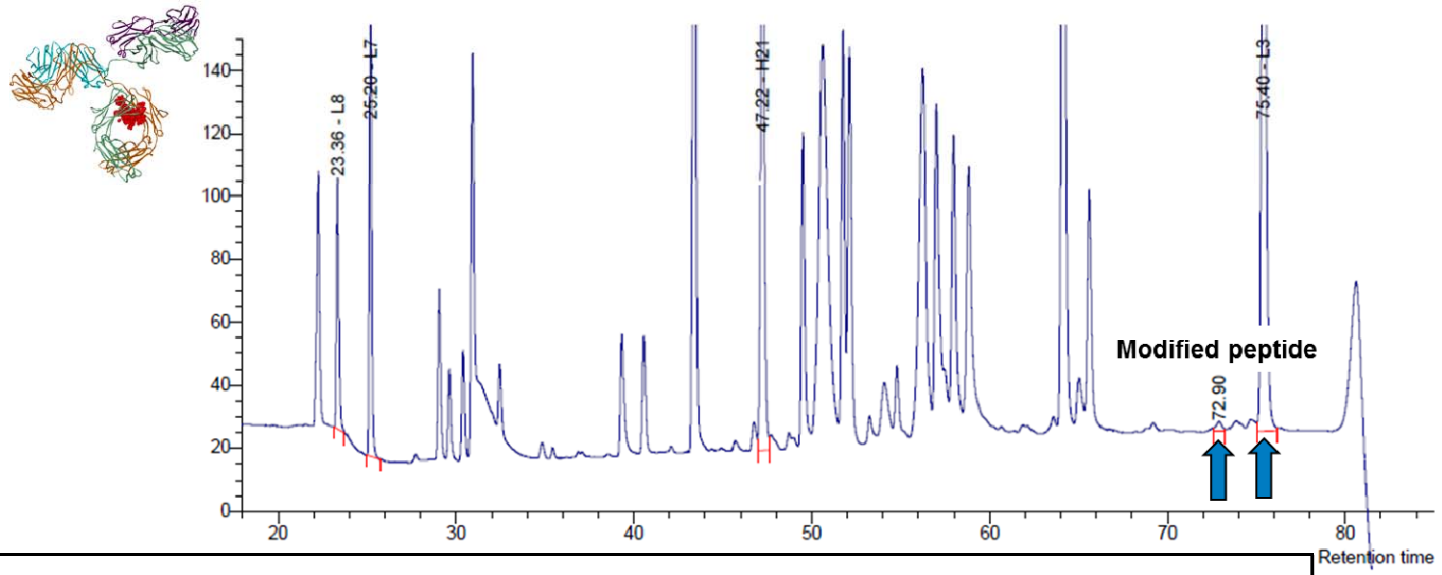
EXAMPLE OF A TARGETED PEPTIDE MAP WITH UV DETECTION PROVIDES RESULTS FOR ONE SINGLE ATTRIBUTE

Quantitation of modification of a peptide in CDR of a monoclonal antibody by reduced and alkylated Lys-C map



$$\% \text{ Modified pep.} = \frac{\text{Area (Modified pep.Peak)}}{\text{[Area(Modified pep. Peak)+Area (Unmodified pep. Peak)]}} \times 100$$

DRIVERS FOR APPLICATION OF MULTI-ATTRIBUTE METHOD

- Selective and specific monitoring of biologically relevant Product Quality Attributes rather than less specific monitoring by traditional methods (eg. CEX, reduced CE-SDS) better ensures product quality.
- All covalent PQAs are captured, though not reported, which speeds investigations of process deviations.
- Reduced number of assays for process development, product disposition and in-process control lowers costs and improves cycle time.
- Modality independent method speeds process development and embraces the principles of Quality-by-Design (applicable for mAbs, Fc-fusions, BiTE®s, bi-specifics, ADCs).
- Smaller footprint due to reduction in number of types of instruments
- Immediate data flow when executed on the manufacturing floor

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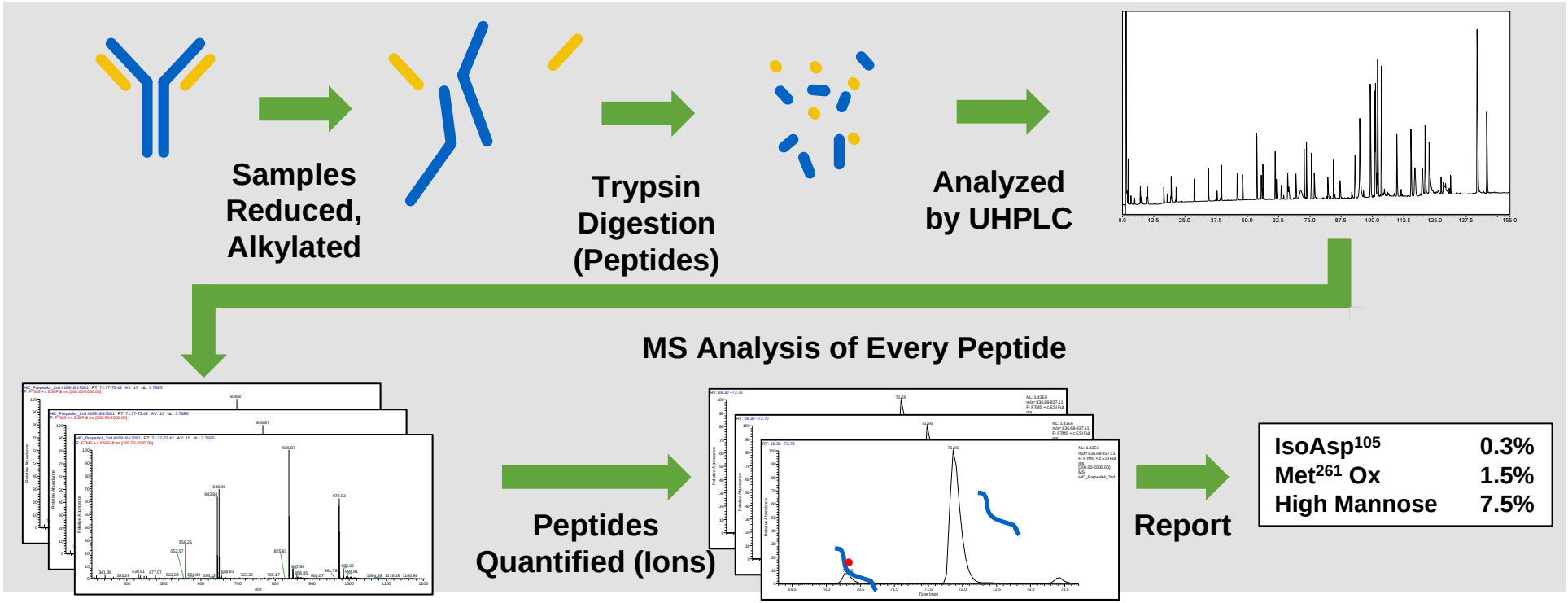
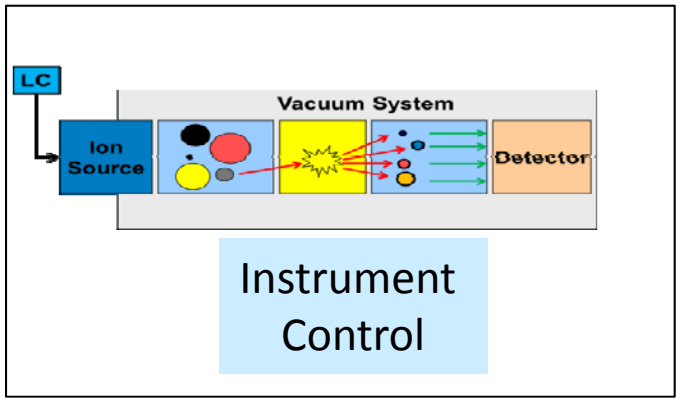
MAM METHOD WORKFLOW



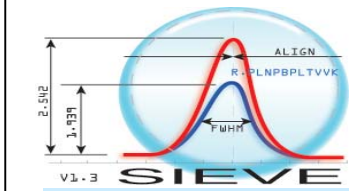
ALL INSTRUMENT CONTROL AND DATA ANALYSIS COMPONENTS ARE IN A SINGLE COMPLIANT PACKAGE

Chromeleon 7.2 SR2
CFR Title 21 Part 11 Compliant Package



Instrument Control

Attribute Quantitation



New Peak Detection

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PINPOINT

- **Software developed for targeted/quantitative analysis of MSn and high-resolution/accurate-mass (HR/AM) data as well as traditional selected reaction monitoring (SRM) transition data.**
- **In MAM application, Pinpoint analyzes protein peptide maps and targets MS1 precursor ions by retention time, accurate mass, and isotopic distribution.**
- **Theoretical and historical knowledge + in-depth characterization studies are combined to build information used by Pinpoint**
- **Pinpoint screening tool is used to interrogate experimental peptide map files**
- **Pinpoint provides automated data processing, outputs the area for the MS1 precursor and quantifies the PQA of interest**

1. Development of a quantitative mass spectrometry multi-attribute method for characterization, quality control testing and disposition of biologics
Rogers RS, Nightlinger NS, Livingston B, Campbell P, Bailey R, Balland A. *MAbs*. 2015; 7(5): 881-890

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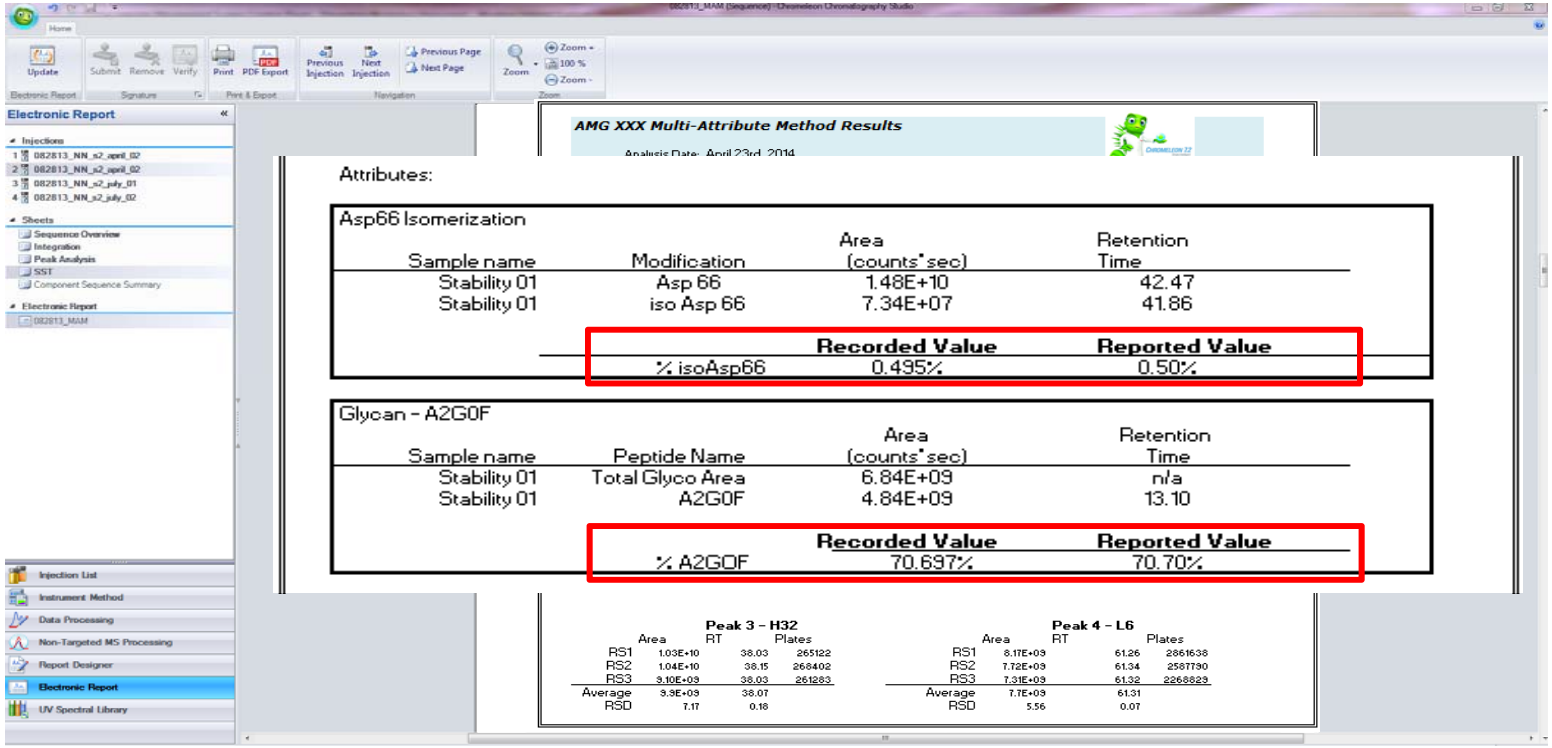
CHROMELEON 7.2 SR2.0: ELECTRONIC REPORTING



AMG XXX Multi-Attribute Method Results

Analysis Date: April 23rd, 2014

Attributes:

Asp66 Isomerization

Sample name	Modification	Area (counts*sec)	Retention Time
Stability 01	Asp 66	1.48E+10	42.47
Stability 01	iso Asp 66	7.34E+07	41.86

	Recorded Value	Reported Value
% isoAsp66	0.495%	0.50%

Glycan - A2G0F

Sample name	Peptide Name	Area (counts*sec)	Retention Time
Stability 01	Total Glyco Area	6.84E+09	n/a
Stability 01	A2G0F	4.84E+09	13.10

	Recorded Value	Reported Value
% A2G0F	70.697%	70.70%

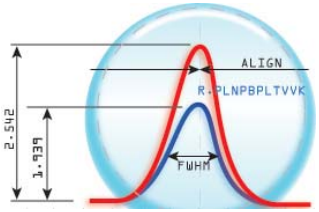
Peak 3 - H32

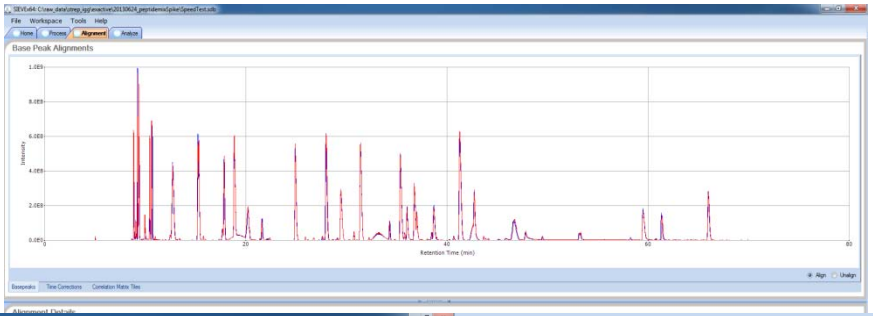
	Area	RT	Plates
RS1	1.03E+10	38.03	265122
RS2	1.04E+10	38.15	268402
RS3	3.10E+09	38.03	261283
Average	9.3E+09	38.07	
RSD	7.17	0.18	

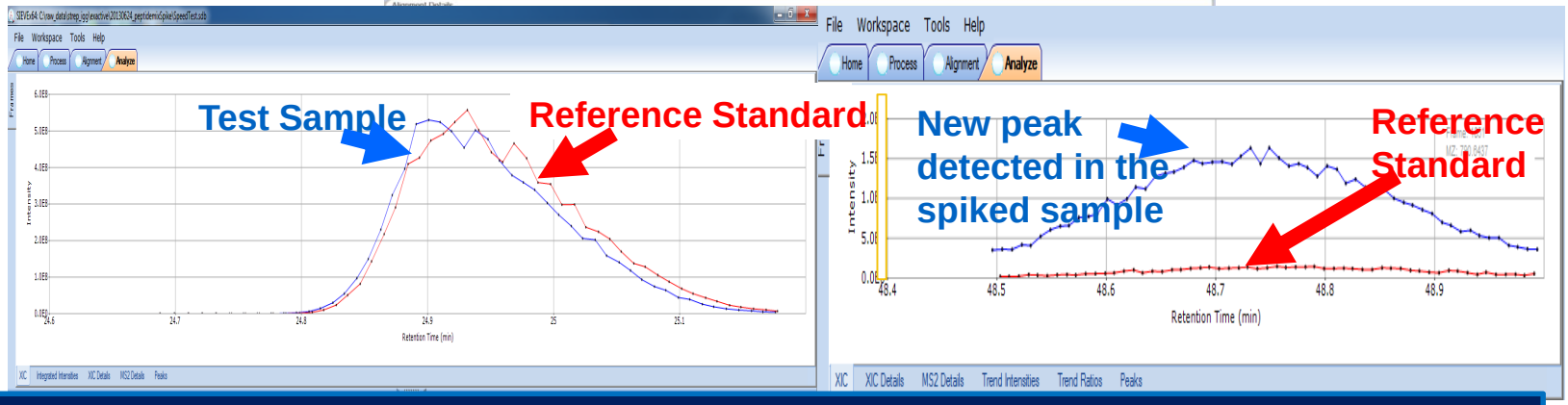
Peak 4 - L6

	Area	RT	Plates
RS1	8.17E+09	61.26	2861638
RS2	7.72E+09	61.34	2587790
RS3	7.31E+09	61.32	2268823
Average	7.7E+09	61.31	
RSD	5.56	0.07	

SOFTWARE: NEW PEAK DETECTION







SIEVE is able to detect new peaks

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MAM METHOD ACCEPTANCE CRITERIA

- **System Suitability**

  Based on a set of Select Unmodified Peptides

  - **Retention time: %RSD < 2%**
  - **Extracted Ion Count Area: RSD of EIC Area < 10%**
  - **Mass Accuracy: < 5 ppm**
  - **Peak Height: 1E6**
- **Sample Acceptance**

AMGEN

CRITERIA FOR EVALUATING A PEPTIDE OR ATTRIBUTE USING THE MULTI ATTRIBUTE METHOD

Development

1. Identification of the peptide/attribute is confirmed by MS^2 fragmentation + orthogonal characterization methods (HILIC-MS for glycosylation)
2. The retention time window for the peptide/attribute is defined
3. Set appropriate filters and threshold for new peak in Sieve

Execution

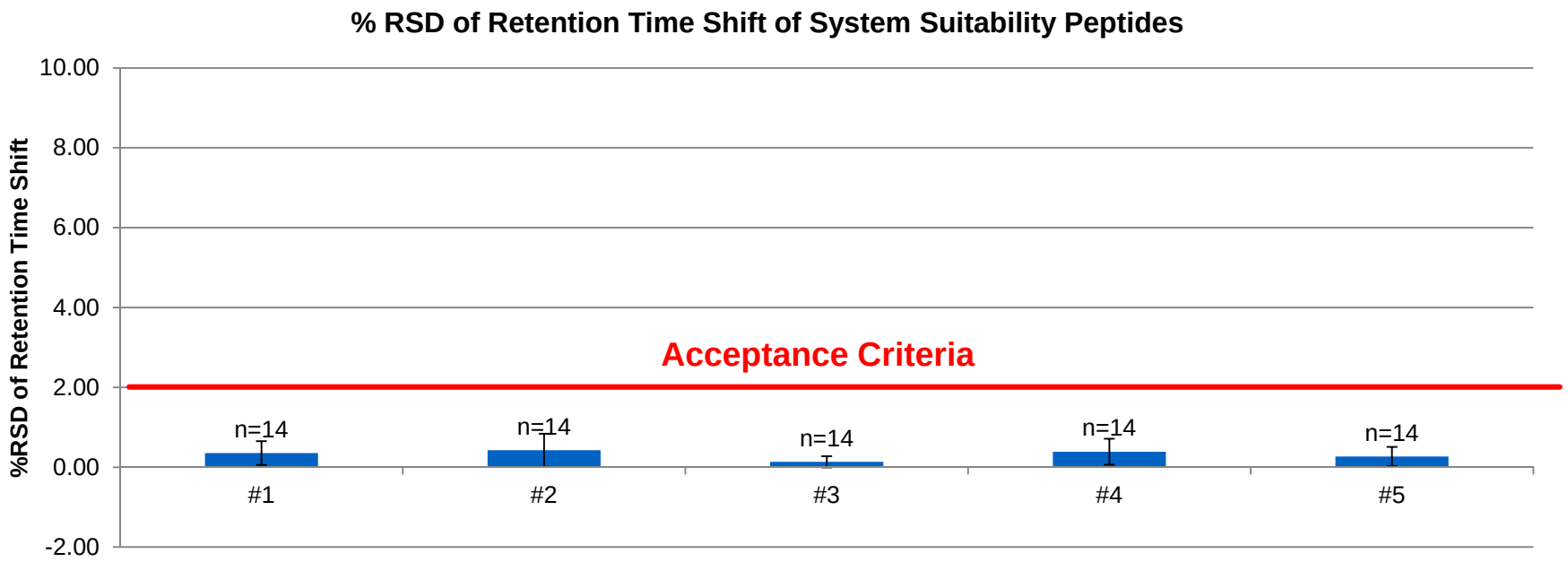
1. **The retention time for the peptide/attribute must be within a set retention time window (determined by characterization of the molecule)**
2. **The experimental mass is less than 5 ppm from the predicted mass**
3. **The experimental isotopic distribution fit to the theoretical must meet pre defined criteria**
4. **Apply filters and Threshold for new peak detection**

AMGEN

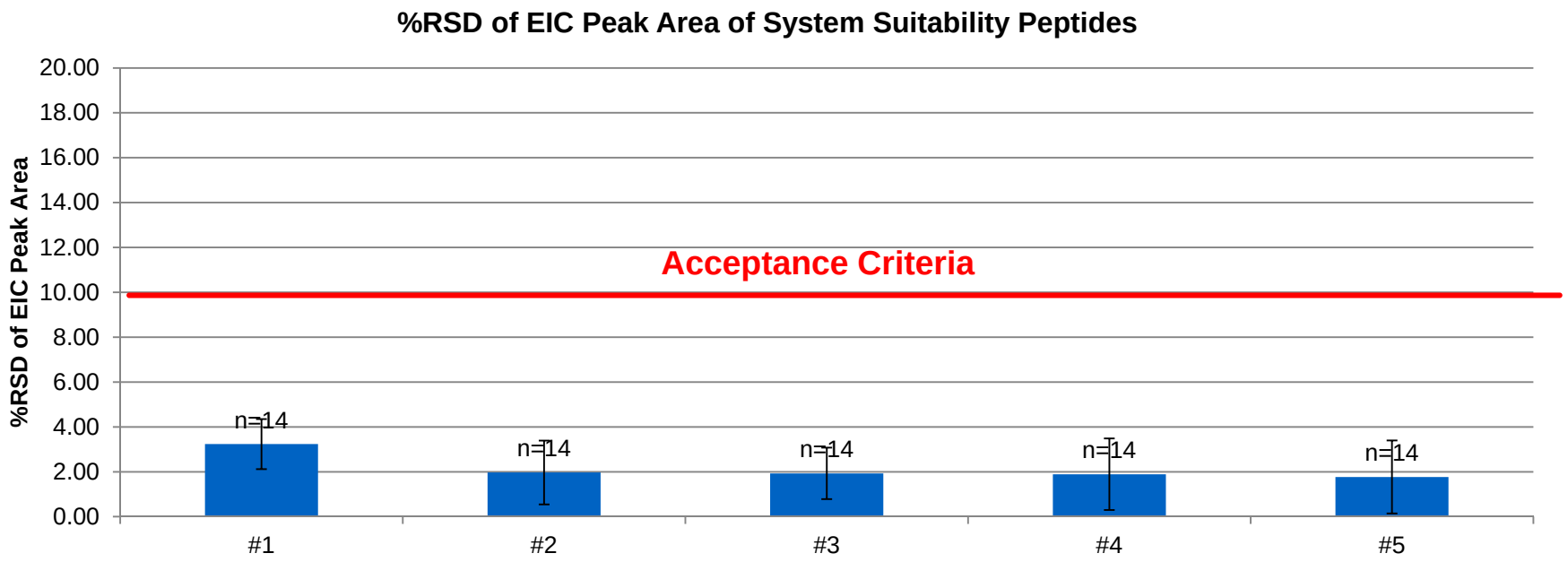
MAM PERFORMANCE: CONSISTENCY AND ROBUSTNESS

- **System suitability test results (5 system suitability peptides) of 14 independently executed MAM testing in the span of 18 months were evaluated:**
  - **Retention time shift**
  - **Extracted ion chromatogram (EIC) peak area**
  - **Mass accuracy**

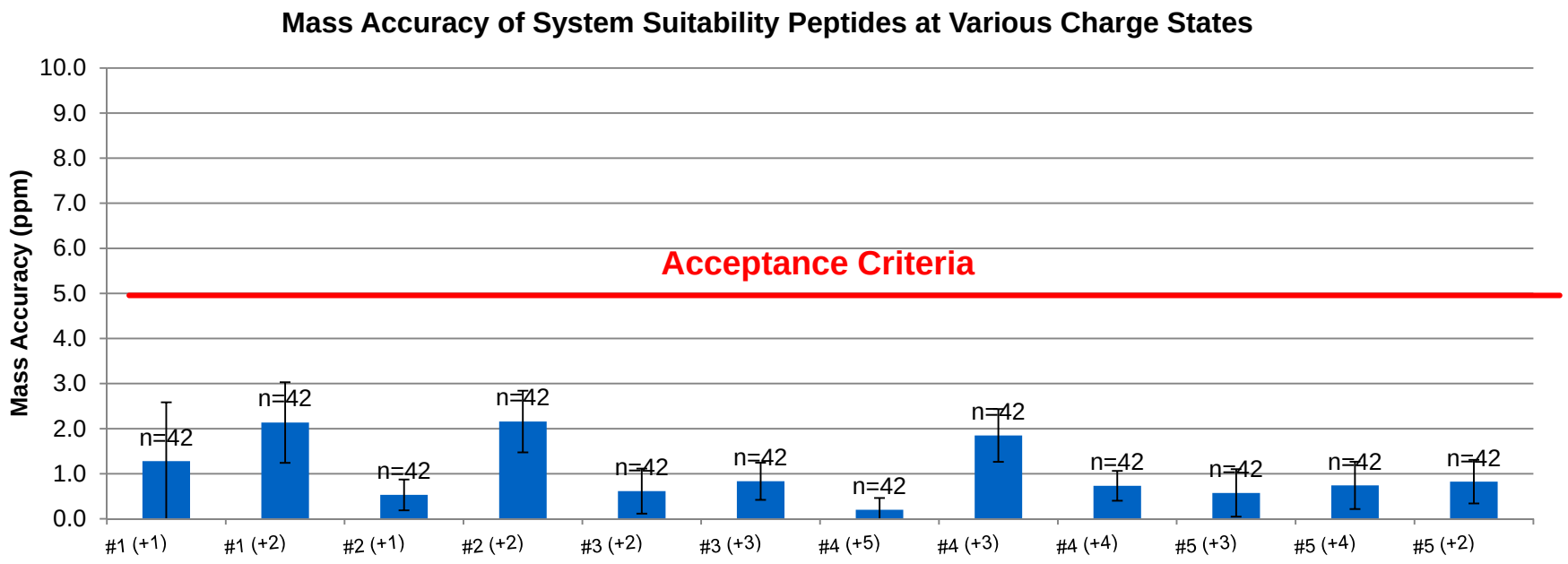
MAM PERFORMANCE: RETENTION TIME



MAM PERFORMANCE: PEAK INTENSITY VARIATIONS



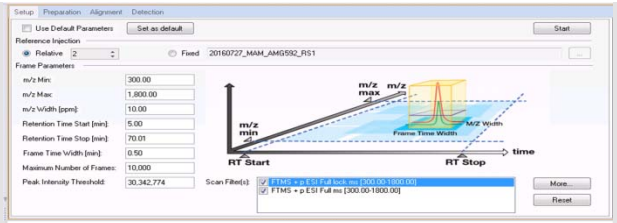
MAM PERFORMANCE: MASS ACCURACY

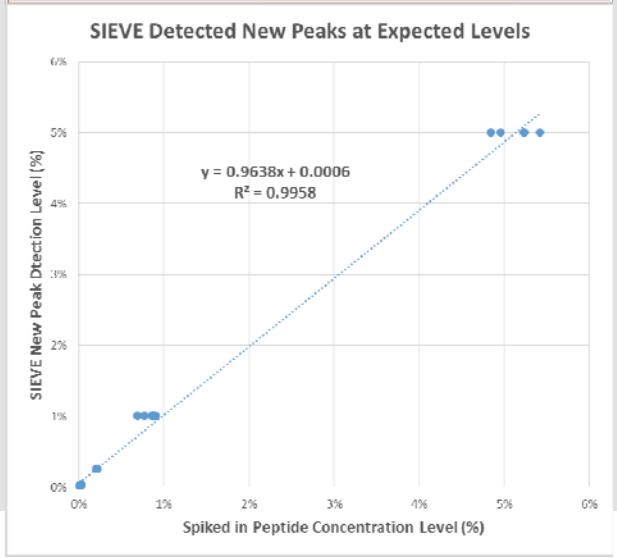


THERMO SIEVE SOFTWARE FOR NEW PEAK DETECTION

- **New peak detection is performed using Thermo Scientific SIEVE software, which is a part of Chromeleon software package**

- **SIEVE can effectively locate compounds with statistically significant abundance differences**
  - uses two-population differential analysis
  - uses aligned chromatograms
  - uses MS intensities from raw LC/MS data to find abundance differences
  - collects all peaks above a given threshold from all raw data, no information is lost





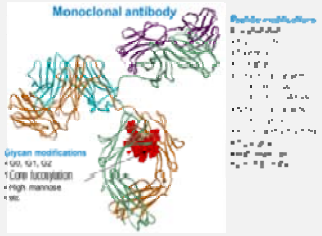
MAM CAN DIRECTLY IDENTIFY AND QUANTIFY PQAS AT AMINO ACID LEVEL WHICH ENABLES AMGEN TO DESIGN RELEVANT QUALITY TARGET PRODUCT PROFILE

Patient Centric Process Development

Target Product Profile

- Indication & use
- Dosage & administration
- Tolerability
- Dosage forms & strength
- Efficacy
- Safety/side effects
- Value & access

Product Quality Attribute Assessments



- CQA identification
- Scoring for potential impact to safety/efficacy

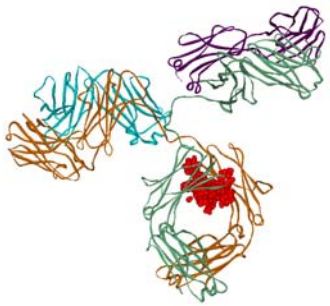
Quality Target Product Profile

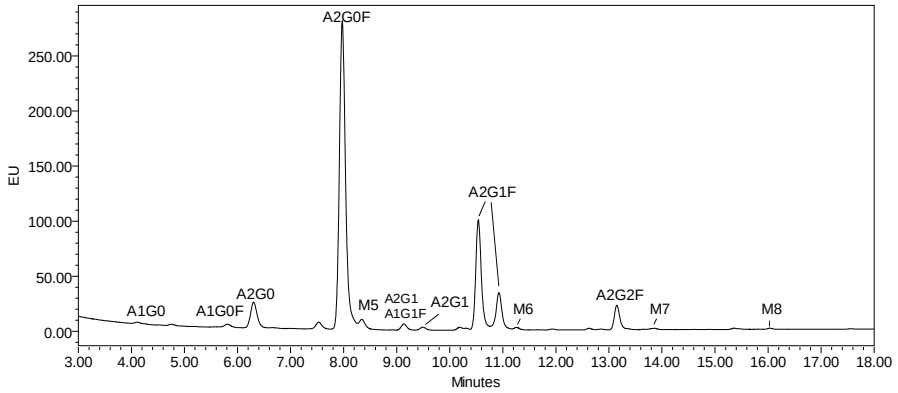
- Critical quality attribute selection
- Attribute range determination
- Designing quality into product during PD

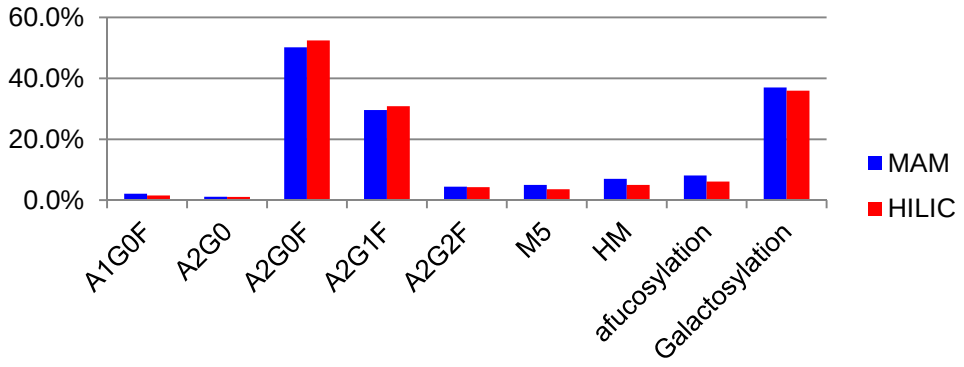
Attribute Measurements

- MAM provides specific attribute measurement
- Allows Amgen to control the levels of individual molecular CQAs

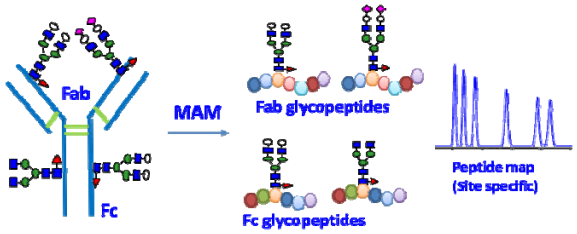
COMPARISON OF TRADITIONAL GLYCAN MAP AND MAM – EXCELLENT AGREEMENT FOR MAB FC GLYCANS

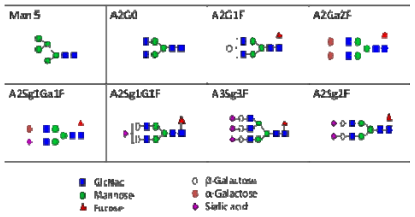




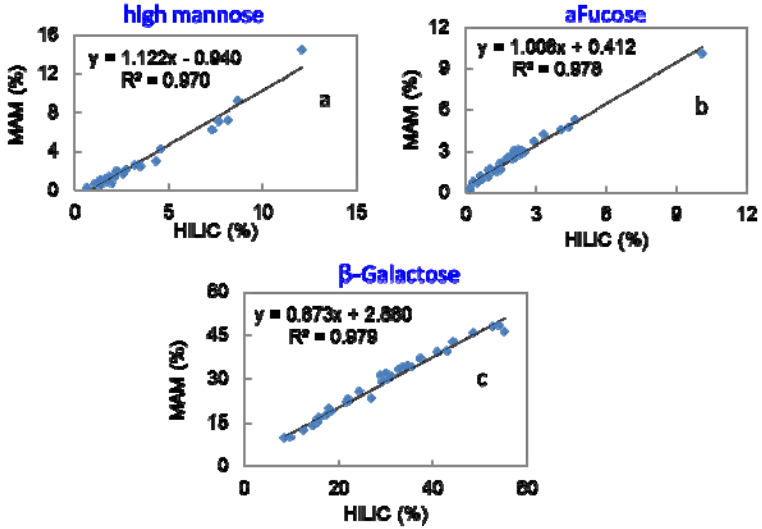


MAM GLYCAN ANALYSIS CORRELATES WELL WITH TRADITIONAL GLYCAN ANALYSIS

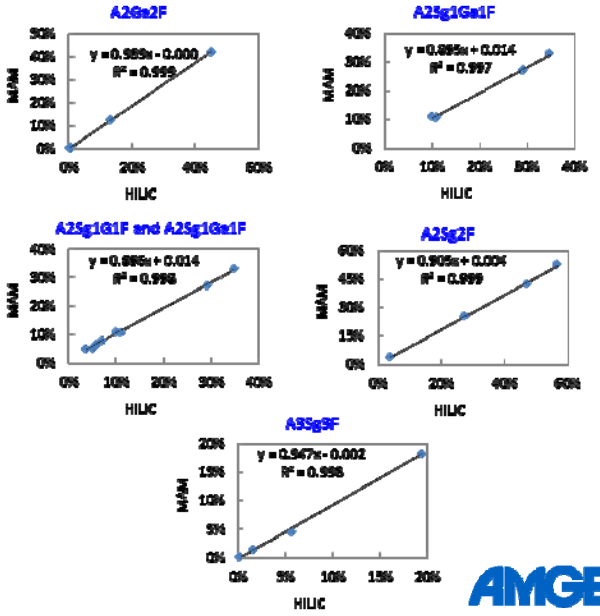




Fc glycan analysis:

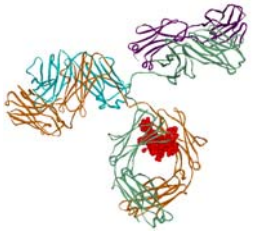


Fab glycan analysis:

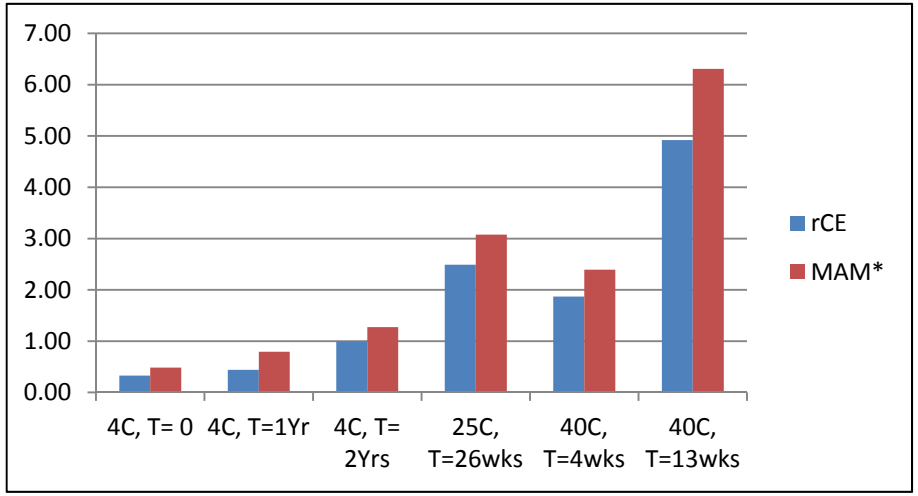


1. Application of a quantitative LC-MS multi-attribute method for monitoring site-specific glycan heterogeneity on a monoclonal antibody containing two N-linked glycosylation sites
Wang T, Chu L, Li W, Lawson K, Apostol I, Eris T, *Analytical Chemistry, 2017*

REAL TIME SAMPLE CLIPPING: MAM VS. REDUCED CE-SDS



	% Clipped Species	
Sample	rCE	MAM*
4C, T= 0	0.33	0.49
4C, T=1 Yr	0.44	0.79
4C, T= 2 Yrs	1.00	1.27
25C, T=26 wks	2.49	3.08
40C, T=4 wks	1.87	2.39
40C, T=1 3wks	4.92	6.31



Relative levels of Clips by MAM and reduced CE-SDS (LMW + MMW species) are in agreement

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MAM HAS POTENTIAL TO REPLACE SEVERAL METHODS AND ASSOCIATED INSTRUMENTS

Current Method	Attribute	Proposed Method
rCE-SDS	Purity - Clips	Multi-Attribute Method (MAM)
CEX-HPLC	Purity – Charge Variants	
Glycan Map	Glycans	
Immunoassay	Identity	

The AAPS Journal (© 2017)
DOI: 10.1208/s12248-017-0149-5

Commentary

A View on the Importance of "Multi-Attribute Method" for Measuring Purity of Biopharmaceuticals and Improving Overall Control Strategy

Richard S. Rogers,[1,3] Michael Abernathy,[1] Douglas D. Richardson,[1] Jason C. Rouse,[1] Justin B. Sperry,[1] Patrick Swann,[1] Jette Wypych,[2] Christopher Yu,[1] Li Zang,[1] and Rohini Deshpande[1]

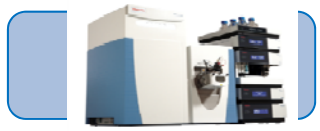
Received 2 October 2017; accepted 3 November 2017

Abstract. Today, we are experiencing unprecedented growth and innovation within the pharmaceutical industry. Established protein therapeutic modalities, such as recombinant human proteins, monoclonal antibodies (mAbs), and fusion proteins, are being used to treat previously unmet medical needs. Novel therapies such as bispecific T cell engagers (BiTEs), chimeric antigen T cell receptors (CARTs), siRNA, and gene therapies are paving the path towards increasingly personalized medicine. This advancement of new indications and therapeutic modalities is paralleled by development of new analytical technologies and methods that provide enhanced information content in a more efficient manner. Recently a liquid chromatography-mass spectrometry (LCMS) multi-attribute method (MAM) has been developed and designed for improved simultaneous detection, identification, quantitation, and quality control (monitoring) of molecular attributes (Rogers et al. MAbs 7(5):881–90, 2015). Based on peptide mapping principles, this powerful tool represents a true advancement in testing methodology that can be utilized not only during product characterization, formulation development, stability testing, and development of the manufacturing process, but also as a platform quality control method in dispositioning clinical materials for both innovative biotherapeutics and biosimilars.

KEY WORDS: biotherapeutic; mass spectrometry; multi-attribute method; quality by design.

HPLC-FLD (Glycan-map) | **HPLC-UV (CEX-HPLC)** | **CE-UV (rCE-SDS)** | **Platereader (immunoassay)**

MAM replaces four instrument types



UPLC/MS (MAM)

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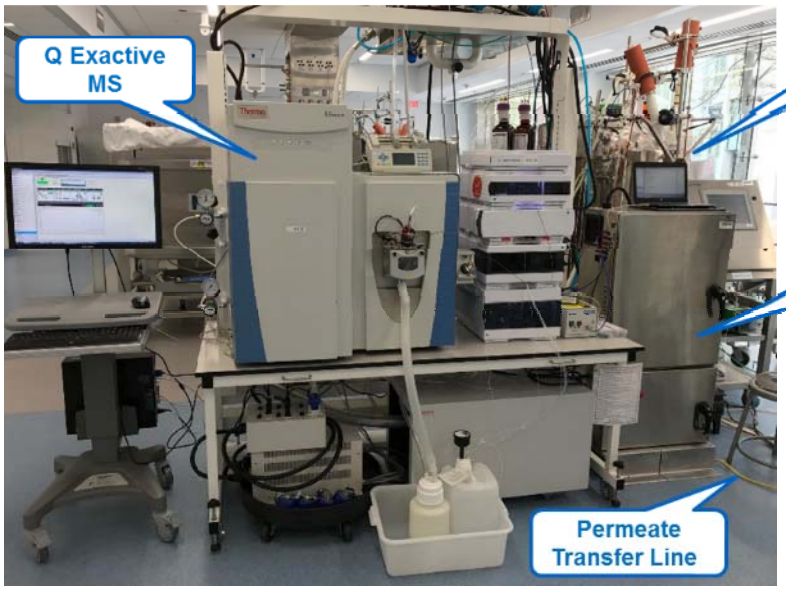
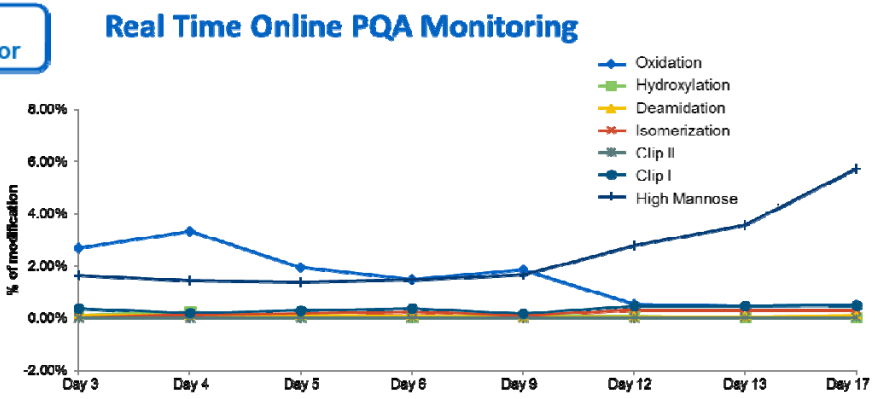
BRING MAM ONLINE: REAL TIME PQA MONITORING





- Evaluate product attributes in real time
- Correlate process parameters with product quality attributes

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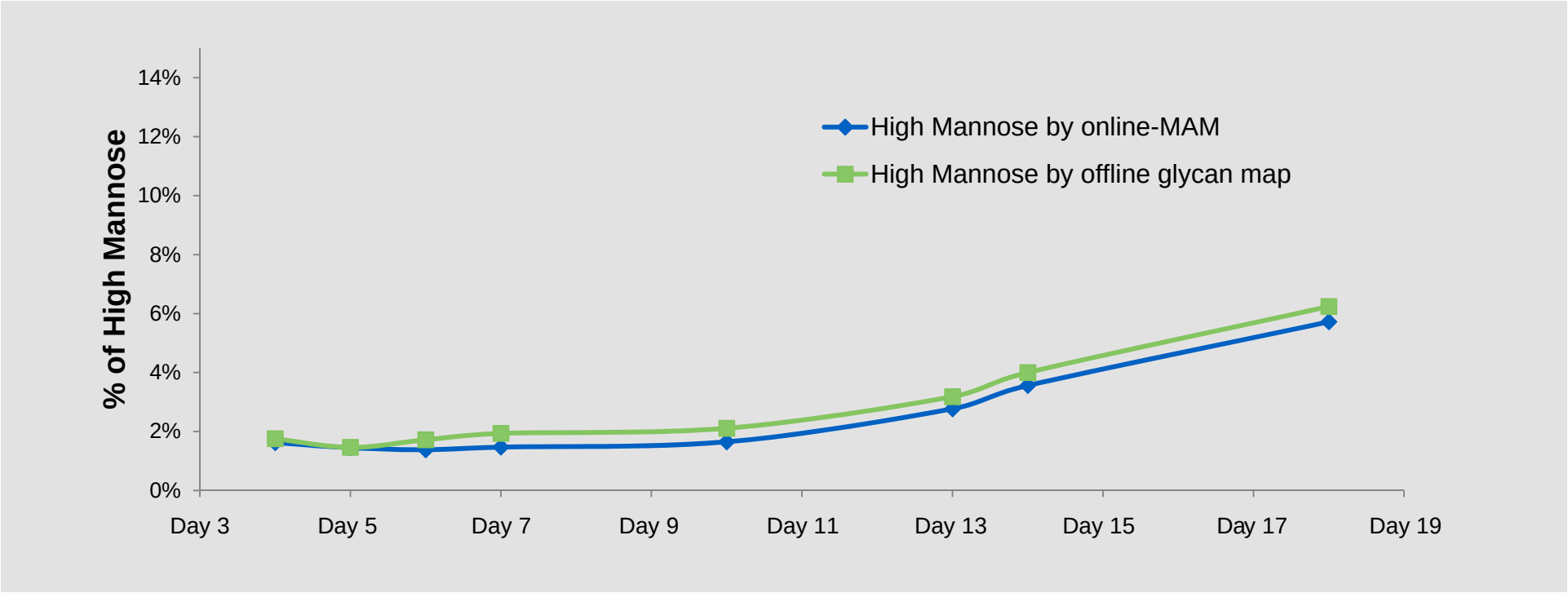
EXCELLENT CORRELATION BETWEEN ONLINE AND OFFLINE METHODS



DIFFERENT MASS SPEC PLATFORMS:
SUITABLE FOR MAM-LIKE APPLICATIONS?

	Orbitrap	ToF	Quadrupole	Triple Quad
Resolution	High	High	Low	Low
Mass Accuracy	High	High	Low	Low
Linearity	Good	Good	Very Good	Very Good
Precision	Good	Good	Very Good	Very Good
Dynamic Range	Good	Good	Very Good	Super Good
Cost	Very High	High	Low	Medium
Footprint	Big	Big	Small	Small to Medium
Specificity	Good	Good	Poor	Good
LOD/LOQ	Good	Good	Poor	Very Good
New Peak Detection	Yes	Yes	No	No
Robustness	Good	Good	Super Good	Very Good

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PUBLICATIONS ON LABEL FREE USE OF MASS SPECTROMETRY FOR QUANTITATION OF PRODUCT ATTRIBUTES

mAbs 7:5, 881–890; September/October 2015; © 2015 Amgen Inc.

Development of a quantitative mass spectrometry multi-attribute method for characterization, quality control testing and disposition of biologics

Richard S Rogers[1,*], Nancy S Nightlinger, Brittney Livingston[†], Phil Campbell, Robert Bailey[#], and Alain Balland[§]

Analytical Sciences, Amgen Inc.; Seattle, WA USA
[†]Present affiliation: Just Biotherapeutics; Seattle, WA USA
[#]Present affiliation: Zymeworks; Seattle, WA USA
[§]Present affiliation: Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany

Keywords: monoclonal antibody, multi-attribute method (MAM), peptide map, product quality attributes, quality by desi

Abbreviations: IgG2, immunoglobulin G2 antibody isotype; PTMs, post-translational modifications; CQAs, critical attributes; QbD, Quality by Design; RP-HPLC, reverse phase, high performance liquid chromatography; MS, mass spectrom MS2, tandem MS or MS/MS; MAM, multi-attribute method; RCESDS, reduced capillary electrophoresis sodium dodecyl su NGHC, non-glycosylated heavy chain; A2G2F, asialo-, bi-galactosylated bi-antennary, core substituted with fucose; A1G0, a agalacto-, mono-antennary; M5, oligomannose 5; A1G0F, asialo-, agalacto-, mono-antennary, core substituted with fucose; A asialo-, agalacto-, bi-antennary; M6, oligomannose 6; A1G1F, asialo-, mono-galactosylated mono-antennary, core substituted fucose; A2G0F, asialo-, agalacto-, bi-antennary, core substituted with fucose; A2G1, asialo-, mono-galactosylated bi-antennary oligomannose 7; A2G1F, asialo-, mono-galactosylated bi-antennary, core substituted with fucose; A2G2, bi-galactosylated bi-antennary; M8, oligomannose 8; M9, oligomannose 9

Regulatory agencies have recently recommended a Quality by Design (QbD) approach for the manufacturing of therapeutic molecules. A QbD strategy requires deep understanding at the molecular level of the attributes that are crucial for safety and efficacy and for insuring that the desired quality of the purified protein drug product is met at the end of the manufacturing process. A mass spectrometry (MS)-based approach to simultaneously monitor the extensive array of product quality attributes (PQAs) present on therapeutic molecules has been developed. This multi-attribute method (MAM) uses a combination of high mass accuracy / high resolution MS data generated by Orbitrap technology and automated identification and relative quantification of PQAs with dedicated software (Pinpoint). The MAM has the potential to replace several conventional electrophoretic and chromatographic methods currently used in Quality Control to release therapeutic molecules. The MAM represents an optimized analytical solution to focus on the attributes of the therapeutic molecule essential for function and implement QbD principles across process development, manufacturing and drug disposition.

MABS
2016, VOL. 8, NO. 8, 1477–1486
http://dx.doi.org/10.1080/19420862.2016.1226715

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REPORT

Simultaneous monitoring of oxidation, deamidation, isomerization, and glycosylation of monoclonal antibodies by liquid chromatography-mass spectrometry method with ultrafast tryptic digestion

Yi Wang, Xiaojuan Li, Yan-Hui Liu, Daisy Richardson, Huijuan

Bioprocess Development, Merck Research Laboratories, Merck & Co., Inc., Ke

ABSTRACT
Monoclonal antibodies are subjected to a wide variety of post- cause structural heterogeneity. Characterization and control of t are critical to ensure antibody quality and to define any poten potency of antibody therapeutics. The biopharmaceutical indu analyze these quality attributes individually, which requires sub report a simple and ultrafast bottom-up liquid chromatography-m 5 min tryptic digestion to simultaneously analyze multipl deamidation, isomerization, glycation, glycosylation, and N-termin occur during antibody production in mammalian cell culture, Compared to commonly used preparation procedures, this uLC-M falsely-increased Met oxidation, Asp isomerization, and Asn deami digestion times in conventional LC-MS methods. This simple, low can be used to quickly and accurately analyze samples at any st particular for clone and media selection during cell culture develop

MABS
2017, VOL. 9, NO. 7, 1186–1196
https://doi.org/10.1080/19420862.2017.1364326

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REPORT

OPEN ACCESS

A Quadrupole Dalton-based multi-attribute method for product characterization, process development, and quality control of therapeutic proteins

Weichen Xu[a], Rod Brian Jimenez[a], Rachel Mowery[b], Haibin Luo[c], Mingyan Cao[a], Nitin Agarwal[b], Irina Ramos[c], Xiangyang Wang[a], and Jihong Wang[a]

[a]Analytical Sciences, MedImmune, One MedImmune Way, Gaithersburg, MD USA; [b]Cell Culture and Fermentation Sciences, MedImmune, One MedImmune Way, Gaithersburg, MD USA; [c]Purification Process Sciences, MedImmune; One MedImmune Way, Gaithersburg, MD USA

ABSTRACT
During manufacturing and storage process, therapeutic proteins are subject to various post-translational modifications (PTMs), such as isomerization, deamidation, oxidation, disulfide bond modifications and glycosylation. Certain PTMs may affect bioactivity, stability or pharmacokinetics and pharmacodynamics profile and are therefore classified as potential critical quality attributes (pCQAs). Identifying, monitoring and controlling these PTMs are usually key elements of the Quality by Design (QbD) approach. Traditionally, multiple analytical methods are utilized for these purposes, which is time consuming and costly. In recent years, multi-attribute monitoring methods have been developed in the biopharmaceutical industry. However, these methods combine high-end mass spectrometry with complicated data analysis software, which could pose difficulty when implementing in a quality control (QC) environment. Here we report a multi-attribute method (MAM) using a Quadrupole Dalton (QDa) mass detector to selectively monitor and quantitate PTMs in a therapeutic monoclonal antibody. The result output from the QDa-based MAM is straightforward and automatic. Evaluation results indicate this method provides comparable results to the traditional assays. To ensure future application in the QC environment, this method was qualified according to the International Conference on Harmonization (ICH) guideline and applied in the characterization of drug substance and stability samples. The QDa-based MAM is shown to be an extremely useful tool for product and process characterization studies that facilitates facile understanding of process impact on multiple quality attributes, while being QC friendly and cost-effective.

ARTICLE HISTORY
Received 19 June 2017
Revised 24 July 2017
Accepted 1 August 2017

KEYWORDS: monoclonal antibody; multi-attribute method; process development; product quality attributes; quality control

Abbreviations: BLA, biologics license application; CDR, complementarity-determining region; CE-SDS, capillary electrophoresis sodium dodecyl sulfate; CEX, cation exchange chromatography; CM, clarified medium; DS, drug substance; DTT, dithiothreitol; EDTA, EDTA; Fab, fragment antigen-binding; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; GuHCl, guanidine hydrochloride; HILIC, hydrophilic interaction chromatography; HL, heavy chain-light chain; IAM, iodoacetamide; ICH, international conference on harmonization; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LOD, limit of detection; LOQ, limit of quantitation; Lys-C, lysyl endopeptidase; m/z, mass-to-charge ratio; mAbs, monoclonal antibodies; MAM, multi-attribute method; Man, high mannose; MS, mass spectrometry; NaCl, sodium chloride; NEM, N-ethylmaleimide; PBS, phosphate-buffered saline; pCQAs, potential critical quality attributes; PTMs, post-translational modifications; QbD, quality by design; QC, quality control; QDa, quadrupole dalton; SIR, selected ion recording; TFA, trifluoroacetic acid

AMGEN

CHALLENGES AND SOLUTIONS FOR IMPLEMENTATION OF MAM

- Technical
  - Sample preparation
  - Robustness of instruments
  - Robustness of software (new peak detection)
- Regulatory/Compliance
  - Acceptance
  - 21CFRpart 11
- Capability as a replacement (instead of additional) release and stability test
  - IEX-HPLC, CE-SDS, ID, conventional glycan analysis i.e HILIC
- Diverse Regulatory Environment
  - Industry meetings and engagement

FUTURE VISION FOR MAM

- Include additional PQAs for quantitation and control
- Data standardization across multiple instrument and software platforms
- On-the-floor real time testing with product attribute control
- Smaller instrument footprint, automation and faster run times
- Raw data submission fore regulatory agencies to evaluate MAM data

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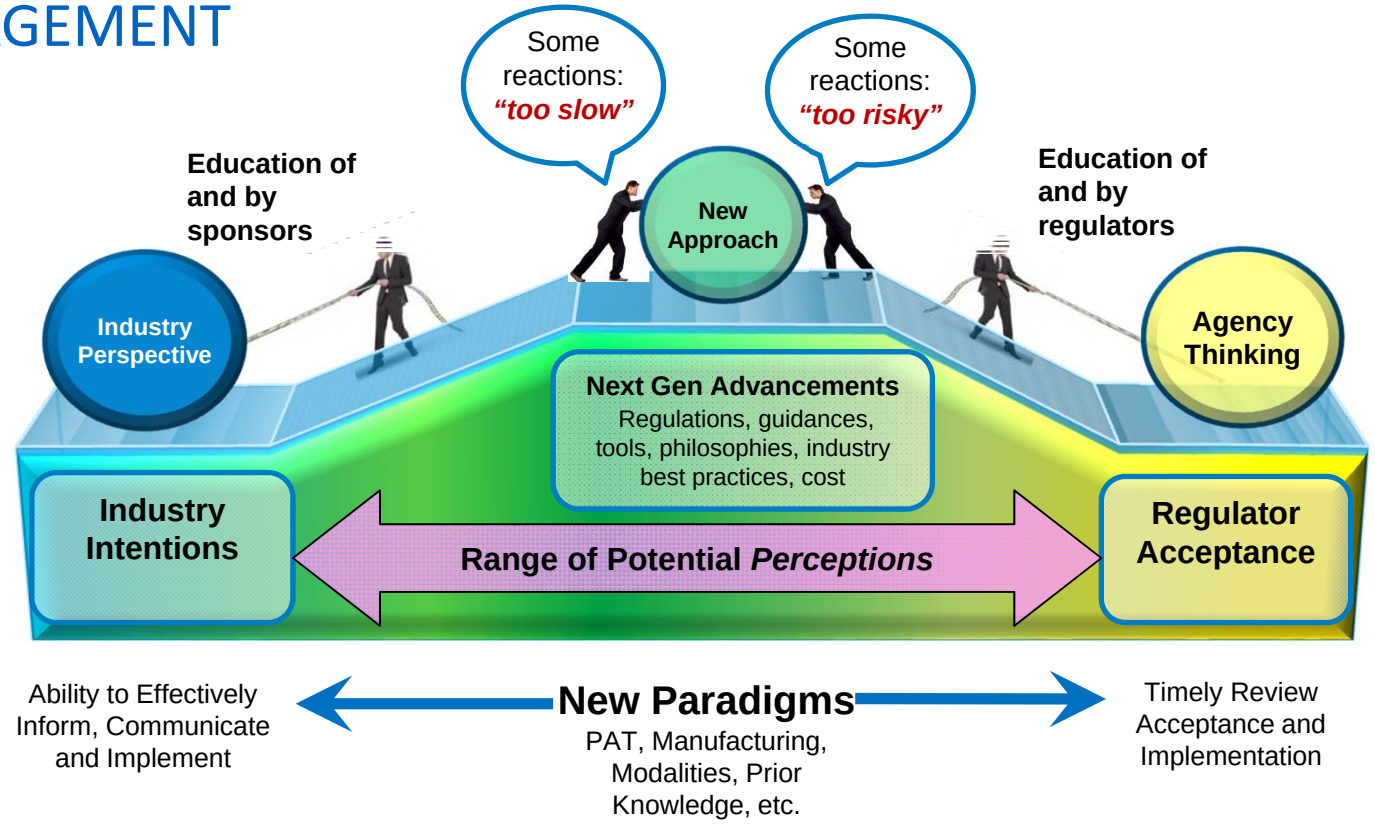
BUILDING AGENCY AND INDUSTRY ACCEPTANCE OF NEXT GENERATION ADVANCEMENTS REQUIRES BALANCED ENGAGEMENT



ACKNOWLEDGEMENTS

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- Zhongqi Zhang
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- Tura Camilli
- Tamer Eris
- Alicia Zeng
- Gang Xue
- Richard Wu

AMGEN

Regulatory Considerations for Gene-modified T cell Products

ASTM International Workshop on Emerging Technologies in Biopharmaceutical Manufacturing

Cambridge, MA

Nirjal Bhattarai, Ph.D.

Division of Cellular and Gene Therapies

Office of Tissues and Advanced Therapies

CBER, FDA

Outline

- Brief introduction of OTAT
- Update on Cell and Gene Therapy Products
- Key regulatory challenges for manufacturing cell and gene therapy products
- Gene Modified T cells: An Emerging Technology
- OTAT Resources

Office of Tissues and Advanced Therapies (OTAT)

- One of the three product offices within CBER.
- Previously known as Office of Cellular, Tissue and Gene Therapies (OCTGT)
- Effective October 16, 2016, OCTGT was reorganized, expanded and renamed as Office of Tissues and Advanced Therapies (OTAT) to meet the needs for reviewing applications for emerging cutting edge technologies such as cell and gene therapies in an efficient and consistent manner.
- During reorganization some resources were transferred from Office of Blood Research and Review (OBRR) to OTAT.

Products Regulated by OTAT

- **Stem cell and stem cell-derived products**
  - Hematopoietic, mesenchymal, cord blood, embryonic, iPSCs
- **Somatic cell therapies**
  - Pancreatic islets, chondrocytes, myoblasts, keratinocytes, hepatocytes
- **Active immunotherapies**
  - Cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies
  - Therapeutic vaccines

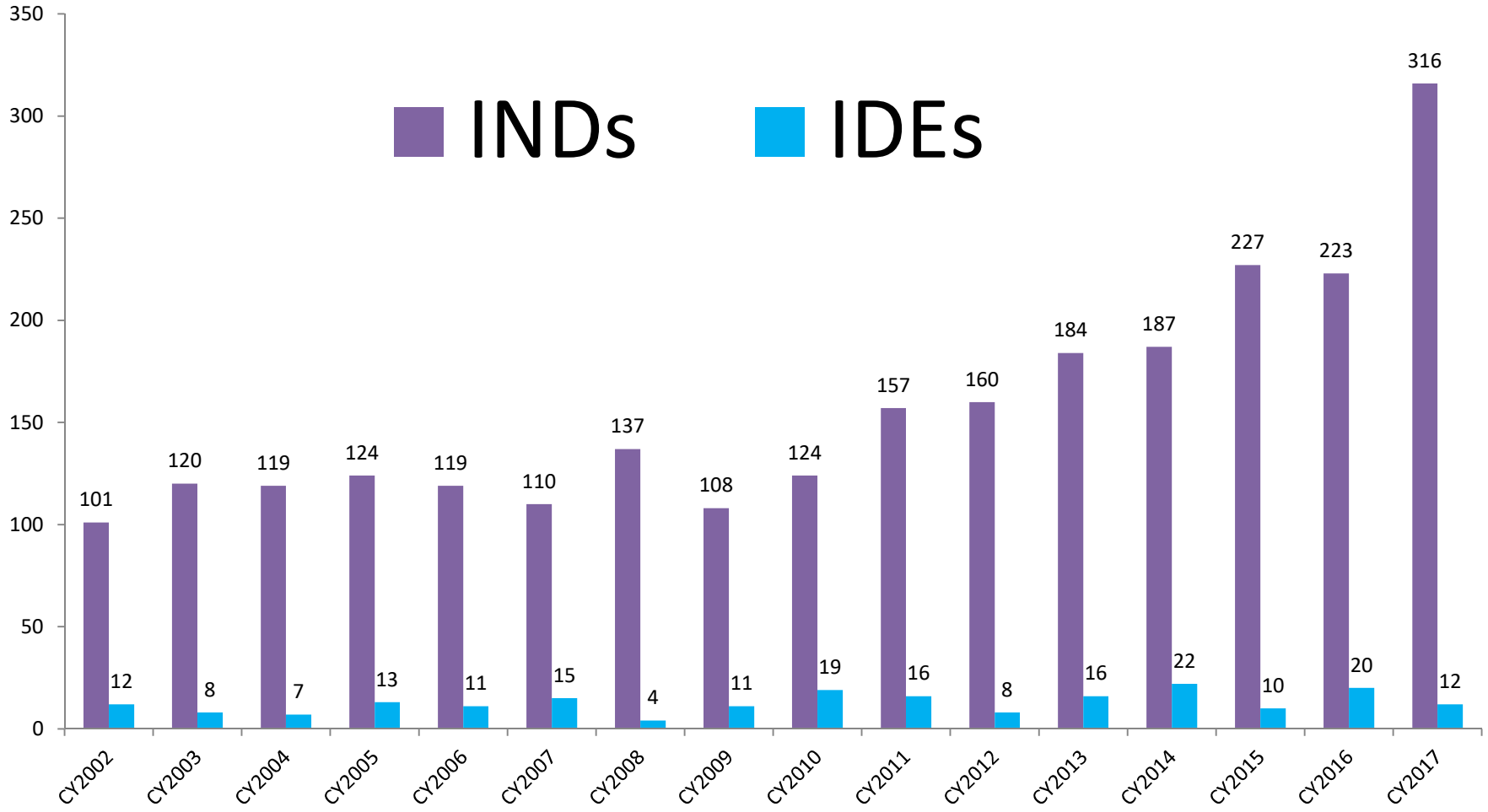
OTAT Products, Continued

- **Gene therapies**
  - Genetically modified cells, e.g., CAR-T cells
  - Plasmids, viral vectors, bacterial vectors
- **Xenotransplantation products**
- **Purified and recombinant proteins** for hematology (e.g., coagulation factors, thrombin, botulism anti-toxin, diphtheria anti-toxin, fibrin sealants)
- **Antivenins**
- **Devices and combination products**
  - Devices with a cellular component
  - Devices used in manufacturing or delivery of cells

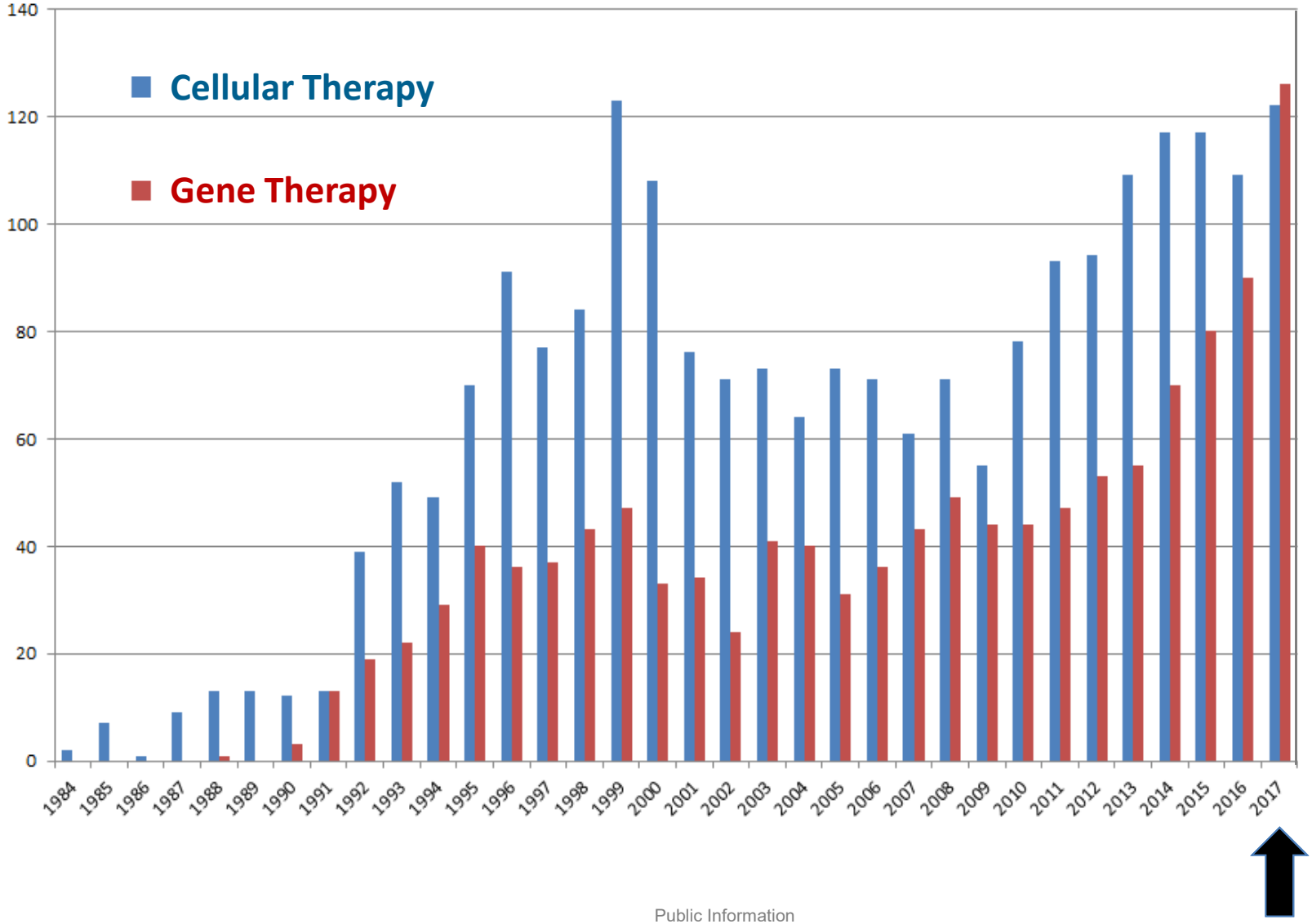
Cell and Gene Therapy Products Approved by OTAT

- HPC (hematopoietic progenitor cells), Cord Blood
- Cellular Immunotherapy
  - Provenge (Autologous DCs)
  - Kymriah (anti-CD19 CAR T cells)
  - Yescarta (anti-CD19 CAR T cells)
- Oncolytic virotherapy
  - Imlygic (HSV-1)
- Viral Gene Therapy
  - Luxturna (AAV2)
- Cellular Products
  - Gintuit (Keratinocytes/ Fibroblasts)
  - Maci (Chondrocytes)
  - Laviv (Fibroblasts)

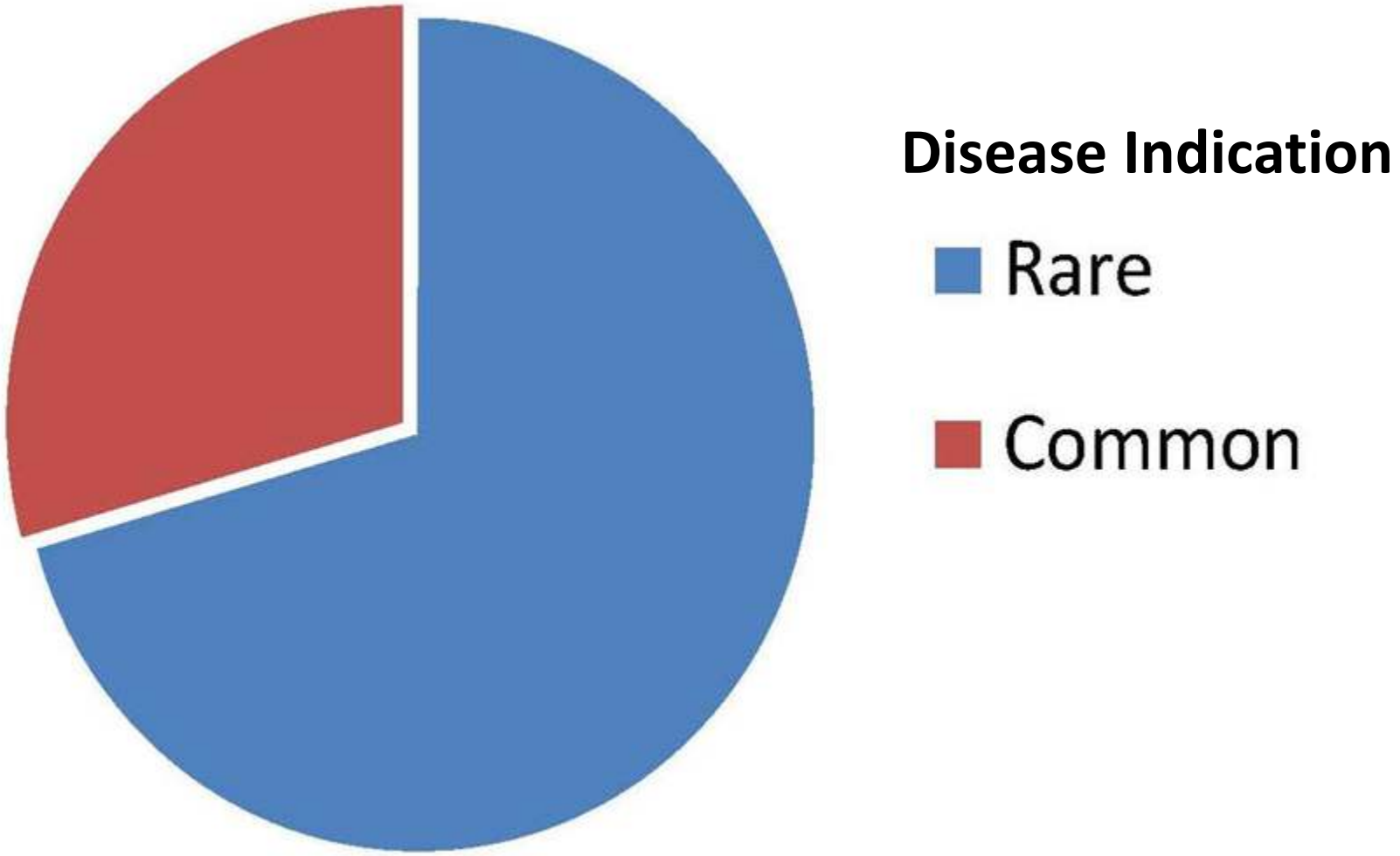
All INDs and IDEs Submitted to OTAT [OCTGT] Calendar Years (CY) 2002-2017



Gene and Cell Therapy Applications 1984-2017



Cellular and Gene Therapy
Investigational New Drug Applications



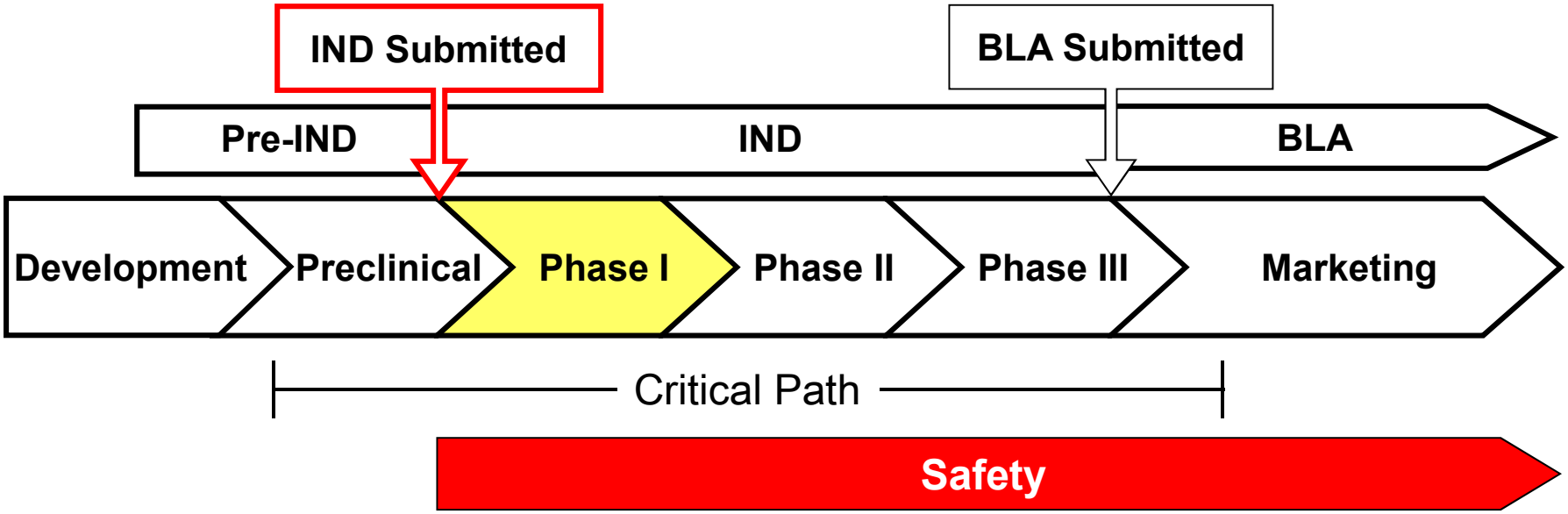
Special Considerations for Cellular and Gene Therapies

- Novel products and technologies
- Often require invasive delivery procedures
- In vivo mechanism of action is not always well understood
- Cells or gene may persist for extended period or produce sustained effect
  - Intensified or prolonged adverse reactions

Potential Risks of Cellular and Gene Therapies

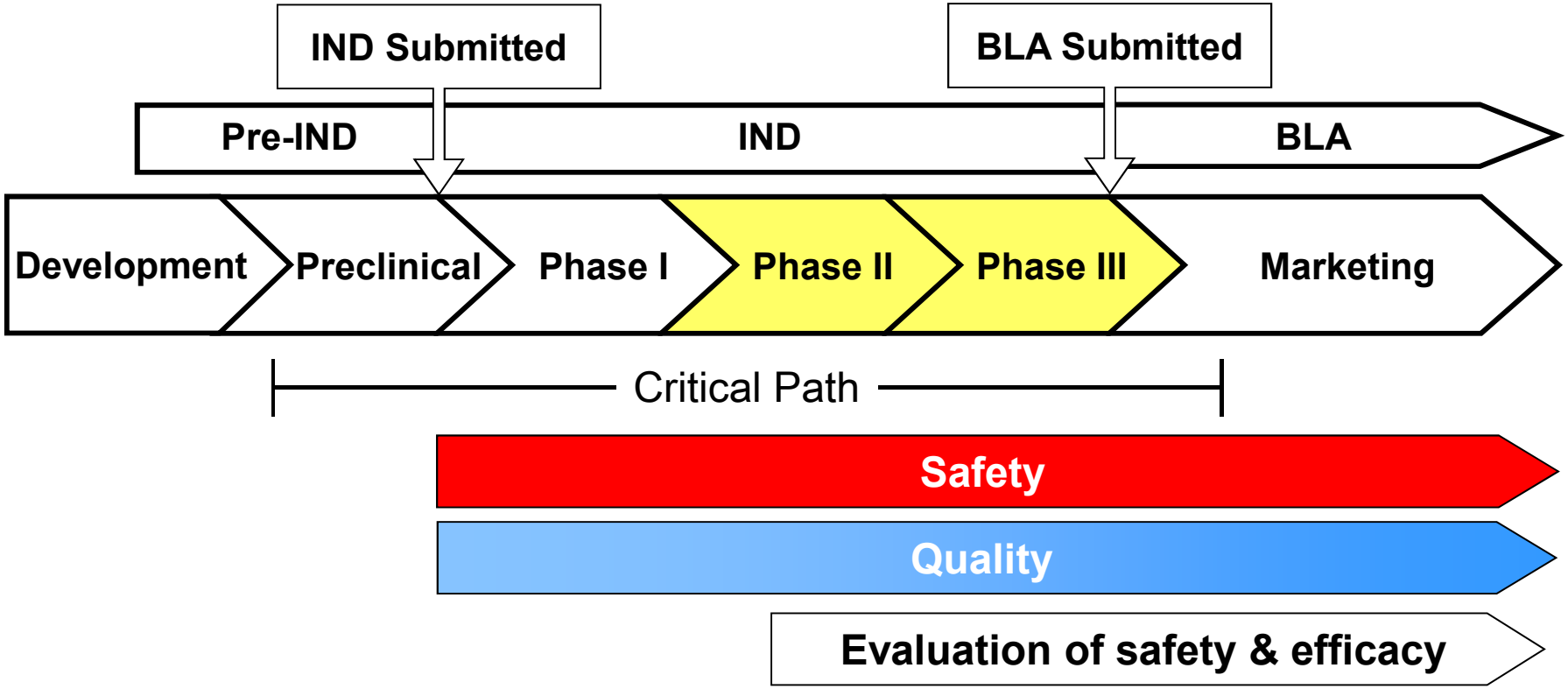
- Cellular Therapies
  - Transformation to form tumors
  - Migration to non-target sites
  - Stimulate immune response against treatment
  - Lymphoid cells may induce graft-vs-host disease
- Gene Therapies
  - Insertional mutagenesis
  - Heritable modification of germline DNA
  - Uncontrolled or unintentionally prolonged activity
  - Adverse reaction (e.g., immune response) to vector/ transgene

Manufacturing Expectations During Product Development



FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects [21 CFR 312.22(a)]

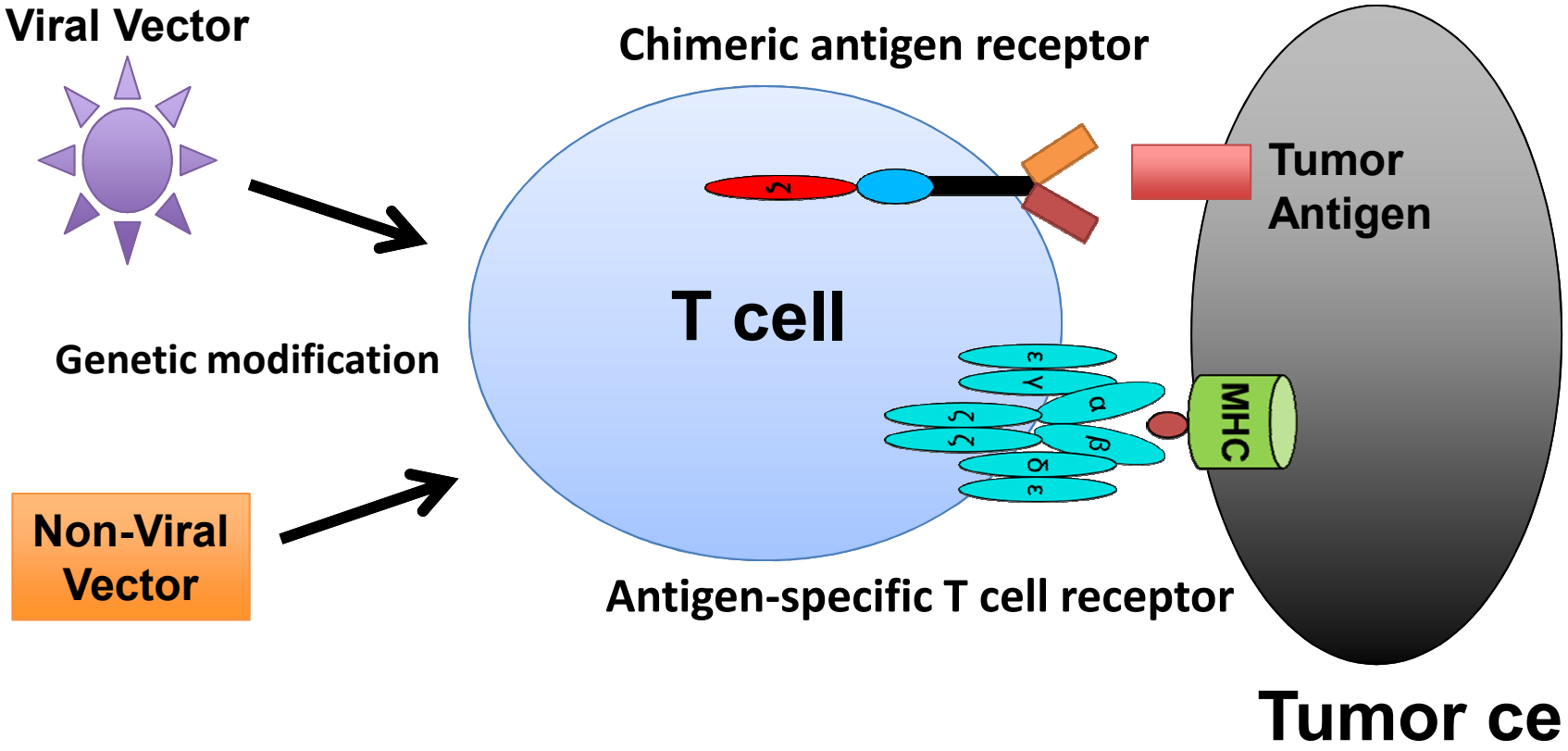
Manufacturing Expectations During Product Development



… in phase 2 and 3, to help assure that the quality of the scientific evaluation is adequate to permit an evaluation of the drug's effectiveness and safety…

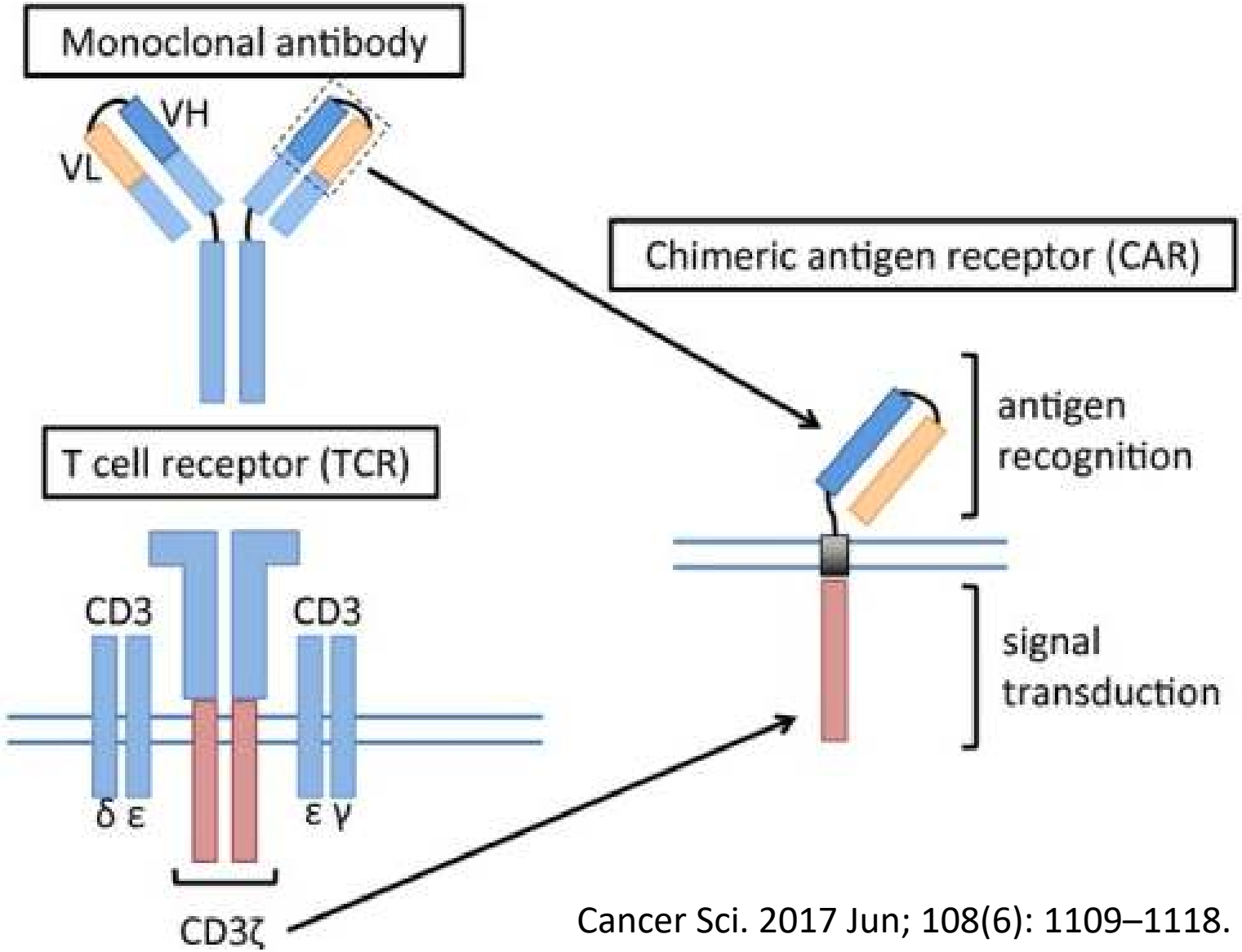
[21 CFR 312.22(a)]

Gene Modified T cell Therapy: An Emerging Technology



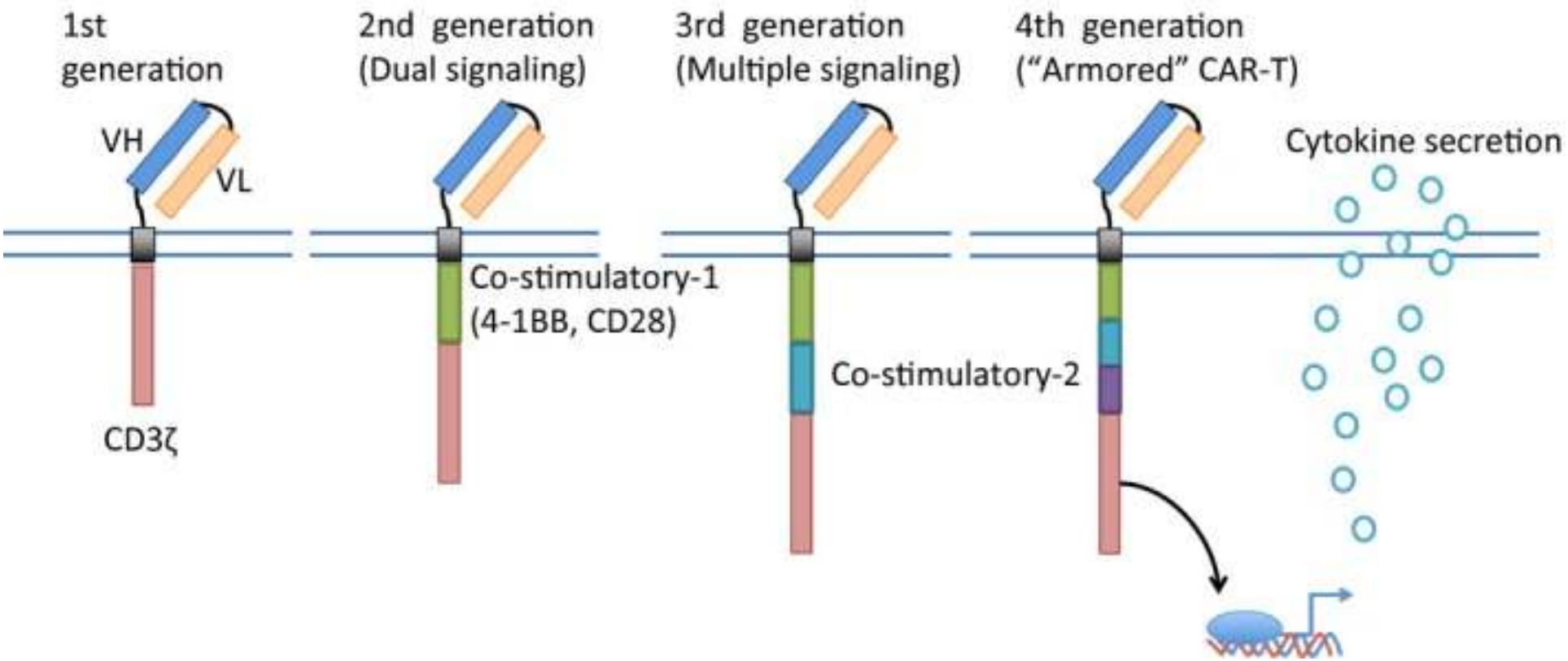
What are CAR T cells?

Chimeric Antigen Receptor T cells



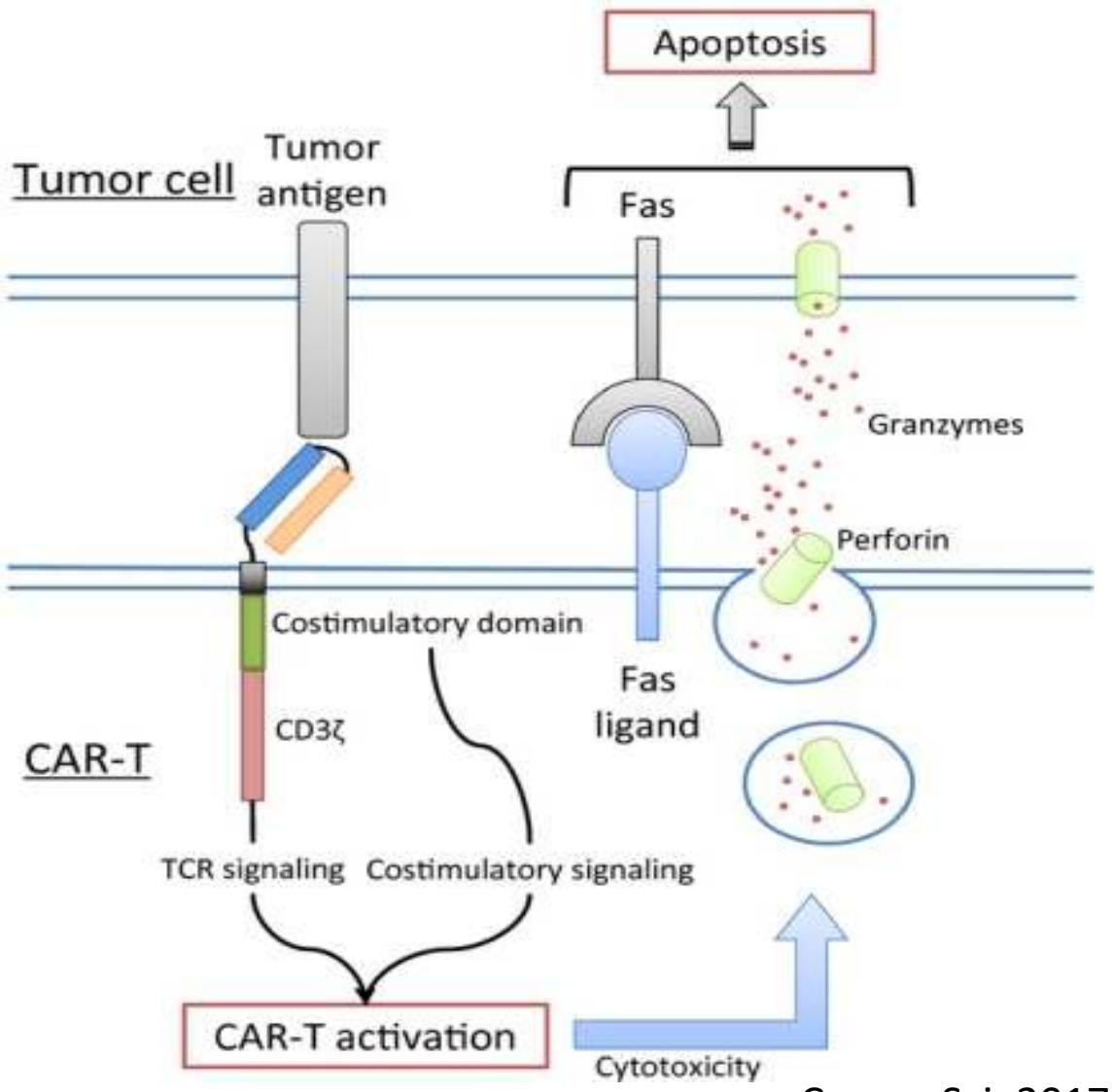
Cancer Sci. 2017 Jun; 108(6): 1109–1118.

Evolution of CAR T cells



Cancer Sci. 2017 Jun; 108(6): 1109–1118.

Primary Mechanism of Action for CAR T cells



Cancer Sci. 2017 Jun; 108(6): 1109–1118.

FDA approves first CAR T cell therapies

Health

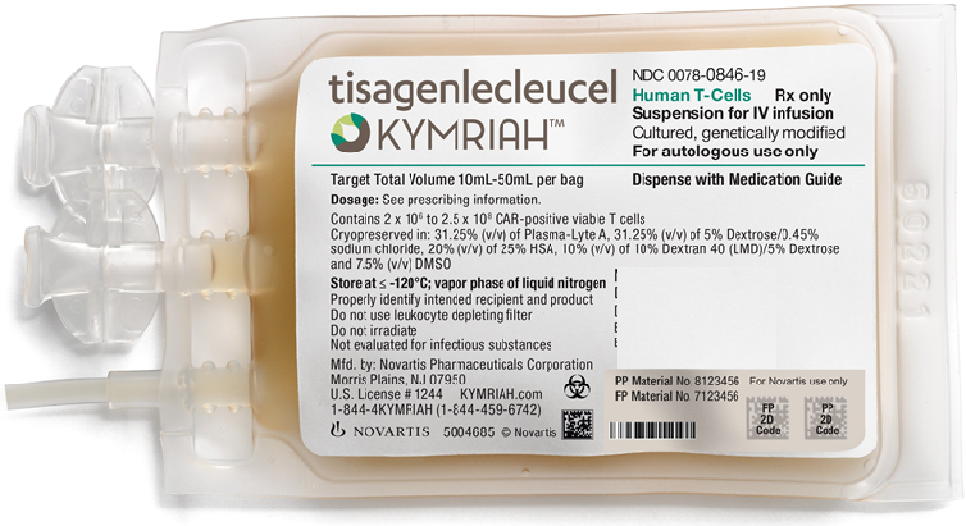
First cancer 'living drug' gets go-ahead

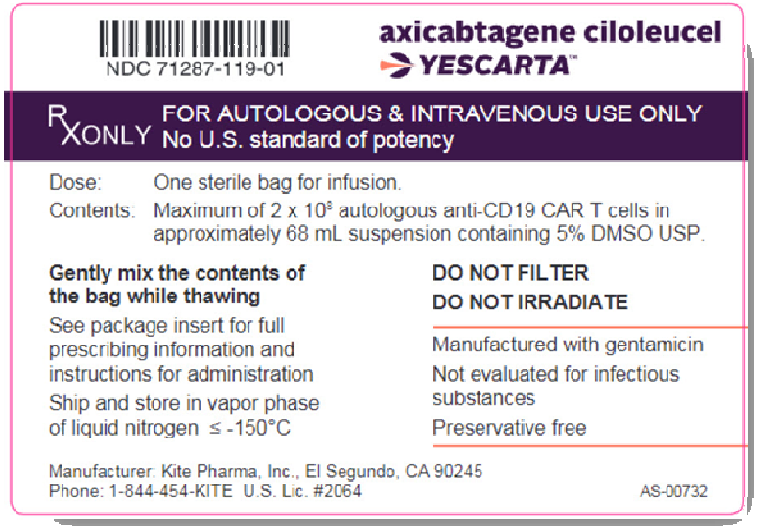
By James Gallagher
Health and science reporter, BBC News website

30 August 2017 | Health -BBC

Modified T cells that attack leukemia become first gene therapy approved in the United States

By Jocelyn Kaiser | Aug. 30, 2017 , 2:48 PM -Science



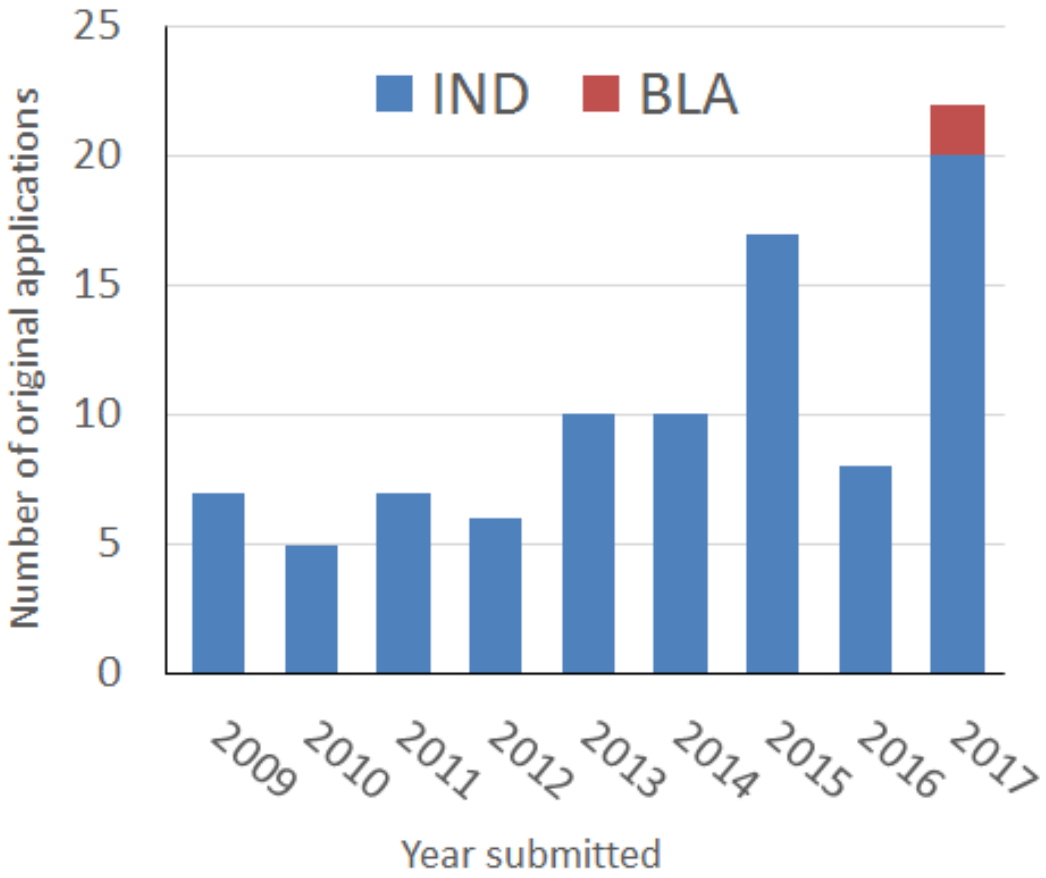


Benefits of CAR T cells

- Offer many advantages over conventional T cells:
  - Modular designs and swappable domains to target any antigen
  - Control of T cell specificity
  - MHC independent mode of action
  - More potent effector function

CAR T cell applications in OTAT

- First CAR T cell IND submitted in 2001

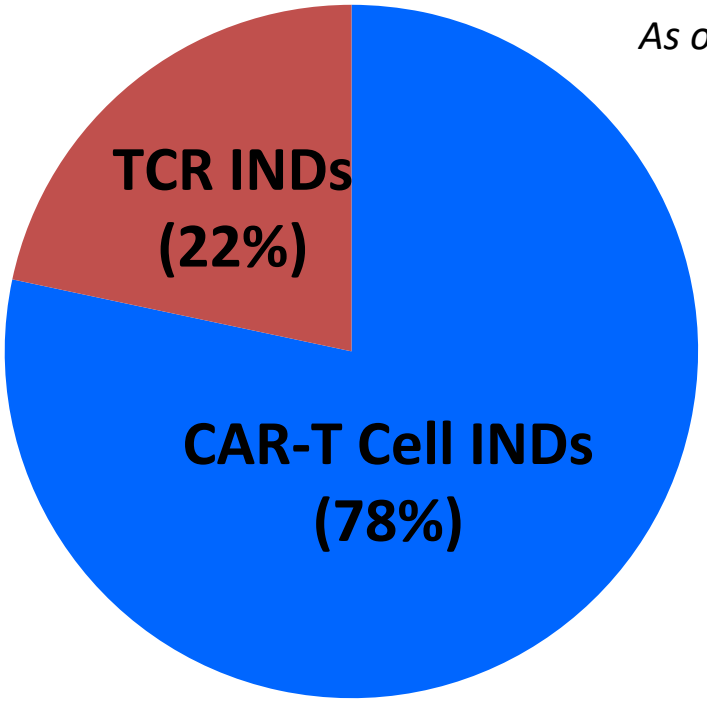


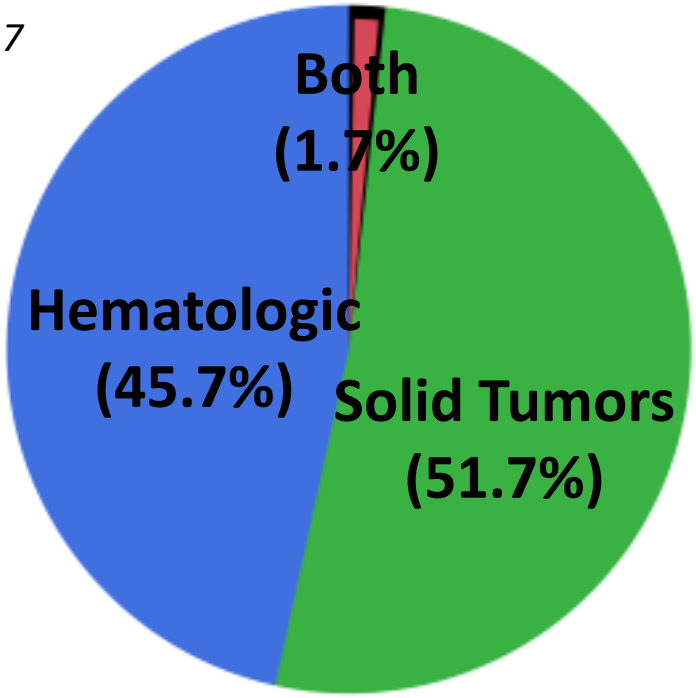
Current as of 12/2017

T cell products in OTAT

A total of ~140 TCR / CAR-T Cell INDs regulated by OTAT/CBER

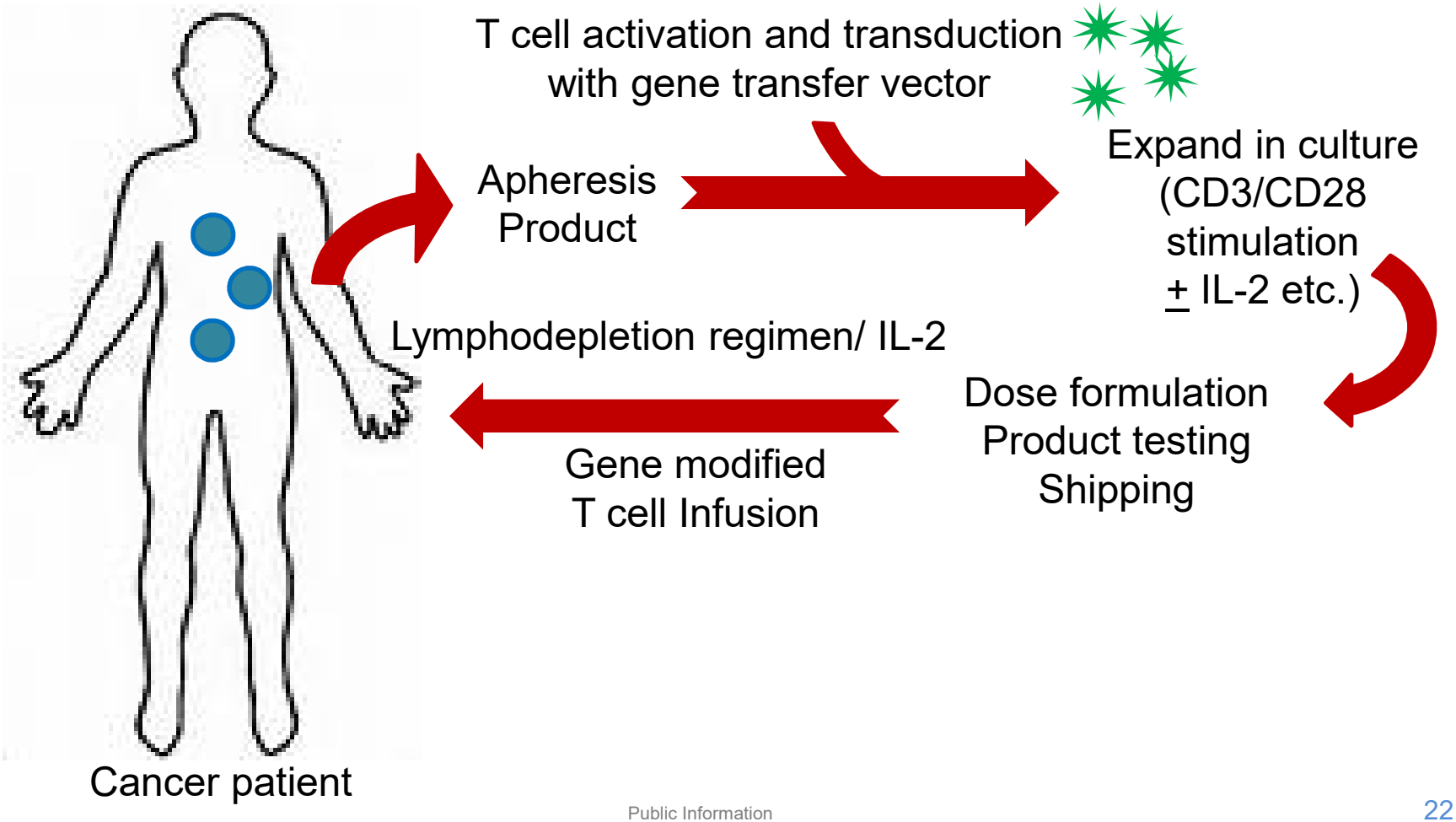
As of October 2017



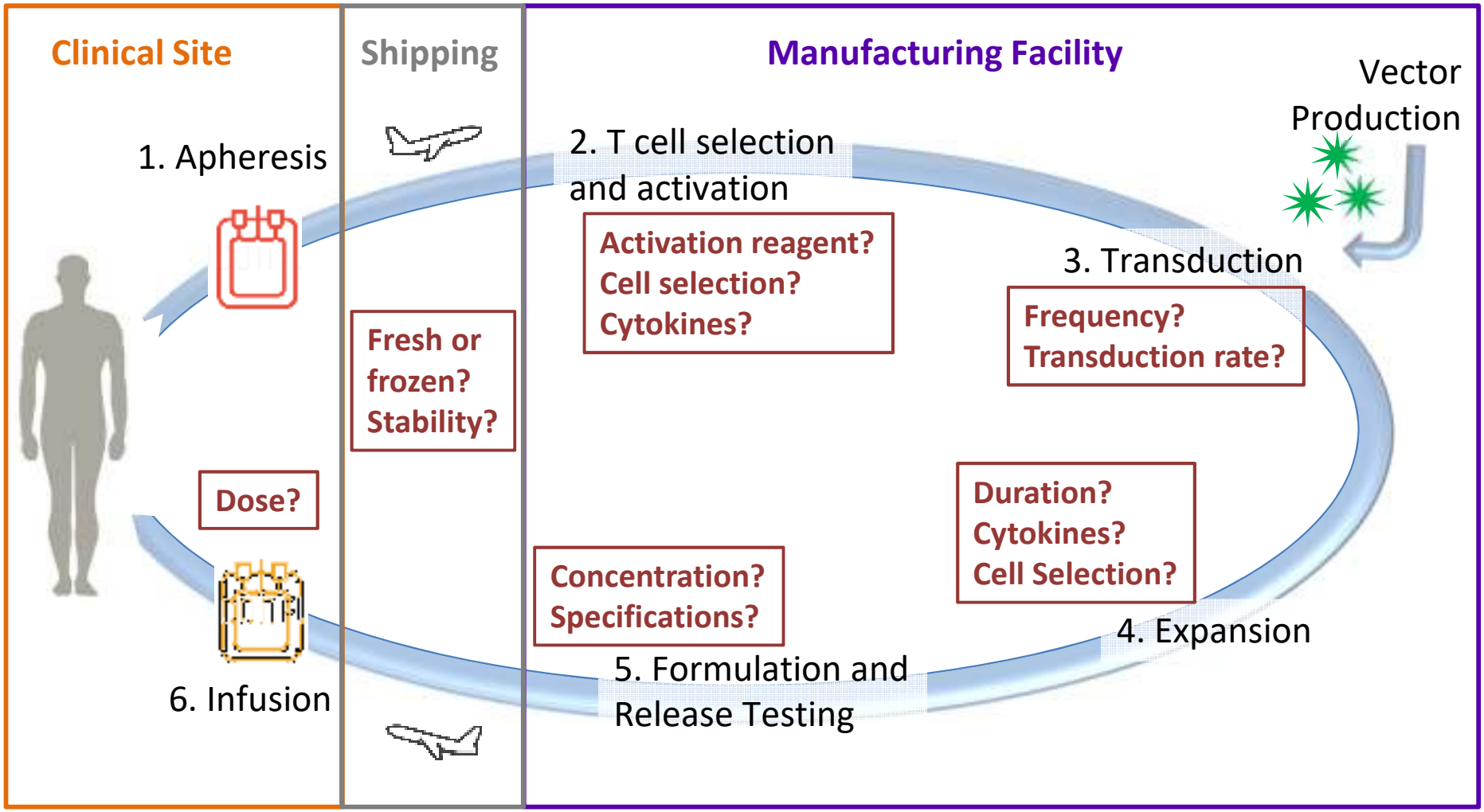


Manufacturing of CAR T cells

In vivo | **Ex vivo**



How does each step affect the final product?



Common Regulatory Concerns during Manufacturing of T cell products

- **Vector Manufacturing**
  - Usually Retroviral or Lentiviral vectors are used
    - Stable virus producer cells (retrovirus)
    - Transient transfection (lentivirus)
  - cGMP manufacturing required
  - Establish producer cell banks
    - requires extensive testing
  - Initiate stability testing program (cell banks and virus)
  - Vector lots must be tested for replication-competent virus (RCR/RCL)

Common Regulatory Concerns during Manufacturing of T cell products

- **T Cell product Manufacturing**
  - Usually autologous cells
  - If allogenic, donor eligibility testing is required
  - cGMP manufacturing required
  - Cell Substrates: history, source, general characteristics, safety testing
  - Reagents testing: human serum, antibodies, etc.
  - Stability testing

T cell product: Manufacturing Challenges

Supply chain vulnerabilities

- Many critical components from 3rd parties
  - Vector, media, serum, cytokines, stimulation reagents, consumables, test kits
  - Quality agreements with vendors
  - Material qualification and acceptance criteria to ensure suitability
  - Substitutes may not exist; if available, how will they affect product?

Product consistency

- Patient to patient variation in autologous T cell substrates
  - May depend on many factors including age, prior therapies
- Lot to lot variation in transduction efficiency

  - Standardization of Retro/Lentivirus vector stocks to give a constant multiplicity of infection (MOI)

Product tracking and labeling (chain of custody/chain of identity)

- Autologous products; critical to ensure patient receives the correct product

Manufacturing Changes

- Scale up
- Facility changes
- Reagents or equipment changed/discontinued

Major changes require comparability testing

- New vector design, process changes, critical reagent changes etc.
- Comparability = similar product quality attributes pre- and post-change; no adverse impact on product quality, safety or efficacy
- Side by side studies of “old” vs. “new” product
- Use relevant biological and analytical assay methods

If comparability cannot be demonstrated analytically FDA may require additional pre-clinical studies or clinical trials

T cell product: Testing Challenges

In process testing

- Monitor cell proliferation/cell quality in real time
- Cell count, viability, (phenotype?)

Lot release testing

Parameter	Tests
Safety	RCR/RCL, sterility, endotoxin, mycoplasma, vector copy number per transduced cell
Identity	Presence of transgene sequence
Purity	Process and product-related impurities (residual BSA, antibiotics, etc.)
Dose	Number of viable T cells expressing CAR/TCR
Potency	Cytokine production, tumor cell killing, phenotype, etc.

Personalized products; time window for release testing may be limited

- Especially if products are to be given “fresh”

T cell product: Potency Assay

- **Guided by proposed mechanism of action and pre-clinical proof of concept data**
- **Conduct product characterization studies throughout product development**
- **Evaluate multiple measures of product potency**
  - Can choose one assay for product release while continuing to collect data on other assays
  - Sometimes a single measurement may not be fully informative and a matrix approach may be needed
- **Assays should be chosen based on successful test method qualification using the product**
- **Validate assay performance prior to licensure**
- **Guidance document on Potency Tests**

T cell products: Challenges in early phase INDs

Preclinical studies

- *In vitro* specificity/characterization studies
- Animal studies of efficacy (where feasible and informative)
- Show proof of concept
- Comparing new products to previous may be useful
- Preclinical guidance documents

Manufacturing

- Ensure quality of all product components (vector, reagents, cells)
- Develop manufacturing experience, show feasibility
- Make changes where necessary
- Develop and begin to refine tests
- Continual product characterization studies to inform testing

Engage with FDA early

- Pre-pre-IND and Pre-IND meetings

T cell products: Challenges during Pathway to Licensure

Access to key reagents/ Intellectual Property issues

- Materials/reagents adequate for product manufacturing
- Certain reagents often only available from a single supplier

Move from academic to industrial manufacturing settings

- Manufacturing capacity (patient-specific products: manufacturing currently labor intensive)
- Central manufacturing facilities?
- Comparability studies needed if manufacturing methods/sites changed between early and late stage studies
- Product characterization is critical

T cell Product: Challenges for Commercial Manufacturing?

- Establish Critical Quality Attributes (CQA)
  - Has to be meaningful measures of potency and characterization
  - Establish specifications based on prior experience
- Establish Critical Process Parameters (CPP)
  - Process Consistency
  - Comparability
- Manufacturing Strategy
  - Centralized or Decentralized
  - Late Phase Changes
  - Comparability
  - Logistics: Storage, Shipping, Stability/Expiration

T-Cell Product: Scientific Challenges

- Immunogenicity and inflammation
- Specificity: On-target Off Tumor and Off Target
- Reported Deaths with CAR T-cells
  - Cytokine Release Syndrome (CRS)
  - Complex reaction with multiple components
  - Renal and cardiac complications
  - Neurologic toxicity
- Long-Term Toxicity Issues
  - Persistence of CAR T cells
  - Potential for secondary malignancies
  - Replication competent viruses?

Summary

- **Gene modified T cells has pontential to treat diverse human cancer**
- **Products moving rapidly from labs to clinics**
- **Products are complex**
  - Many components: Construct, vector, cells
- **Complex manufacturing and testing**
- **Safety and Toxicity is a concern**
- **Many scientific questions need to be answered**
  - What construct components are required for optimal performance?
  - What are better pre-clinical models for safety and efficacy?
  - What in vitro tests better predict in vivo product performance?
- **Upcoming products likely to be even more complex**

Contact Information

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  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber

Thank you


FDA
U.S. Department of Health and Human Services
Food and Drug Administration

Standardization of Emerging Technologies from a NIST Perspective

Dean Ripple, Biomolecular Measurement Division

ASTM E55 Workshop on Emerging Technologies in Biopharmaceutical Manufacturing

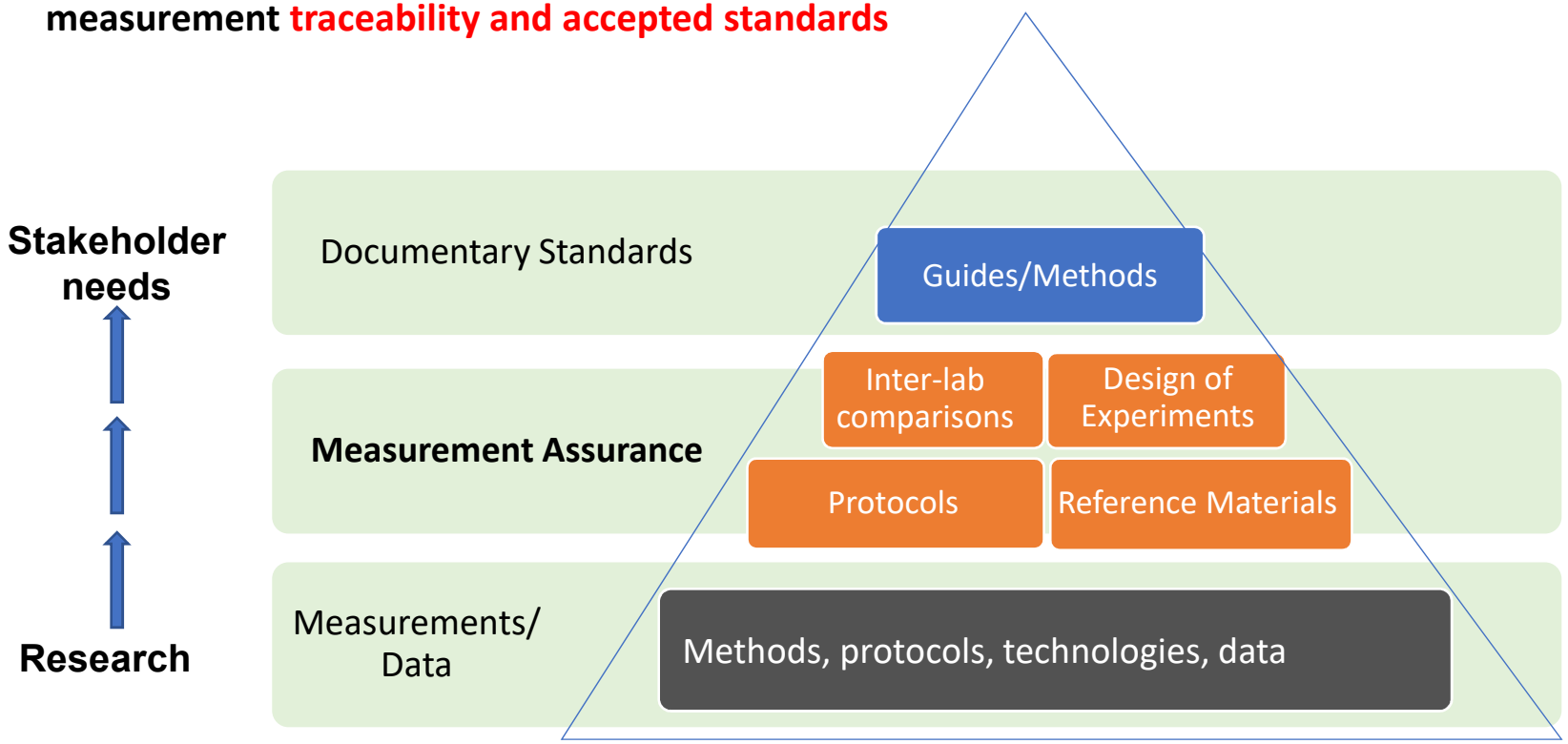
April 17, 2018

NIST
National Institute of Standards and Technology
U.S. Department of Commerce

MATERIAL MEASUREMENT LABORATORY

Critical Role of Measurement Science in Standards Development

The global marketplace is presenting new demands on health care manufacturers for measurement traceability and accepted standards



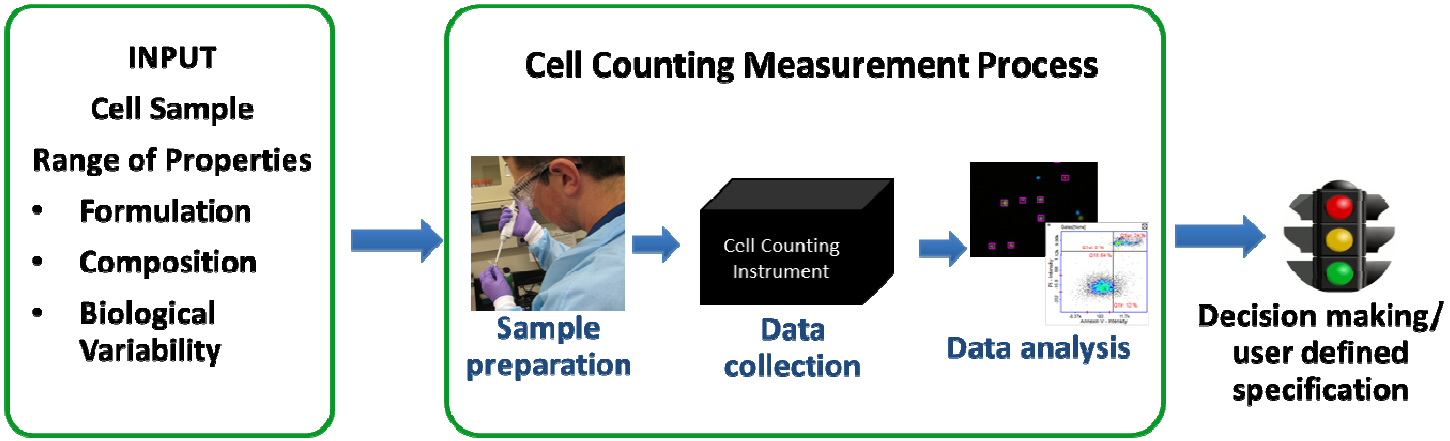
Building Measurement Assurance for Cell Characterization

With the development of cell-therapy products (CTPs), there is an increased need for high quality, robust, and validated measurements for cell characterization.

https://www.nist.gov/programs-projects/building-measurement-confidence-cell-characterization

Building Confidence in the Quality of a Cell-Counting Measurement Process

Need confidence in the measurement process over the range of samples that are intended to be measured in order to enable decision making based on cell count



Challenges:

- There are very limited fit-for-purpose reference materials currently available for cell counting
- Difficult to envision a single standard reference material or reference method to support all cell counting conditions

Absence of a "reference value" for cell number to assess accuracy

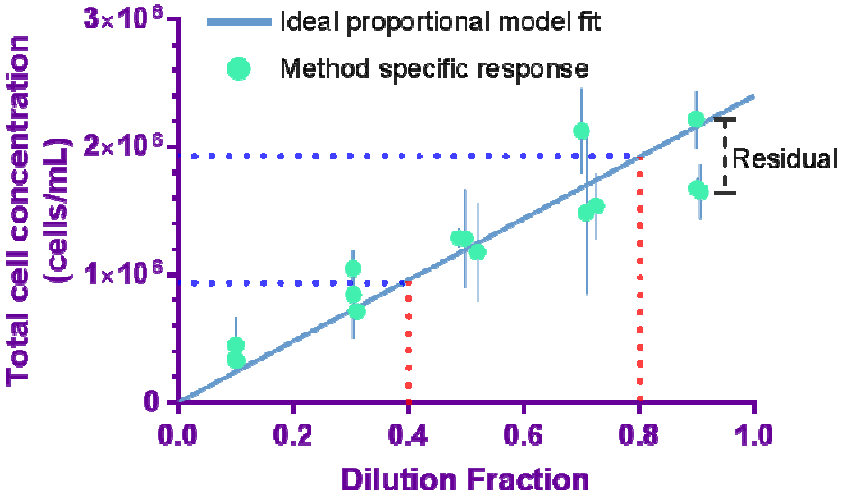
Approach:

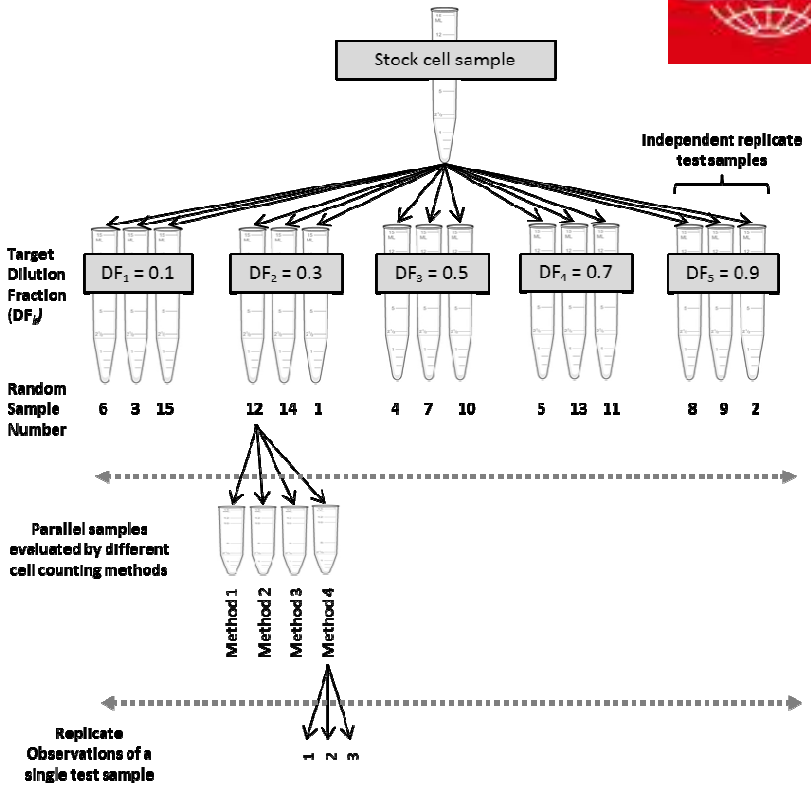
- Develop a framework to quantify measurement process performance, independent of measurement platforms and in the absence of a reference materials/reference measurement

ISO/CD 20391-2, Biotechnology — Cell counting — Part 2: Experimental design and statistical analysis to quantify counting method performance

Under development: https://www.iso.org/standard/67892.html

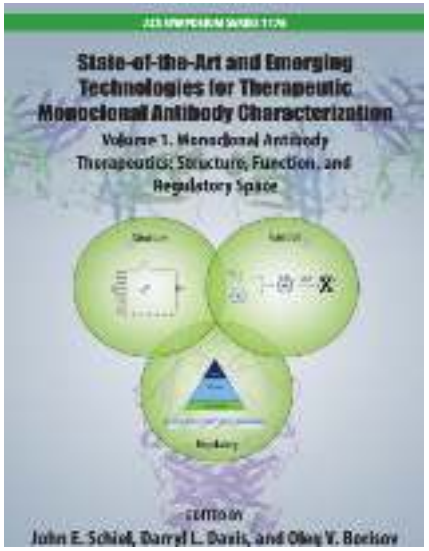
- Statistical analysis provides insight into cell counting uncertainties
- An achievable step towards absolute counts





Sarkar et al. Cytotherapy 19.12 (2017): 1509

NISTmAb Reference Material



NISTmAb Attributes:

- Open Innovation Humanized mAb (IgG1κ) RM 8671
  - 10 mg/mL, 800 µL per unit
  - 12.5 mM L-His, 12.5 mM L-His HCl (pH 6.0)

Unique Approach for IgG RM:

- Completed rigorous interlaboratory characterization
  - Results used for book compilation
- Reference Material 8671
  - Product Lifecycle --> Quality and Availability
  - Attribute-specific methods rigorously qualified
  - Value assignment incorporating method experience
  - Homogeneity, purity, stability based physicochemical method control ranges

Representative of IgG1κ Therapeutic Class

- Peptide mapping by LC-MS/MS
- Primary Sequence
- S-S Bridge Analysis
- PTM analysis
- Intact, middle down MS
- Glycosylation Analysis
- LC: SEC, RP, IEX, HIC
- CE: cIEF, cSDS, CZE
- SDS-PAGE
- MS/MS library compilation
- HOS: NMR, HDX, XRD
- Neutron scattering
- Biophysical: CD, FTIR, DSC, DLS, AUC, SLS, DSF
- Protein particulates
- Many emerging technologies

http://pubs.acs.org/isbn/9780841230262, http://pubs.acs.org/isbn/9780841230293 , http://pubs.acs.org/isbn/9780841230316

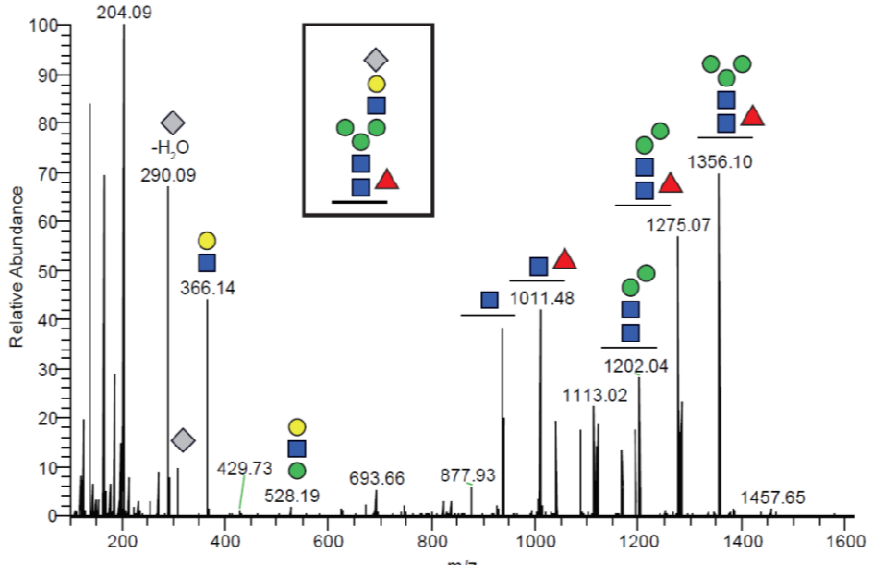
NIST Interlaboratory Comparison on mAb Glycans

Motivation for Comparison:

- Structural analysis of glycans is challenging, but necessary for biopharmaceuticals
- No standard method of glycan analysis (e.g. derivatizations)
- No standard way of naming or writing, and monosaccharide compositions

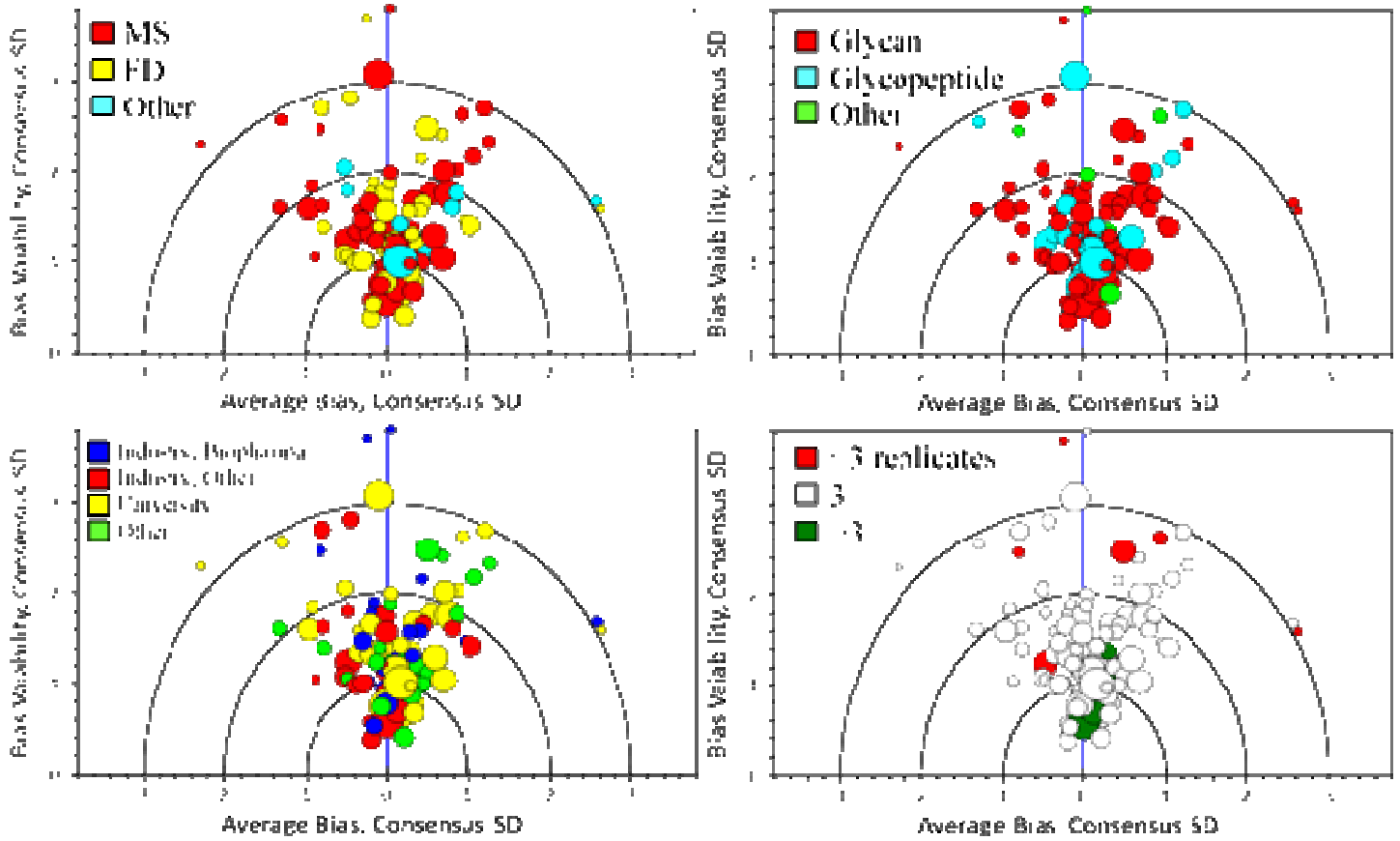
Data Obtained:

- 103 reports from 76 labs, mostly Europe and North America
- 43% Industry labs
- Entities studied ranged from intact to fully released glycans
- Wide range of derivatization & analysis



Deviations of Glycan Measurement Bias & Variability from Consensus Values

Scores <2 are good; >3 questionable

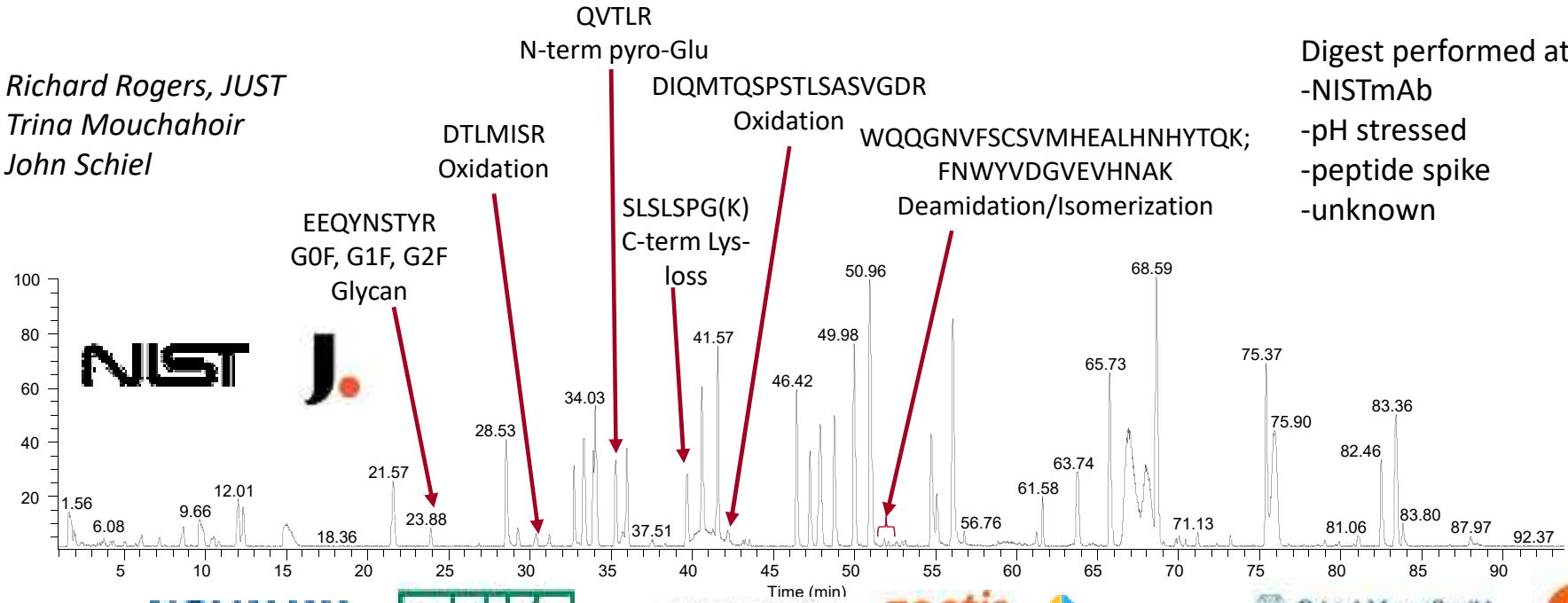


- Significant fraction of scores > 2 means opportunity for improvement
- Different sectors; different methods can all work
- Standardization should focus on optimizing each method, not prescribing one method

Multi-Attribute Method and New Peak Detection Round Robin
Strength in Numbers

- NISTmAb Inter-laboratory LC-MS peptide mapping method to evaluate
  - Ability for LC-MS to perform industry-relevant purity evaluation
  - Detection of spiked peptides and PTMs on the NISTmAb when stressed
- Evaluate LC-MS peptide mapping lifecycle-appropriate implementation

Richard Rogers, JUST
Trina Mouchahoir
John Schiel



Digest performed at NIST
-NISTmAb
-pH stressed
-peptide spike
-unknown

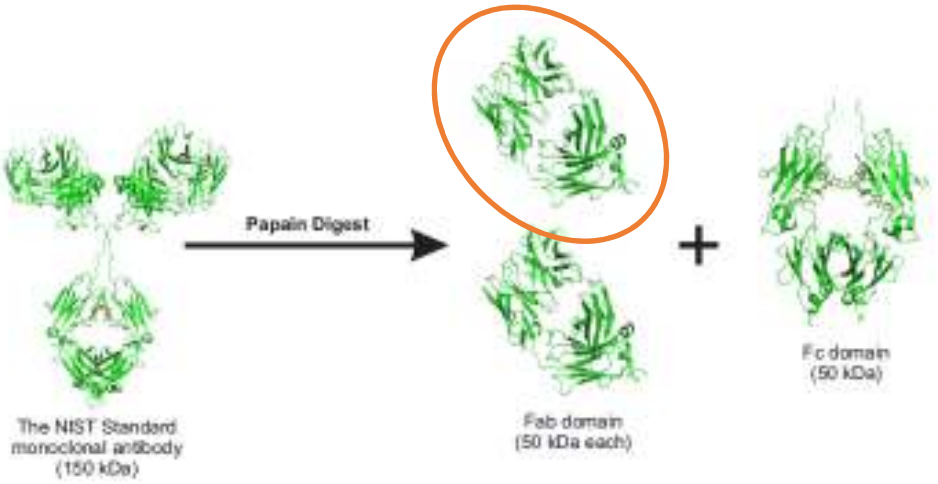
mam consortium

Pathway for Robust Implementation of Higher Order Structure Assessment of mAbs by 2D-NMR

Goals:

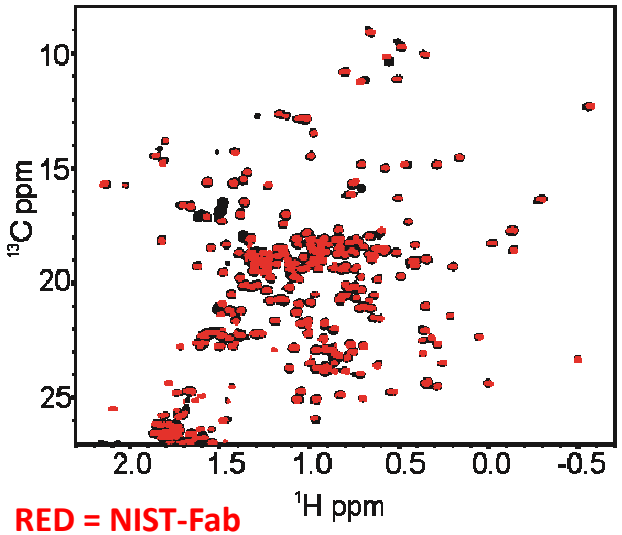
- Establish a community standard for the measurement of the higher order structure (HOS) critical quality attribute (CQA) by 2D-NMR
- To provide assurance for industrial and regulatory agencies that 2D-NMR characterization can have high repeatability & reproducibility
- To develop chemometric tools to aid method translation into the biopharmaceutical lab

25 institutions
3 continents
39 magnets
Room temperature & cold probes



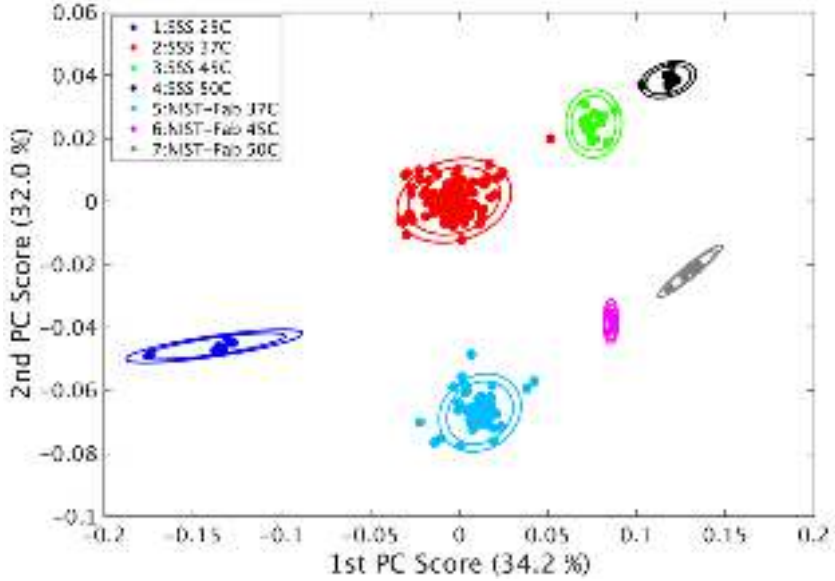
Fingerprint Comparison at 900 MHz: System Suitability Sample (SSS) vs. NIST-Fab

Methyl Spectral Map: less dense & easier to separate peaks



RED = NIST-Fab
Black = SSS

Principal Component Analysis distinguishes fingerprints

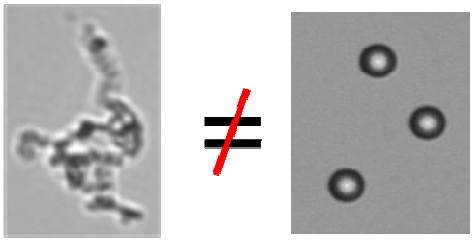


- Intercomparison demonstrates that Methyl-group NMR & PCA are applicable across wide range of labs
- Exploration on different mAbs, different proteins, different formulations prior to standardization?

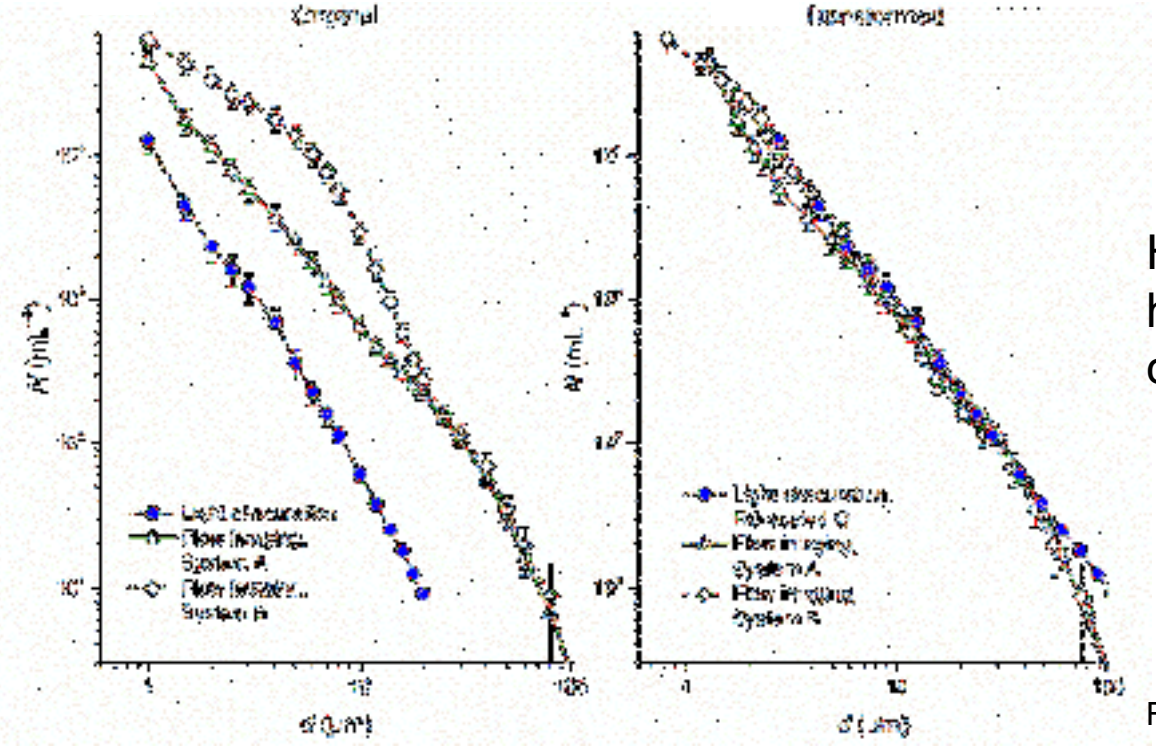
Subvisible Particle Measurements in Pharmaceuticals

- Subvisible particle counts in pharmaceuticals may differ by factor of 10x or more in different particle counters
- Beads used for calibration do not mimic common, actual particles (silicone oil, protein aggregates

Protein aggregate



Polystyrene bead



Harmonization is possible for homogeneous, well-characterized particles

Ripple & Hu (2016) Pharm. Res. 33:653-72

Standardization of Subvisible Particle Counting

Particles in actual samples are heterogeneous & not well-characterized.
Harmonization options:

- Accept differences in instruments
- Characterize particle populations & apply corrections
- Reach consensus on 'typical', approximate corrections
- Develop/use more advanced instruments

Using a reference material instead of a model doesn't simplify matters:

- How do we match the reference material to the test sample?

Standards Path:

1. General guides to promote good practices & consistent interpretation
   - ASTM E3060 *Standard Guide for Subvisible Particle Measurement in Biopharmaceutical Manufacturing Using Dynamic (Flow) Imaging Microscopy*
   - USP <1788> *Methods for the Determination of Particulate Matter …* (draft)
2. Protocols to answer "How do I …?" questions (next ASTM standard)
3. Workshops with vendors & other interested parties to establish consensus on diameter corrections

Thoughts & Conclusions

Gaps between research & standardization:

- Technical complexity
- Robustness of procedure & equipment
- Lack of consensus
- Different visions of final goal

Intercomparisons & Reference materials

- Both uncover new measurement science or unknown issues
- Can identify achievable scope of standards
- Implement prior to standardization

What documentary standards are achievable?

- Overly prescriptive standards can inhibit further technology growth
- Standards need to be realistic about scope of consensus & robust methods
- Need Guides & “How-to” documents that bridge the gap between research papers & pharmacopeial documents

Acknowledgments & Contacts

- Lorna De Leoz, D. Duewer, S. Stein (glycans, marialorna.deleoz@nist.gov)
- Sumona Sarkar, Sheng Lin-Gipson (cell counting, sumona.sarkar@nist.gov)

https://www.nist.gov/programs-projects/building-measurement-confidence-cell-characterization

- John Schiel (multi-attribute methods, john.schiel@nist.gov)
- Rob Brinson, L. Arbogast, J. Marino (NMR, robert.brinson@nist.gov)
- Zhishang Hu (particles), Chinese Academy of Sciences
- Dean Ripple (particles, dean.ripple@nist.gov)

UMD | NIST
INSTITUTE FOR BIOSCIENCE & BIOTECHNOLOGY RESEARCH

ASTM International Workshop
BPSA and BPOG Activity Summary

Jeff Carter (BPSA and BPOG)

What is the BioPhorum Operations Group (BPOG)?

unique global collaboration

powerful vehicle for change

6 Phorums

>50 industry changing initiatives

industry leaders and experts working in concert

delivers results by pooling knowledge, practices and ideas

53+ MEMBER COMPANIES

2060+ ACTIVE PARTICIPANTS

6 THRIVING COMMUNITIES

1 PHORUM FOR CHANGE

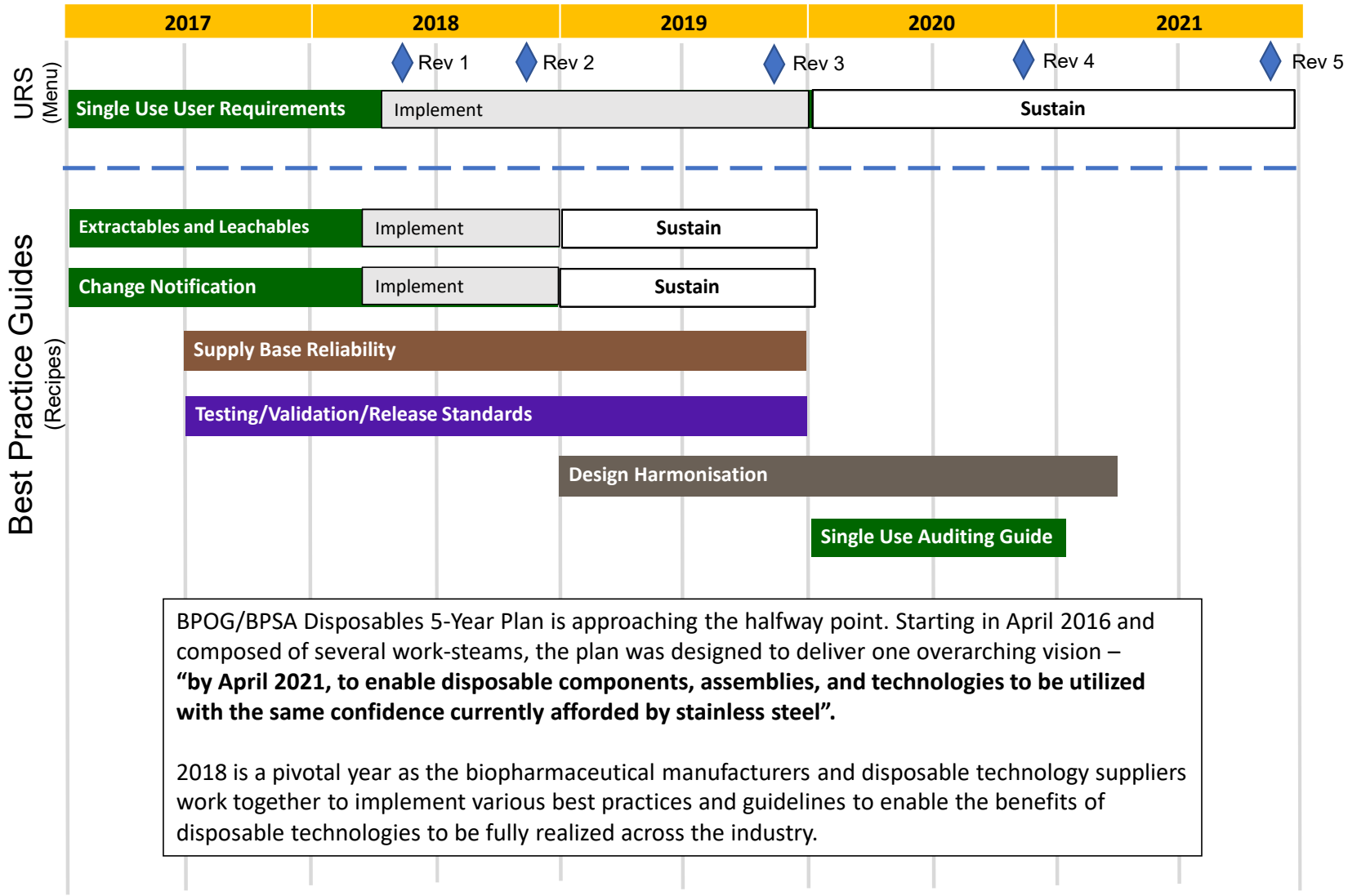
Bio-Process Systems Alliance

BPSA MISSION

To facilitate, globally, the development and manufacturing of biopharmaceuticals through the implementation of robust, safe and sustainable Single-Use Technologies.

SOCMA
Society of Chemical Manufacturers & Affiliates

BPOG Disposables 5 year implementation plan @ 26th Feb 2018



BPOG/BPSA Disposables 5-Year Plan is approaching the halfway point. Starting in April 2016 and composed of several work-steams, the plan was designed to deliver one overarching vision – **"by April 2021, to enable disposable components, assemblies, and technologies to be utilized with the same confidence currently afforded by stainless steel".**

2018 is a pivotal year as the biopharmaceutical manufacturers and disposable technology suppliers work together to implement various best practices and guidelines to enable the benefits of disposable technologies to be fully realized across the industry.

BPSA Activities leading to Standards

• Change Notification (with BPOG)	ASME-BPE 2018 edition
• Integrity Assurance	WK 43741, WK NNNNN
• Particulates	WK54630, WK43724
• Cell therapy – eqpt extractables	Pursue standard?
• Cell therapy – eqpt particulates	Pursue standard?

Opportunities

- Single Use User Requirements (BPSA and BPOG).
  - Contains a comprehensive list of user needs
  - By analogy to “USP 788 for equipment” or “USP 1207 CCIT for equipment,” are there other borrowed standards that need clarification with respect to their application to single use equipment?
  - For example:

• Endotoxin	USP 85/161	WFI or medical device focus
• Residual solvents	ICH Q3C (R6)	pharmaceuticals focus

AMERICAN SOCIETY OF MECHANICAL ENGINEERS BIOPROCESSING EQUIPMENT STANDARD 2018 UPDATE

ASTM WORKSHOP ON EMERGING TECHNOLOGIES IN BIOPHARMA MANF

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ASME BPE

TOM LARKIN

Legal Standard Setting Organization

ASME BPE Overview

- **ASME BPE is an international industry consensus standard**
- **Approved by ANSI as meeting the criteria for American National Standards**
- ***Requirements for specification, design, fabrication and verification of bioprocess equipment as being fit for their intended use and minimize risk to product quality[1]***
- **Typically required in specifications from the owner /user**
- **Currently on a 2 year revision cycle**

[1]- ASME BPE, Part SD, section SD-1 paragraph 2

ASME BPE – New for 2018

- New Mandatory Appendix for Single Use Systems
  - Content taken from Section PM (*POLYMERS AND OTHER NONMETALLIC MATERIALS*)
- Incorporating BPOG recommendations for Change Management and Particulate