Expectations on Development of ICH Guidance Regarding Manufacture of Biotechnology Products

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History of ICH Q5 (Biotech) EWG

- 1992 - Started Q5C (Product Stability)
- 1993 - Started Q5A (Viral Safety) & Q5B (Genetic Expression Construct)
- 1996 – Started Q5D (Cell Substrates) & Q6B (Specifications)
- 1997 – Started CTD (M4Q)
- 1998 – Added a chapter on Biotech API to Q7A (API GMP)
- 2002 – Started Q5E (Comparability)

History of ICH Q5 (Biotech) EWG

- Q5 EWG has been a very productive and collegial group of industry & regulatory scientists with great respect for each other, and for data, and for truth
- Since we finished Q5E in 2004, Q5 EWG has been trying to find a suitable technical topic with broad support

History of ICH Q5 (Biotech) EWG

- 2005, 2006 saw several meetings held to attempt to find a topic which the Q5 group could work on next, and there were several attempts to produce a concept paper
- 2006, 2007 saw several meetings driven by the needs of the ICH Steering Committee to further the concept of Quality by Design (Q8, Q9, Q10) for all products (Biotech & NCE)
- Yokohama 2007 – ICH SC approves development of a concept paper on Drug Substance along the general themes of ICH Q8, to capture best practices for CTD/S2

What Did ICH SC Agree to?

ICH Quality Roundtable September 2007

Issues identified as crucial and addressed

- Systematic approach to pharmaceutical development (Quality by design)
- Quality Risk management
- Pharmaceutical Quality System
- Control strategy(ies)
- Design Space: Q8 definition acceptable
- Real Time Release
- Lifecycle approach

ICH Quality Roundtable

Agreements and Understandings

- Principles of Q8, Q9, Q10 are applicable to chemical and biotech drug substances and drug products
- Broad spectrum of process and molecular complexity rather than type of product could impact implementation
- Principles provide significant opportunities (and challenges) for more complex molecules and processes

ICH Quality Roundtable

Agreements and Understandings (2)

- Fundamentals of good product development need to be addressed regardless of ‘traditional’ or ‘new’ development paradigms
- Focus should be on enhancing the process for ensuring quality rather than specific terminology
- Lack of guidance on drug substance still a remaining gap

ICH Quality Roundtable

Recommendations

- Development of an ICH guideline on Development and Manufacture of the Drug Substance (Section ‘S2’ of CTD-Q)
- Follow process used by CTD-Q EWG where biotech & chemical experts work together and in parallel (if necessary)
- Core group (1-2/party + 1/observer) to develop concept paper and business case

US Industry View of What Might Happen Next

- Concept paper to be developed in Portland June 2008, perhaps to include
  - General concepts for API process development consistent with Q8 - Q10
  - As needed, specific guidances to be given for NCE and biotechnology-based APIs
  - If ICH SC accepts concept paper, then EWG would be formed and rapporteur selected to start work in late 2008-early 2009
  - Step 2 might be possible in 2010 or 2011

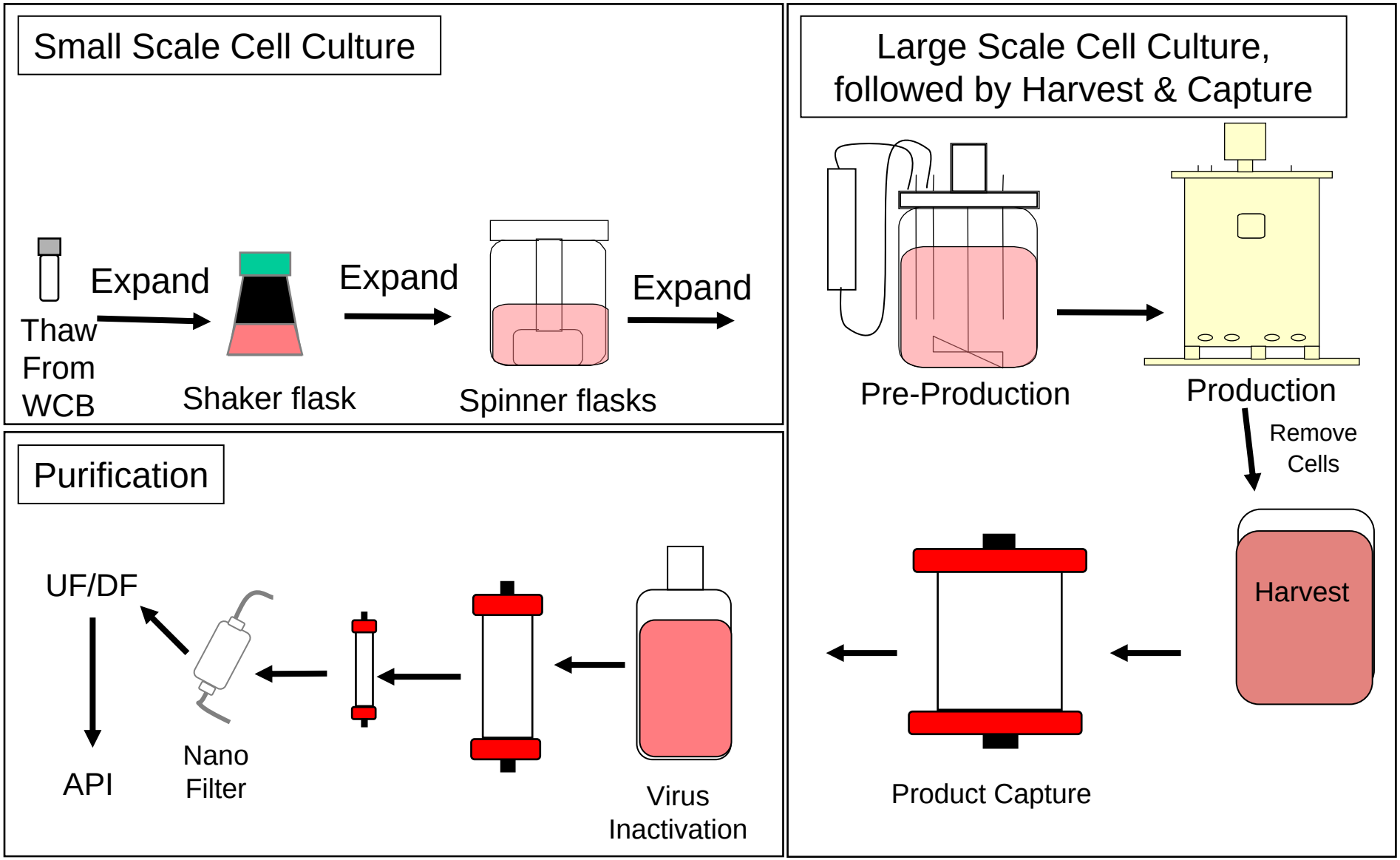
What Are Possible Differences between NCE and Biotechnolgy –based APIs?

(Why will different approaches be necessary for some biotechnology issues?)

Typical API Manufacturing Process Stages

NCE	Biopharmaceutical
➢ Chemistry	Biology
➢ Isolation	Harvest & Capture
➢ Crystallization	Purification
➢ Drying/Milling	Formulation/Freezing
➢ API	API

Typical Biopharmaceutical API Manufacturing Process



Typical Environments for API Manufacturing Process Stages

Biopharmaceutical Stage	Environment
➢ Biology	Aseptic or Contained
➢ Harvest & Capture	Contained
➢ Purification	Controlled bioburden
➢ Formulation/Freezing	Controlled bioburden
➢ API	Controlled bioburden

(In cases where API cannot pass 0.2um filter, all environments are aseptic or contained)

Key Differences between NCEs & Biopharmaceutical APIs

Attribute	NCE	Biopharm	Effect
Structural basis	Covalent	Covalent & weak	Delicate structures
Raw Materials	Defined chemicals	Some complex materials, cells	Less control
Solvent	Organics	WFI	Viral safety
Process	High temp & pressure	Physiological	Viral safety
Homogeneity	>99% single chemical entity	Microhetero-geneity	Power of Analytical tools
Process	Fewer unit ops	More unit ops	Complexity of Pro Val, QRM, & QbD

Viral Safety

- NCEs have robust structures based on covalent chemical bonds, enabling use of process conditions which inactivate viruses present in raw materials; NCEs have no history of transmission of viruses
- Biopharmaceuticals have delicate 3-D structures based on weak interactions which require physiological processing conditions, & which determine safety & efficacy
- Earlier versions of biological technology (conventional vaccines & plasma derivatives) relied on processes which could not assure freedom from contamination, resulting in innumerable episodes of transmission of viral agents to patients
- Modern biopharmaceutical processes are deliberately designed to preserve delicate structures while ensuring viral safety by a combination of raw material controls, testing, inactivation, physical removal of virus particles, and procedural & engineering controls to prevent viral contamination; perfect viral safety record to date

Illustrations of Why Viral Safety Concerns Exist for Biological Products

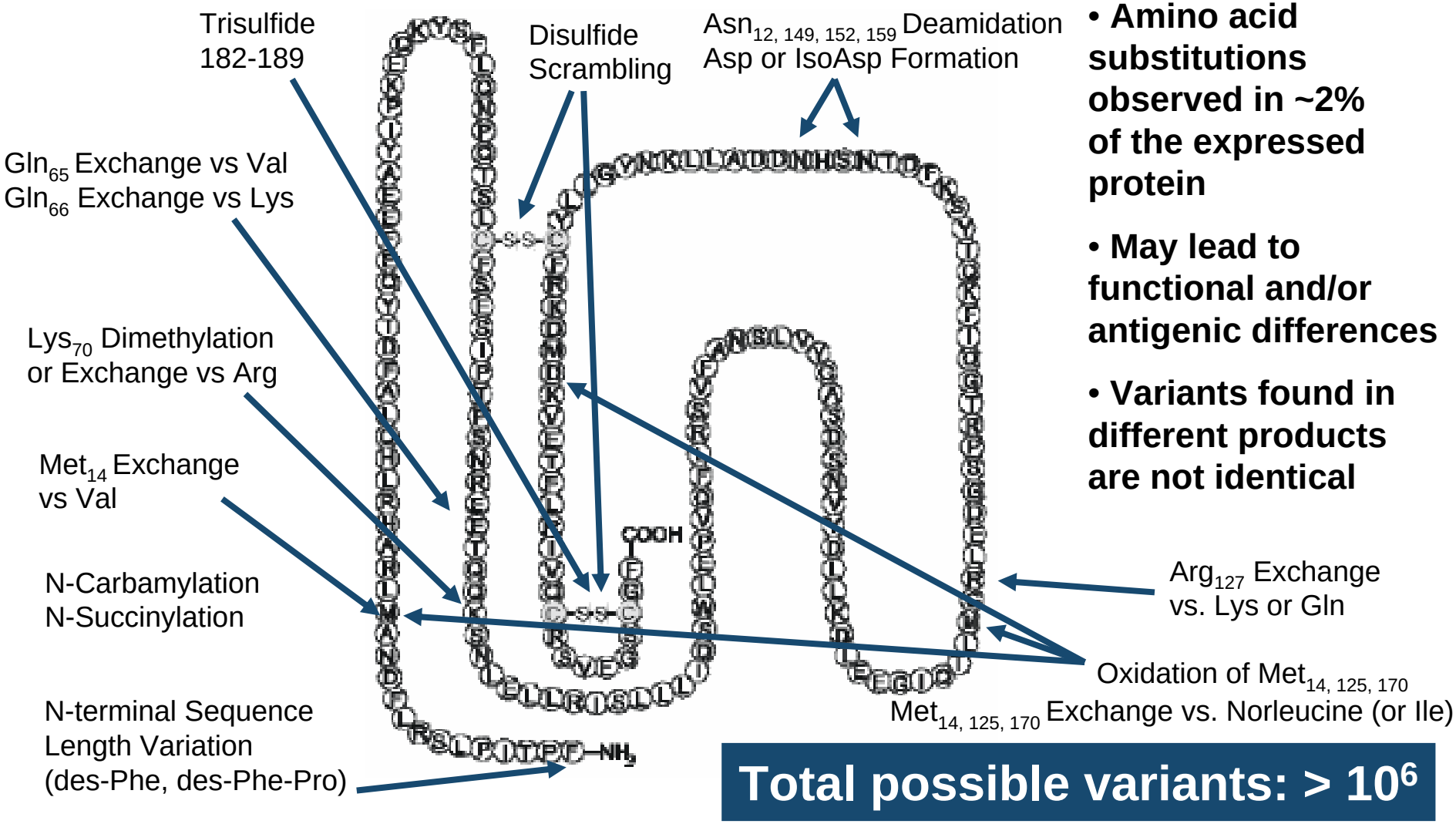
- Several hundred recipients of irradiated dura mater grafts and pituitary-derived hGH developed CJD
- Approximately 20,000 US residents who received HIV-contaminated blood and plasma derivatives before 1985 developed AIDs; the vast majority have died
- Although none of the many hundreds of millions of recipients has been known to have been infected by a biotech product , existing vigilence systems have detected the presence of parvoviruses, orbiviruses, rhinoviruses, bunyaviruses, adenoviruses, and retroviruses in cells or in process materials

Homogeneity

- NCEs are typically composed of >99% single chemical entity; analytical tools can define every atom, impurities, contaminants
- Biopharms are microheterogenous, and even simple ones have 10E4 different chemical entities in API (complex ones may have 10E8 to 10E9); analytical tools cannot usually define every atom, and definition of product-related substances, product-related & process-related impurities, & contaminants can be very complex & imperfect
- Combination of delicate structure and microheterogeneity also prevent accelerated & stressed conditions from accurately predicting stability of biopharmaceuticals, which typically rely on real time/storage condition data for product expiry & handling labeling
- Measurements of purity/impurities are relative to both the method of measurement and the process used to produce the API

Microheterogeneity of non-glycosylated proteins - hGH

A 191-amino acid protein with 2 S-S bridges



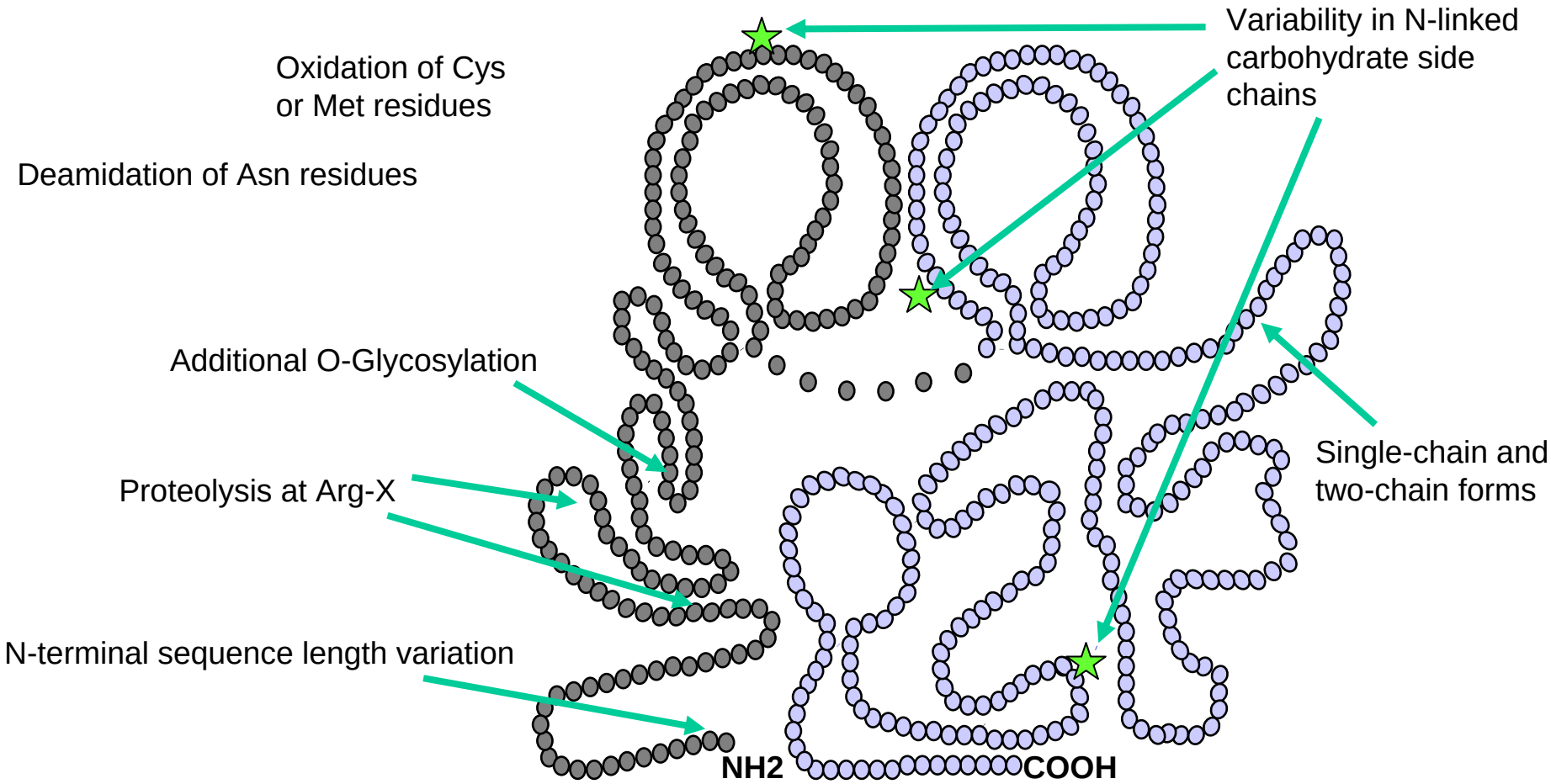
- **Amino acid substitutions observed in ~2% of the expressed protein**
- **May lead to functional and/or antigenic differences**
- **Variants found in different products are not identical**

Total possible variants: > 10^6

A. Eshkol, Serono & L. Fryklund, Pfizer

Microheterogeneity of glycosylated proteins - t-PA

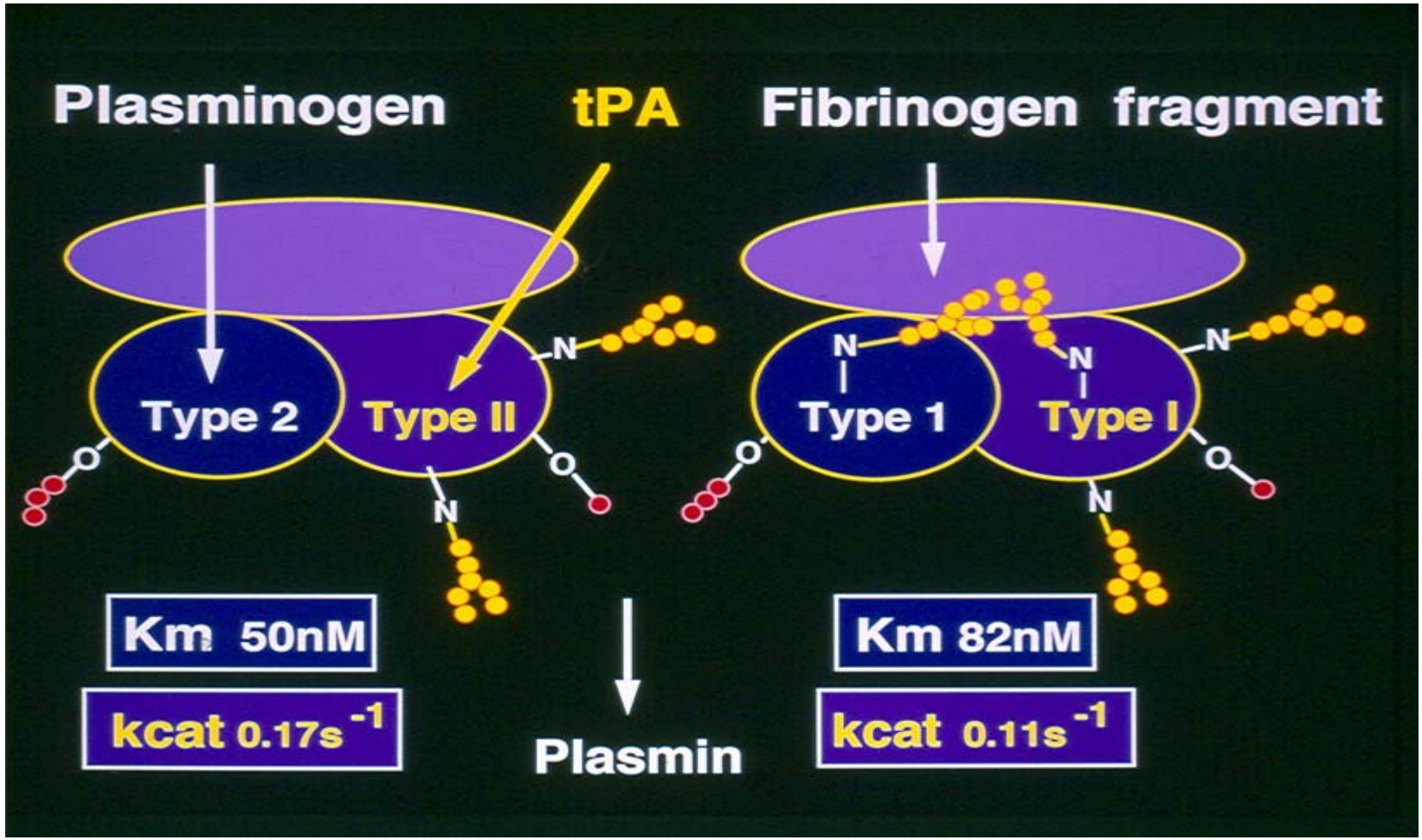
A 527-amino acid protein with 17 S-S bridges and 3 glycosylation sites



Georg-Burkhard Kresse, Roche

Total possible variants: 1.09 x 10^9

Variable Glycosyslation of tPA at One Site Leads to Different Biological Activity



Process & Product Complexity

- NCEs typically have relatively few unit operations, with relatively few CPPs and CQAs, and it is usually straightforward to relate CPPs to CQAs, enabling process validation.
- Biopharmaceuticals have typically 10 or more manufacturing stages, encompassing 18 – 30 unit operations, with several hundred process parameters, large numbers of CQAs, and considerable ambiguity in defining CPPs and their relationship to CQAs, limiting the power of process validation.
- Combination of delicate structure, complex raw materials, living processes, environmental effects, less analytical power, and complex processes leads to complex biopharmaceutical APIs where less can be known or assured by testing or by process validation.
- Complex APIs plus wide variety of mechanism of action (as well as variable state of knowledge regarding MoA) leads to need for considerable diversity in approach to product & process control strategy, process validation, quality risk management, and design space.

Illustrations of Greater Process & Product Complexity for Biotech

- Control points: 25 – 100 for NCE vs 250 – thousands for biotech
- Batch record size reflects the number of control points

API Batch Records: NCE

Biopharmaceutical

Complexity Interacts with Inhomogeneity & Patient to Give Rise to Immunogenicity

- Some biopharmaceuticals are inherently immunogenic (especially replacement Rx)
- Some product – related impurities can be immunogenic (interferon alpha with oxidized Met, others with some deamidations)
- Some process – related impurities can have adjuvant effect, enhancing immunogenicity (host cell proteins, leachables/extractables, silicones)

Illustration of Design Space Complexity for Biopharmaceuticals

- Cation exchange step needs to consider
  - Interaction of multivariate input parameters
  - Maintenance of microheterogeneity profile (Removal of product-related substances ?)
  - Removal of product-related impurities
  - Removal of DNA
  - Removal of host cell proteins (dozens to 100s)
  - Removal of putative viral agents
  - Yield

Factors Increasing Difficulty of QbD Approach for Biotech APIs

- Clinical safety & efficacy not always linked to mechanism(s) of action or CQAs
- Bioavailability is not transparently linked to biological effect, even though most biotech products are administered parenterally
- Many products have multiple mechanisms, and these often have different structural basis (e.g., IFNalpha, some IgGs)
- Measurement of biological activity (e.g., bioassay or potency assay) may or may not have known relationship to mechanism(s) of action
- Knowledge of many molecular changes comes late in development
- Measurement of molecular change is more straightforward than assignment of impact of molecular change to biological properties (and safety & efficacy)

Factors Increasing Difficulty of QbD Approach for Biotech APIs (cont'd)

All these factors interact to make it very difficult to fully understand the relationships among PPs, CPPs, CQAs, and clinical performance. When combined with little manufacturing experience at commercial scale for MAA filing, predictability is limited.

Opportunities for QbD in Biotech

- Despite these difficulties, there have been many successful applications of QbD & QRM principles
  - Sound scientific principles as the molecular basis of API & product design
  - Multifactorial DOE applications in process design
  - Viral safety evaluations (process design & control, engineering & operational controls, risk analysis)
  - Numerous applications of comparability principles to manufacturing changes in development and after approval
  - Numerous applications of formal & informal risk analysis in
    - Evaluations of relationships among PPs, CPPs, & CQAs
    - Evaluations of possible myriad analytical tools for QC controls
  - Use of automation & PAT concepts where justified

Summary

- Any ICH approach to incorporate QbD into APIs for biotechnology products has to give clear guidance on many topics which are different or more complex than for NCEs
- The EWG will need to successfully address this complexity to produce a useful guidance