BioManufacturing, CMC aspects of the biotherapeutics and associated reagents

Jacques Dumas, Advanced BioInnovation & Technology /Biotherapeutics, sanofi Vitry Research Center, France

23-24 September 2015, Romainville

SANOFI

Global Biotherapeutics

Global Biotherapeutics

- Introduction – complexity of proteins
- Regulatory context (FDA regulation)
- Importance of the processes –Comparability – QbD
- Impact of changes (examples)
- Conclusion

SANOFI

Qu'est-ce que la « CMC » ?

Chemical Manufacturing and Control

Global Biotherapeutics

- = Développement pré-clinique d'un médicament
- Propriétés physico-chimiques de la "NCE": caractérisation, stabilité, solubilité
- Procédé de fabrication optimisé pour passer de l'échelle de paillasse (mgs) au manufacturing (kgs)
- Formulation: capsules, tablettes, aérosols, injectable (iv, sc, im)
- ***NCE: New Chemical Entity***

Recombinant Proteins

Global Biotherapeutics

de 1980 à 1990

Produits de remplacement = protéines synthétisées pour éviter leur extraction à partir de sources animales ou végétales

☺ **Amélioration de la sécurité** du produit et de l'**accès au traitement** pour un plus grand nombre de patients

Exemple : insuline à action rapide (*Insuman rapid®*, Sanofi), rasburicase (*Fasturtec®*, Sanofi)

de 1990 à 2000

Protéines optimisées = protéines modifiées par chimie ou génie génétique

☺ **Amélioration des propriétés** des protéines précédentes

Exemple : insuline glargine à action lente (*Lantus®*, Sanofi)

de 2000 à 2013

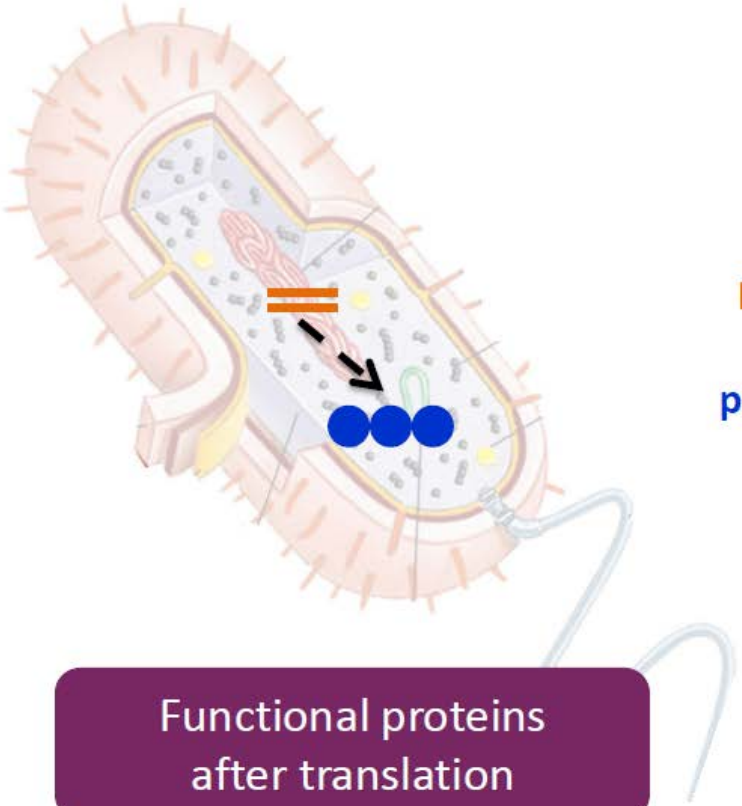
Anticorps monoclonaux = protéines se fixant sur une cible de manière spécifique

☺ **Thérapies ciblées** et **nouveaux traitements** (cancer, maladies rares, maladies auto-immunes, maladies infectieuses…)

Exemple : aflibercept (*Zaltrap®*, Regeneron/Sanofi), anticorps anti-PCSK-9 (Regeneron/Sanofi)

PROGRAM EXECUTION : FROM GENE TO PROTEIN

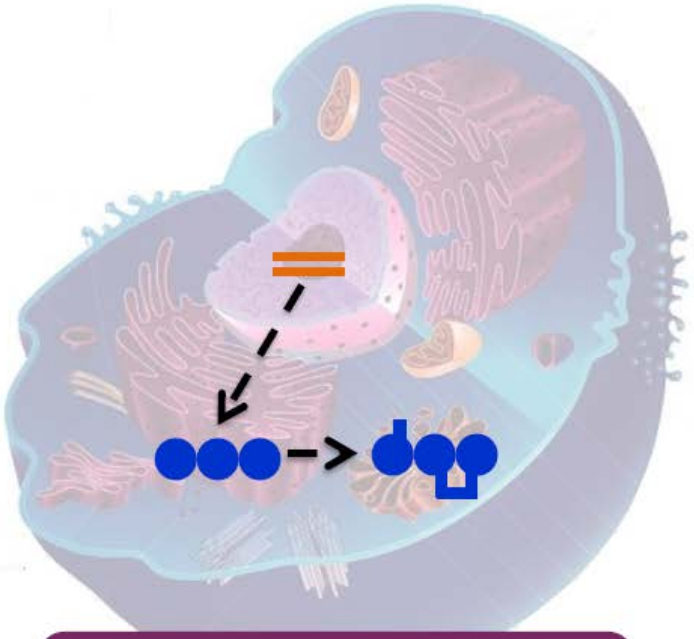
Prokaryotic cell



DNA

protein

Eukaryotic cell



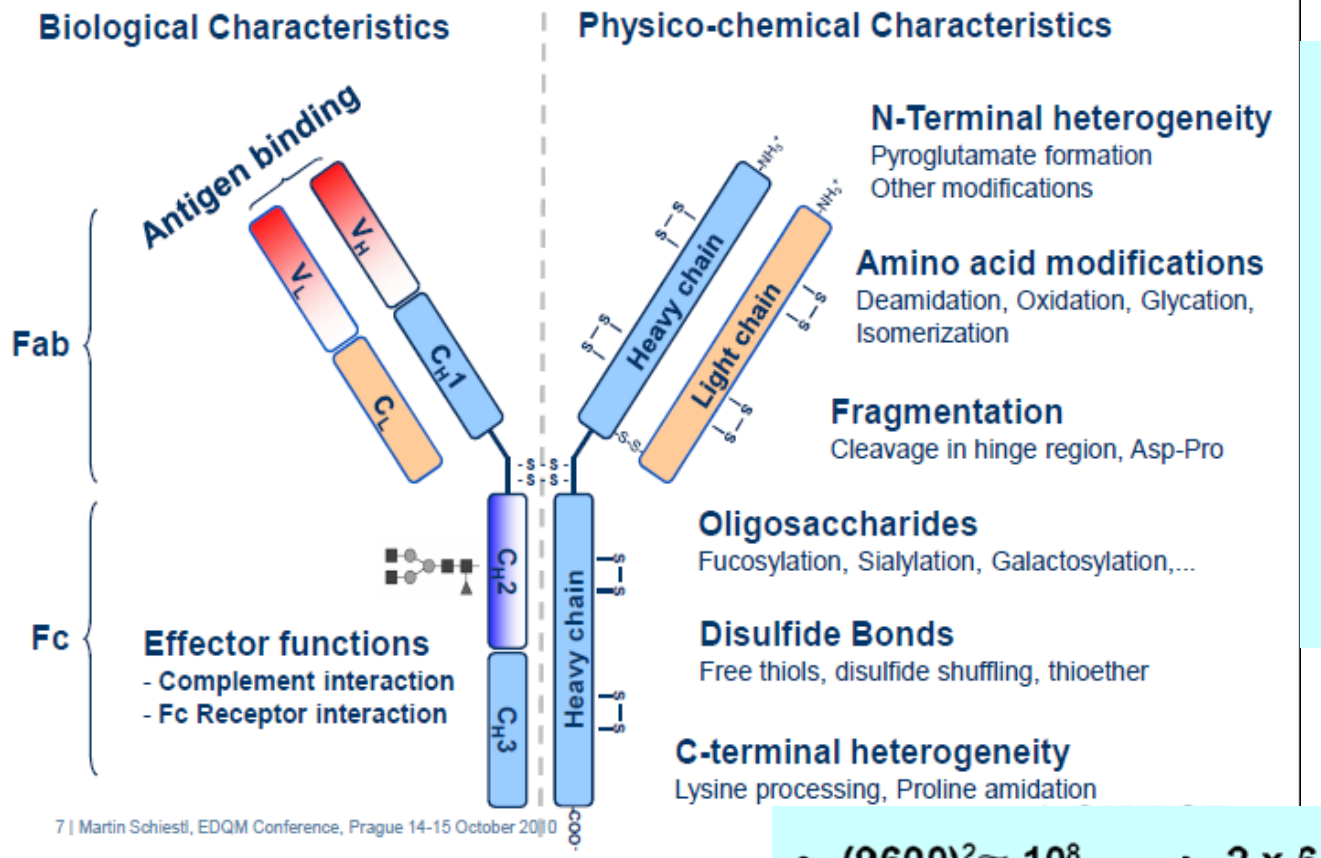
Functional proteins after translation

Functional proteins after **modifications**

Antibody heterogeneity

Global Biotherapeutics

Which quality attributes to consider? Example IgG1 type mAb

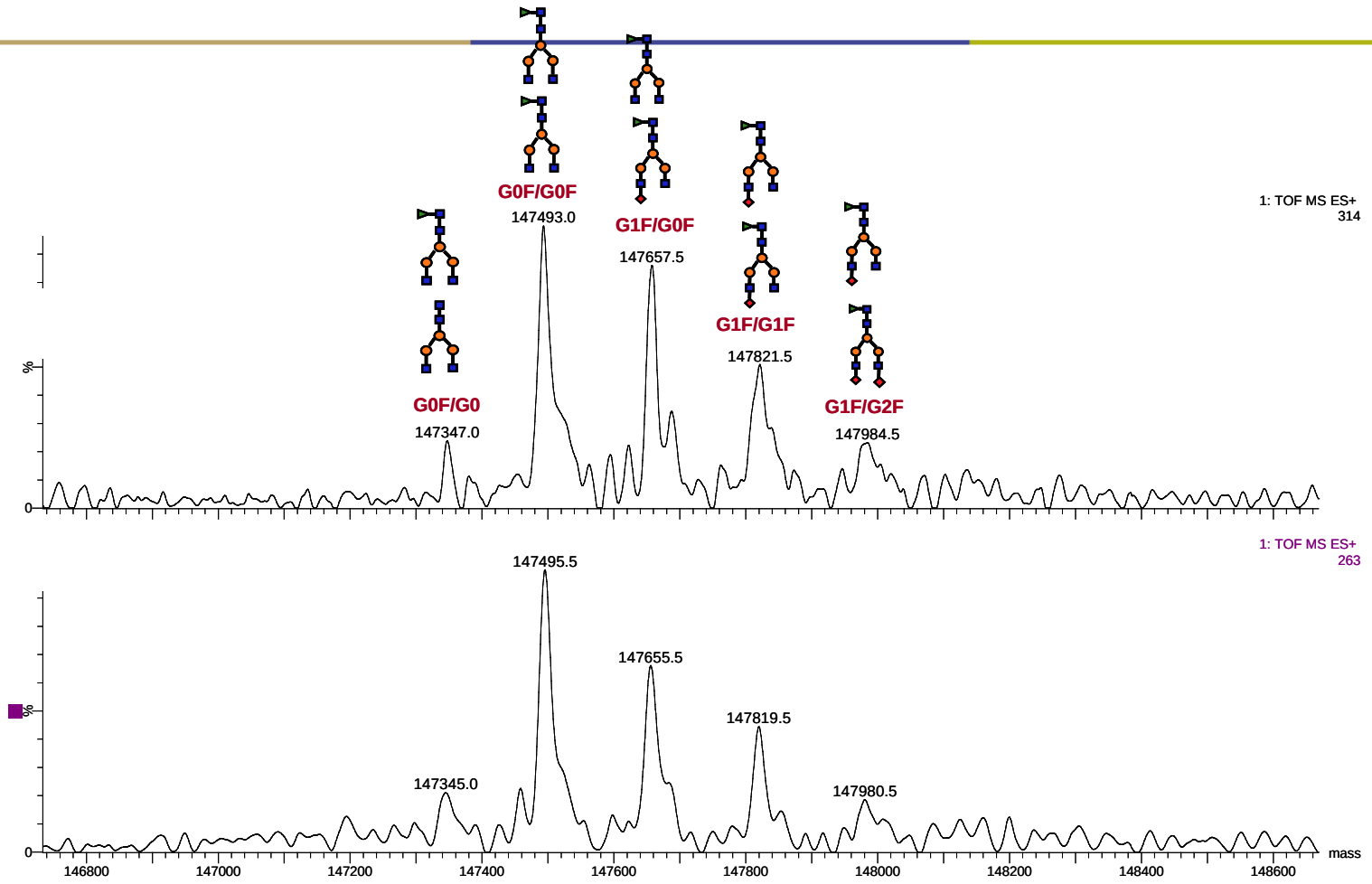


- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose, G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)

- $(9600)^2 \approx 10^8$
- 2 x 6 x 4 x 4 x 5 x 5 x 2 = 9600

Complexité des Biologiques (glycosylations) (3)

Global Biotherapeutics



SANOFI Research & Development

FDA Process Validation Guide
General concept

Global Biotherapeutics

Stage 1 – Process Design

Building and Capturing Process Knowledge and Understanding

Risk analysis

…it is essential that activities and studies resulting in product understanding be documented…

DOE

Critical Quality Attributes

Establishing a Strategy for Process Control

…process controls address variability to assure quality of the products…

PAT

Stage 2 – Process Qualification

Design of a Facility and Qualification of Utilities and Equipment

Performance Qualification Approach

Performance Qualification Protocol

Protocol Execution and Report

Stage 3 – Continued Process Verification

Process drifts

In-process monitoring

…continually assure that the process remains in a state of control…
…data should be statistically trended and reviewed…

Statistical expertise

SANOFI

General Overview of a Production Process

Global Biotherapeutics

Production:
Décongélation d'une ampoule
Culture initiale
Expansion: fermentation, bioréacteurs
Production

Upstream processing

Extraction → Concentration/ Purification primaire → Purification par Chromatographie résolutive → Formulation du produit → Conditionnement → Etiquettage Emballage Stockage de lots

Downstream processing

FROM R&D TO PRODUCTION

Lab scale	Pilot scale	Production scale
Erlenmeyers/Bioreactors	Bioreactors	Bioreactors
0,1 - 30L	30 - 300L	300L - 300m^3

Change is the Nature of Development

- Biologics Development is about managing process changes
- Key data are generated starting with Research, all along the development path
  - Pharmacology results
  - Safety data (animal studies, but also e.g. human IHC data)
  - Safety in patients
  - Dose finding in patients
  - Pivotal clinical studies

- It is unusual to have the final process ready for the first key experiments
- Different processes (raw materials, scale, growth, and purification) will be used
- Analytical methods become more refined
- Formulation (e.g. from lyo to liquid, from i.v. to s.c.) might change
- Need to manage this change (show „comparability“ of the different drug qualities)

- Changes describe the move from platform technology to more tailored approaches
- Major changes are typically performed when establishing the final process

Comparability

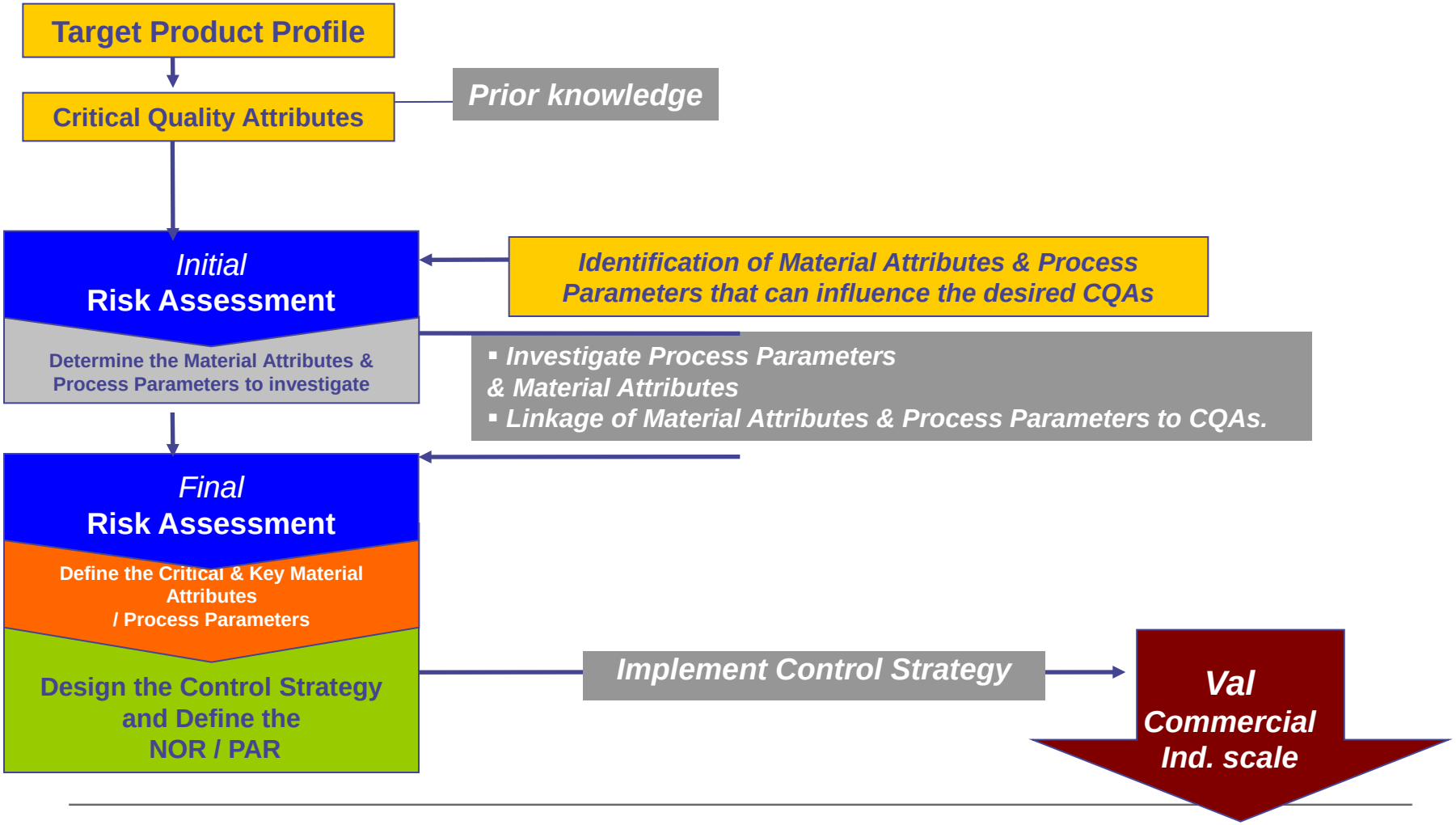
- **Building the bridge between different qualities / processes**

- A prominent example is the use of **„representative“ material** (i.e. not the final clinical material) for GLP toxicology studies.
  This requires an analytical dossier and position paper (to be generated later) to justify representativeness.

- **Comparability is not necessarily analytical identity**. When differences are seen, their relevance must be assessed by a risk analysis (what parameters are critical to efficacy and safety).

- **Larger heterogeneity is more difficult to keep constant.**

Quality by Design Development

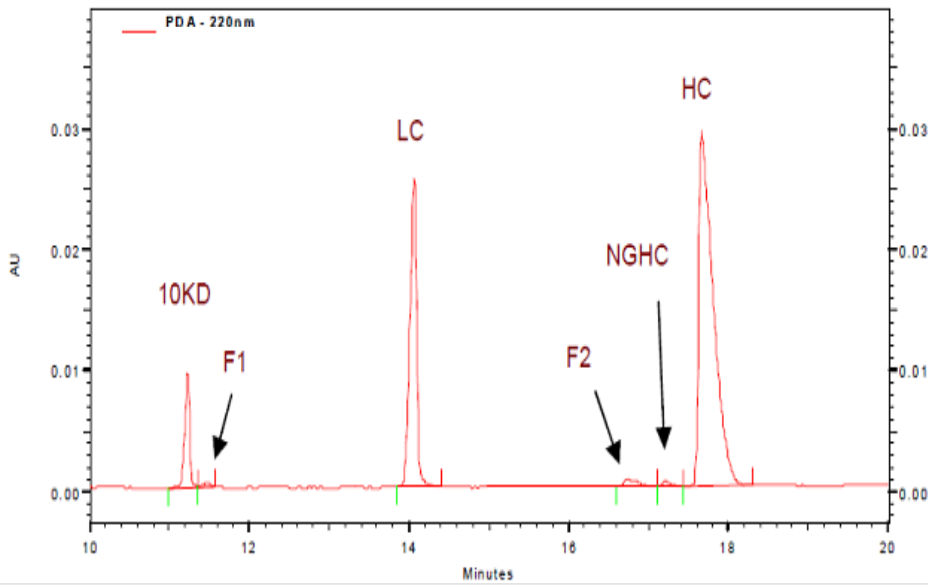


DS/DP - Impact of process changes from USP

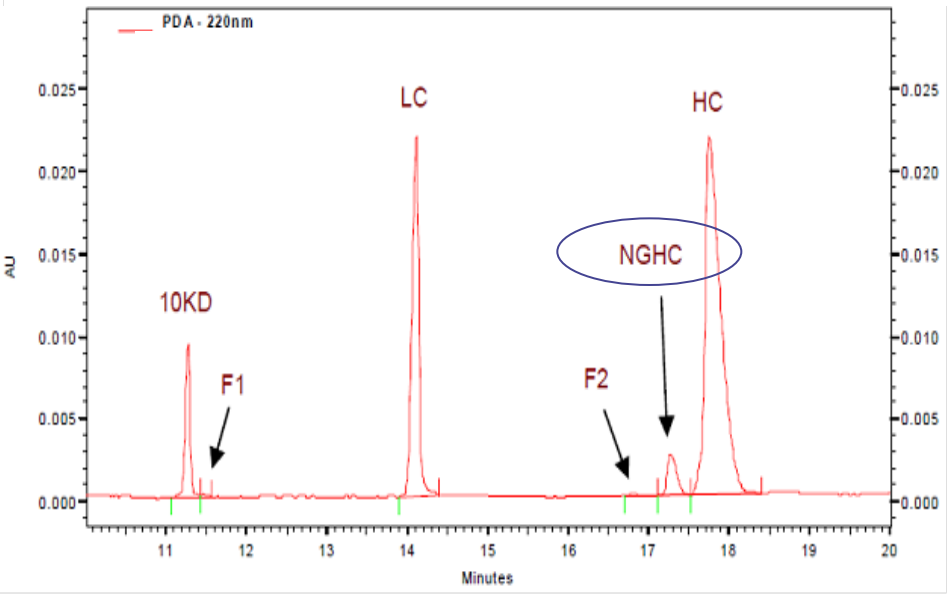
Global Biotherapeutics

- Non glycosylated HC content by cGE (reduced condition)

P1 (pre-change)



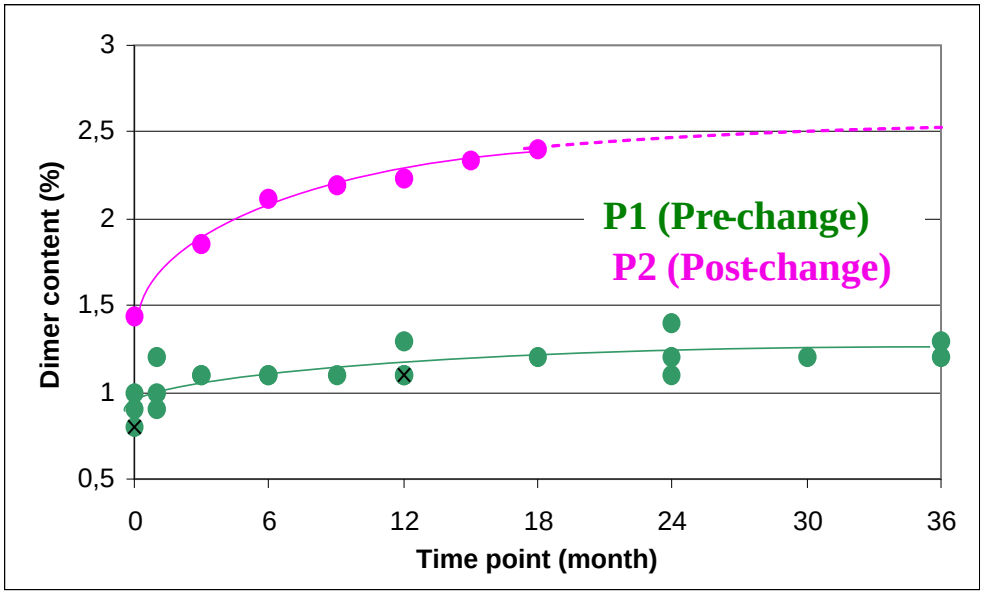
P2 (post-change)



SANOFI Research & Development

DS/DP - Impact of process changes from mAb/DS Conjugation

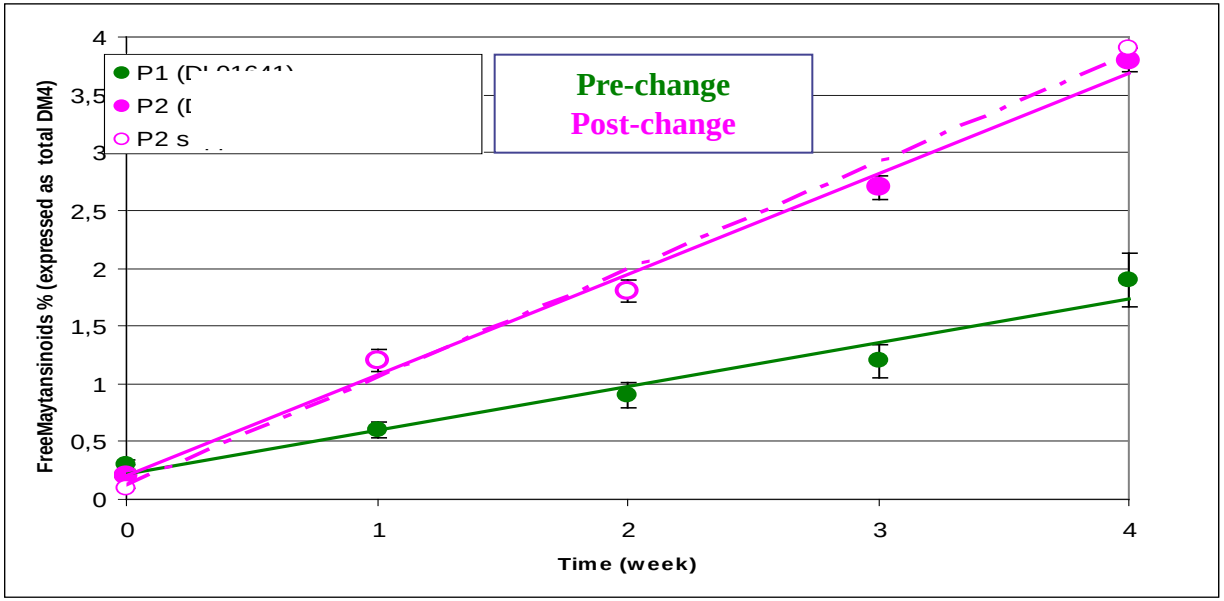
- Impact on soluble aggregates formation (dimer) on DS/DP level only
- **3-fold more dimer expected at end shelf life**



- Potential impact on immunogenicity

DS/DP - Impact of overall process changes

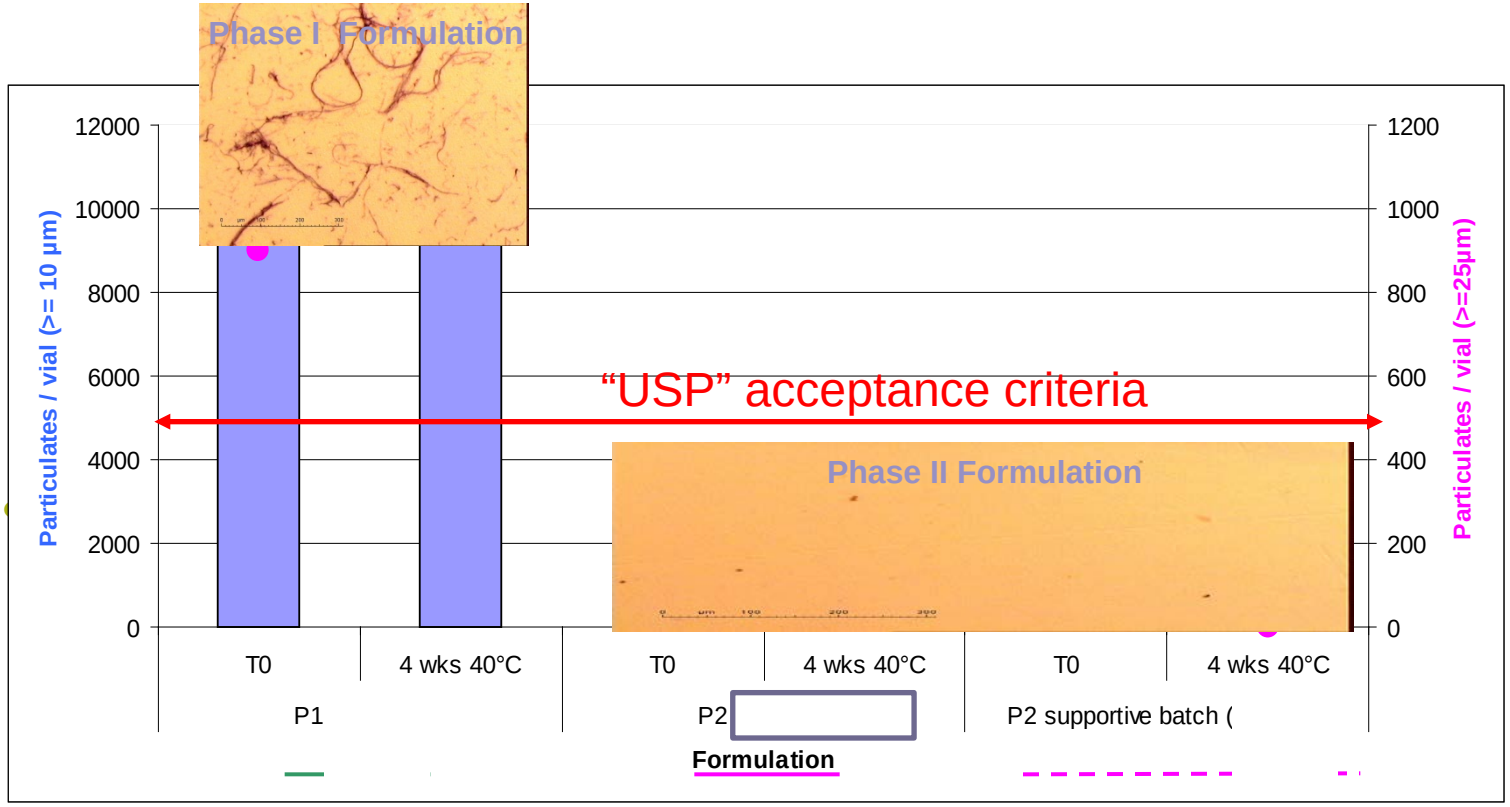
- Higher rate of free drug released demonstrated
- **2-fold increase in free drug under stressed conditions**



- Change in the stability profile
- **Potential impact on toxicity not expected based on DSAR assessment**

DS/DP - Impact of process changes from DP Formulation

- **Sub - Visible Particles decrease with conformity to Pharmacopeia**



Risk assessment of analytical differences between Phase I and Phase II processes: example of an ADC

Global Biotherapeutics

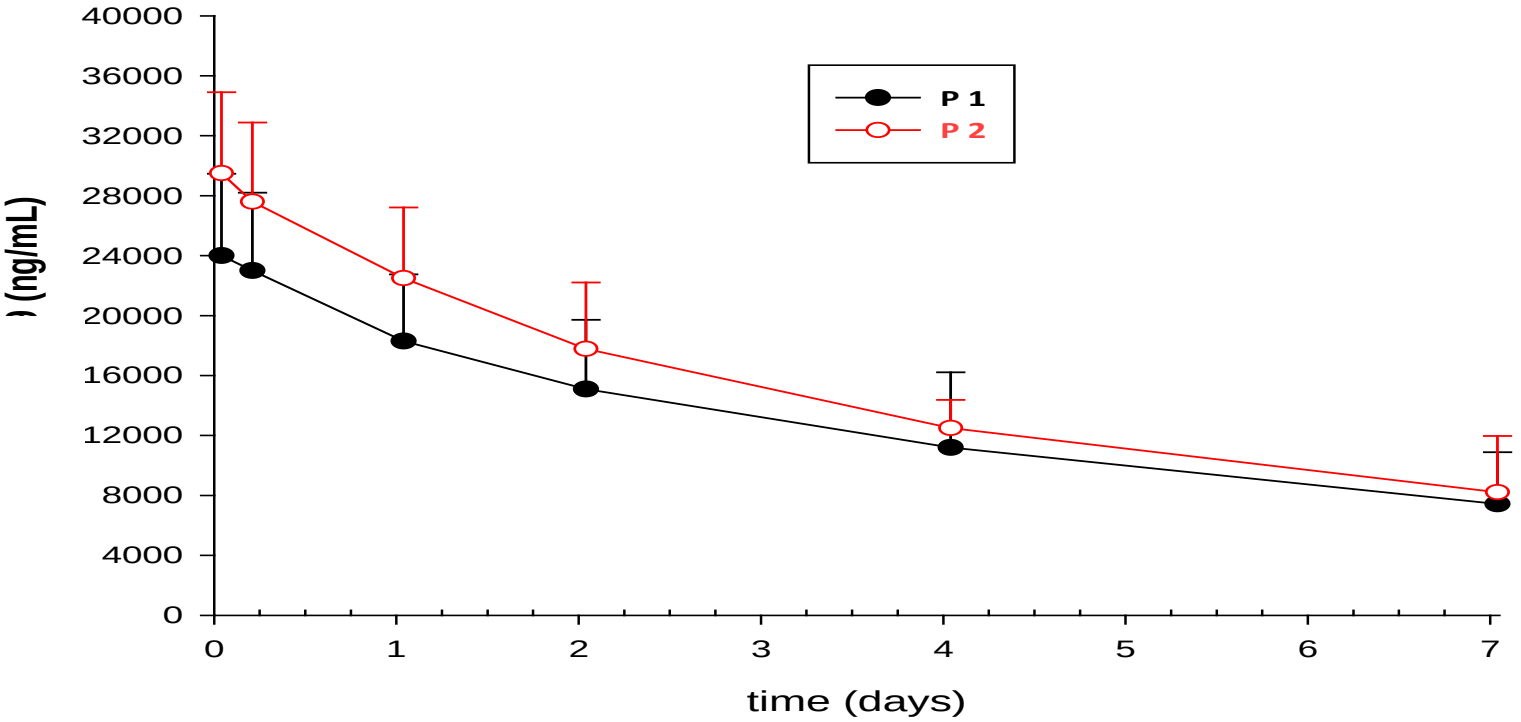
- **Risk of impact of observed analytical differences, as well as change in drug product formulation, on the pharmacokinetic parameters, pharmacodynamic effects, immunogenicity and safety was assessed.**
  - Risk took into consideration :
    - **product structure,**
    - **current understanding of mechanism of action,**
    - **disease-related factors,**
    - **route of administration,**
    - **immunogenicity data from Phase I and**
    - **overall similarity of materials derived from Phase I and Phase II processes.**
- Risk associated with each of the observed analytical differences was categorized as either Low, Moderate or High.
- Conclusion from this risk assessment
  - **on safety and efficacy profile when compared to Phase I process material used in Phase I studies**
  - **Assessment can be used to justify a study to further demonstrate comparability**

SANOFI

Clinical data : human PK profiles comparison

Global Biotherapeutics

PK profiles following a single administration of P1 & P2 quality Drug Product



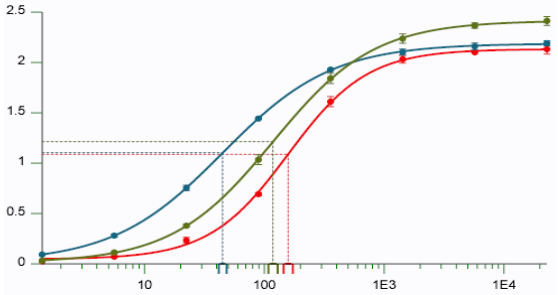
- No impact of different DP qualities on PK profile to human
- Comparability fully demonstrated for P1 and P2 quality

SANOFI

Importance of reactives stability
Binding ELISA: variability related to the antigens

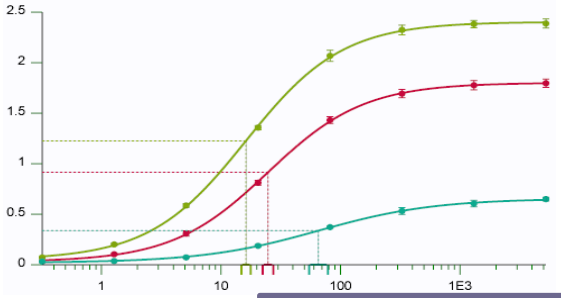
Global Biotherapeutics

Ag1



Prospec 1µg/mL_1/25k
Tebu 1µg/mL_1/25k an
Prospec (new) 1µg/mL_

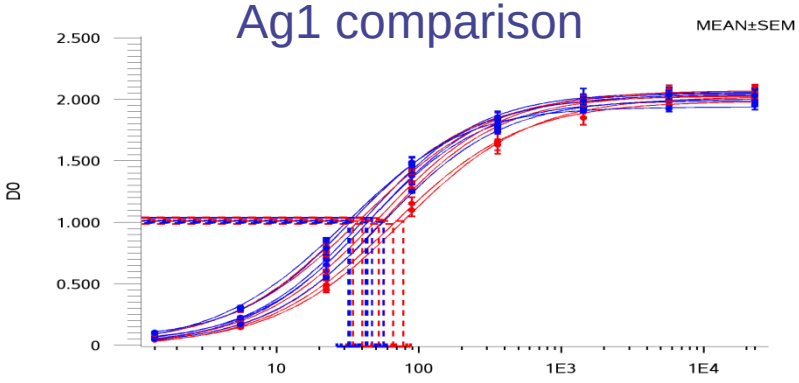
Ag2



Prospec 1µg/mL_1/12.5k
Tebu 1µg/mL_1/12.5k an
Prospec (new) 1µg/mL_1

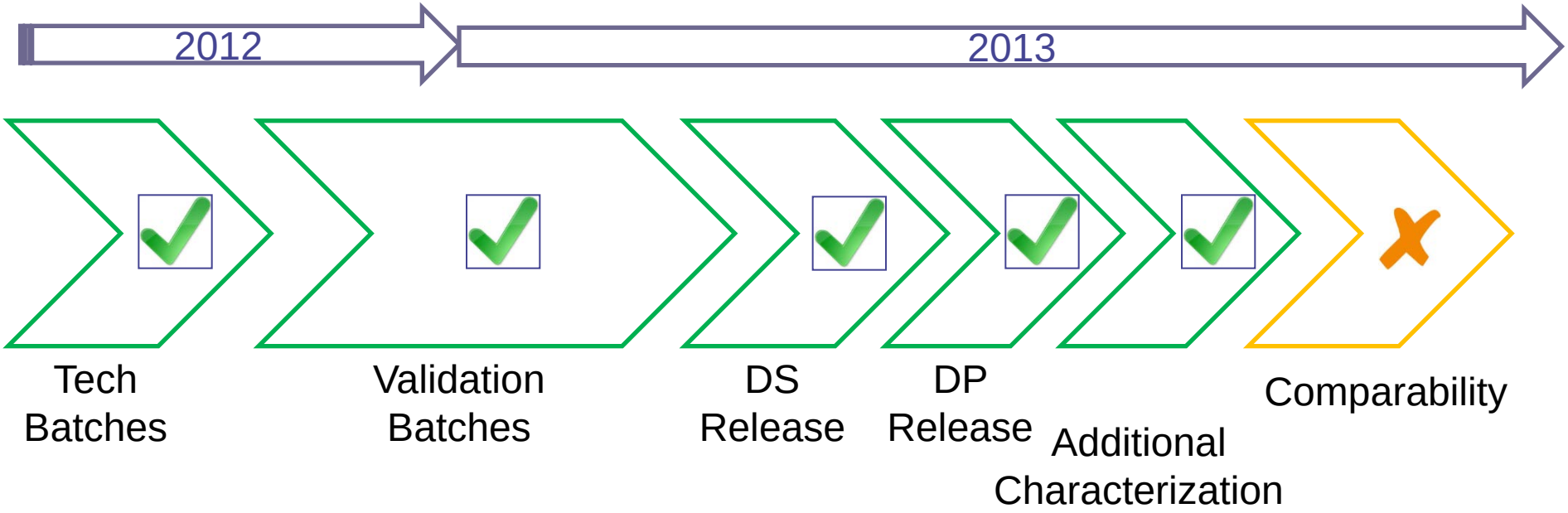
Dose-response comparison
His-Ag1 Tebu-Bio vs Ag1-His sanofi
3 independant analyses

Ag1 comparison



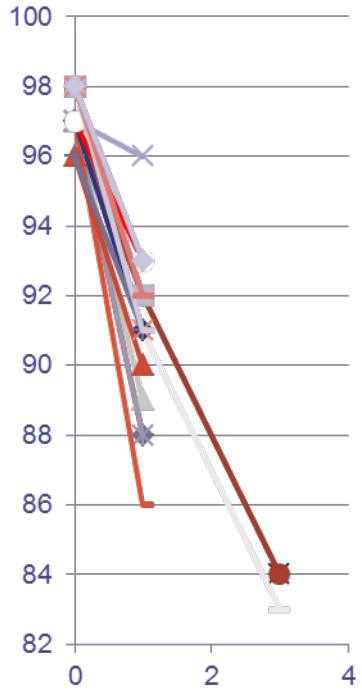
SANOFI

Process validation where the issue started

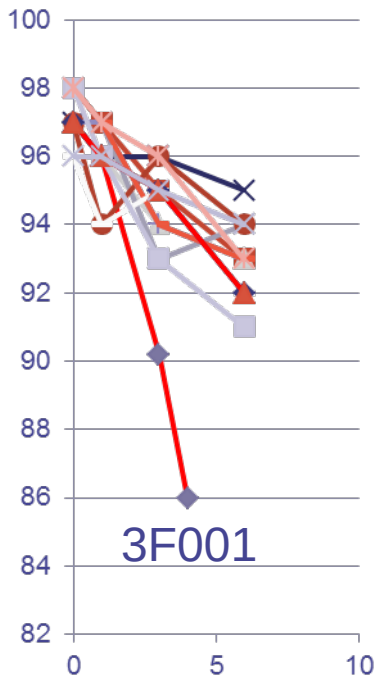


→ Task force to address the issue

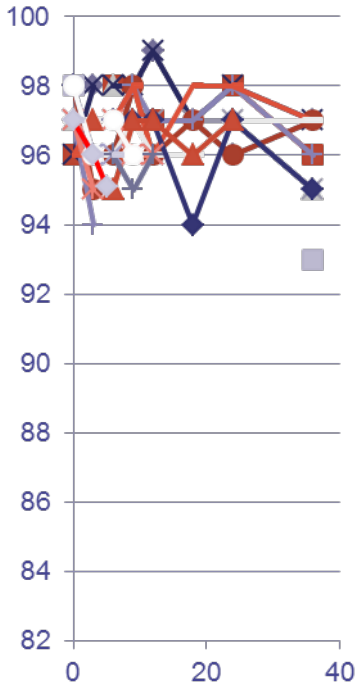
DP Stability studies: NR SDS-PAGE main band



40°C

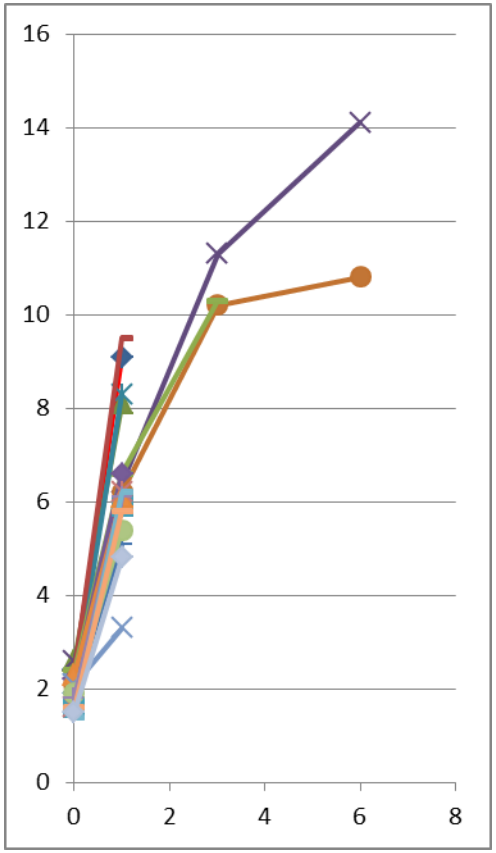


25°C

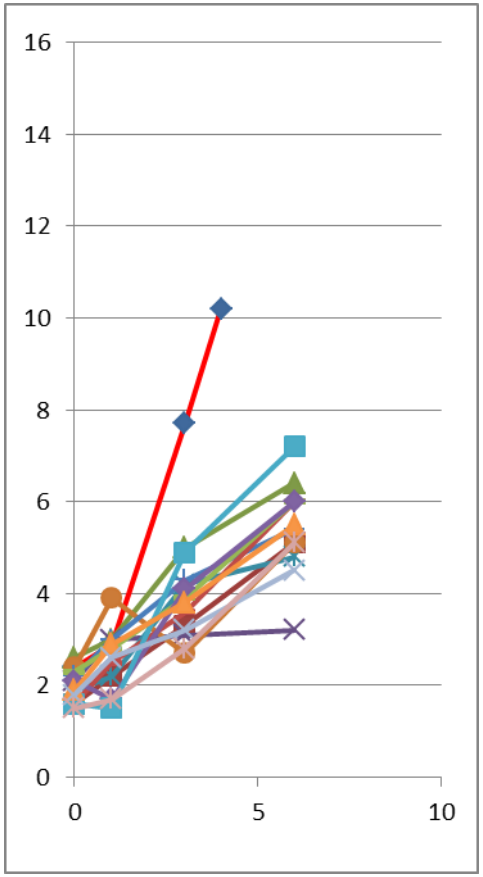


5°C

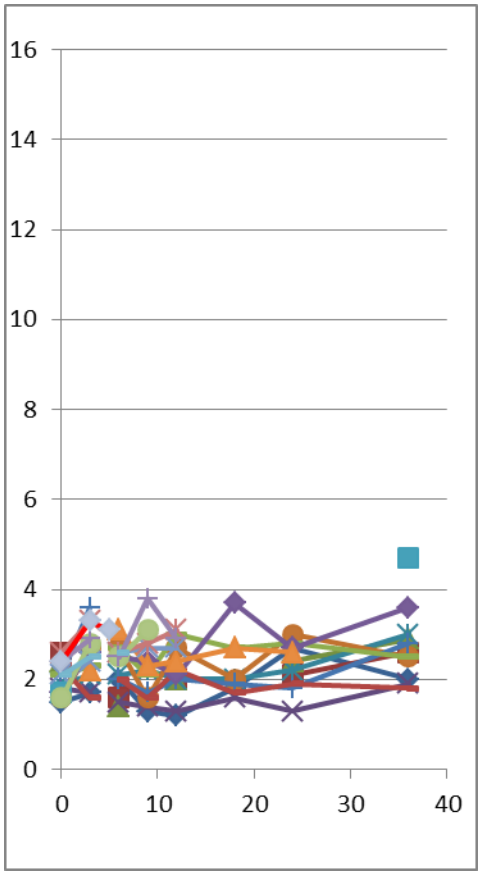
DP Stability studies: NR SDS-PAGE degradation band



40°C



25°C



5°C

Process investigation

- Lean approach to identify potential root causes (3 months)
  - **Definition of the problem**
  - **Process mapping**
  - **Evaluation of critical parameters**
  - **Conclusion and action lists**

- List of potential root causes to use a basis for subsequent studies
  - **Small scale studies (9 months)**
  - **Technical batches at scale**

Conclusion

- Unstability issue could come from several different changes in the process: USP, DSP, formulation…
- Any change of the process needs a risk assessment in the stability perspective for comparability
- Comparability studies are keys with good knowledge of the protein and the process (cirtical parameters, mapping, QbD)
- DS/DP forced degradation studies are time consuming and difficult to interpret
- Robustness of analytical methods is critical

Thanks

Global Biotherapeutics