Addressing Uncertainties in Complex Biologics: Enhanced vs. Conventional Approaches

IABS-GHS case studies, June 23rd, Tokyo

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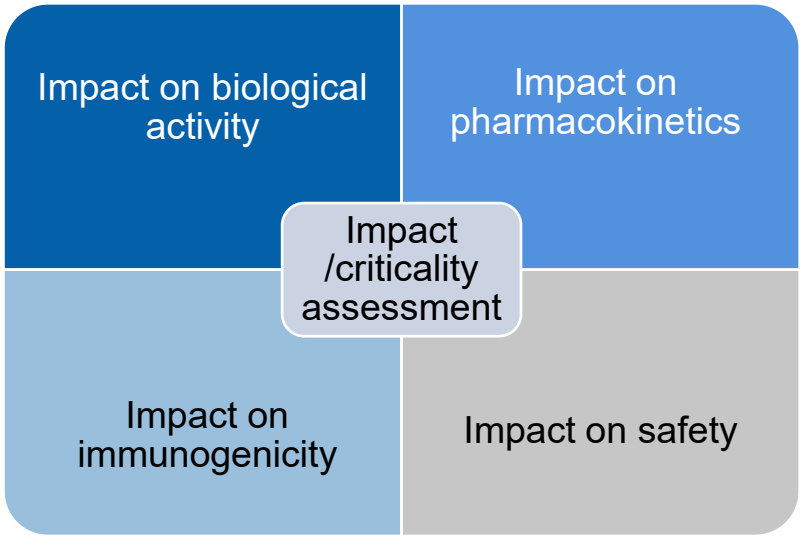
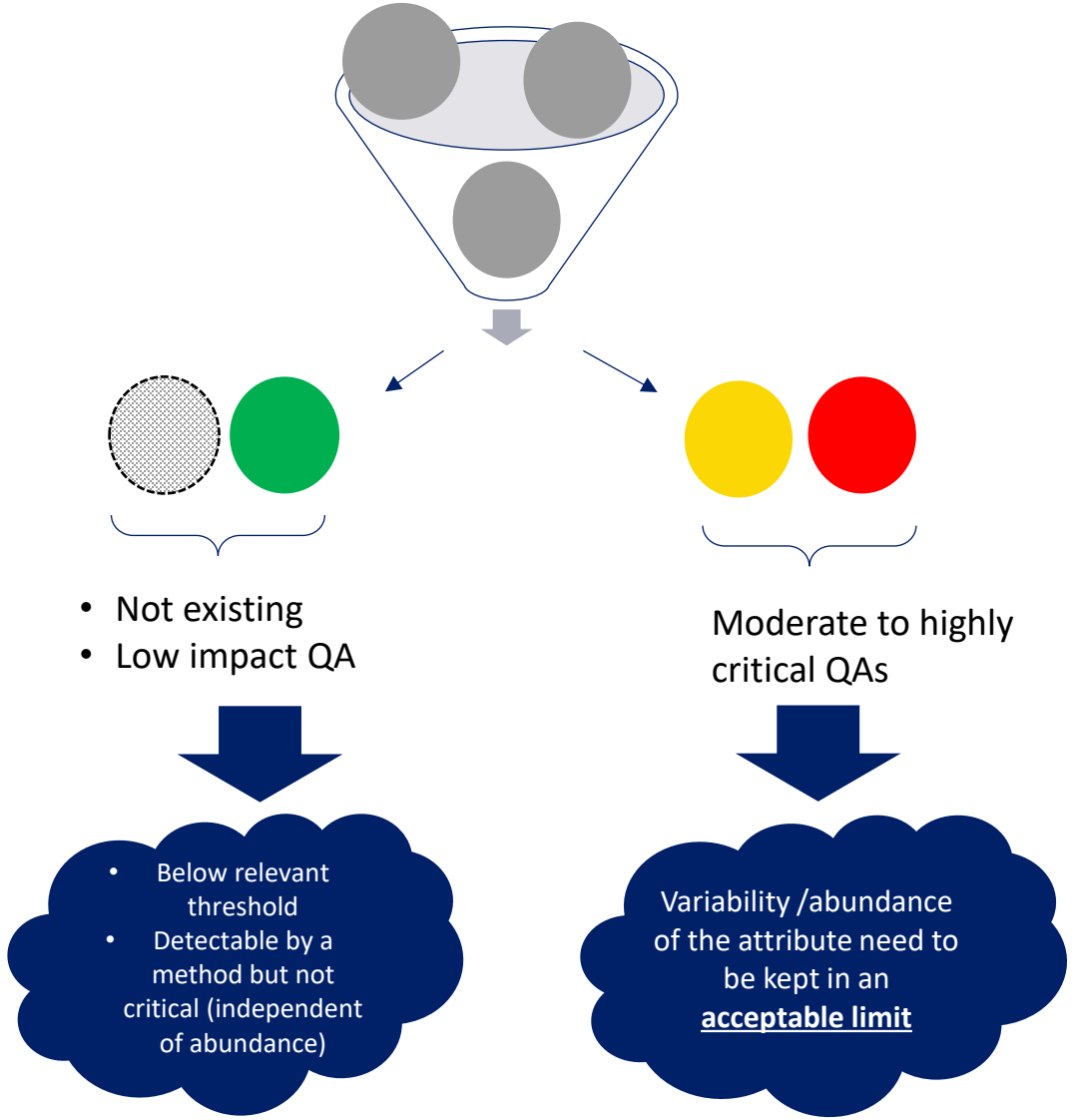
Addressing uncertainties by product characterization and conservative Critical Quality Attribute determination

Product Characterization

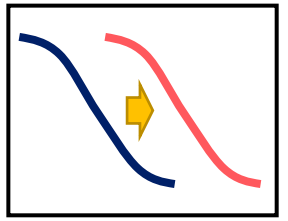
- **Reliable stress** studies **covering** all the stress the molecule could see during its lifecycle until administration
- **Sensitive, scientific sound** physicochemical and biological assays
- **Threshold**: 0.1 %, not applicable to any variant with potential impact on safety and immunogenicity

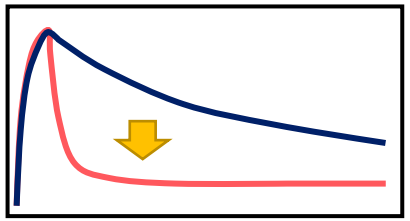




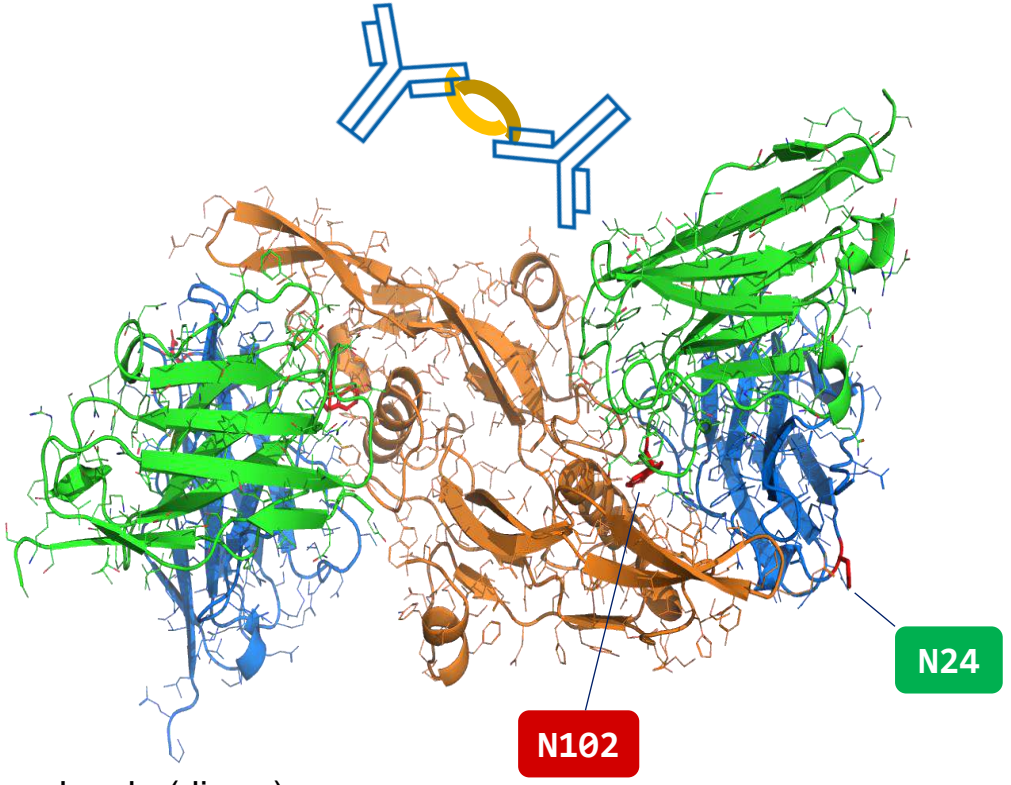
Technology advances and elucidation of structure-function

- **Forced degradation studies to elucidate liabilities and test them in functional assays**
- **Sensitive functional binding assays and cell advance cell-based bioassays**
- **Peak fractionation and MS**
- **In vitro and in vivo animal models**





- **X-ray diffraction, cryo-EM high resolution structures of target bound drugs, HDX-MS**
- **In silico structure modeling (Alphafold3)**



Brown = target molecule (dimer)
Green = light-, blue = heavy-chain

Product and process understanding

Scientific/product Acceptance Criterion that ensures no clinical impact: the desired pharmaceutical quality

Amount of CQA (N102)

10 %

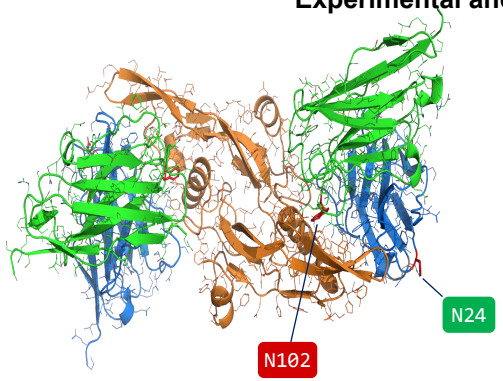
7 %

6 %

5 %

4 % -

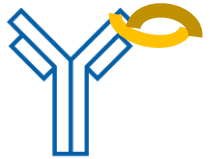
Experimental and Prior Knowledge



Brown = target molecule (dimer)
Green = light-, blue = heavy-chain

- **Impact on PK?** → **No,** not in PK relevant region
- **Impact on immunogenicity and/or safety?** → **No,** based on relevant clinical experience from this molecule, other molecules as well as its natural occurring variant found in human molecules
- **Impact on potency: Yes,** N102 deamidation reduces affinity to target

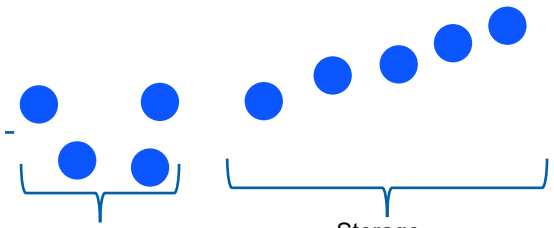
Understanding the mechanism



Experimentally confirmed: **one intact** Fab sufficient

- Amount in **reference** material = **4.0 %**
- **Reference** material is **100% potent**
- **CQA-AC** = **10%,** allows an increase of 6%
- 6% increase results **only in marginal impact on potency** (<1.0%, as only molecules with modification on both Fab cannot bind)
- Upon careful evaluation, this impact is **not expected to have a clinical relevance**
- **No impact on other properties** (e.g. immunogenicity, stability)

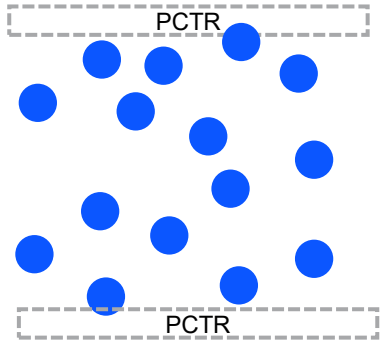
Clinical experience based on clinical batch manufacturing and storage prior administration



Manufacturing

Storage (administered aged material)

Process development and characterization



Definition of:
- CPP vs non-CPP/KPP
- Proven acceptable manufacturing ranges

DS validation

Executing commercial process

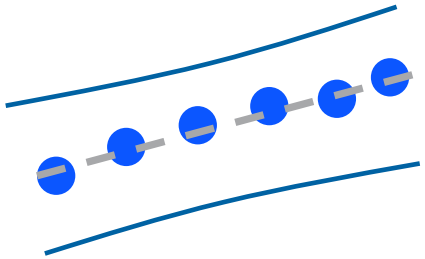
DS stability

Batch testing

DP validation

Executing commercial process

DP stability



Worst case slope models
Real time, predictions

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PCTR = Process Characterization Target Range

Product and process understanding

Scientific/product Acceptance Criterion that ensures no clinical impact: the desired pharmaceutical quality

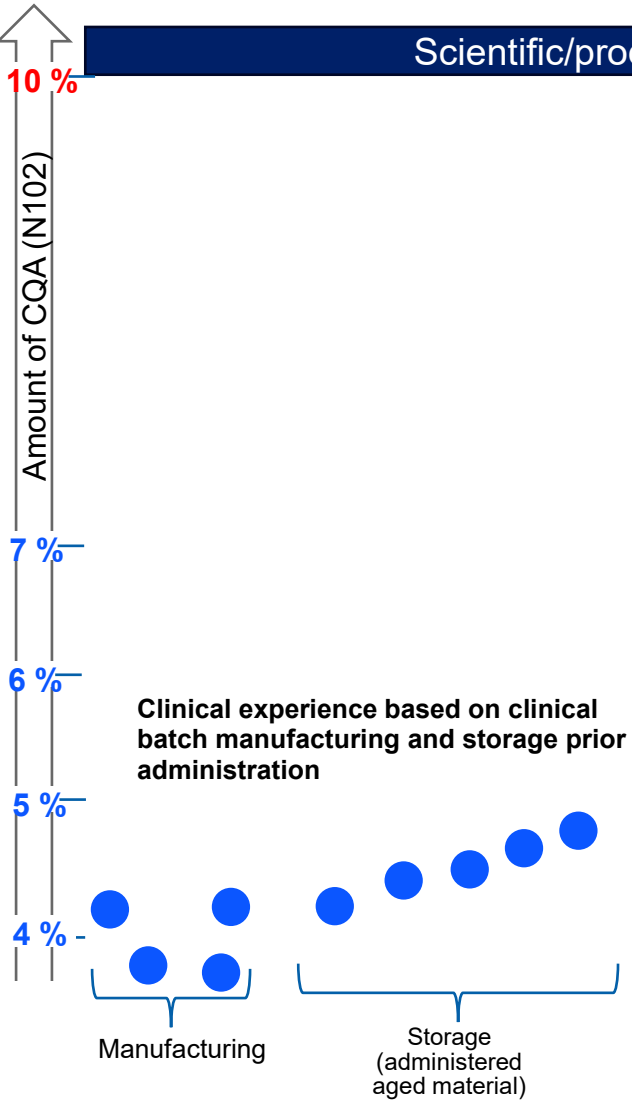
Safety margin

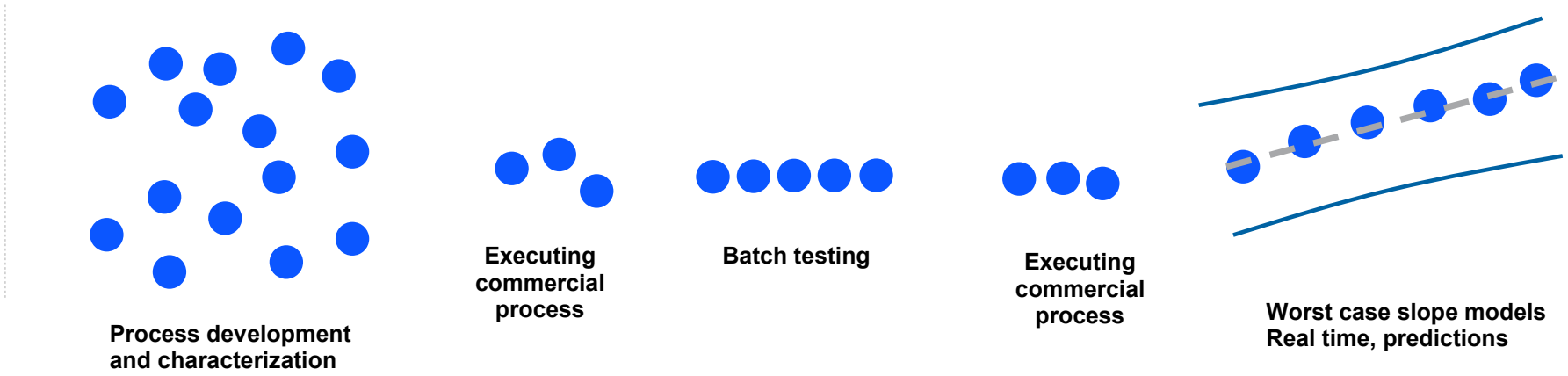
Maintaining "safety margin" (CQA level) **during commercial lifecycle:**

- Monitoring process parameters (e.g. CPPs and KPPs)
- Monitoring process outputs using sensitive analytical techniques as product-related Performance Indicators (e.g. "purity" of acidic or basic variants by CEX or CZE)
- Change and deviation management using predefined assessments routes to confirm safety margin

Safety margin

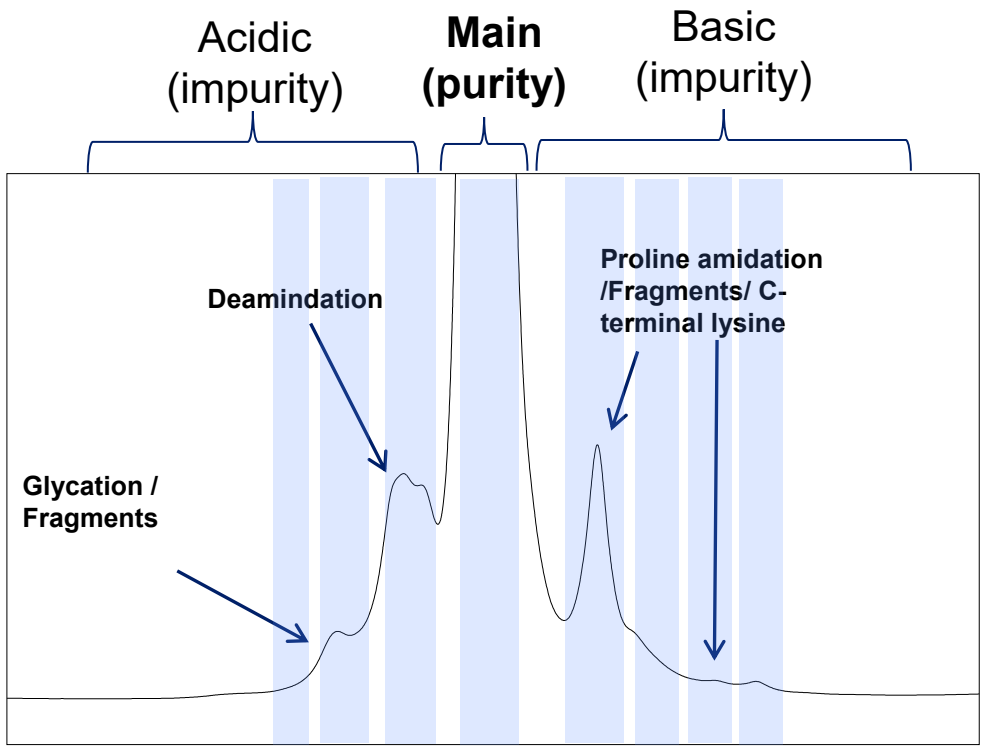
Under routine manufacturing, N102 clearly remains below 6 % *(or 7 % considering combined pre-assessed worst cases)*





Well characterized analytical procedure for quality control of CQAs or process consistency monitoring ?

Charge based separation assay (CEX) and peak fractionation



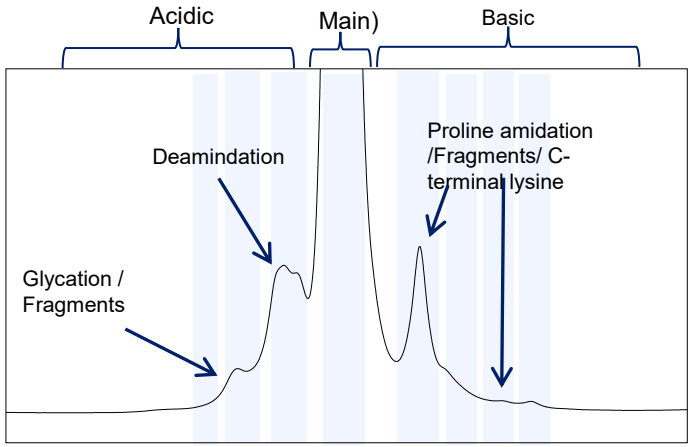
Variant identification

Variant / peak	Product understanding based on characterization experiments
Glycation	Forcedly highly glycated samples did **behave comparable to the non-glycated** IgG1 in representative drug to target binding studies.
Deamidation	Deamidation under various stress conditions occurred mainly in residues that **are not involved** in binding or effector function. These modifications are visible in the labeled peaks. N102 deamidation which is less sensitive to stress occurs at lower levels
Proline amidation /c-terminal lysine	Residues not involved in binding to target and effector functions not relevant for this IgG. Changes in charge are lower than what is described as risk for PK *(Bumbaka et all., 2012)*
Fragmentation	Fragments show changed bioactivity and PK properties in experimental *in vitro* studies Required analytical performance to control of fragments is achieved by other technologies such as **CE-SDS** that better separates the fragments that occur in accordance with the characterized degradation pathways

→ CEX monitors general product consistency, but does not need to be employed to restrict the amount of a CQA in a batch

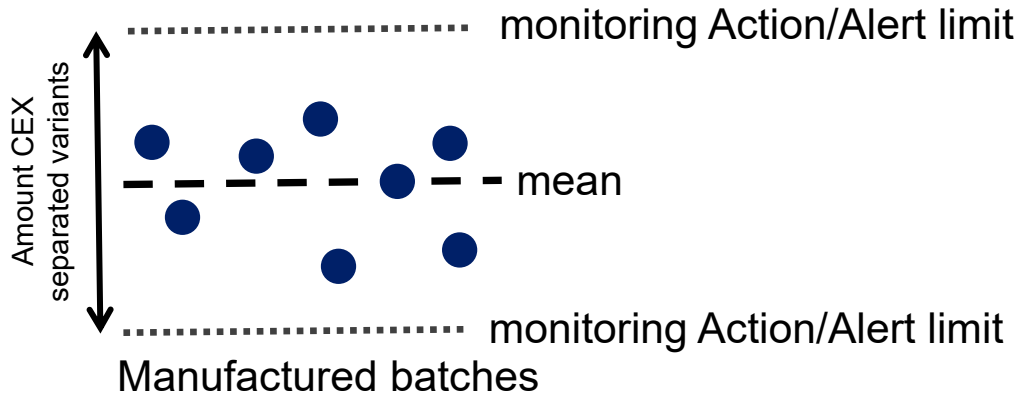
Routine process output monitoring using sensitive “performance indicator (PI)”

Well characterized PI: CEX



Executed at relevant place of the manufacturing chain for every batch (e.g. DS production)

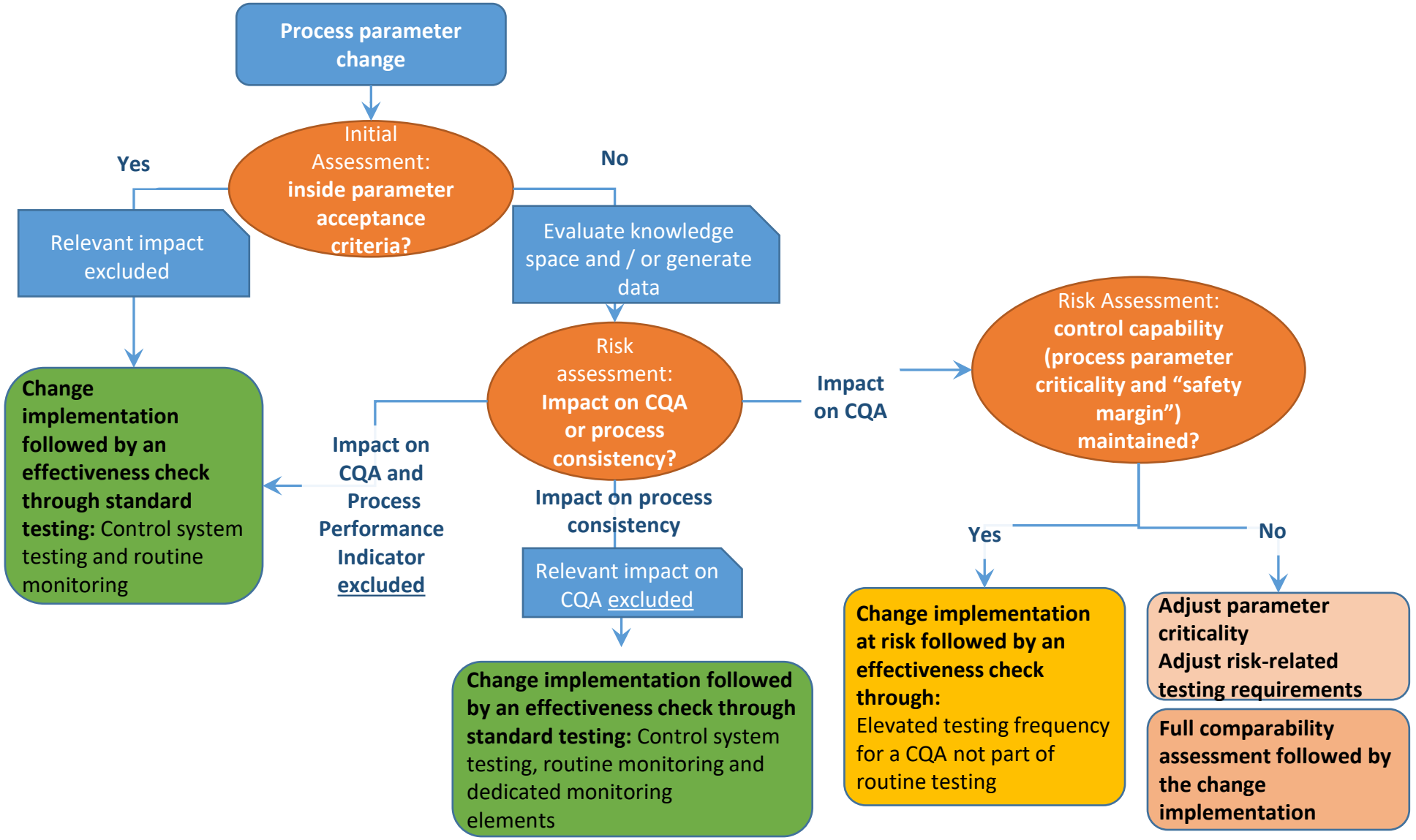
Monitored against historical manufacturing consistency



Actions

- Violation of Nelson Rules, monitoring action limit, peak pattern change triggers **an investigation**
- In confirmed cases (not analytical method related), the investigation includes an **assessment of potential impact on the “safety margin” for N102**
- Case dependent, **assessment is done risk based or data driven** using an in-depth characterization method such as peptide mapping LC-MS analysis for multi attribute monitoring (MAM)
- If assessment concludes that N102 **CQA-Acceptance Criterion is not violated, batch is released**
- **If impact on N102 “safety margin”** is observed, the investigation is extended and might include potential adaption of parameter settings, action limits and can trigger a change

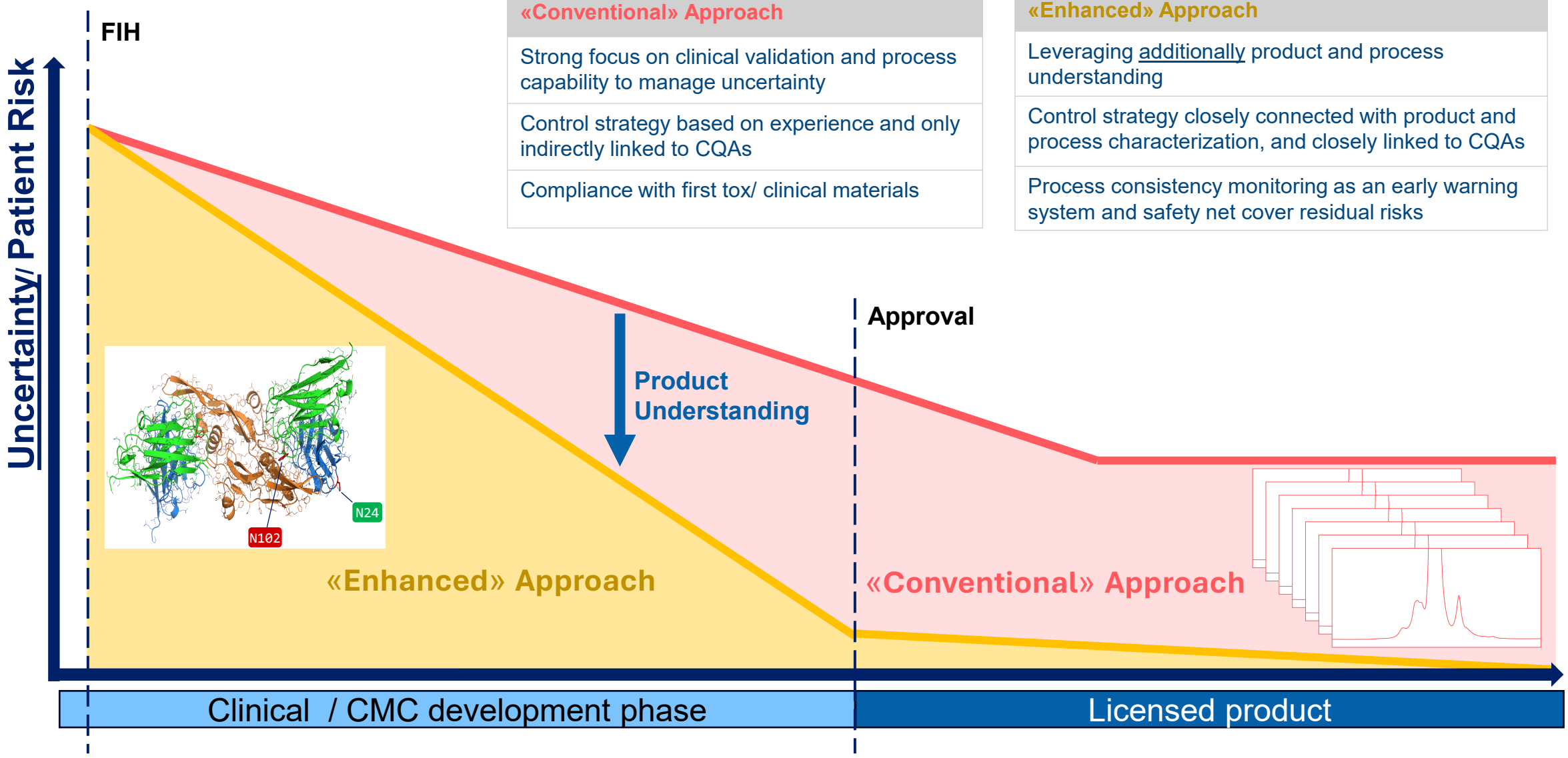
Maintenance of risk control upon change



The “enhanced” approach includes the “conventional” approach to Pharmaceutical Quality but reduces uncertainties

«Conventional» Approach
Strong focus on clinical validation and process capability to manage uncertainty
Control strategy based on experience and only indirectly linked to CQAs
Compliance with first tox/ clinical materials

«Enhanced» Approach
Leveraging additionally product and process understanding
Control strategy closely connected with product and process characterization, and closely linked to CQAs
Process consistency monitoring as an early warning system and safety net cover residual risks



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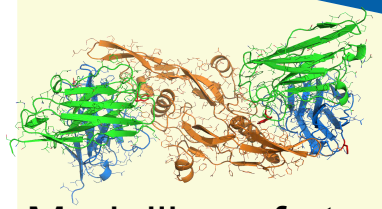
G. Gellermann, A. Mischo, R. Koeck, s. Kirsch, “Do Patient Needs Define Biologic Product Specifications,” Bioprocess Online 14. March 2025 https://www.bioprocessonline.com/doc/do-patient-needs-define-biologic-product-specifications-0001

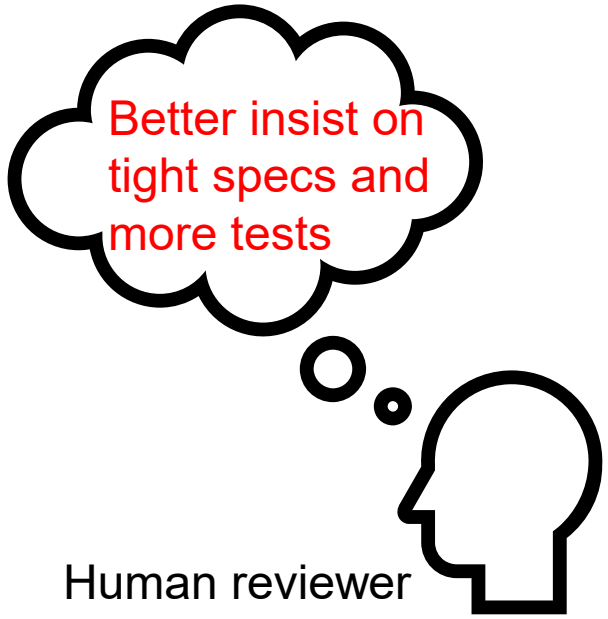
Finding the sweet spot of sharing information



Modelling of structure function relations
CQA and claiming “scientific”- based acceptance criteria outside clinical exposure
CQA control via enhanced product understanding

Specifications for conventional methods but little information what limit for specific CQAs such as e.g. a deamidation is appropriate and how it is controlled

Company claims product understanding of a **complex biomolecule** and uses modern approaches to **propose fewer binding controls**



Company **doesn't understand the product and process**
They overlook CQAs and maybe the Control Strategy is not complete

How can we increase regulatory acceptance of the “scientific-specifications” and “enhanced” control strategy approach

- Specifications based on scientific and product understanding **might go beyond actual clinical exposure** due to **comprehensive product characterization**. This helps improve control and lifecycle management.
- A broader limit **might justify less frequent routine** analytical batch release testing (as is generally accepted for CQAs like DNA). However, less frequent testing should not lead to less control over process variability.
- Hence, the enhanced control strategy **includes monitoring process consistency** using sensitive technologies like a charge-based separation assay. However, this is **handled with different consequences** (specification vs. action/warning limit).
- The PQS ensures **the low-risk state** (safety margin) is maintained.
- For **increasing the acceptance of the enhanced approach**, it may be useful to **disclose and commit the measures** for deviations from an action or warning limit of process consistency monitoring limits as well as the change management and effectiveness check for the risk control? What is the expectation from regulators?

Acknowledgements

- **Novartis / Biologics CMC Strategy Team:**
  F. Unterluggauer, S. Zierow, T. Stangler, L. Staud, N. Kaup, B. Mayr, B. Latal, A. Huber-Toth, N. Heigl, R. Mayer, B. Trenktrog, A. Mischo, J. Ritter, R. Tasler, H-J. Wallny, R. Koeck, M. Vetsch, B. Schmelzer, M. Horvat, S. Kirsch, T. Pohl. S. Gursenkov, ***et al.***

- **CMC Teams of case studies and pilots**: L. Flores Ortiz, R. Mende, N. Rederstorff, N. Kaup, N Ravi, J. Ritter, S. Tomer, H. Wu, Y. Wang, S Pahlich, U. Knof, T Meissner, M. Frank, K. Tuor, W. Mueller, W. Kern, D. Kuzman, D. Salinas, J. Cerar, G. Milicic, M. Boncina, P. Merkle, F. Griaud. A. Quintal, M. Zinko, S. Soret, S. Jevsevar, ***et al.***

- **ICHQ12 (Q14) implementation team:** S. Kyritsis, T. Kieckbusch, A. Reines, L. Staud, H-P Mennet, B. Latal ***et al.***

- **TRD Analytical Development**: M. Bluemel, J. den Engelsman, D. Chelius, T. Pohl, S. Kirsch, T. Faller, ***et al.***

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Thank you

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