Biologics Development

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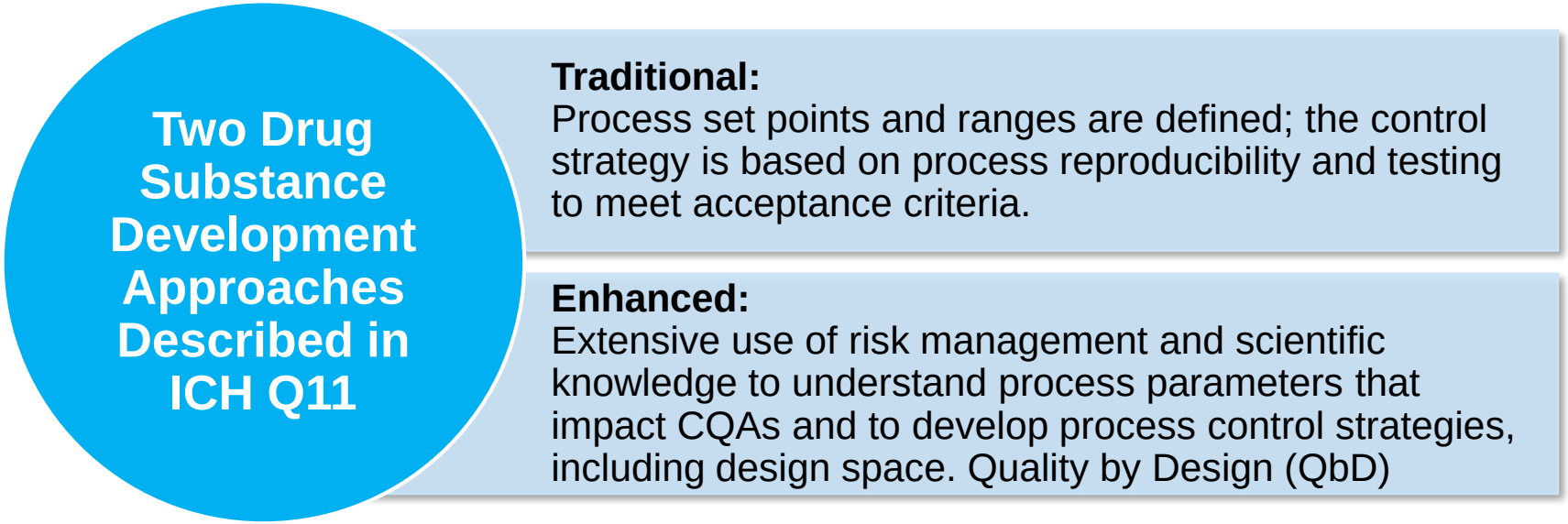
SANOFI

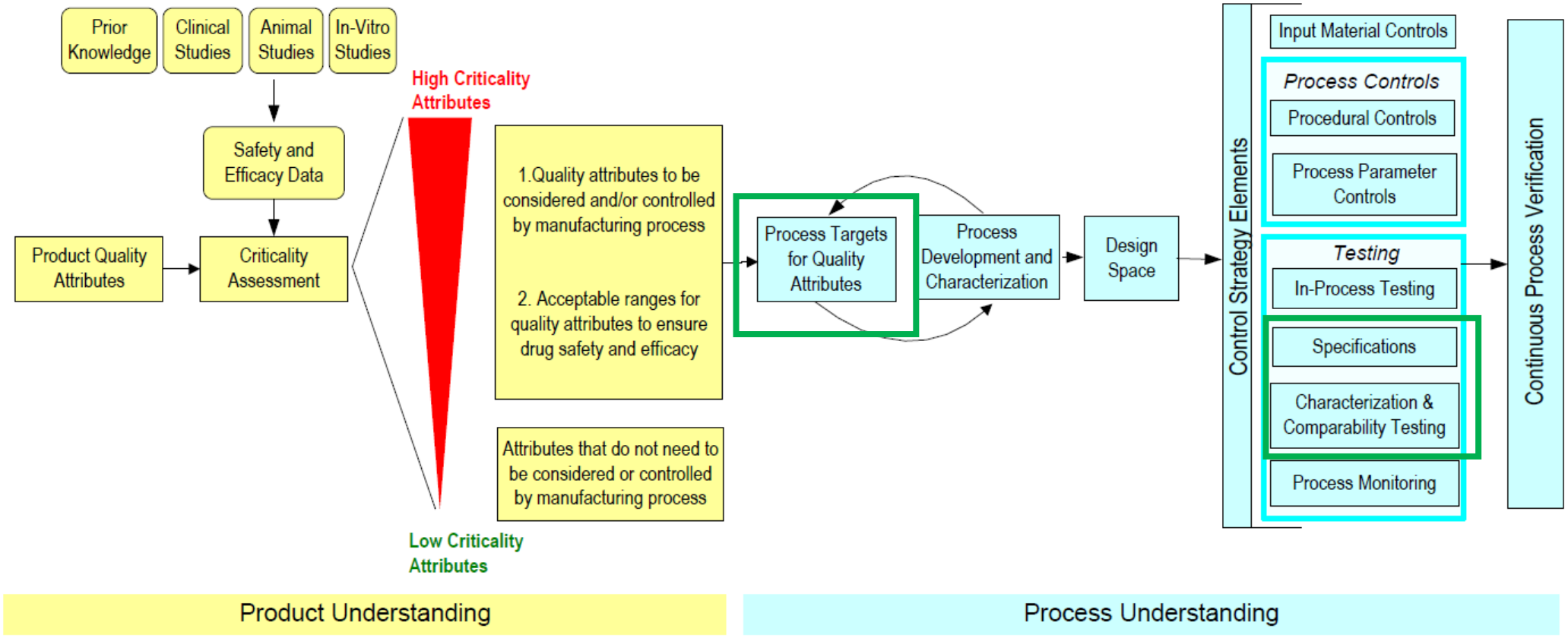
PRODUCT UNDERSTANDING: CONNECTING THE DOTS

Drug Development Approaches



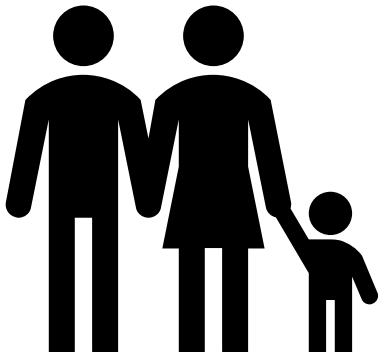
These approaches are not mutually exclusive and companies can use either the traditional or enhanced approaches or a combination.

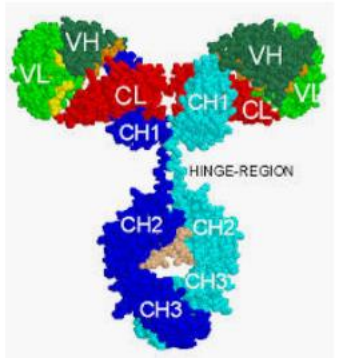
Product & Process Understanding: Keys to Product Quality



- Process developed with clinical importance in mind
- More clinically relevant specifications and comparability criteria

Critical Quality Attributes & The Patient





Uncertainty

?

x

Impact

Safety

Immunogenicity

Potency/Efficacy

PK/PD

Potential to cause adverse events?

Critical Quality Attributes

Safety e.g. Bioburden

Product Variants e.g. glycosylation

Purity e.g. Half antibody

Potency

Strength

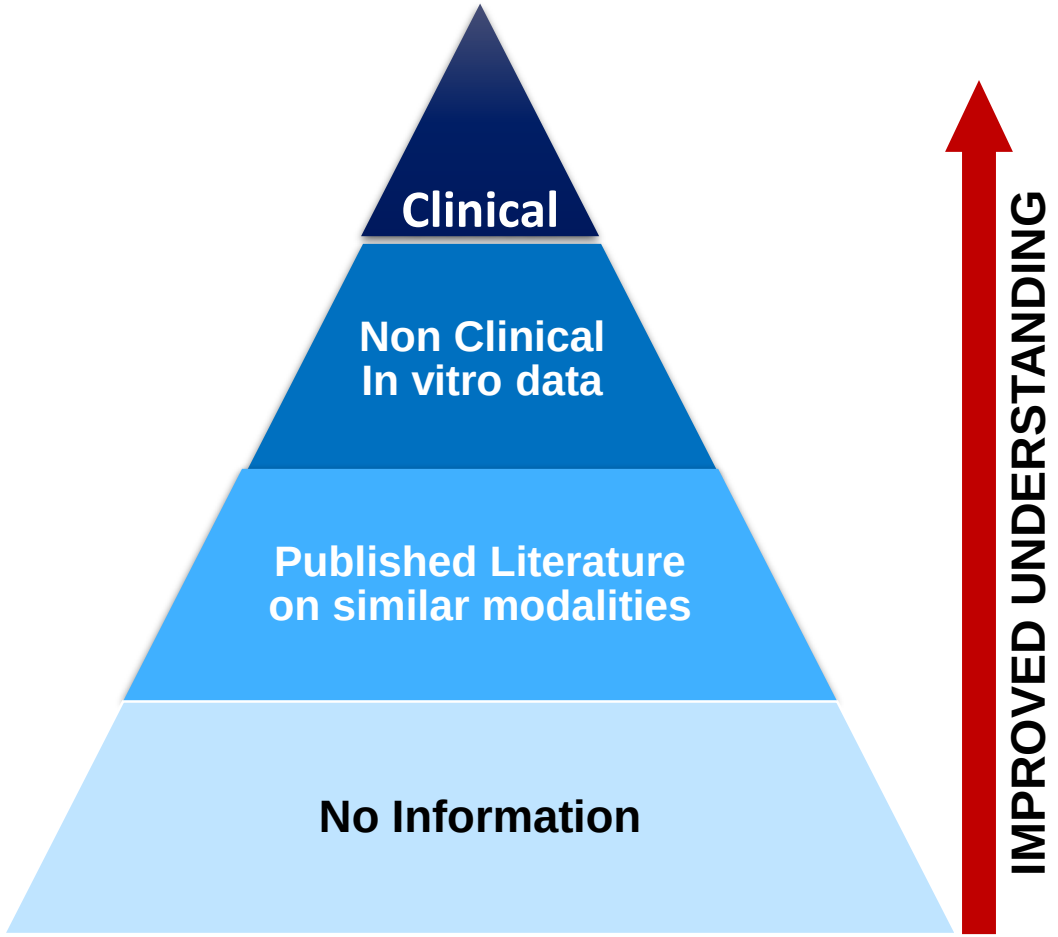
Process Residuals e.g. HCP

Identity

- Decrease uncertainty with improved attribute understanding

Reducing Uncertainty & Predicting Patient Outcomes

- Product attributes sciences and non clinical data are key to predicting patient outcomes
  - In vitro cell based data
  - Serum studies to understand impact in vivo
  - Non clinical data to understand impacts on PK/PD
  - Clinical prior knowledge with similar molecule
  - Clinical knowledge with molecule
- Therapeutic products are complex
  - Quality attributes (QA) are often interlinked
  - QA inverse relationships with each other
  - Studying one attribute at a time clinically can be challenging
- Dosing patients with higher than expected levels carries considerable patient risk



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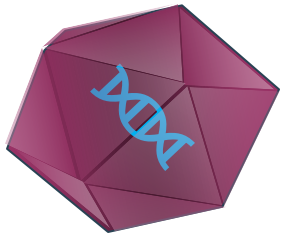
SAFETY

CASE STUDY 1: TUMOR DERVIVED OR TUMORGENIC PHENOTYPES IN GENE THERAPY PRODUCTS

Rigorous Confirmation of Patient Safety needed

CMC Information for Human Gene Therapy INDs

"If you are using cells that are tumor-derived or with tumorigenic phenotypes or other characteristics that give rise to special concerns, more stringent limitations of residual DNA quantities may be needed to assure product safety."



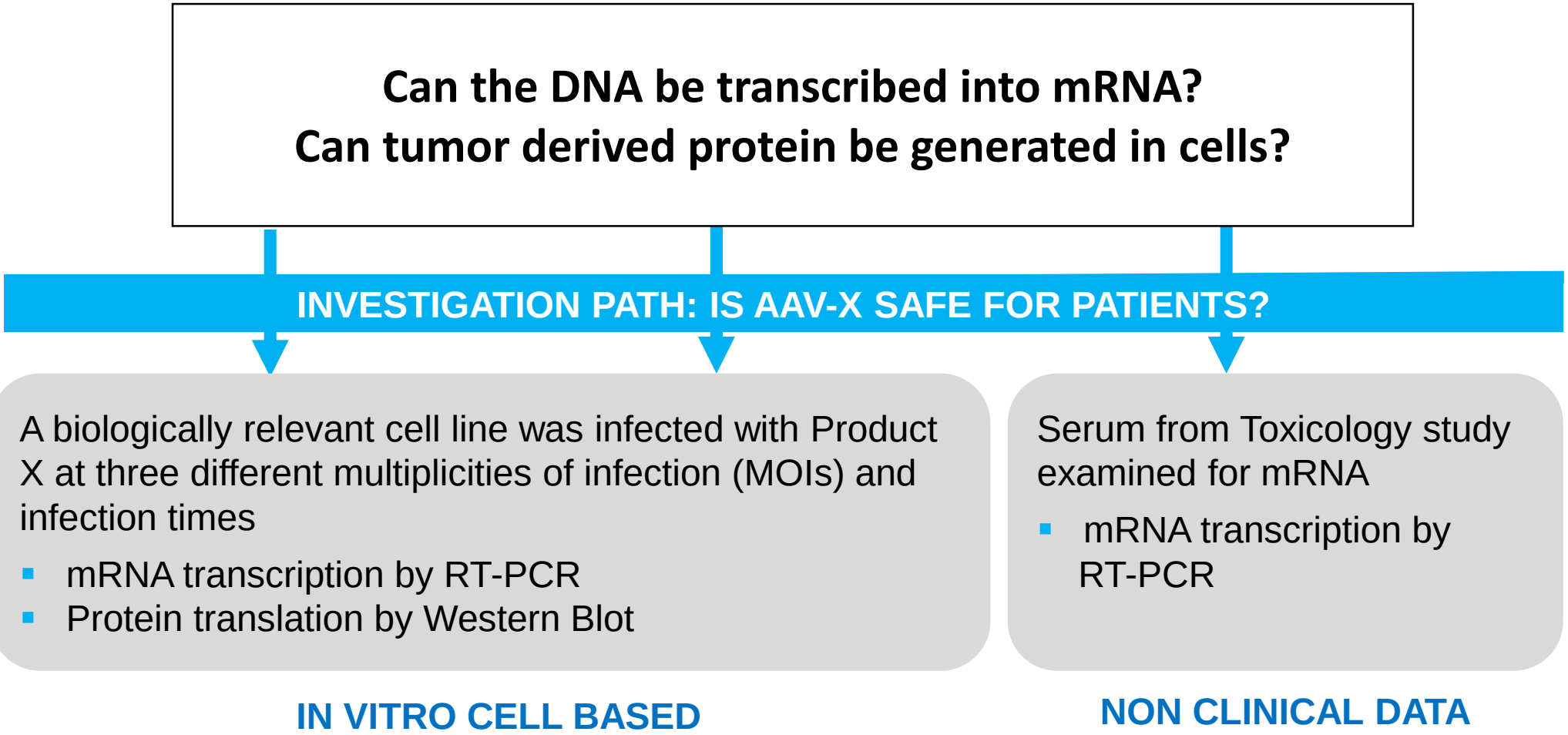
Product AAV Vector

Case Study

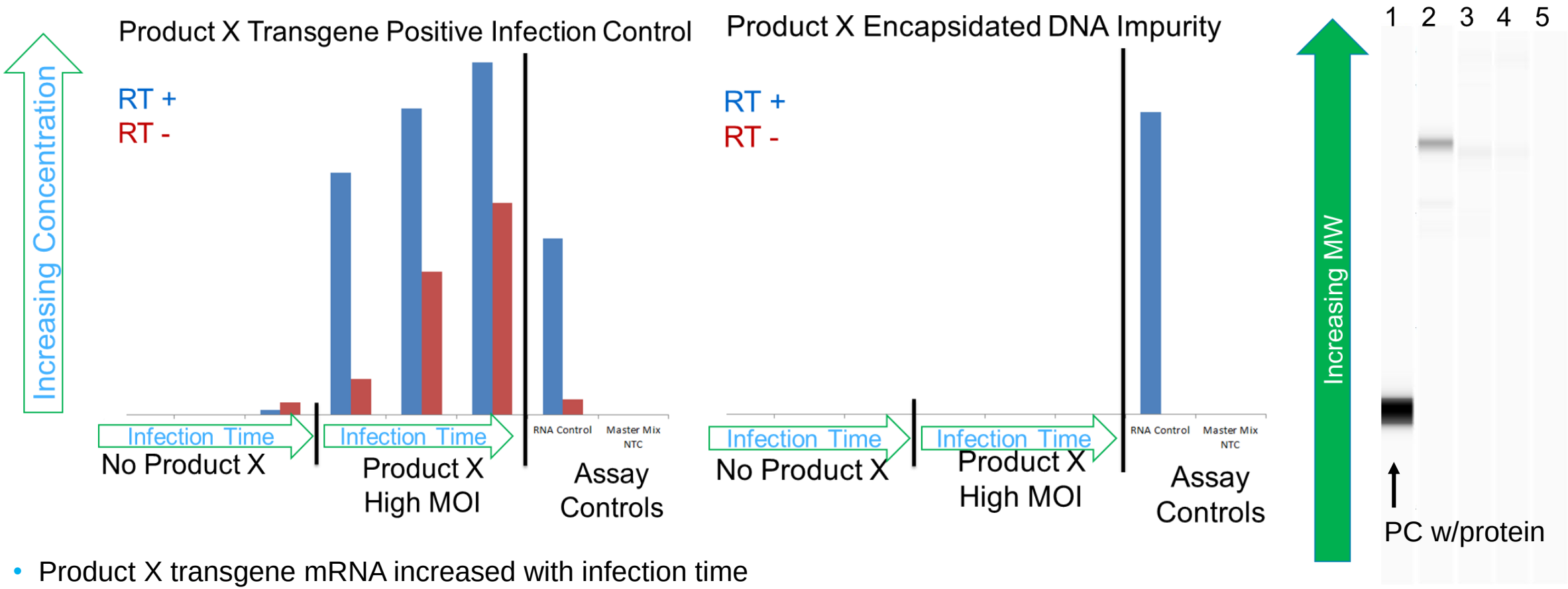
- DNA sequences from master cell bank were found to be encapsidated in DS
- Assays monitoring the presence of these sequences are included as part of characterization testing
- Results confirmed full length sequences were present

Due to high impact of safety concerns uncertainty needs to be removed

Can DNA be transcribed/translated into oncogenic protein?



Safety Confirmed In Vitro and In Vivo Animal Model



- Product X transgene mRNA increased with infection time
- No encapsidated DNA impurity mRNA was detected under any infection condition
- No encapsidated DNA impurity mRNA detected in Tox samples
- No impurity protein detected

✓ **PRODUCT SAFETY CONFIRMED**

DNA impurity promoter likely not encapsidated

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POTENCY& EFFICACY

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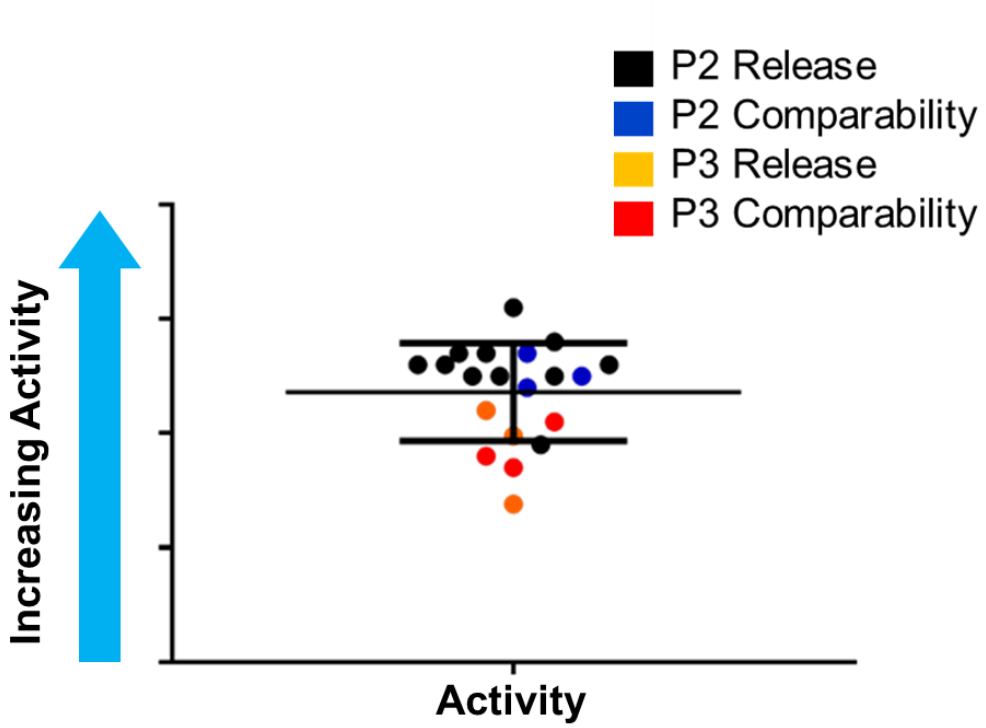
CONNECTING THE DOTS TO PROPOSE CLINICAL RELEVANT SPECIFICATION

Using Product Knowledge to Setting Clinical Relevant Specifications

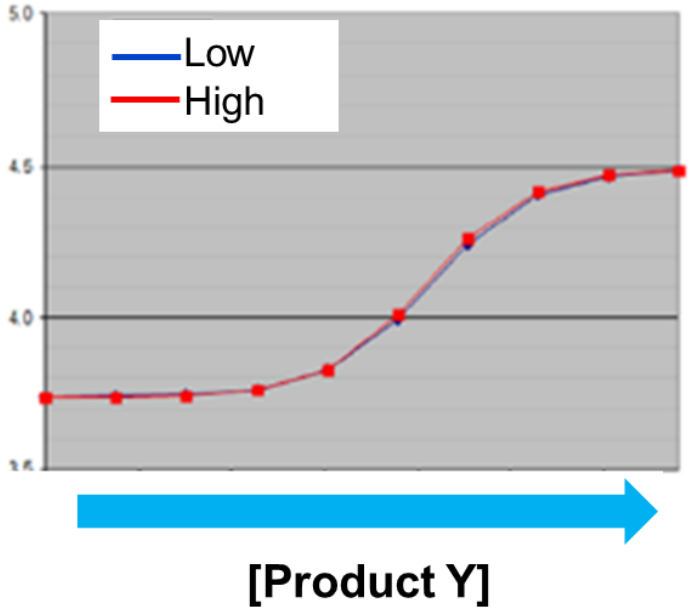
- Product Y P3 vs P2 comparability
  - Product Y activity was found to be slight lower in P3 vs P2
  - All other attributes found to comparable
- How should the P3 specifications be justified, if confirmed comparable?
- What information can be gathered?
  - Cell based potency vs activity
  - Non clinical data in efficacy model
  - Clinical experience



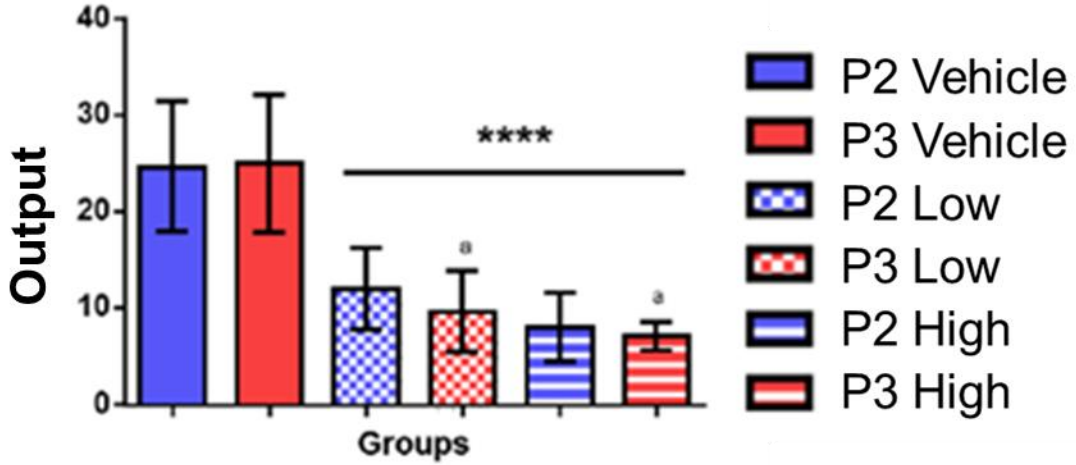
Product Y Activity & In Vitro and In Vivo Data

- Product Y samples generated with high and low activity levels
- Samples studied in in vitro potency assay and non clinical efficacy model

Cell Based Potency Assay

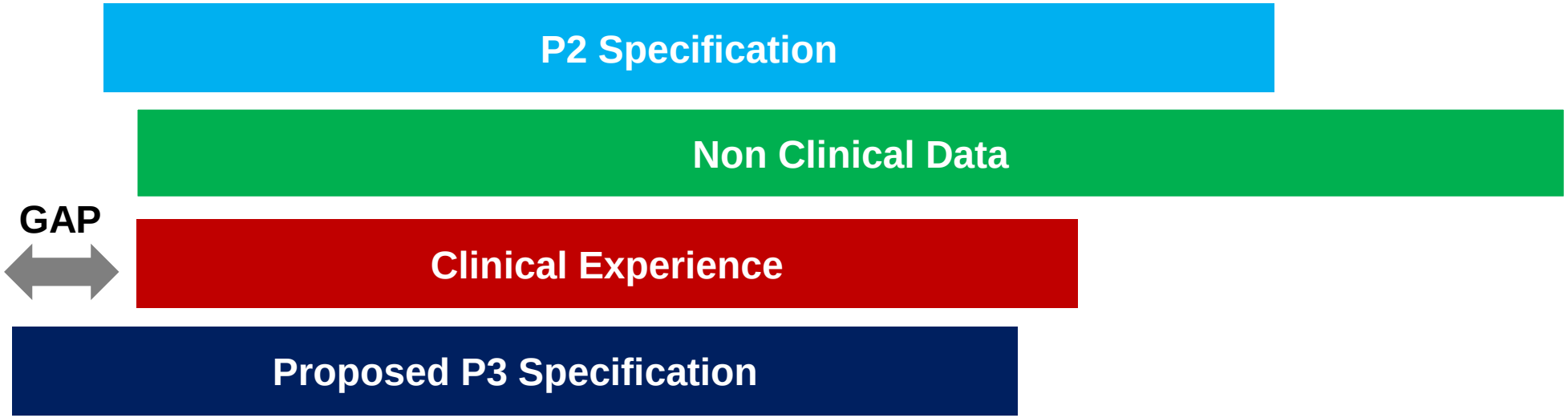


In vivo efficacy model



- *In vitro* potency & non clinical data illustrate differences are normalized in the *in vivo* animal model and cell based potency assay

Proposing a clinical relevant specification



- Difficult to dose samples at the edge of the clinical specifications and cover the whole range
- Generate additional non clinical data to cover the range
  - Can material be made at lower activity levels?
  - Can we understand the in vivo relevance of the in vitro activity data?
- Qualify the animal model and potency with clinical data

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IMMUNOGENCITY

CASE STUDY 2: EVALUATING IMMUNOGENCITY FOR NEW HCPS

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Case Study: New HCP Detected After Process Changes

Background

- Intensified cell culture process developed as P2 process
- Lower HCP levels by HCP ELISA in P2 vs P1 process
- MS-HCP profiling from P1 vs P2
  - Moderate changes in HCP1
  - HCP2 present above QL

Considerations

- Potential risk of HCPs to the patient
  - Immunogenicity
  - Toxicity
  - Adverse impact on the efficacy of the therapeutic
- Limited guidance on the quantities of HCPs that are acceptable
- Risk-based approach

One HCP Risk-Assessment Tool – Factors to Consider

Impact	Identity of HCP	Exposure to HCP	Clinical Indication	Therapeutic MOA	Phase of Devpt	Route of Admin	Duration of Treat	Dose Frequency
Very High	Not homologous with human	No experience	Autoimmune, Pediatric	Immune activating	Phase III	Interderm, IM, Inhale, Ocular	Chronic	Intermittent
High	Homologous with human		Immunology		Phase II			Daily/Weekly
Moderate		Non-clinical experience		Not immune-modulating		IV		
Low	Human homolog is inaccessible	Clinical experience	Oncology, Elderly	Immune suppressing	Phase I or Pre-clinical		Single dose	

- The identification of these risks forms the “basis for cross-functional discussion”and informs process development and decision-making.
- It is wise to comprehensively assess HCP profiles early to facilitate a strategy for mitigating changes in HCPs.

Zafra, et. al. 2015. Biotech and Bioeng 112(11):2284

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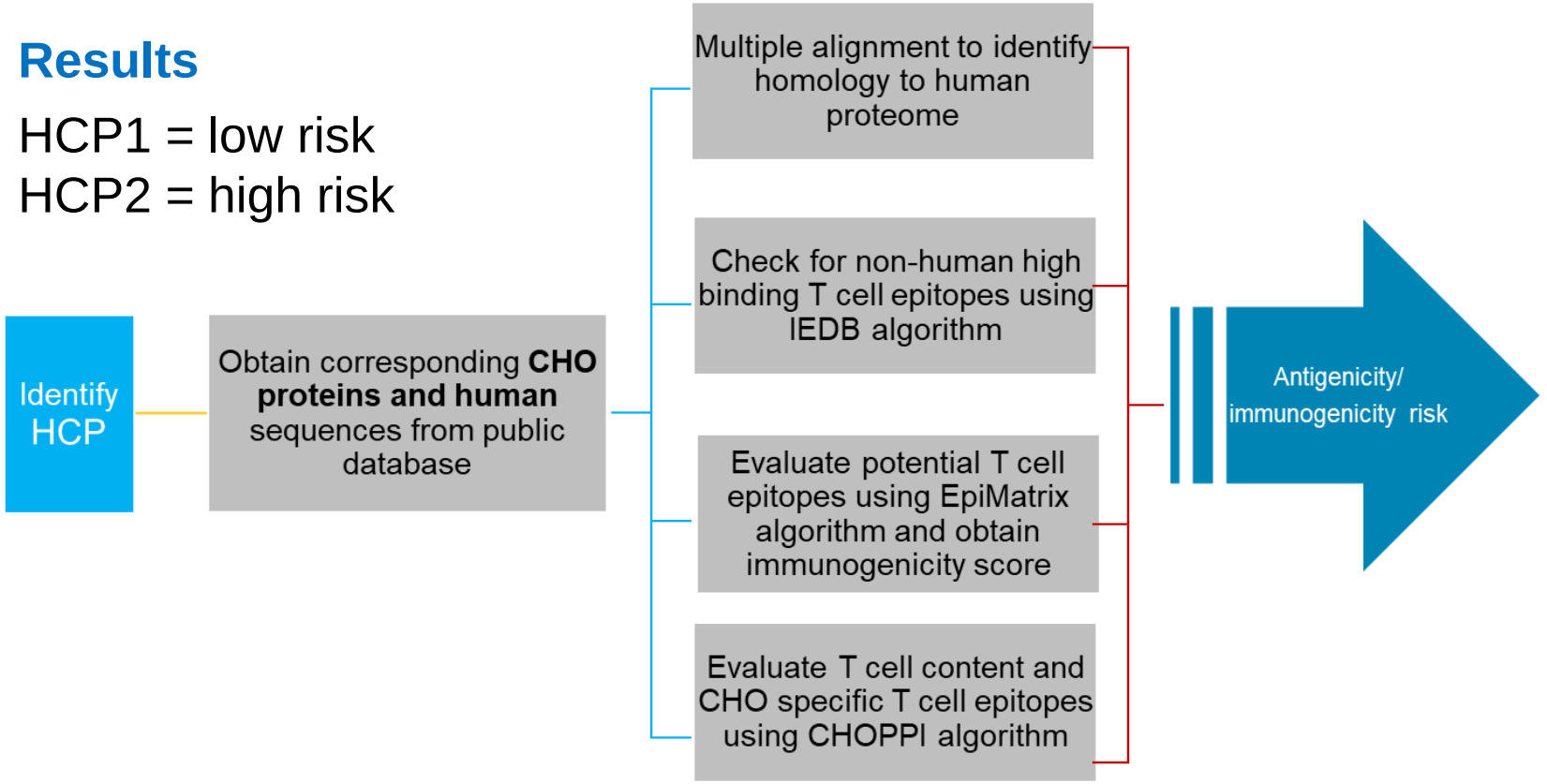
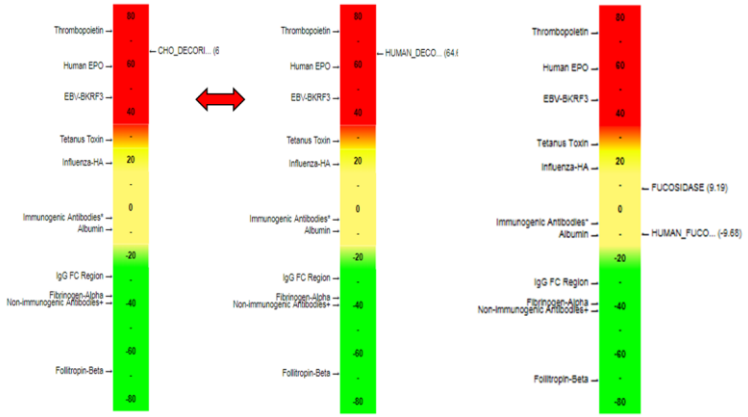
Human homology & In silico Antigenicity Profiling

Results

HCP1 = low risk
HCP2 = high risk





Rate Immunogencity Risk using EpiMatrix Immunogenicity scale

Linking it to patient outcomes

- Leverage using clinical adverse event information
- Use clinical experience from multiple products to understand safe limits for high risk HCPs?

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PRIOR KNOWLEDGE MANAGEMENT

PRODUCT UNDERSTANDING: CONNECTING THE DOTS

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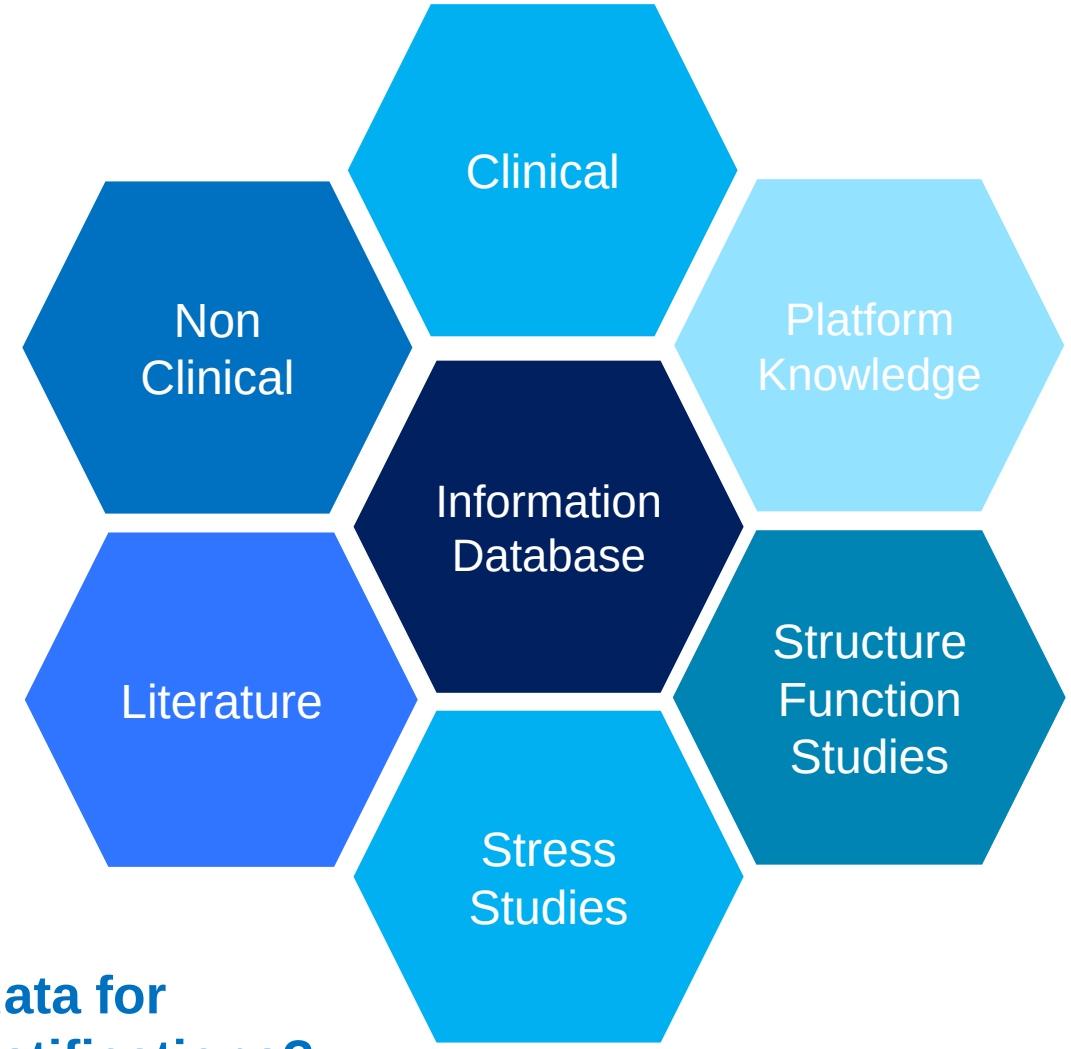
Prior Knowledge Management

Challenges

- Lots of information from multiple sources
- Collecting information across projects & function groups can be challenging & time consuming
- Project often re-invent the wheel

Mitigation

- Data lake generation
- Information database development with advanced data analytical apps
  - Quality attribute driven
  - Different from data sources



Any regulatory concerns for using data for specification and control strategy justifications?

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Conclusions

- Product attribute sciences are important for building understanding of CQAs
  - Easier to study single attributes at a time
  - Need to be bridge to clinical and non clinical studies to ensure relevance
- Prior knowledge is powerful,
  - Study relationships between attributes
  - Link clinical data across projects e.g HCPs to understand impact at a larger scale
  - Well organized, seachable & secure
- Understanding is imperative to providing well controlled products
  - Enhancing holistic control strategy & relevant specifications

Acknowledgments

- Analytical Development
- Characterization
- Upstream Development
- Downstream Development
- Clinical Development
- DMPK

Thankyou