Enhanced Approach to Analytical Method Development for Vaccines

Cristiana Campa
GSK, Siena, Italy

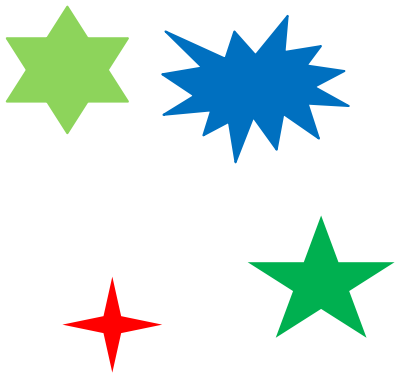
CASSS CMC FORUM
SUMMER 2021

Outline

1. **Vaccines- challenges and opportunities related to analytical testing**
2. Why QbD-driven analytical strategy is critical to address challenges
3. Learnings from COVID-19

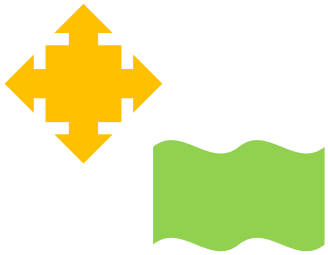
Vaccine Products

Antigen(s)



- Typically, complex and multiple antigens with different structural features and doses
- Needed for **specificity of the immune response**

Adjuvant



- Aluminum salts or Adjuvant Systems (combination of immunostimulatory molecules).
- Needed for most of the inactivated (whole or subunit) vaccines to **enhance and modulate immunogenicity of the vaccine antigen**

Administered Vaccine

- All components in an appropriate formulation/ carrier
- May require reconstitution/ mixing of different component solutions before administration
- Typically filled in vial or syringe, depending on formulation composition and patient needs

Vaccines analytical strategy

Example of complexity and number of tests

10 Buildings

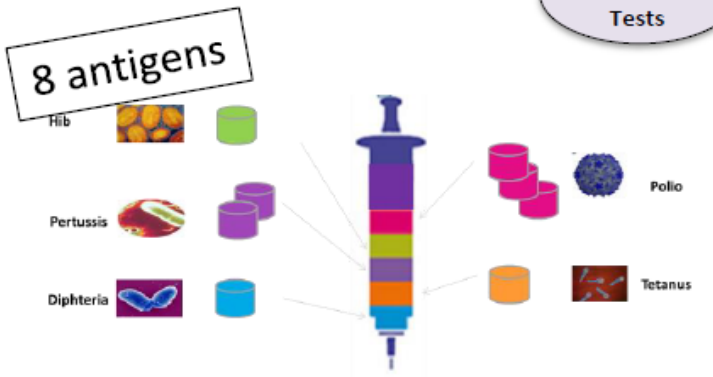
49 Mfg steps

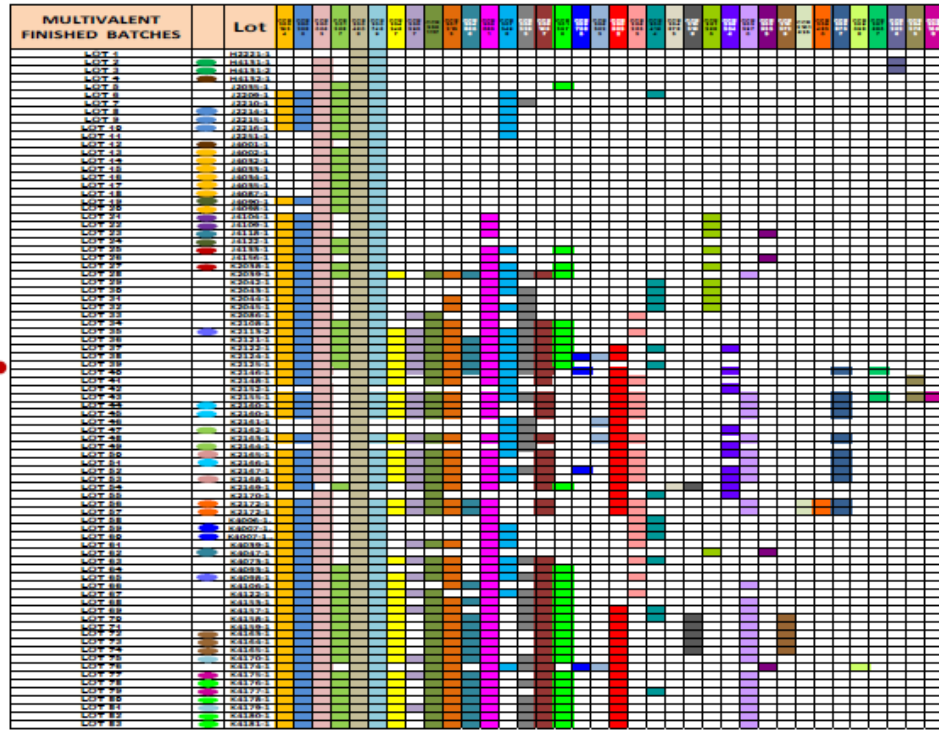
141 Raw Mat.

222 Test methods

1265 Tests

COMPLEXITY





In one year: **83 batches, 55 processes**

Changes include: new autoclave, new raw material supplier, new reference standard, new pharmacopoeial requirements

Registered in 100+ countries

From PDA Vaccine Europe Conference (2018), M. Colao (GSK) and A. Vinthers (Sanofi in 2018)

Vaccines analytical strategy

Points to consider

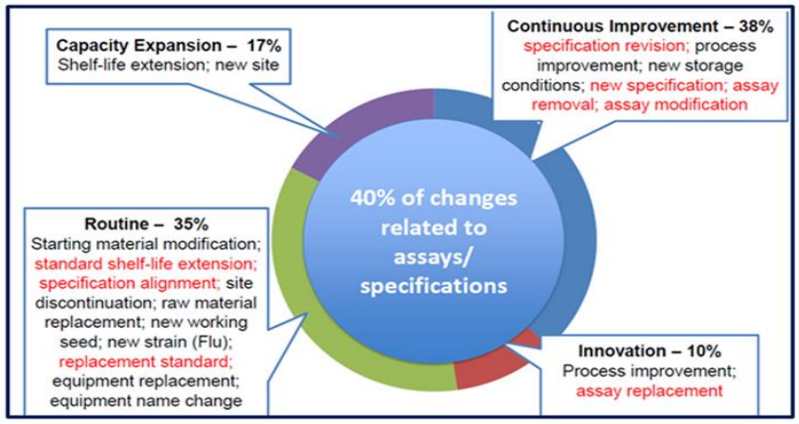
Complexity of products and processes, and consequent challenging characterization, and multiple tests especially for multi- valent vaccines

Wide **variety of possible vaccine categories**/ structural features, implying relatively limited possibility to leverage information from different product types

Heavy **post- approval life cycle management** of analytical strategy due to optimization/ replacement of methods

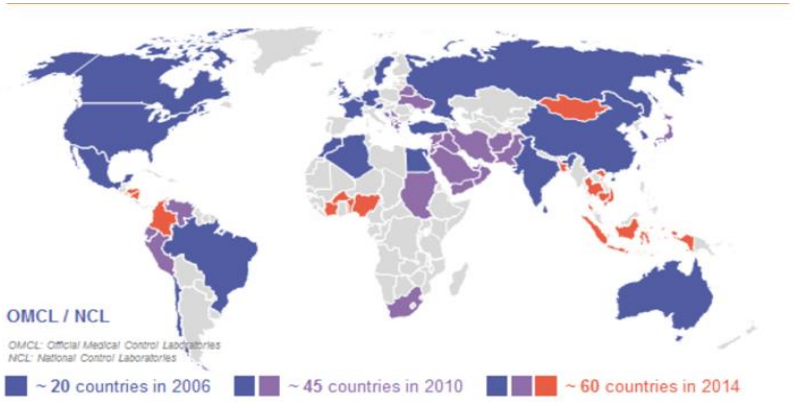
National Control Laboratory testing (depending on the vaccine market, several labs and methods for the same attributes)

Aggressive timelines for product, process and analytical development may be needed, especially in case of disease outbreaks



From PDA Vaccine Europe Conference (2018), A. Deavin (GSK) and T. Gastineau (Sanofi)

Data is taken from one year –2017 –covers all change controls that led to regulatory action in Europe (IA, IB, II) for GSK Vaccine products categorised into continuous improvement, innovation, routine and supply (together with sub- categories describing the type of change)



From PDA Vaccine Europe Conference (2018), M. Colao (GSK) and A. Vinthers (Sanofi in 2018)

Outline

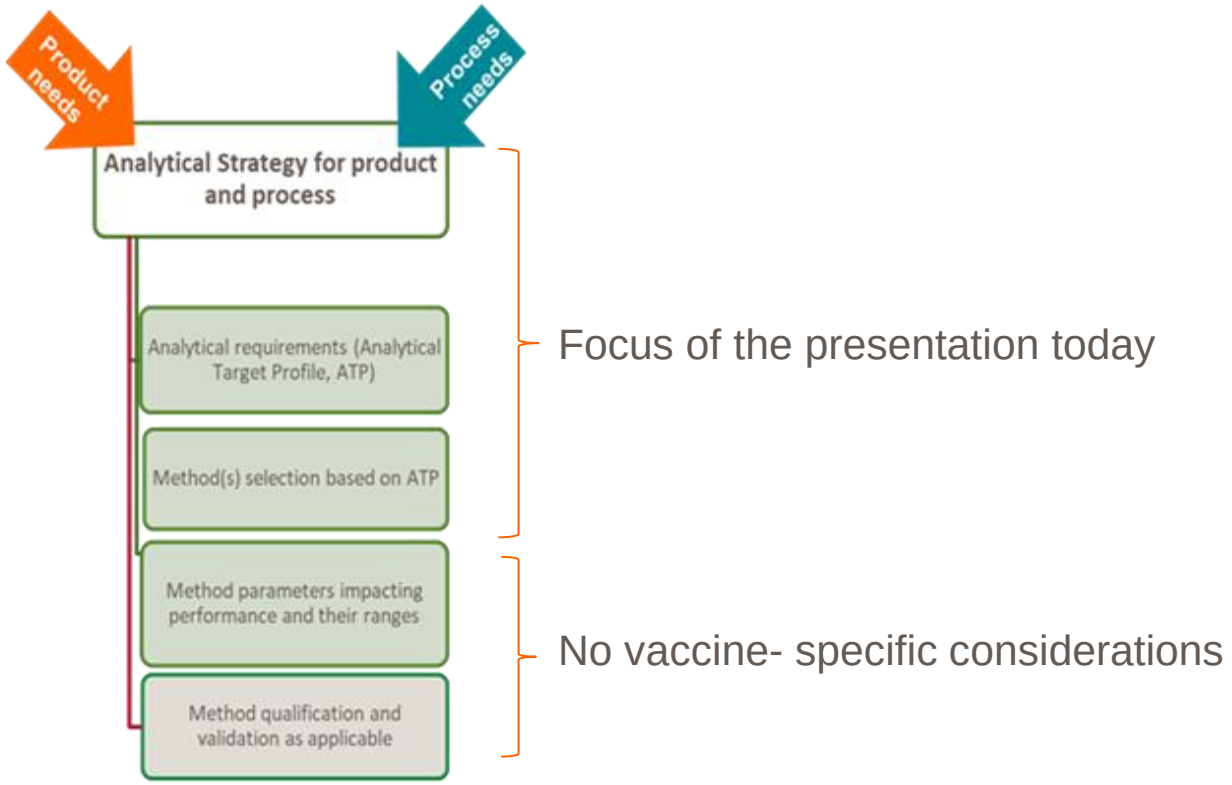
1. Vaccines- challenges and opportunities related to vaccine analytical testing

2. **Why QbD-driven analytical strategy is critical to address challenges**

3. Learnings from COVID-19

How to manage such challenges? Two options

1. **Never change a method…. EVER!...**
2. **More realistically, define a structured approach to analytical methods lifecycle management – Performance- driven Approach**



Adapted from the book *Quality by Design— An Indispensable Approach to Accelerate Biopharmaceutical Product Development*, PDA, March 2021, edited by M. Amin Khan and Cristiana Campa

ATP establishment during development allows fit- for purpose technologies/ methods at filing and minimizes the risk of re-work during lifecycle

Case study: glycoconjugate vaccine- saccharide content

Expectations	Colorimetric sialic acid		HPAEC-PAD with CarboPac PA1		HPAEC-PAD with CarboPac PA20Fast	
ATP requirements ↓	Observed value	ATP requirement check	Observed value	ATP requirement check	Observed value	ATP requirement check
Selectivity / Specificity (Able to discriminate analyte from matrix signals)	Analyte not separated from other components; ultrafiltration needed for complex matrix phases	Met only upon sample UF	Analyte peak separated from the other matrix components	Fully met, no UF	Analyte peak separated from the other matrix components	Fully met, no UF
Accuracy (bias) (80-120%)	82-100% (pre-validation data)	Met	97-108% (pre-validation data)	Met	95-99% (validation data)	Met
Precision (CV ≤ 8%)	2-10% Possible variability between different lots and analyses performed at different time (pre-validation data)	Not fully met	CV 3-10% (pre-validation data)	Not fully met	CV 3% (validation data)	Met
Business/ supply requirements ↓	Observed value	Business requirement check	Observed value	Business requirements check	Observed value	Business requirements check
Cycle Time (< 1 day)	2 hours (no ultrafiltration) 5 hours (ultrafiltration required)	Met	10-12 hours	Met	4-5 hours	Met
Throughput (NLT 8 samples)	Up to 20	Met	Up to 15	Met	Up to 30	Met
Sample volume required for the analysis	1 ml	-	20 µl	-	5 µl	-

Product development stages →

F. Merangolo, S. Giannini, M. Gavini, S. Ricci, C. Campa, *LCGC Applications of Ion Chromatography* (2015)

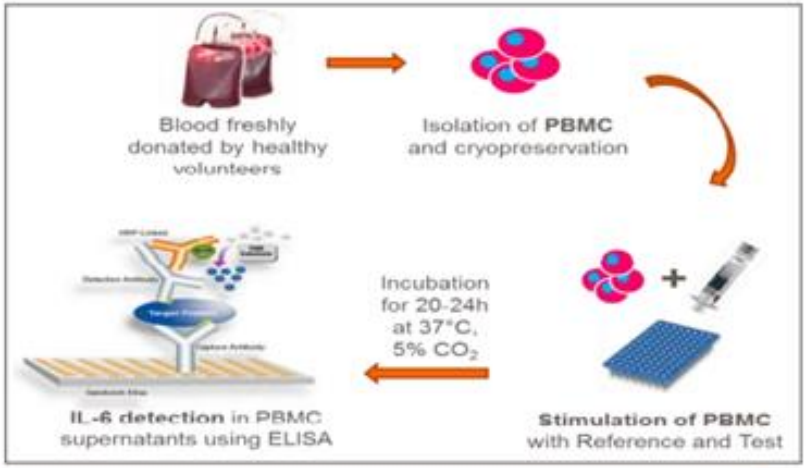
ATP can also support some needed method changes during lifecycle

Case study: from Rabbit Pyrogenicity Test to Monocyte Activation Test

ATP definition for evaluating the pyrogen content of Bexsero			
Project	Attribute	Version	PDVS Stage
Bexsero	Pyrogen content	01	Life-cycle management
Sample	Intended Purposes of Measurement	Scope Category	Output (ICH group)
Final container	Quantitatively measurement of intrinsically pyrogenic components (both endotoxin and non-endotoxin) in the drug product	Measure a quality attribute (safety) Not applied on stability	Quantitative test for safety attribute

Monocyte Activation Test (MAT)

- Based on the human reaction to pyrogens
- Quantitative *in vitro* test
- Specific for both endotoxin and non-endotoxin pyrogens
- Low variability with high sensitivity and accuracy
- No animal use (in line with 3Rs)



Implementation of MAT as pyrogen test for Bexsero in replacement of both RPT and LAL allowed a better evaluation of vaccine pyrogen content (CQA) together with a reduction of animal use and lead-time for lots testing and release

Clear benefits from some method changes during lifecycle, with several post- approval changes needed

Case study: from Rabbit Pyrogenicity Test to Monocyte Activation Test

- US – March 2021
- Brazil- February 2019
- Israel- April 2018
- Canada- December 2017
- Australia and Argentina- June 2017
- Europe- April 2017

Approval of MAT applied to Bexsero by International regulations

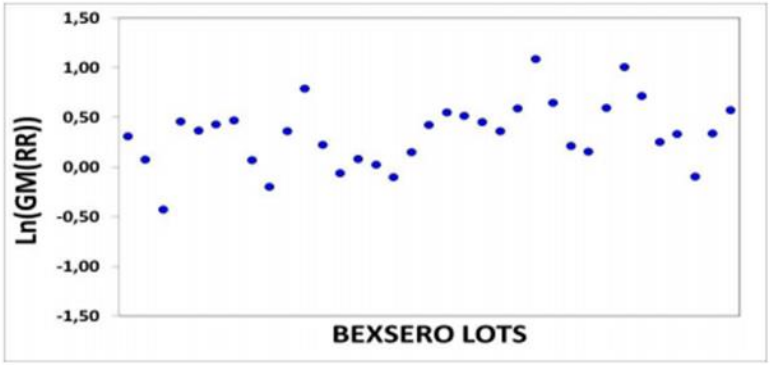
194 rabbits saved

in 1 year due to MAT implementation

Reduction of lead-time

for lots testing and release

MAT results for a representative set of Bexsero batches



More detail on MAT for Bexsero: Sara Valentini et al., Monocyte Activation Test to reliably measure pyrogenic content of a vaccine: an in vitro test to overcome in vivo limitations, Vaccine Volume 37, Issue 29, 27 June 2019, Pages 3754-3760

Outline

1. Vaccines- challenges and opportunities related to vaccine analytical testing

2. Why QbD-driven analytical strategy is critical to address challenges

3. **Learnings from COVID-19**

Significant increase of post- approval changes is expected due to COVID-19 crisis

- Manufacturing processes for COVID-19 vaccines are moving swiftly
  - Execution of process development with considerably reduced timelines
  - **Evolving knowledge on product, analytics and process**
  - Potential deferral of activities (e.g., optimization/ validation) until after launch to minimize timeline

- To make billions of doses, post-launch supply will likely require:
  - **Use of multiple manufacturing sites**
  - **Need for many post-approval changes**

- Such increase of PACs may have an impact on all vaccines post- approval lifecycle management (due to the increased workload and worldwide harmonization issues)- includes the analytical space, also critical to support product comparability…

For manufacturing changes:

- Need to **show post-change product is comparable to the pre-change product**
- Ensure that the pre- and post-change products perform equivalently

** From COVAX Comparability (Sept 2020) and Tech Transfer (Jan 2021) workshops*

COVAX Regulatory Advisory Group (RAG) reflection on analytical strategy for Comparability*

- RAG members stressed that there is a need for **very strong analytical packages and that the analytical package must be focused on the proposed changes in the manufacturing process**. Moreover, it will be important to include stability data and characterization tests in the analytical package.

- In addition to the routine release tests used in a comparability exercise, developers should consider **additional characterization tests** to support comparability over the life-cycle of the vaccine.

- **If analytical methods are changed during the development of the product, then comparability of the old and new method must be well characterized, or the assessments could prove difficult.** […]

- **As far as possible, the analytical methods should not be modified significantly all along the clinical development phases in order to have a solid baseline for the comparability exercises.** […]"

** Extract from WHO Technical Brief- Regulation of COVID-19 vaccines, Synopsis from the August 2020 – February 2021 COVAX RAG meetings*

More info on COVAX:
COVAX Overview • Epidemic Preparedness Innovations (tghn.org)

How to deal with evolving analytical strategy?

- Considering the small number of lots, and the often limited time for process understanding/ robustness experiments, analytical testing is critical to support safety and efficacy monitoring of COVID-19 Vaccines

- Ideally, method changes should be avoided, however:
  - for some **(product- specific) attributes testing**, **key innovation** may be needed
  - **manufacturer's different testing sites** may have different analytical capabilities
  - **National Control Laboratories (NCLs)** may have different analytical capabilities (vs industry and across NCL labs)

What is the impact?

How to deal with evolving analytical strategy in heavily accelerated scenarios?

Technology-agnostic method expectations (ATP)!

	Identify CQAs…	Define robust reference standard strategy to…	Focus on tests purpose/ performance to…
Comparability	…impacted by the specific change … tested with orthogonal methods if needed	… ensure clinically proven lots selection comparability (linked to patient) … support analytical bridging e.g., in case of updated attribute testing	….right-first-time method selection … support bridging e.g., in case of updated testing panel
Spec/ NCL testing	…relevant to release & stability (safety/ efficacy monitoring, phase appropriate) … building prior knowledge for vaccine platform …for NCL testing, considering company panel/ results	… support analytical bridging e.g., in case of updated specification testing panel	… right-first-time method selection … support bridging e.g., in case of updated testing panel, minimizing impact on specs ranges … support interactions NCLs/ industry and global recognition for NCLs

Reference Standard & Control Samples Strategy is key to support reliable analytical strategy and method performance control

Uses

- Used as **comparator to verify structural changes associated to process changes** (ICH Q5E)
- **Standard** in analytical procedures (eg for calibration in quantitative tests, reference for identity etc)
- **Control samples** in analytical procedures; **real- time method performance assessment**, with data to supporting continued method performance verification and bridging in case of procedure change.

Lots selection

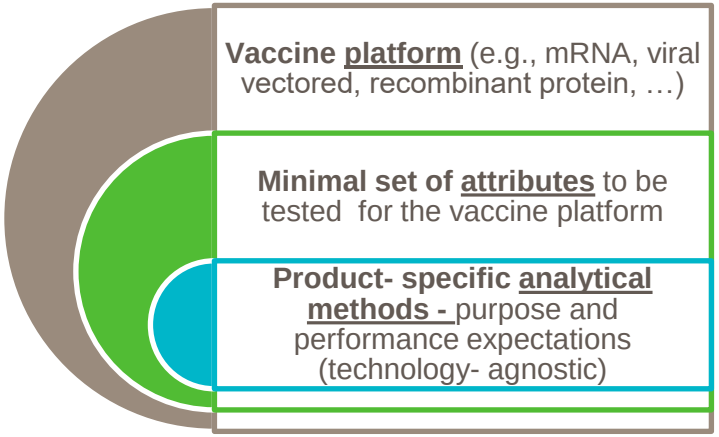
- During development, reference standard **lots suited/ used for clinical trials** are important to support comparability across different clinical stages – representing the link with the patient.
- In late development, **lots used/ suited for pivotal Phase 3 clinical trials** (establishing safety and efficacy) serve as ideal reference standards for comparability studies **vs PPQ/ commercial lots**
- Lot size needs to be large enough to sustain release and NCL transfers; working standard strategy should also be established asap

Suitability requisites

- **Batches representative** of the respective life cycle stage of the product
- **Extensive characterization**
- **Stability** and **storage conditions** defined
- **Qualified** to support use and bridging in case of procedure changes

** From COVAX Best practices for tech transfer workshop,*
https://media.tghn.org/medialibrary/2021/02/012720_Tech_transfer_workshop.pdf

Shift the focus to expected method performance (as opposite to specific tests/ technologies) → support method bridging and NCL mutual recognition establishment



- Publicly disclosed and ideally agreed by Health Authorities globally
- Supporting rapid establishment of analytical strategies for manufacturers and NCLs

(e.g., *Analytical strategy options proposed by EDQM on recombinant viral vectored vaccines for human use*, https://www.edqm.eu/sites/default/files/medias/fichiers/COVID-19/recombinant_viral_vectored_vaccines.pdf or *WHO Evaluation of the quality, safety and efficacy of RNA-based 5 prophylactic vaccines for infectious diseases: regulatory 6 considerations (DRAFT)* https://www.who.int/docs/default-source/biologicals/ecbs/reg-considerations-on-rna-vaccines_1st-draft_pc_tz_22122020.pdf?sfvrsn=c13e1e20_3)

- Based on information and rationales discussed with individual manufacturers (not necessarily publicly disclosed).
- Supporting
    - comparability/ specs testing in case of method changes
    - analytical transfer across different facilities with different technologies
    - alignment/ info transfer/ reliance across NCLs

** From COVAX Best practices for tech transfer workshop, https://media.tghn.org/medialibrary/2021/02/012720_Tech_transfer_workshop.pdf*

Conclusion

- **Performance- driven approach** to analytical method development for vaccines is much needed to **support right- first time selection of analytical technologies & procedures**, minimizing the changes during lifecycle management

- Nevertheless, due to the need for continuous improvement on legacy products and introduction of innovation, **a structured approach to analytical methods changes is critical to ensure a sustainable supply of vaccines worldwide**

- The knowledge built through application of AQbD principles helps to manage the risks represented by changes in assays (e.g., through (i) tests comparisons supported by pre-defined performance expectations and (ii) understanding of key variables to be controlled within a procedure).

- **ICH Q14** represents a unique opportunity to set a **global framework for defining the analytical enhanced approach**, and to show concretely **how to support method development and lifecycle management** in an agile way, safeguarding quality, safety and efficacy.

Acknowledgement

- Jean- François Dierick
- Koen De heyder
- Phil Borman
- Raffaella Cecchi
- Sabine Leclercq
- Shahjahan Shaid

& the Authors of the mentioned publications

Questions?

This work was sponsored by GlaxoSmithKline Biologicals SA

Cristiana Campa is a permanent employee of the GSK group of companies – cristiana.x.campa@gsk.com