Using platform approaches with vaccines to support rapid development and launch

Cristiana Campa
Vaccines Technical R&D
GSK

CASSS CMC Strategy Forum 2023,
Session I- The Art of Specification Setting

Outline

How to set specifications supporting rapid development and global supply of a vaccine?

- Patient- centric strategies for sound justification of specifications, cross- company discussions
- Use of prior knowledge for specifications setting of vaccines
- Examples
- Concluding remarks

Patient- centric strategies for sound justification of specifications, cross- company discussions

How to define Specifications addressing patient needs, access and global harmonization?

- Deep and early product characterization & QTPP definition, leading to patient- driven identification of Critical Quality Attributes/ acceptance criteria (including stability)
- Reliance on prior and platform knowledge as appropriate
- Collaboration and early engagement between CMC and preclinical/ clinical areas (within Companies and Regulatory Agencies)

- Process understanding, analytical robustness & holistic Control Strategy to ensure manufacturing consistency in routine setting
- Promoting acceptance of PQS/ QMS to manage consistency through trending analysis/ internal limits (CPV), independently from specifications

- Communication/ alignment important to support cultural shift to «patient centric» specifications from specifications as tool to «control process»
- Cultural shift (both at Companies and within Regulatory Agencies) needed to ensure consistent approaches/ Regulatory feedbacks across different products and life cycle stages.

- Shared vision as a basis for harmonized implementation at launch and during lyfecyle
- Continued dialogue through trade associations & meetings involving both Regulators and Industry, including Publications
- Support of ICH Q6 revision and update/ issuing of other relevant and interconnected guidances
- For individual products/ companies, driving of more dialogue among the involved Agencies

EFPIA/ Vaccines Europe position, aligned with key takeways from conferences involving companies and Regulators

https://www.vaccineseurope.eu/news/position-papers/efpia-vaccines-europe-position-paper-on-ich-q6-a-b-revision

Patient- centric specifications

- A patient-centric (or clinically relevant) specification is a set of **CQAs** and **acceptance ranges** to which product quality attributes should conform for the product to be **safe and effective when used as labeled.** Justifications for acceptance ranges focus on risk/knowledge-based assessment of the impact to patient and improve access to medicines through reliable, robust supply chains.

- **Potential impact on safety and efficacy** should be assessed in the context of the overall control strategy, and **justified by thorough understanding of molecular attributes, clinical relevance, reliance on nonclinical (in vitro/in vivo) models, and use of prior knowledge** (e.g., on safety of some impurities, to be used across different products).

- **Consistency is assured through direct process controls** (input material controls, process parameter controls, in-process controls, etc.) **and ongoing process verification** within an appropriate quality management system to meet **cGMP requirements**

- In case of patient-centric approach for specifications definition, **tightening of specification acceptance criteria solely based on process capability/historical data (e.g., as post- approval commitment) does not fit with setting quality expectations based on product safety and efficacy**. Thus, such restrictions would become unnecessary under the patient- centric paradigm

Impact of Traditional vs Patient-Centric Specifications

Application of “minimal” or “enhanced” approach elements for specifications (attribute, method and acceptance criteria) depends on the level of relevant knowledge available on a given product/ quality attribute and associated control strategy.

Traditional (minimal) approach

Inappropriately established specification due to **limited understanding of attribute impact on safety and/ or efficacy**

Specification tied explicitly to manufacturing performance consistency at the initial site; **risk of rejecting safe and effective batches due to unnecessarily tight specifications**

Different markets favor different statistical approaches leading to **global divergence of specifications, hampering lifecycle management**

Supply concerns can arise for lifecycle changes to manufacturing process

Patient-Centric (Enhanced Approach)

Specifications are based on desired **quality and clinical performance as supported by scientific and risk-based knowledge of CQAs**

Specifications **not to be re-assessed with more batches** (never tied to manufacturing performance)

Reduced reliance on statistics/batch data can lead to **improved harmonization**

Knowledge- driven acceptance criteria facilitate **continual improvement during lifecycle, leading to more robust supply chains and patient experience**

Scientifically sound justification and well- structured lifecycle plan to **support accelerated access**

Key points of attention for successful patient- centric specifications setting

- Principles related to patient- centric specifications can be valid for all pharmaceutical modalities and enable accelerated development to support unmet medical needs.

- Implementation approach depends on several factors, including

  - The ability to ensure appropriate structural characterization
  - The confidence in nonclinical models, to support structure- function relationship and acceptance criteria for CQAs
  - The level of integration of CMC and preclinical/ clinical design and expertise, as appropriate
  - **The level of prior knowledge**
  - The control strategy (process and analytical performance understanding), to ensure manufacturing consistency, and depending on the lifecycle stage (development vs routine manufacturing)
  - The maturity of the QMS/ PQS to support consistency demonstration, and clarity of regulatory framework

Use of prior knowledge for specifications setting of vaccines

Platform quality attributes & patient- centric strategies drive harmonization of specifications

Example: Endotoxins testing

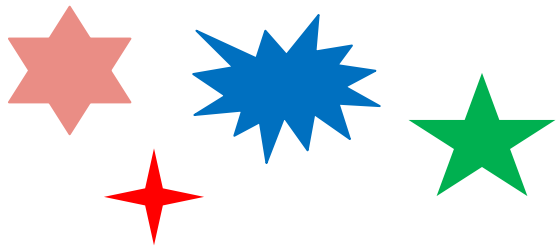
- Acceptance criteria based on safety expectations (eg pharmacopoeia limits)→ opportunity for patient- centric platform specification

- **Platform & clinically justified acceptance criteria set the basis for specifications harmonization**

To which extent is this concept broadly applicable to other vaccine attributes?

Vaccines

Antigen(s)



- Needed for **specificity of the immune response**
- Depending on the vaccine platform, may be **directly administered** (e.g., subunit vaccines, inactivated or live attenuated vaccines) **or generated in the body after administration** (e.g., mRNA and viral vector vaccines)
- **Complex and multiple antigens** (with different structural features and doses) **may be combined** (e.g., some glycoconjugate/ protein subunit vaccines)

Adjuvants & delivery vehicles

Depending on the vaccine platform, **adjuvants or delivery vehicles** may be needed.

- **Aluminum salts or Adjuvant Systems** (combination of immunostimulatory molecules) may be a component. Needed **for most of the inactivated (whole or subunit) vaccines to enhance and modulate immunogenicity of the vaccine antigen**
- **Delivery vehicles (e.g., lipid nanoparticles, LNPs)** to increase stability and ensure adsorption and fusion with the cell membrane

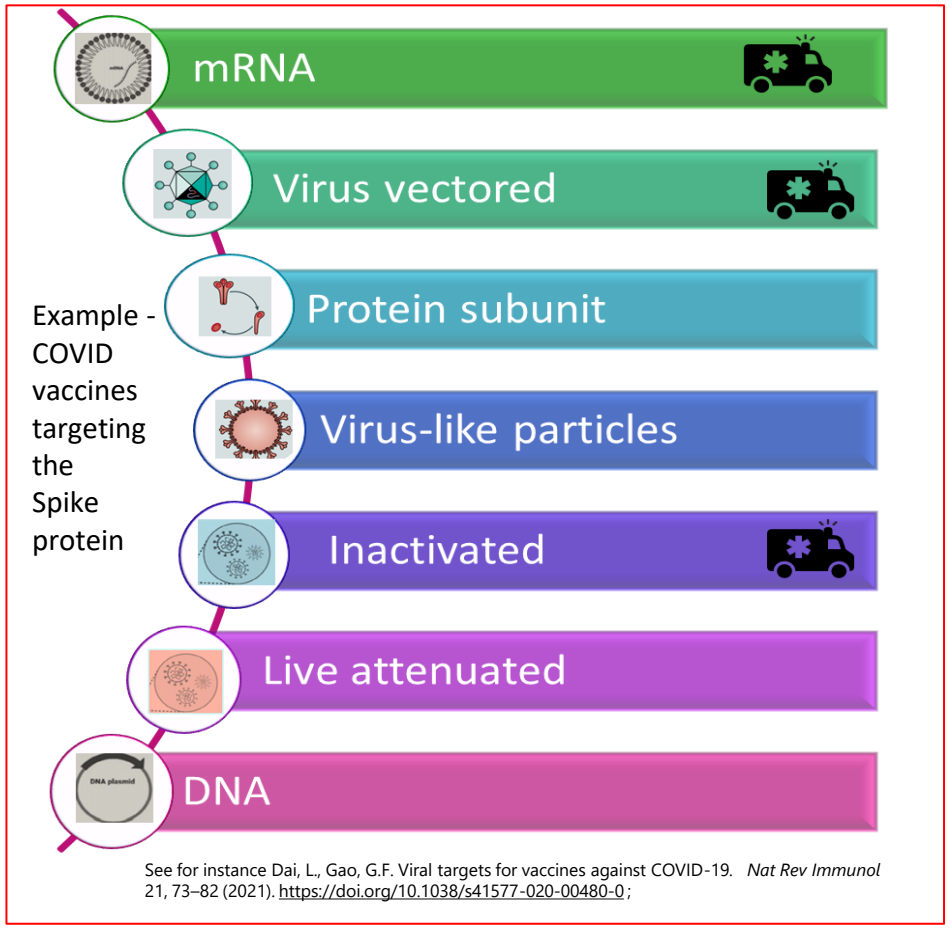
Administered Vaccine

- All components in an **appropriate formulation**
- **May require reconstitution/ mixing of different component** before administration
- **Typically filled in vial or syringe, but other administration routes are/ will be possible** depending on the product characteristics and medical need (e.g., oral solutions, microneedles, inhalation)

Yingzhu Li, Rumiana Tenchov, Jeffrey Smoot, Cynthia Liu, Steven Watkins, and Qiongqiong Zhou, *ACS Central Science* **2021** 7 (4), 512-533
DOI: 10.1021/acscentsci.1c00120

Carmine D'Amico, · Flavia Fontana,· Ruoyu Cheng,· Hélder A. Santos, *Drug Delivery and Translational Research* (2021) 11:353–372
https://doi.org/10.1007/s13346-021-00924-7

For a given medical need, multiple «vaccine platforms» are possible



See for instance Dai, L., Gao, G.F. Viral targets for vaccines against COVID-19. *Nat Rev Immunol* 21, 73–82 (2021). https://doi.org/10.1038/s41577-020-00480-0 ;

- In general, one or more vaccine platforms may fit with the medical need, depending on factors like
  - the nature of the disease (e.g., viral vs bacterial)
  - the supply rapidity
  - the supply spread (global/ local) and areas.

- For specifications setting, **the extent of CMC prior knowledge that can be used depends on the vaccine platform and on the tested attribute**

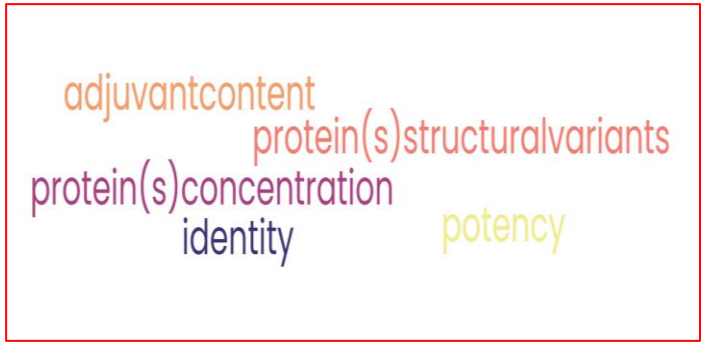
Full platform specifications are not broadly applicable across vaccines

Due to the broad set of structural features, **each vaccine platform may have some very different critical quality attributes and acceptable ranges**, supporting the justification of appropriate purity, potency, identity etc.

Examples

Some speciifications attributes for mRNA vaccines*

Some speciifications attributes for protein subunit vaccines*



*EPAR COVID vaccines

Elements of prior knowledge may be applicable within a vaccine platform

DP	Quality Attribute List	Critical Quality Attributes	CQA ranges	Analytical strategy
mRNA	**Yes**	**Yes**	**Yes** for typical safety attributes **No** for some product – specific attributes/ formulation (e.g. depending on dose, storage/ stability, target)	Generally **yes**, with product- specific considerations as per CQA ranges
subunit	**Yes** (for a given subunit category, e.g., protein, glycoconjugate, etc)	**Yes** for typical safety attributes and generic formulation attributes **No** for some product-specific attributes (especially for structural variants, product-specific epitopes)	**Yes** for typical safety attributes **No** for some product-specific attributes/ formulation (e.g. depending on dose, storage/ stability, target, nature of antigen)	**Yes** for typical safety and generic formulation attributes **No** for some product-specific attributes

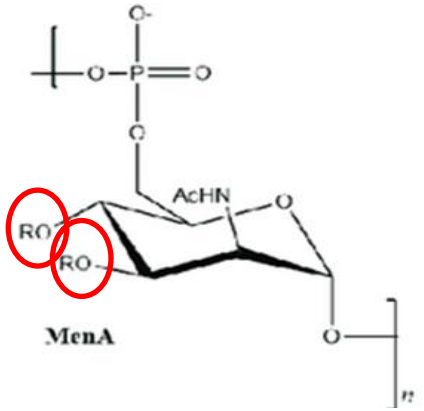
GSK

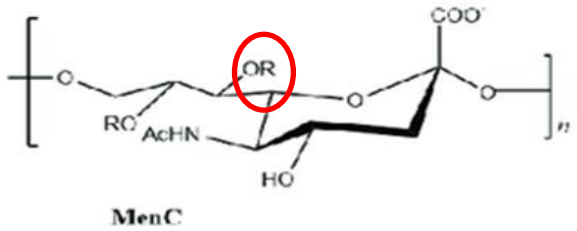
Examples

use of prior knowledge to support CQAs identification and testing for vaccines

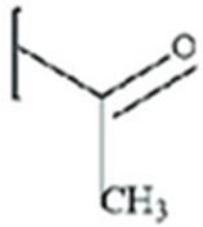
Prior knowledge may support justification of specifications attributes choice→ exclusion of non-CQAs from routine testing

O- Acetyl content for meningococcal glycoconjugate vaccines (MenA/ MenC)





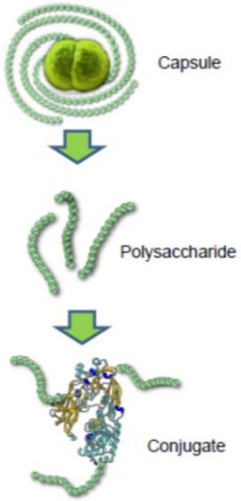
R and Ac = acetylation



Well- established knowledge for meningococcal vaccines

For MenA, O-Acetyl is a CQA

For MenC, O- Acetyl is not a CQA



Patient- centric approach & platform knowledge use applied to a new presentation of a meningococcal vaccine:

- **For MenC glycoconjugates, O-Acetyl is not routinely tested**
- For MenA glycoconjugates, O- Acetyl is routinely tested when degradation is known to occur

Exclusion of O-acetyl from MenC specification has been generally agreed with several Authorities, on the basis of well- established prior knowledge and real- world evidence

In the absence of prior knowledge, removal from specifications of attributes deemed as non- critical is more difficult

- For a newly developed subunit vaccine, a structural variant was demonstrated to be non- critical, based on *in-vivo* immunogenicity data showing comparable results for structural variant and target antigen.

- The company consequently proposed to remove the attribute from the specifications.

-**Different feedbacks received from different Authorities, finally decision was to add in the specifications panel for all the relevant countries, to simplify submission strategy**

- The company will propose removal of the test after demonstration of consistent levels of the product- related substance at commercial level.

Open questions

- Was this a problem with nonclinical models/ criticality confirmation study?
- What kind of information should be shared with Authorities to demonstrate reliability of nonclinical models for criticality confirmation for vaccines quality attributes?

GSK

Examples

use of prior knowledge to support CQA acceptance criteria

Use of platform knowledge for product- specific vaccine CQAs acceptance criteria

- For any vaccine platform, specific considerations may be needed for release and stability ranges associated to attributes like content, potency, and structural integrity.
- This may require dedicated end of shelf life studies/ inclusion of some intentionally modified material in clinical studies, especially if reliance on nonclinical models, prior knowledge elements or control strategy is not possible.
- Dose finding studies may also be a relevant support for justification of some specifications ranges

GSK

MenACWY liquid formulation- specifications for MenCWY

Commercial product with MenA lyo component

FROM

MenA lyo + MenCWY liq

TO

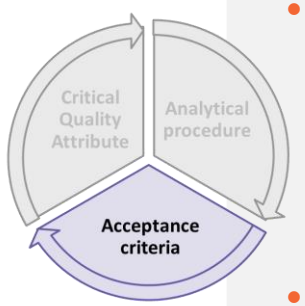
MenACWY liquid – one vial

New product (1 vial) with MenA In full liquid formulation (no changes for MenCWY)

MenCWY Product understanding was high at the beginning of the development

Product knowledge indicates no impact to safety or efficacy within proposed range

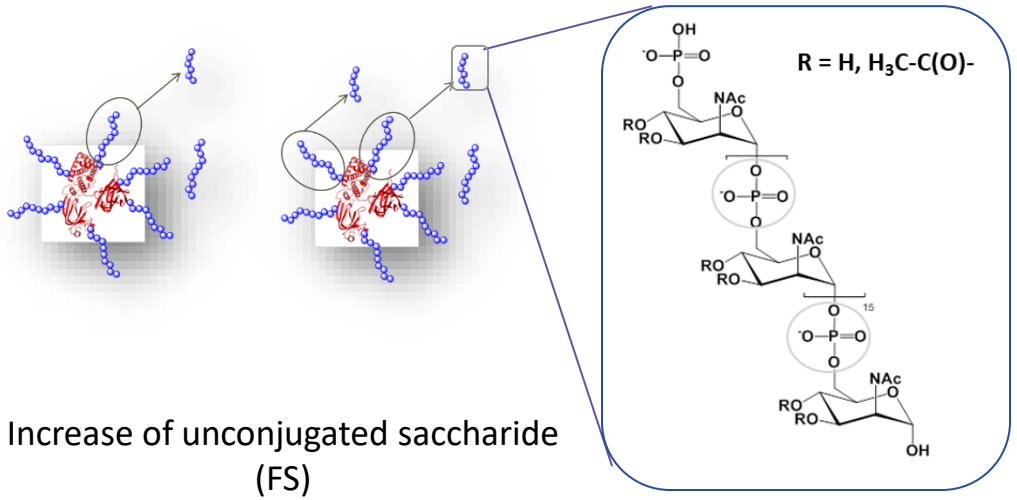
- Previous knowledge applied to identify CQA/QA and acceptance criteria
  - Extensive clinical and manufacturing experience
  - MenCWY stability very well known – no hydrolytic reactions in solution
  - Toxicology/safety data available
- Analytical methods for testing Drug Product in liquid presentation available
- MenCWY comparability full liquid vs lyo/liquid demonstrated



- Acceptance criteria *for the well controlled attributes* set using historical data collected on lyo/liquid product
- No dedicated clinical study needed

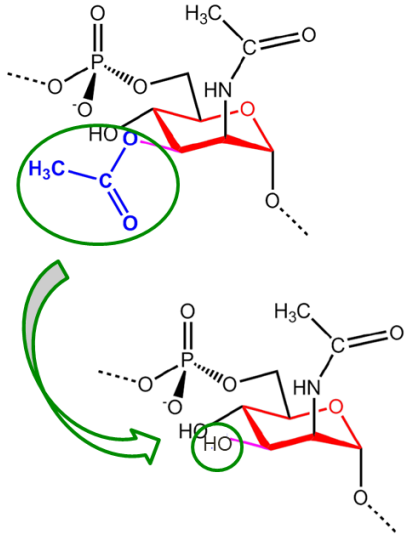
Content from M. Aggravi/ E. Fragapane, IABS GHS conference, Jan 2023

MenACWY liquid formulation- specifications for MenA



Increase of unconjugated saccharide (FS)

Loss of O-Acetyl group in solution. Reaction is temperature dependent



Modification in the epitope

Previous knowledge :

Free (unconjugated) saccharide (FS) and O-acetylation (OAc) contents are CQA for immunogenicity of conjugate vaccines

The relationship between the change of FS and O-Ac *over time* and efficacy for CRM-MenA glycoconjugate is unknown

→

Changes in the attributes are related to *the intrinsic nature of the product*

No prior knowledge on impact available

→

Clinical qualification of acceptable ranges of these two attributes was performed

Vaccine, *40*(24), 3366–3371. https://doi.org/10.1016/j.vaccine.2022.04.053; *Vaccine*, *38*(23), 3930–3933. https://doi.org/10.1016/j.vaccine.2020.04.005; ACS Omega 2019, 4, 7, 12827–12832

Content from M. Aggravi/ E. Fragapane, IABS GHS conference, Jan 2023

Use of platform knowledge for product- specific vaccine CQAs acceptance criteria

- For any vaccine platform, specific considerations may be needed for release and stability ranges associated to attributes like content, potency, and structural integrity.
- This may require dedicated end of shelf life studies/ inclusion of some intentionally modified material in clinical studies, especially if reliance on nonclinical models, prior knowledge elements or control strategy is not possible.
- Dose finding studies may also be a relevant support for justification of some specifications ranges

GSK

Importance of dose finding and use of prior knowledge to streamline dose study design

- A way to de-risk knowledge evolution on specifications setting (e.g., during accelerated development) is the use of appropriate dose selection, when applicable.
  - For example, for a sub-unit protein- based vaccine, the actual antigen amount in the product may be lower than the targeted amount due to unforeseen structural variant(s) impacting efficacy (or due to changes in analytical tests).
  - **The product can still be considered effective if the actual amount is higher than the minimum active dose** [see for instance, *EMA-FDA stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies (2018)*]

- Recently, **modeling strategies have been proposed to guide the optimal dosing of COVID- 19 vaccines, thanks to the prior knowledge on dose- finding and clinical response of existing vaccines** [Could computer models be the key to better COVID vaccines? (nature.com) https://www.nature.com/articles/d41586-022-00924-8].

Open Question

Would it be appropriate to use clinical readouts to feed preclinical models/ studies and confirm retrospective or future reliability assessment?

GSK

Use of prior knowledge to support stability specifications of vaccines

- Prior Knowledge can help identifying the stability- indicating CQAs and related analytical strategies

- Prior knowledge of platform-based stability data may be leveraged for shelf-life projection with scientific justification- e.g.:
  - ✓ Reliance on prior knowledge for **stability modeling** to support assignment of shelf life of biologics [Vaccines. 2021; 9(10):1114; Quality by Design—An Indispensable Approach to Accelerate Biopharmaceutical Product Development; PDA: Bethesda, MD, USA, 2021; pp. 133–168].
  - ✓ Shelf- life establishment for **COVID viral vector vaccines** [AAPS Open (2021) 7:6]
  - ✓ Examples of **Regulatory Guidance for COVID variants**
    - Registered shelf-life conditions for COVID variants would be applicable under certain conditions, and provided confirmatory real-time stability data post- approval [e.g., https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-vaccines-intended-provide-protection-against-variant_en.pdf].
    - "Consideration of platform stability data, prior knowledge from early clinical batches or statistical modeling may also be applied to forecast expiry of product or COVID vaccine variants, in principle, the registered shelf -life conditions/period would be applicable." [https://cdn.who.int/media/docs/default-source/in-vitro-diagnostics/covid19/considerations-who-evaluation-of-covid-vaccine_v25_11_2020.pdf?sfvrsn=f14bc2b1_3&download=true]

GSK

Concluding remarks

Use of prior knowledge to support specifications of vaccines

- Use of prior knowledge for specifications setting, in the framework of patient- centric strategies, is key to support accelerated access and harmonization
- For vaccines, the extent of use of prior knowledge depends on the nature of the vaccine and on the tested attribute
- Examples have been reported on use of prior knowledge elements for CQAs identification and acceptance criteria including stability considerations
- Best use of prior knowledge to support optimal design of nonclinical and clinical models for vaccines requires further reflection.

GSK

Acknowledgement

- Marianna Aggravi
- Elena Fragapane
- Barbara Capecchi
- Mathieu Vasselle
- The EFPIA/ VE ICH Q6 team (slides with EFPIA logo)

GSK

Cristiana Campa is employed by the GSK group of companies