Regulatory Considerations for Adjuvanted Vaccines - From Characterization To Global Access

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TALK OUTLINE

- Adjuvant landscape
- Current regulatory frameworks
- Emerging regulatory themes and challenges
- Global deployment
- Key regulatory takeaways

Adjuvant Landscape

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Adjuvants Through a Regulatory Lens

- Important tools in modern vaccine development
- May be co-formulated with the antigen(s) or combined prior to administration
- From a regulatory perspective, adjuvants may:
  - Add complexity to the final formulation
  - Broaden evidentiary expectations for quality, safety, and efficacy
  - Require more extensive characterization, control strategies, and product/process understanding

Where Adjuvants Add Value

1

Enhancing immunogenicity

- Vaccines with low inherent immunogenicity
- Vaccines targeting vulnerable populations

2

Broadening immune responses

- Vaccines requiring strong cellular immunity
- Mucosal vaccines

3

Improving formulation and delivery

- Pandemic vaccines (antigen-sparing)
- Stability-limited vaccines

Recent Developments in the Adjuvant Landscape

- Rationally designed adjuvant systems (e.g., PRR agonists)
- Combinations of adjuvants (e.g., AS01, AS03)
- Multifunctional delivery systems (e.g., LNPs, Matrix-M)
- Self-adjuvanted/integrated platforms (e.g., mRNA-LNP vaccines)
- AI/data-driven discovery

These approaches can increase complexity across CMC, non-clinical, and clinical evaluation

Current Regulatory Frameworks

Regulatory Landscape for Adjuvanted Vaccines

Multiple guidance documents available across regions

- WHO TRS 987 Annex 2, guidance from regional and national regulatory authorities
- Broadly aligned in principles

Gaps and challenges

- Some were developed with earlier adjuvant systems in mind (e.g., aluminum salts)
- Differences in interpretation and data expectations across jurisdictions

Core Regulatory Principles

- Adjuvants are not licensed as standalone products
- Not classified as an active ingredient
- Inclusion must provide clinical benefit
- Each antigen-adjuvant combination is a distinct product

Data must support each specific antigen-adjuvant combination

Emerging Regulatory Trends and Challenges Across the Product Lifecycle

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1. Blurring of Antigen and Adjuvant Boundaries

Self-adjuvanting integrated platforms where the boundaries between antigen, adjuvant, and delivery system are not always well-defined

- **What constitutes the active component/ingredient?**
- **Can components be independently evaluated?**

Case Examples

BEXSERO

- Antigen and intrinsic immunostimulatory activity embedded in the same structure (OMV)

mRNA-LNP Vaccines

- LNP may function primarily as a delivery system, but can also influence immunogenicity and reactogenicity

Component classification can influence data expectations, comparability strategies, and IP considerations

2. Emergence of Licensable Adjuvants

Adjuvants are increasingly being developed independently from the final vaccine product

- **Who owns lifecycle data and platform knowledge?**
- **How much information do manufacturers have access to?**
- **Who is responsible for post-market commitments?**

Case Examples

GSK Adjuvant Systems

- Multiple proprietary adjuvant systems (e.g. AS01, AS03, AS04)
- Used across different vaccine programs/partnerships

SEPPIC / SWE

- Open-access squalene emulsion adjuvant platform
- Used across several clinical programs

Shared adjuvant platforms may facilitate broader access but distribute regulatory responsibilities across multiple stakeholders

3. Leveraging Platform Data/Prior Knowledge

Adjuvant platforms are increasingly being used across different products

- **How transferable is platform data/prior knowledge?**
- **When to supplement with product-specific data/evidence?**

Case Study – Platform Data *vs*. Product-Specific Data

- New vaccine using licensed adjuvant (e.g., Adjuvant A)
- Platform data may be leveraged for the adjuvant
- Product-specific data required for the antigen-adjuvant combination:
  - CMC: Compatibility, Characterization, Stability
  - Non-clinical: Proof-of-Concept and Safety
  - Clinical: Safety and Immunogenicity/Efficacy, as appropriate

Platform data and prior knowledge may be used to streamline data packages and regulatory evaluation

4. Reliance on Global Supply Chains

Multiple sites across the globe involved in manufacturing and testing of the adjuvant, DS, and DP across the product lifecycle

- **How can comparability be maintained across sites and development stages?**
- **How should evolving assays be bridged without losing linkage to clinical experience?**
- **How should observed differences in quality attributes be interpreted?**

Case Study – Assay Evolution and Material Comparability

Adjuvanted Vaccine A: Potency assay evolved throughout development. Different assay formats and reference standards were used across sites and across Phase 1–3 and commercial lots.

Regulatory Assessment:

- Formulation was based on protein content
- The totality of data supported comparable clinical performance across lots manufactured and tested at different sites

A broader analytical package can help distinguish true material differences from assay-related effects

Case Study – Comparability after Scale-up

Adjuvanted Vaccine B: Commercial vaccine lots used adjuvant lots from new manufacturing site. Significantly higher particle counts observed when compared to clinical lots.

Regulatory Assessment:

- Data from non-clinical studies did not show a difference in immunogenicity
- Clinical data demonstrated no meaningful impact on safety or efficacy

Differences in quality attributes should be assessed in the context of clinical relevance

5. Leveraging Stability Data from Stressed Studies

Data from accelerated stability studies and forced-degradation studies are increasingly used to inform regulatory decisions

- **Which stability dataset should drive interpretation?**
- **Are stress-induced changes clinically meaningful?**
- **What role should forced-degradation studies play?**

Case Study – Interpreting Accelerated and Forced-Degradation Data

For vaccines, shelf-life assignment relies on real-time, real-condition stability data

Accelerated study

- May inform interim decisions when real-time data are limited
- Particularly relevant in pandemics or early clinical development

Forced-degradation study

- Can help characterize degradation patterns
- Can support comparability after CMC changes

Stressed studies can inform regulatory decisions, but they are supportive tools and should be interpreted in context

6. Leveraging Dose-Ranging Studies to Support Antigen Sparing

Dose-ranging studies with adjuvants may be used to support lower antigen doses particularly in the context of pandemics

- **How can adjuvants support lower antigen doses while maintaining acceptable immunogenicity?**
- **What level of clinical data is needed to justify an antigen-sparing strategy?**

Case Study – Early-Stage Studies for Antigen-Sparing Strategies

H1N1 Flu Vaccine

- Phase 2 study evaluated
  - 3.75 µg, 7.5 µg, and 15 µg HA with AS03
  - 7.5 µg and 15 µg HA without adjuvant
- Acceptable safety and immunogenicity supported selection of 3.75 µg HA + AS03

NUVAXOVID

- Phase 1/2 study evaluated
  - 5 µg and 25 µg rS protein with 50 µg Matrix-M
  - 25 µg rS protein without adjuvant
- Data supported selection of 5 µg rS protein + 50 µg Matrix-M

Lower antigen content per dose can help extend limited vaccine supply and support broader population coverage

Jackson LA et al. J Infect Dis. 2012 Sep 15;206(6):811-20

Keech C et al. N Engl J Med 2020;383:2320-2332

7. Use of RWE to Address Residual Safety Uncertainty

Post-market (PM) studies and real-world evidence (RWE) are increasingly used to address residual uncertainty around safety

- **When can post-market evidence help address residual uncertainty at licensure?**
- **How can post-market data help confirm or refute early safety concerns?**

Case Study – HEPLISAV-B and Residual Uncertainty

- Contains CpG adjuvant
- Imbalance in cardiovascular events observed in a clinical study
- Regulatory review was prolonged and complex
- Licensed with a commitment to conduct a sufficiently powered post-market (PM) study
- The post-market study did not identify an increased risk of AMI

Post-market studies can help confirm the safety of novel adjuvants or platforms where residual uncertainty remains

Reflections on an Evolving Adjuvant Space

- Scientific and regulatory questions continue to evolve
- Science-based regulation can help bridge gaps where there is a disconnect between existing regulatory frameworks and newer adjuvant approaches
- Regulatory alignment can help facilitate broader use of adjuvants and adjuvanted vaccines

Global Deployment

Multi-country Licensing Strategies

To support broad registration:

- Understand regional requirements early
- Build a common core dossier
- Clearly justify platform data/prior knowledge
- Harmonize specifications
- Use reliance-based pathways where available

Early alignment reduces downstream delays and supports global access

Challenges in Multi-jurisdictional Alignment

- Differences in:
  - Country-specific documentation/requirements
  - Interpretation of analytical and clinical data
  - Risk tolerance
- Result in:
  - Divergent specifications
  - Additional data/bridging requirements
- Opportunity: Early alignment, especially on clinically meaningful ranges

WHO Prequalification – Where Regulatory Acceptability Meets Programmatic Reality

- Evaluated against mandatory, critical, and preferred characteristics
- Additional focus around:
  - Programmatic suitability (e.g., fit within immunization schedules and delivery contexts)
  - Thermostability (e.g., stability during storage at 2-8°C and protection against freezing damage, where relevant)
  - Presentation format and usability (e.g., single dose *vs*. multi-dose, preservatives, dose volumes, delivery devices)
  - Supply reliability and scalability

World Health Organization | Prequalification of Medical Products
IVDs, Medicines, Vaccines and Immunization Devices, Vector Control

Assessing the programmatic suitability of vaccine candidates for WHO prequalification. Revision 2014.

Key Regulatory Takeaways

Analytical understanding is increasingly central to lifecycle management

Platform familiarity helps but product-specific evidence still matters

Early development choices increasingly shape global access

Global deployment depends on shared data and shared interpretation

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Think early, think globally, think lifecycle

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