Vaccines are Biologicals with Unique Specificities

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Agenda

01 Enhanced approach

02 Vaccine QTPP

03 Host-Cell Proteins
CASE STUDY

04 Potency
CASE STUDY

05 Uniformity of dosage units
CASE STUDY

06 Subvisible particles
CASE STUDY

07 Conclusion

The Enhanced Approach

From QTPP to Specification Test

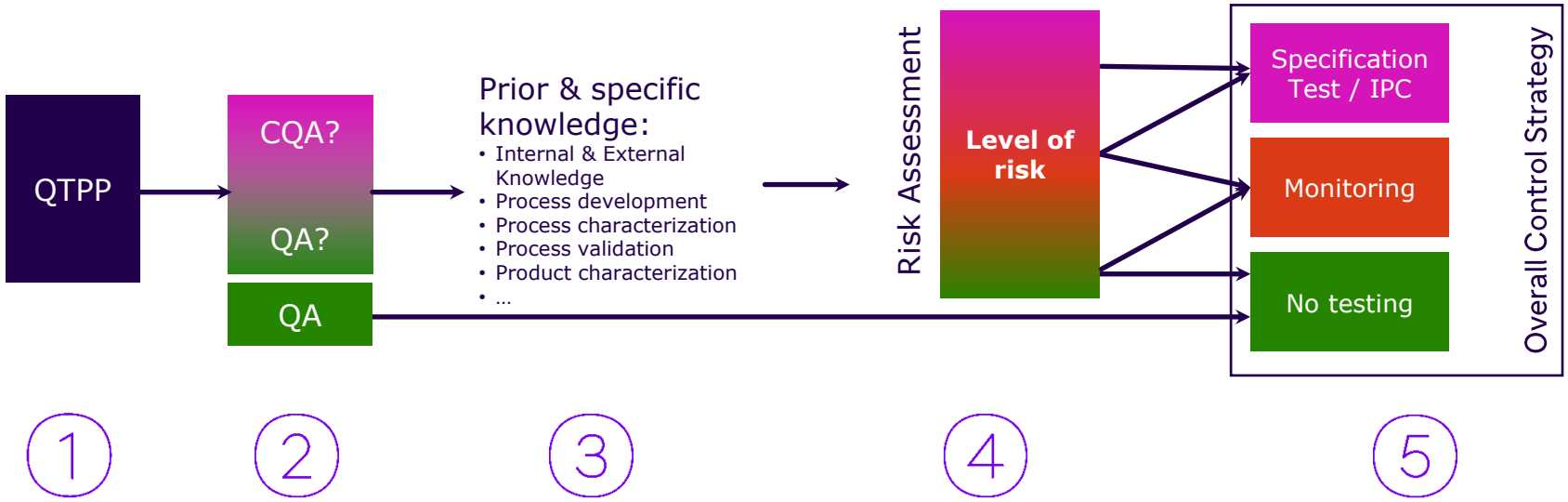


Figure adapted from Emma Ramnarine (Pharmaceutical Technology 47 (10) 30-46)

Vaccine QTPP

QTPP: quality Target Product Profile

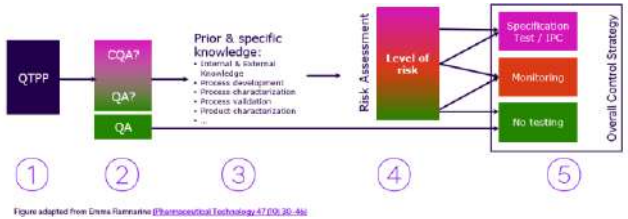
① Vaccine Quality Target Product Profile

Product Attribute	Target
Modality(ies)	**Multiple modalities**: Virus-based vaccines (vector, or live, or inactivated), bacteria-based vaccines (whole-cell live or inactivated, or subunit incl. polysaccharide, conjugate, toxoid), recombinant protein-based vaccines (expressed in bacteria or yeast, or in animal cells, or in baculovirus), mRNA-based vaccines
Intended Use in Clinical Setting	**Active immunization** against XXX
Route of Administration	**IM,** SC, oral, nasal
Vaccination schedule	E.g., for DTP vaccine **10-12 doses** maximum in a lifetime
Dosage Form	Liquid or freeze-dried
Delivery Systems	Prefilled syringe or vial + syringe, specific device for non-parenteral route
Formulation/dosing	XX units of each of **1 to 21 antigens** in a single dose, **0.5 mL/dose,** with or without **adjuvant**
Shelf-Life and Storage	At 2 to 8 °C, ideally for 36 months or more
Drug Product Quality	Sterility, Purity, Potency/Activity/Strength, Stability, etc.
Countries for registration & LCM	Canada, China, Europe, Japan, USA, etc. **> 100 countries**

Host-Cell Proteins (HCPs)

Process-related impurity – HCPs 1/4

② *CQA or not CQA?*



Identification of theoretical risks associated with host cell proteins in vaccines:

- Theoretical risk associated with protein function in human:
  - Auto-immunity
  - Allergic reaction
  - Growth promotion/oncogenicity (negligible given the quantity)
- Potential risk for the stability of the product due to presence of enzymes

But also, a positive role of host cell proteins in vaccines:

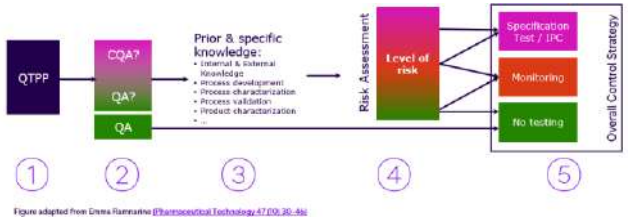
- Can play a role in vaccine antigen stability
- May have an adjuvant effect, increasing the immunogenicity of the vaccine

Conclusion: risk associated with HCPs is considered lower for vaccines compared to biotherapeutics, due to:

- Immunogenicity as the basis of the mechanism of action of vaccines;
- Lower doses administered, less frequently/fewer doses in lifetime;
- Decades of clinical experience

Process-related impurity – HCPs 2/4

③ ④ *Process & Product Knowledge and Risk Assessment*



Even if the risk is considered lower for vaccines compared to biotherapeutics, **characterization testing for HCP content and/or identification is performed during development**:

Data are generated to document the **process performance**:

- HCP removal by the process
- HCP batch-to-batch consistency
- Comparability

HCP **characterization**:

- Identification of HCPs
- Quantification of HCPs

Risk assessment

- Identified HCPs are typically assessed for function (potential toxicity), human sequence similarity, and T cell epitope prediction (potential auto-immunity), using proteomics tools.

Process-related impurity – HCP 3/4

⑤ *Overall Control Strategy – Specification test or not?*

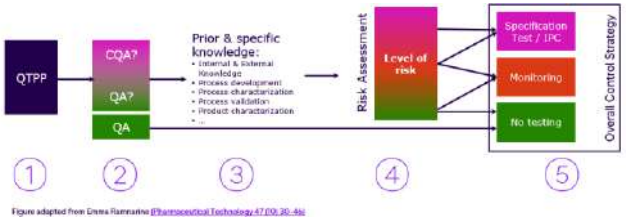


Figure adapted from Drema Ramnarine [Pharmaceutical Technology 47 (10) 30-4s]

Key considerations for HCPs **Overall Control Strategy**:

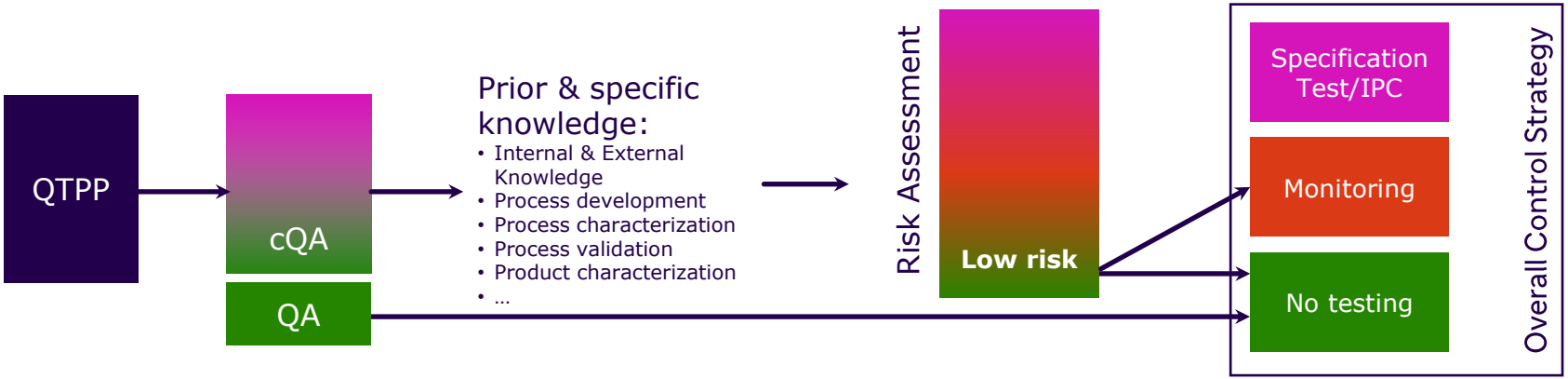
- The low level of risk associated with HCPs in vaccines in general
- Risk assessments performed with process and product knowledge

Overall Control Strategy:

- Process monitoring of HCPs during clinical development
- In case of manufacturing change, for comparability

Process-related impurity – Host Cell Proteins 4/4

Conclusion



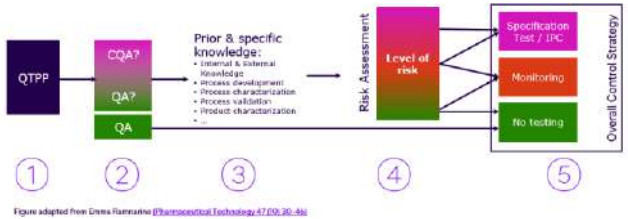
Conclusion:

- Safety risk from HCPs is lower in vaccines versus biotherapeutics
- Established process controls and product characterization during vaccine development can reduce this risk to negligible levels
- In a CTD dossier following the Enhanced Approach, HCPs testing can be managed tactically as a CQA(s), even if the criticality of the attribute for vaccine is considered as low, to show that it is managed and the risk is reduced to a point where routine release testing is not needed

Note: Historically, vaccine guidance has required removal/specific levels of residual DNA, but not HCPs.

Potency

Potency



Potency is a **CQA controlled in specifications on DP**

- Ensure efficacious product is injected to the patient in a sustainable manner
- Potency assay dependent on vaccine type

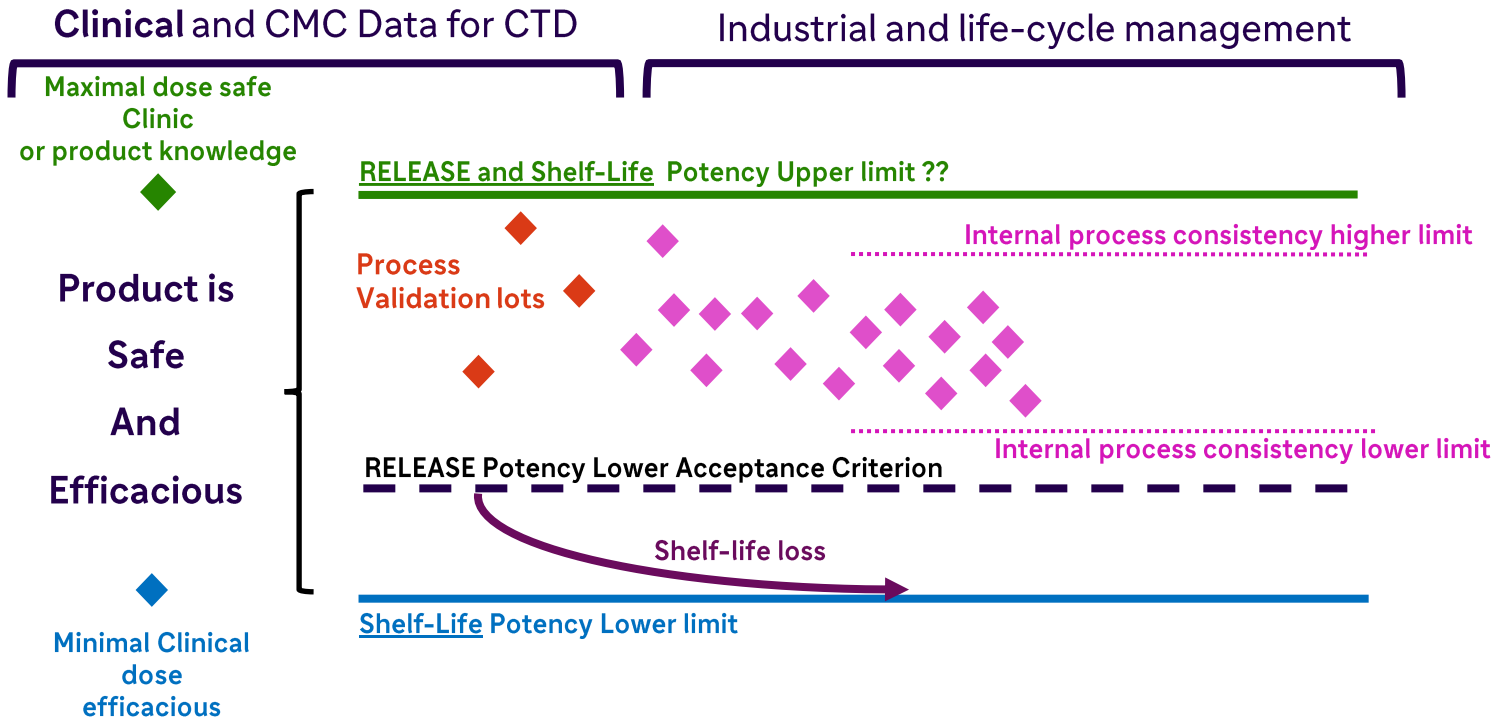
Vaccines have a long legacy of ***in vivo* potency assays** (Tetanus, Diphtheria, Pertussis, Rabies, Polio....)

- Potency assay mimicking injection in human
- Assumption that animal will predict what will happen in human

***In vitro* assay(s) for potency** are being implemented (new vaccines & legacy)

- Based on specific elements of vaccine mechanism of action
- To better document vaccine quality and consistency of production (less variability)
- To improve vaccine availability for sustainable access for patient (more robust and shorter time to result)
- To reduce our impact on environment and comply with 3Rs policy encouraged by EMA

New Vaccines
Potency Specifications acceptance criteria definition



Commercial legacy vaccines – Verorab™ case study
Potency acceptance criteria when switching to *in vitro* test

Not possible to apply the same methodology as for new vaccine

- Clinical trials were performed decades ago

Sanofi Rabies vaccine Verorab™

- Inactivated viral vaccine produced in Vero cells
- Product efficacy and safety demonstrated for decades
- *In vivo* NIH Test successfully replaced by *in vitro G* protein ELISA (EMA, TGA….)

New ELISA potency acceptance criteria define based on:

- Statistical analysis of Rabies G protein ELISA data on 279 Drug Product batches
- Confirmation of proposed acceptance criteria on lab-scale subpotent batches

ELISA Potency acceptance criteria for VERORAB™ DP

Strategy

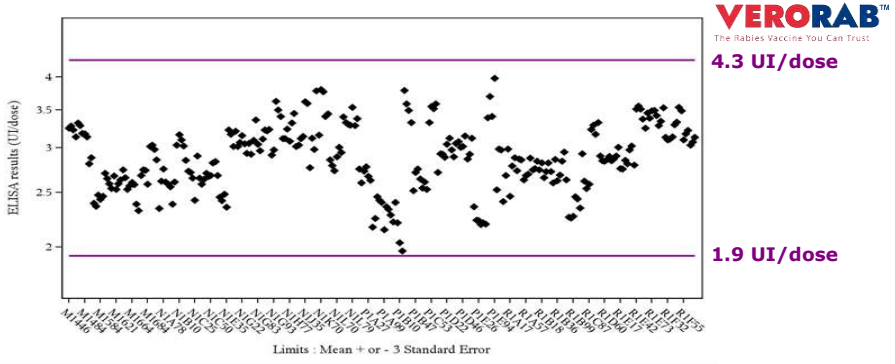
Consistency approach of the **VERORAB™** product with the *in vitro* ELISA

> ***Calculation of the new acceptance criteria : mean ± 3 standard deviations***

Results

Representative batches of VERORAB™ vaccine production
(*i.e.,* well-established safety and efficacy profile, with consistent manufacturing)

279 batches covering 3 years of manufacturing



Agreement Study

Assess the proposed acceptance criteria with sub-potent batches tested in both NIH & ELISA

Verorab™ Vaccine is a “best case”
Not applicable for all vaccines

Inactivated viral rabies vaccine

- Monovalent non adjuvanted
- No antigenicity/potency loss observed over shelf life
- Rabies G protein Potency ELISA in vitro potency assay is versatile, robust, accurate & precise, stability indicating and **fully in agreement with *in vivo* potency**

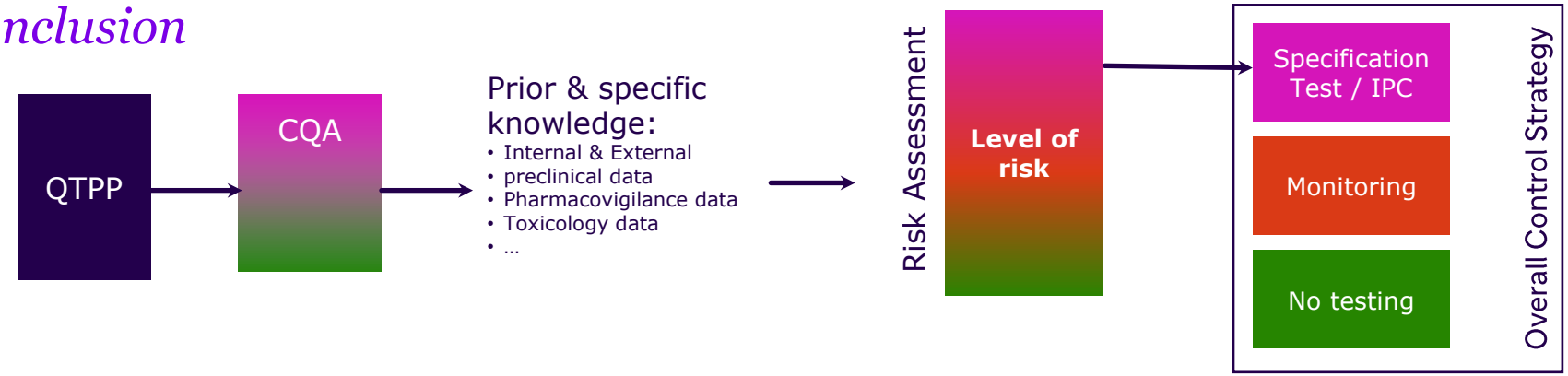
Other products such as for Diphtheria, Tetanus, Pertussis containing vaccines, are more complex

- Multicomponent: 4 to 7 different antigens
- Adjuvanted with aluminum salts
- 4 to 7 different *in vitro* assays that may detect antigen behavior and trends not observed by *in vivo* assay

Strategy for D, T, aP new potency acceptance criteria under definition/discussion

- Based on the bridging with *in vivo* potency including use of subpotent batches
- Confirmed by process consistency analysis (to set internal limits)
- Lower limit only

Potency
Conclusion

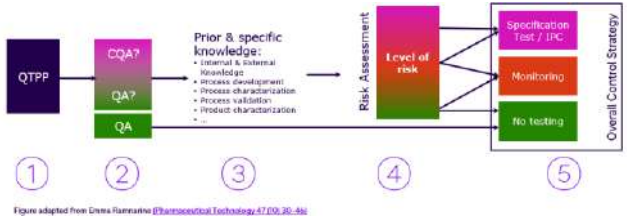


- Potency assay is a specification test for DP
- The Enhanced Approach for setting acceptance criteria is applicable for new and for legacy vaccines
- For legacy vaccines when switching to *in vitro* potency the strategy for setting new acceptance criteria can be a challenge
  - Manufacturing consistency data should be used for process monitoring
  - Specification limits must be carefully defined to ensure sustainable and reliable patient access, with meaningfulness for CQA potency
- Relevance of a potency release upper limit?

Uniformity of dosage units

Uniformity of dosage units

② *CQA!*



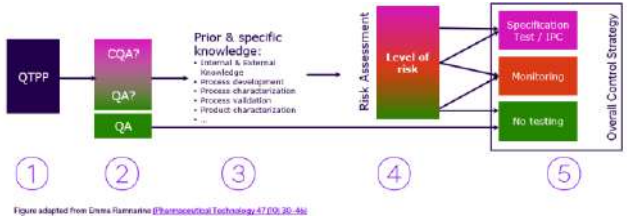
It is critical that **each unit in a batch** (tablet, capsule, injection, etc.) contains the **intended amount of active substance** to:

- Ensure Patient safety and Product efficacy
- Demonstrate process consistency (minimizing variability between units/vials/syringes)
- Demonstrate compliance to label claim

As for any other medicinal product, it is a CQA.

Uniformity of dosage units

⑤ *Overall Control Strategy: alternative strategy*



Pharmacopoeias

- Assays required in parenteral dosage form monographs:
  - Weight Variation (WV)
  - Content uniformity (CU)

Question: Are these Pharmacopoeia methods well controlling the CQA for vaccines?

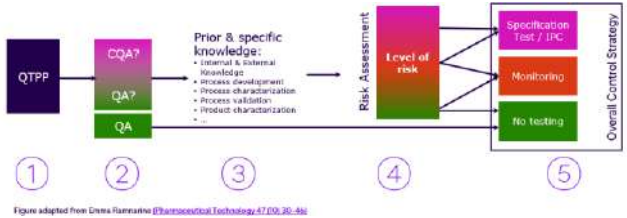
Alternative Overall Control Strategy

- Uniformity of dosage units can be demonstrated by DP **formulation and filling process validation:**
  - Liquid Final Bulk product homogeneity demonstrated by formulation process validation
  - Filling machine validated filling volume and filling process validated

- **Process monitoring**
  - For each lot 100% of the vials are weighed to check filling volume for routine process monitoring

- **Specific tests** addressing content and dosage included in Specifications (DP)
  - Extractable Volume
  - Antigen content & critical excipient content
  - Potency assay

Uniformity of dosage units
Conclusion

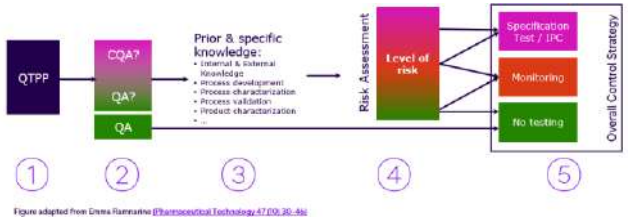


- **Use of alternative methods is possible in Pharmacopoeia – (General Notices)**
- **Is an alternative Overall Control Strategy possible? – E.g., based on process control and other release tests (see previous slide) rather than the strategy described in the Pharmacopoeia?**

Subvisible particles

Subvisible particles (1/2)

② *not a CQA for vaccines*



Identification of risks generally associated with presence of subvisible particles in injections:

- Safety: Immunogenicity, contamination, capillary occlusion
- Efficacy: Loss of active ingredient(s) due to immunogenicity, aggregation/precipitation

The above-mentioned factors are not considered risks for vaccines

- Immunogenicity against the target antigen(s) is a desired outcome for vaccines rather than a risk
- Parenteral vaccine injection routes are IM or SC; not a risk for capillary occlusion
- Subvisible particles are inherent to some vaccine types

The underlying potential risk of aggregation can be assessed and controlled by more appropriate methods rather than through the control of subvisible particles in the DP specification, using the compendial methods.

Subvisible particles (2/2)

⑤ Overall Control Strategy

Overall Control Strategy:

- Presence of subvisible particles could be used to monitor product quality and batch to batch consistency during clinical development only (outside of the specification)

Note that oligomerization, aggregation, and/or particle size, where inherent to the product (VLPs, LNPs…) are assessed by specific appropriate methods (HP-SEC, DLS…)

Conclusion

Conclusion on Vaccine Specificities

Modalities & Clinical Use

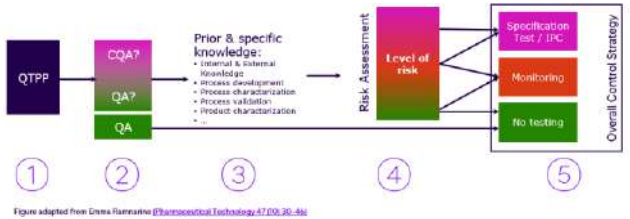


Figure adapted from Drews Ramnarine [Pharmaceutical Technology 47 (10) 30-4s]

2

QA or CQA?

- Criticality of the quality attribute is based **on clinical use** and modality
- Subvisible particles – *not a CQA for vaccines, not in the specification*

3 4

Knowledge and risk assessment

- HCPs – *lower level of risk for vaccines, not in the specification*

5

Test method

- Uniformity of dosage unit – *method provided in general monograph on dosage form not adapted to vaccines*

CQA controlled outside of the specification

- Uniformity of dosage unit – *can be better controlled using an alternative Overall Control Strategy*

Acceptance criteria definition

- Potency – ***enhanced approach*** *supported by clinical data for* ***new vaccines***
- Potency – ***adapted approach*** *for* ***legacy vaccine*** *when moving to* ***in vitro***

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