

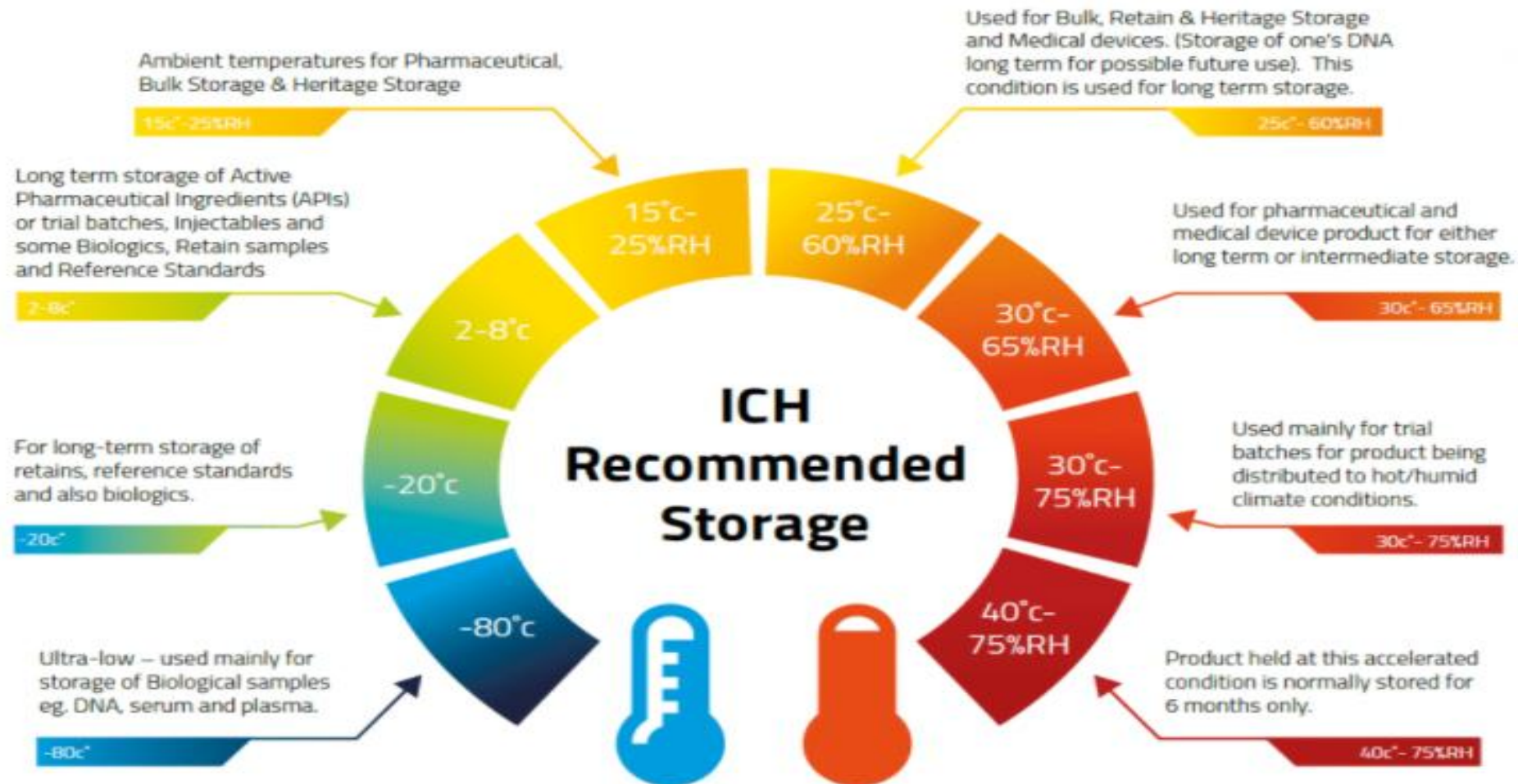
Stability Testing of Vaccines: Developing Countries Vaccine Manufacturers Network (DCVMN) Perspective

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DCVMN e-workshop: Statistical Analysis of Stability Testing

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Stability testing is an integral part of the vaccine manufacturing process and is crucial for success of immunization programs.



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- **WHO** published guidelines on **Stability evaluation of vaccines** enlisting scientific basis and rationale at various stages.



❖ *We here highlight viewpoints, possible roles and global expectations of DCVMN in the area of **Stability testing of Vaccines**.*

❑ Vaccines and Stability testing

Vaccines

- A heterologous class of preparations consisting of proteins, polysaccharides, toxoids, r-DNA antigens, and both inactivated and live attenuated microorganisms.

Vaccine formulation

- Contains stabilizers, adjuvants, preservatives and other excipients contribute to overall stability of product.

Stability testing

- Aims to establish shelf-life, degradation rate of vaccine at real time, accelerated and stress conditions.
- Evaluation of product ability to retain chemical, biological and physical specifications

Thermal stability introduced in 1980s as part of lot release for MMR and Rabies vaccines.

□ Methods and View points

Methods

- ✓ Based on consultations with DCVMN members, here we present the network viewpoints on stability testing of vaccines.
- ✓ Some of the view points are presented using case studies.
- ✓ Case studies are based on Manufacturer's experience in this field, especially during the initial phase of development and manufacturing of vaccines.

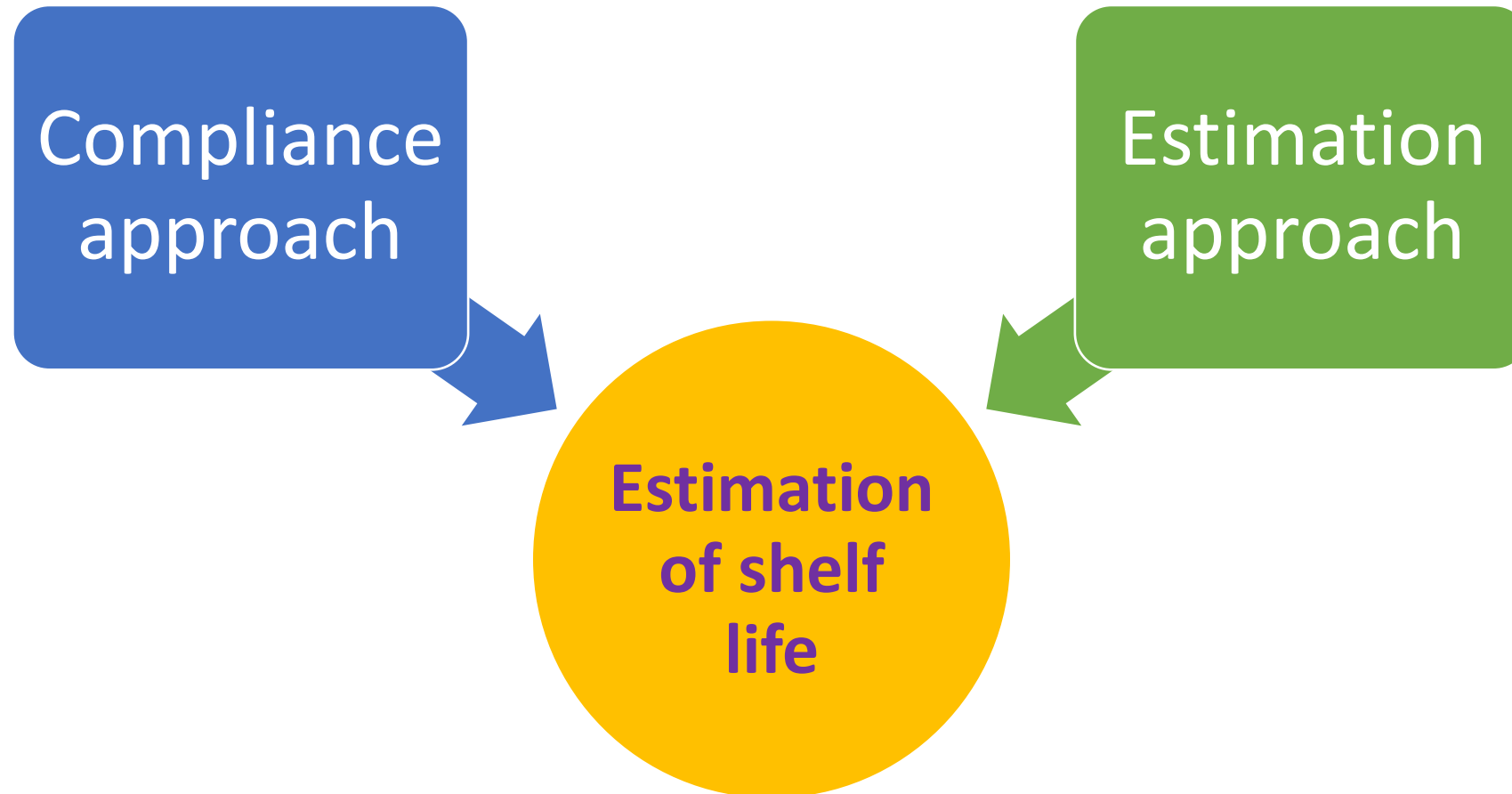
View Points

- ✓ International agencies, such as WHO, have remained an important interface in enhancing the acceptability of products, globally.
- ✓ WHO has released guidelines on stability testing of vaccines at various stages of development and manufacturing.

DCVMN view points on stability testing are presented in following slides...

❑ Models and approach: Expiry period and minimum release specifications

Stability testing uses various approaches towards estimation of the shelf life of the product.



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❑ Models and approach: Expiry period and minimum release specifications.

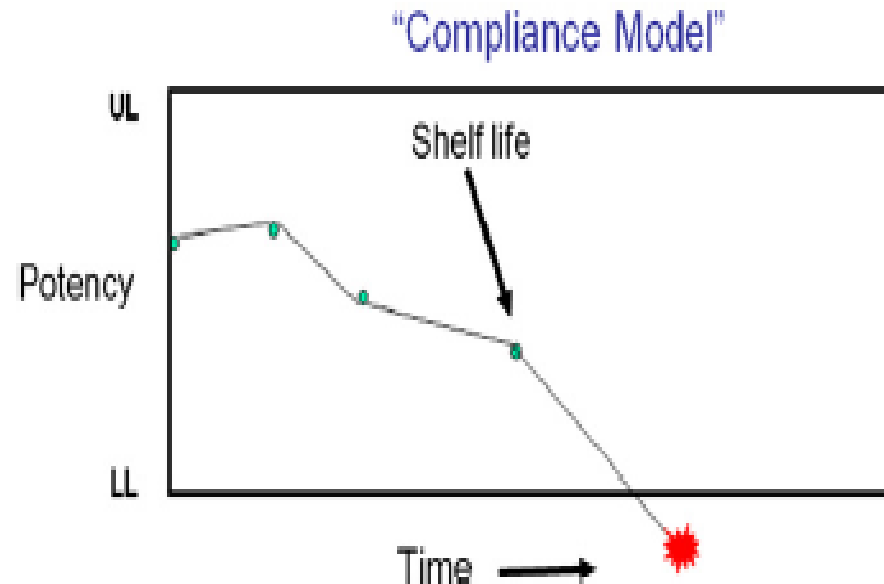
Compliance approach

Shelf life is designated as the last time period at which stability measurement falls above prescribed specifications.

Estimation approach

In this approach the manufacturer may establish minimum release specifications, which assures that the batch will remain within specifications throughout the vaccine shelf life.

In ***Compliance approach***, product shelf life is monitored over the time until the potency measurement falls below the pre-established allowed lower limit is indicated in red colour. The time for which the last potency determination was within specifications (UL & LL) is considered to be the product's shelf life.



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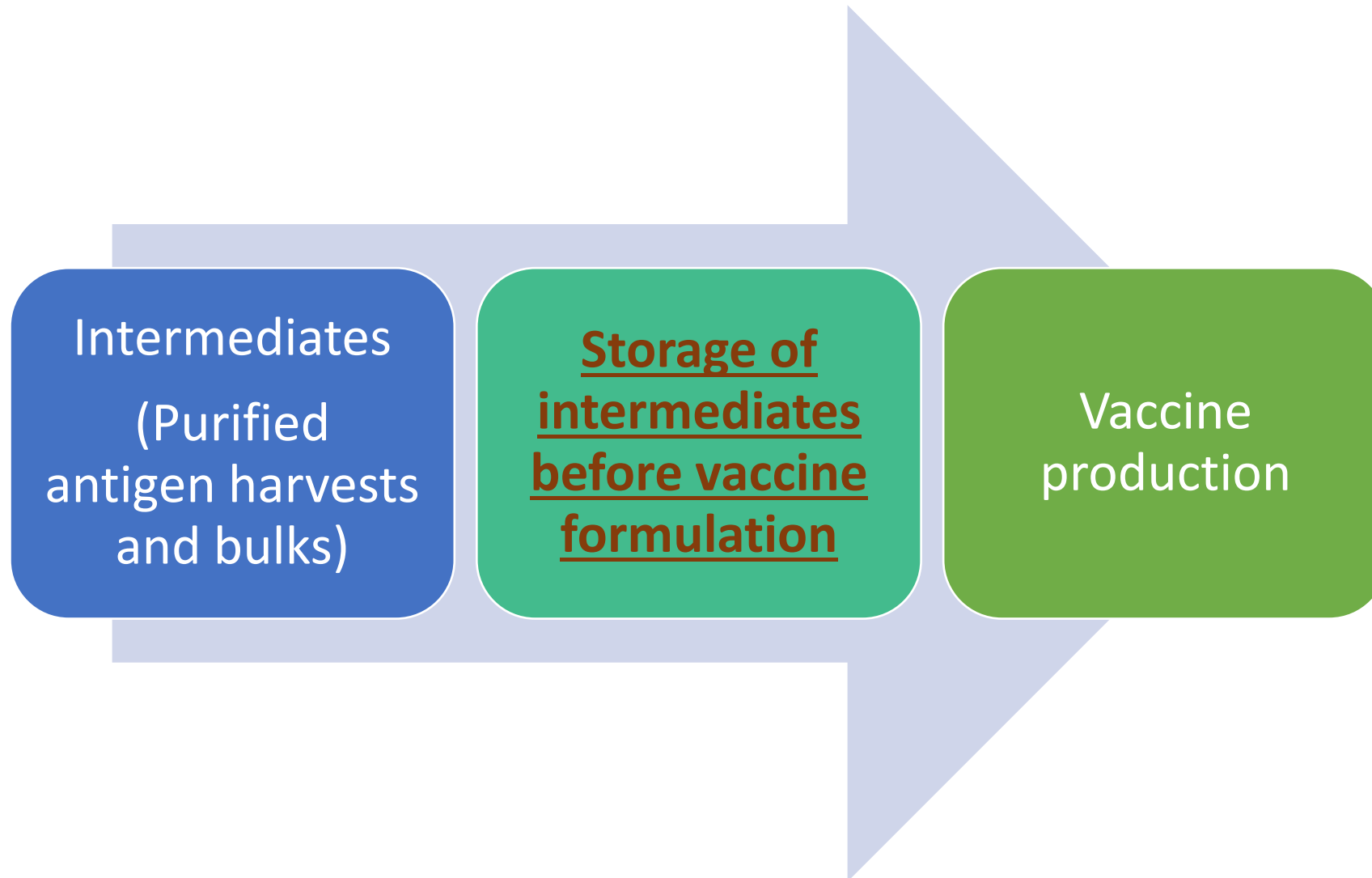
❖ *Compliance approach:*

- Does not take care of uncertainties such as assay variabilities and loss rate.
- Does not provide an optimal estimate of the vaccine's true shelf life.
- Compliance model discourages data collection. If additional data are collected, the probability increases that one or more of these additional data points, due to assay variability, will lie outside the specification range.
- Based on a single data point, does not provide a measure of confidence in the established shelf life.

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- WHO Guideline does not give reference to products, where such approaches should be applied.
- DCVMN network believes that *Estimation approach* should be encouraged in stability testing, as it allows detailed stability profiling of product including assay variability and loss rates and gives actual estimates of shelf life and degradation rates of product.

❑ Cumulative age of intermediates



❖ *WHO guideline advocates the role of accelerated stability testing on intermediates to support the storage before formulation.*

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❑ Cumulative age of intermediates

- ✓ DCVMN supports the role of stability testing, with the belief that any policy on intermediates should be designed on product-by-product basis.
- ✓ Examples of two such antigens which support our view points are provided below:

Example (a): Pertussis Pools

Example (b): Hib conjugate vaccine

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Example (a): Pertussis pools

Mature pools of Pertussis antigens are preferred for formulation owing to relatively reduced inherent toxicity.

In such cases,

Determination of cumulative age becomes utmost important, as it will allow manufacturer to develop effective correlations between age of pools, toxicity and potency.

Example (b): Hib conjugate vaccine

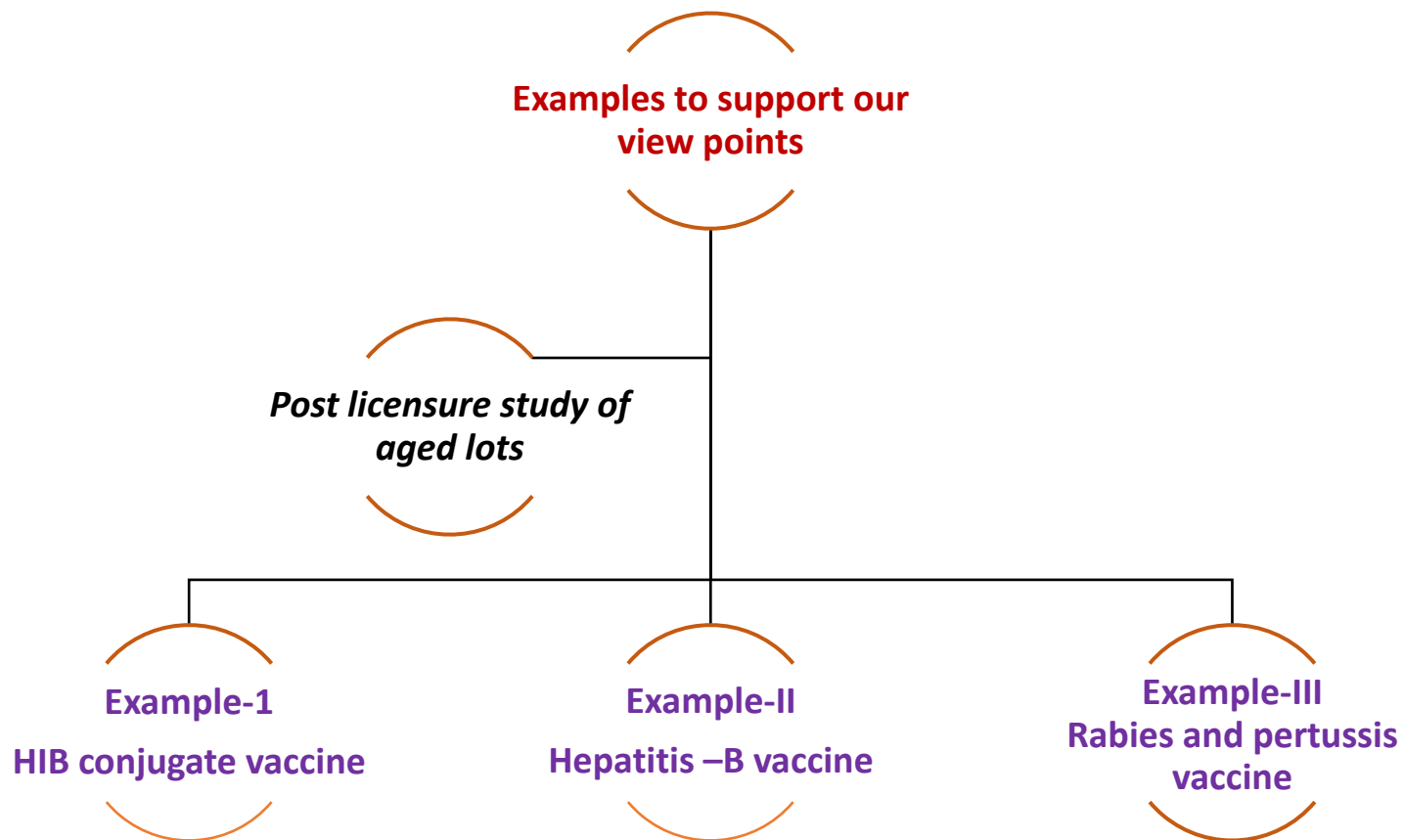
- WHO and British Pharmacopoeia recommend a release specification of 20% free PRP at conjugate bulk and final lot levels.
- Some manufacturers observed that the conjugate bulk shows a free PRP release of up to 7% during routine bulk release testing, which increases up to 9% in the final finished lots.
- Increase of 2% free PRP is attributed to the formulation and lyophilization process.
- Further the manufacturer's has observed free PRP up to 11% in final finished lots during real time stability studies, up to 3 years from date of manufacture.

Based on these observations, manufacturers have set minimum acceptance criterion at 7% for conjugated bulks and 9% for final finished lots which is very much stringent in comparison to British Pharmacopoeia and WHO specifications.

This approach takes care of both cumulative age of intermediates and overall stability of vaccine formulation.

❑ Post licensure study of aged lots

- ✓ Post-licensure stability studies are important to support shelf life specifications and to further refine the stability profile of vaccine.
- ✓ Clinical studies on vaccine lots nearing expiry will be helpful to establish clinical relevance of minimum release potencies.
- ❖ *In such cases, DCVMN has a viewpoint that its rationale and the applicability should be decided on product-by-product basis.*



□ Examples-Post licensure study of aged lots

Example-I: *Polysaccharide conjugate vaccines: H. Influenza type b conjugate vaccine*

- Quality control and stability testing of Hib vaccine is largely dependent on physio-chemical analysis on routine basis.
- **Size exclusion chromatography** is used routinely for monitoring batch-to-batch consistency and ensuring vaccine stability.

However, no clear picture of immunogenicity is available owing to lack of suitable biological assays.

Example-II: *r-DNA Hepatitis-B vaccine*

- Potency estimation on routine basis is done by an *in vitro* estimation of antigen (HBsAg) and *in vivo* estimation of antibody response (relative potency).

However, these assays do not provide the actual protective efficacy of vaccine, which is correlate of functional protective antibody levels in immunized animals.

Example-III: *Anti-rabies and Pertussis vaccines*

- Potency estimation on Anti-rabies and Pertussis components is carried out by mouse protection tests on routine basis.
- Potency tests are based on **challenge methods**, which are performed using live organisms, and **thus provide a true measure of protective immune response.**

❑ Conclusions-Post licensure study of aged lots

- ❖ In our view, the post licensure clinical studies should be preferred for products mentioned in **example-I** and **example-II** category. This may help in developing important correlations between existing quality control methods and clinical efficacy at or near expiry of products.
- ❖ However, for products mentioned under **example-III**, clinical studies may be exempted as challenge assays are capable of giving final account of protective efficacy of vaccine in animal models.

Therefore, the implementation of this recommendation may considered on case to case basis.

❖ Guidelines suggest that ;

- ✓ A case-by-case approach in selection of testing frequency and parameters to be adopted during the stability studies.
 - ✓ Manufacturer's may define the stability profile and propose stability indicating parameters for vaccine in question.
- ❖ Role of **National Control Authorities** becomes important in such scenarios. Additionally, it may create hurdles in harmonization of testing requirements among different countries.
- ❖ DCVMN believes that the WHO guideline should give a clear mandate by giving product specific model as case examples on *testing frequency*, *temperature* and *stability indicating parameters* during all stages of product life cycle to make guidelines more illustrative.

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Points may be considered in designing case examples for product specific models

a) If in a combination vaccine, any single component loses its stability, further study for all components may be stopped.

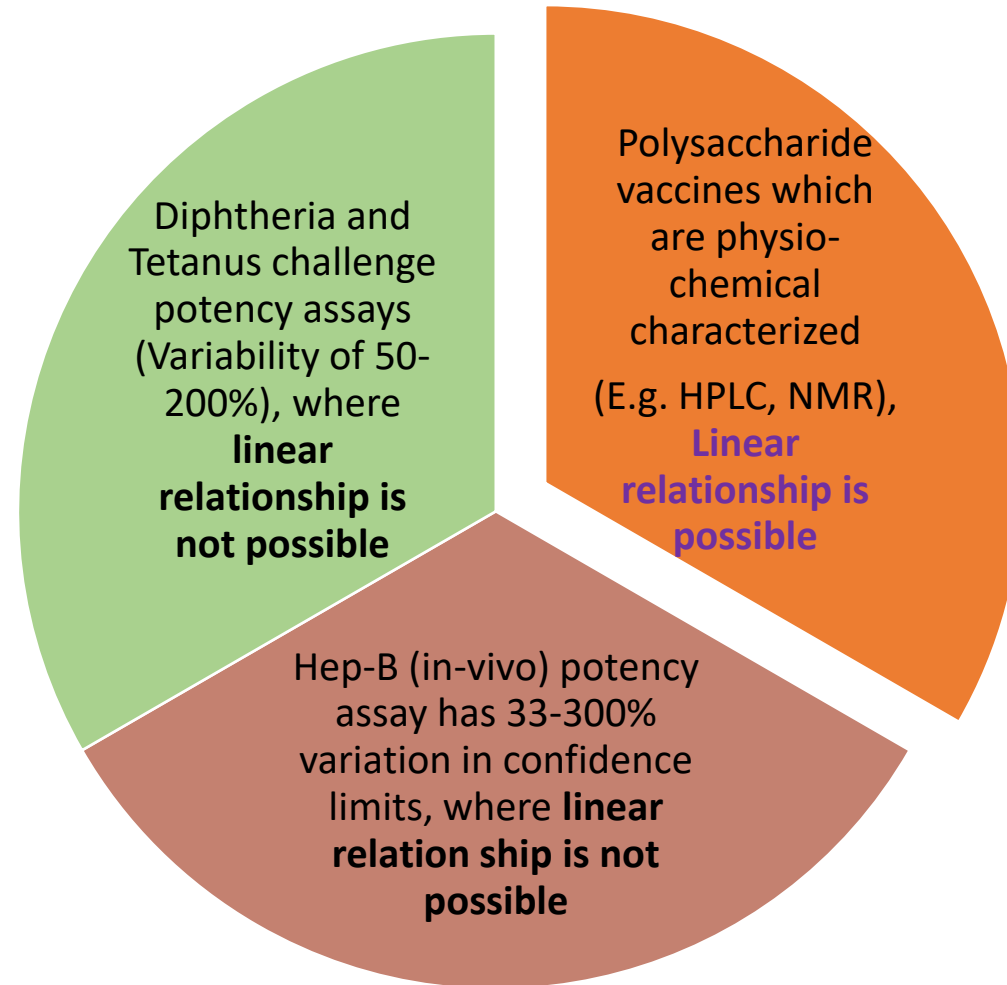
b) In follow up stability cases e.g., post-licensure, stability of most critical component may studied in (e.g., Pertussis potency and Hib (free PRP)) components in pentavalent (DTP-HB-Hib) vaccines.

c) Batches prepared for clinical studies should be monitored for their stability.

d) Representative batches may be taken on stability studies annually as part of compliance to Annual Product Quality Review (APQR).

□ Linear degradation versus assay variability

- Guidelines highlight the challenge of assay variability in stability testing.
- DCVMN network supports WHO view point and suggest that vaccines are complex preparations and need both linear and non-linear assay kinetics for reliable estimates of potency or efficacy.



□ Thermal stability testing

WHO guidelines on stability evaluation of vaccine (WHO/BS/06.2049) says,

Thermal stability should be considered as a vaccine characteristic that provides an indicator of consistency of production in **context of lot release**. Thermal stability is not designed to provide a predictive value of real time stability.

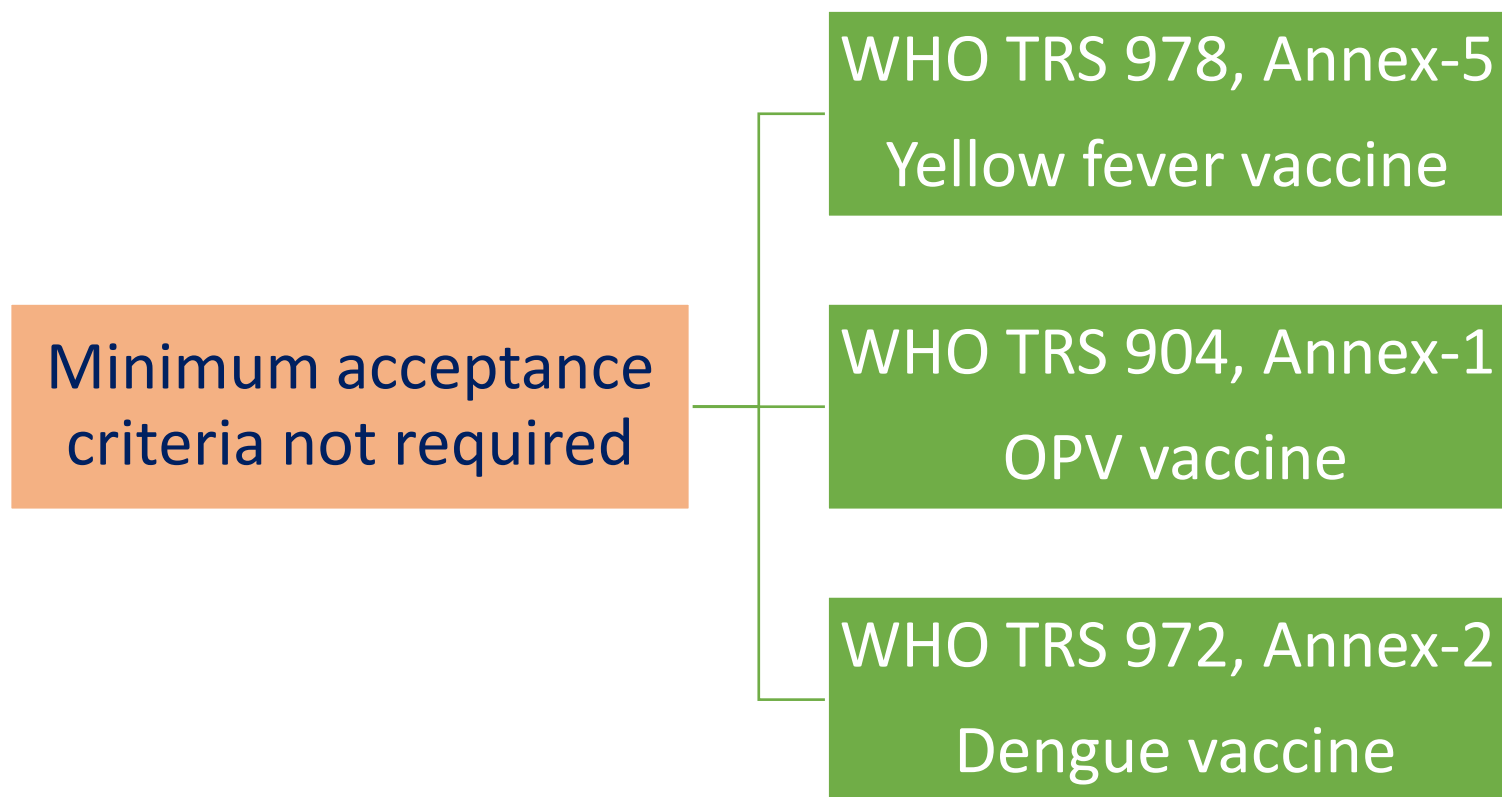
MMR Vaccine (WHO TRS 840), Annex-3

- ✓ Vaccine vials shall be stored at 37°C for 7 days.
- ✓ Geometric mean infectious virus titer of heated vials shall be equal to or greater than the required minimum number of infectious units ($3.000 \log_{10} CCID_{50}/Dose$).
- ✓ Geometric mean virus titer of the vaccine shall not have decreased by more than $1.0 \log_{10}$ infectious units during the period of incubation.
- ✓ Titration of non-exposed and exposed vials shall be made in parallel.

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❑ Thermal stability testing

- WHO TRS for MMR vaccine states that the **heated vaccine should meet the minimum acceptance criteria of $3.000 \log_{10} \text{CCID}_{50}/\text{Dose}$.**
- WHO TRS requirements of other pertinent viral vaccine does not require this criteria to be met.



□ Thermal stability testing: View points

- Requirement of minimum number of infectious units per human dose for heated vaccine has no significance, as thermal stability testing is an **indicator of production consistency**.
- Specification of “ the geometric mean titer of heated vaccine shall not be decreased by more than $1.0 \log_{10}$ infectious units during the period of incubation” shall meet the cause.
- If **shelf life specification** is applied on thermal stability test then the heated vaccine has to meet the requirement of “minimum number of infectious units per human dose” **until the end of shelf life**.
- To meet this requirement, the vaccine manufacturer has to formulate the vaccine with high virus titers, which in turn may cause the adverse events in the vaccinees.

WHO should harmonize the specification for Thermal stability testing of Viral vaccines.

- Stability of vaccine is determinant of efficacy and WHO has taken steps to facilitate harmonization in stability testing requirements of vaccine.
- DCVMN strongly feels that efforts of WHO in harmonization of stability guidelines can only be achieved through a network of national and international manufacturers and regulatory agencies.
- DCVMN can play a important role as facilitator as most of the member countries states are major suppliers and closely co-ordinate with local NRAs / NCLS.

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□ DCVMN: Possible roles

- Further DCVMN, is well represented in at GAVI, WHO, and other national and international organizations.
- Additionally, DCVMN is emerging platform for capacity building of developing countries by facilitating technology transfers, knowledge sharing, collaborations and IPR issues.
- DCVMN can also play an important role in policy advocacy by effective liasoning with local governments, public health ministry, national regulatory agencies, national immunization programmes and intellectual property offices.

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- ✓ DCVMN expects collaborations from international agencies such as WHO in capacity building, resource mobilization, funding for strengthening human resource and local regulatory authorities.
- ✓ For instance, a consortium of WHO, DCVMN, IFPMA and other suitable bodies may be formed, which works together towards the promotion and facilitating knowledge and resources among network members, national regulatory authorities, WHO, etc., which facilitate better compliance to regulatory provisions.

- ❖ DCVMN welcomes WHO initiatives in this important area of product development.
- ❖ DCVMN network suggests that vaccines are complex preparations and testing requirements should be devised on case-by-case basis.
- ❖ Further DCVMN, envisages a bigger role as facilitator amongst national regulatory agencies (NRAs and NCLs), WHO and other stakeholders, to assure better and effective policies in the areas relevant to vaccine manufacture, regulation, supply and quality.

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