NARAYANA
MEDICAL COLLEGE

Narayana Translational Research & Incubation Centre

Conducted webinar entitled

Developing Formulations for Game Changing Multivalent Vaccines

on April 3, 2021 at 3 pm

Speaker -

Dr. K.S. Jaganathan, Ph.D.

Deputy Director & Head of Vaccine Production Department

Serum Institute of India Private Limited, Pune, India.

Patron

Dr. Surya Prakasa Rao, MD,
Professor and Dean, Narayana Medical College,
Nellore, Andhra Pradesh, India.

Convenor

Dr. Sivakumar Vijayaraghavalu, PhD,
Professor and Head,
Narayana Translational Research and Incubation Centre

Registrants Profile - Total 372 registrants from India (95%) and other countries (5%) – which includes Sweden, Saudi Arabia, Bahrain and Japan. Indian registrants were from across the country with higher percentage from Andhra Pradesh (72%), followed by Tamil Nadu (10%); rest of the 18% are from the following states – Telangana, Karnataka, Uttar Pradesh and Kerala.

Panelist –

1. Guest Speaker - Dr. KS Jaganathan, Deputy Director, Serum Institute of India.
2. Patron - Dr. Surya Prakasa Rao, Dean, Narayana Medical College, Nellore, AP
3. Dr. Balasubramanian Thangavel, Chettinad Academy of Research and Education, Chennai, Tamil Nadu.
4. Convener – Dr. Sivakumar Vijayaraghavalu, Professor and Head, Narayana Translational Research and Incubation Centre, Narayana Medical College, Nellore, AP

Convener, welcomed the registrants and introduced the speaker to them as follows -

Good afternoon and greetings to all – with immense pleasure; on behalf of our institution, Narayana Medical College, Nellore, AP, India and our honorable Dean Dr. Surya Prakasa Rao, welcome you all for the webinar entitled – *Developing formulations for game changing multivalent vaccines by Dr. KS Jagananthan,* Deputy Director and Head of vaccine production department at Serum Institute of India (SII).

In SII, he works on Formulation development, Commercial manufacturing and Troubleshooting activities for vaccines and vaccine adjuvants. He obtained his Ph.D. in Pharmaceutical Sciences under the guidance of Prof. S.P. Vyas from Dr. H.S. Gour University, Sagar, India, in collaboration with National Institute of Immunology (NII), New Delhi. He did his post-doctoral studies at Tokyo University, Japan and worked in collaboration with Kowa Pharmaceutical Ltd, Japan. Prior to joining SII, he worked 14 yrs. for Sanofi India on various projects related to Biologics, Vaccines, Monoclonal antibodies and Protein / Drug delivery.

Dr. Jaganathan is a recipient of Best Scientist award by Ministry of Science and Technology, Government of India and was chosen as key scientist to attend the Nobel Laureate Meeting at Germany. He is also a recipient of several awards. To highlight a few – got Bio-Asia Innovation award from the Hands of Prof. Martin Evans - Nobel Laureate, University Grants Commission (UGC) – Junior Research Fellowship (JRF), AICTE-National Doctoral Fellowship (NDF), Young Scientist Award by DST, Government of India, Japan Science & Technology Post-Doctoral Fellowship award by Government of Japan and Best Employee award – Platinum Category by SANOFI group of company.

As a researcher he published several research articles in International journals, presented his findings in International conferences and symposia; he also has many US patents. He has more than 20 years of experience in Pharma Industry at various roles of Product Development and Operations. We are honored to have you in our forum; with this note Convenor asked Dr. Jagannathan to take over the session and deliver his presentation.

Dr. KS Jaganathan, thanked the organization, Dean and the convener for providing an opportunity to talk about vaccines. He started his talk with a statement that the topic chosen is a vast field; in fact, it is a separate department in pharma industry; hope I will cover the most in 45 min; prior to going in detail about formulations, he gave an overview about vaccines, and highlighted the importance of vaccines and the benefits that the humanity attained in the last century. He also cited some examples to support his overview; for instance, small-pox and polio eradication by vaccination. Further he stated that polio is most cost effective, safe and powerful tool to medicine and prevents suffering, disability and death from the infectious diseases. He further told that the immunization in children prevents up to 5 million deaths in a year due to rubella/polio.

He quoted several other examples to support his notion on vaccination and cited the reduction in number of deaths post – mass vaccinations in the past centuries as an example. He advised that the anti-vaccine groups should consider the risk-benefit ratio and should not escalate the minimal risk/allergies as major concern and should not do negative propaganda about immunization. Further, he told that unlike the past we have well written regulatory guidelines that govern the production and safety of the vaccines used. Automated production facilitates safe and mass production 24 by 7. Once vaccines are prepared; rigorous testing was done to evaluate the toxicity and adverse events. Then the test reports will be sent to National Regulatory Authority (NRA) to get approval for marketing. He told that we have classical pathway of safety – efficacy studies; it is evaluated through different phases of clinical trials (phase I – IV). He said that the vaccine development technology is advancing at rapid phase, earlier di- & tri-valent vaccines were there, then tetra-valent vaccines emerged and then penta-, hexa – and now hepta-valent vaccines are developed. He told that vaccine preparation is not easy like preparing any other formulation; one has to acquire experience in the field by working on it years together. We have

conventional FDA approved aluminum based adjuvants. He explained in detail about such adjuvants; screen shot of his presentation can be found below. He also spoke about the novel drug delivery systems (NDDS), which are currently in the laboratory stage; can be in the market in near future as cargo for different antigens. He started to talk about micro-particles based drug delivery systems, once the therapeutic product is purified the formulation scientist will formulate it into a product, such products should have long –shelf life for months together, at –least 6 months or can even up to a year. Mostly liquid formulations are much preferred, so that the need for lyophilization and re-constitution at the time of injection can be avoided. However, most of the vaccines have proteins as antigens in such cases the lyophilization and storing them in the powder form is a requisite. He also informed that the selection of excipients is important and it depends on the regulations of that particular country. For example, beta-cyclodextrin is used as excipient in Europe and USA; but not in Japan. He emphasized that the quality of the product between different batches, as well between the small and large scale batches should not be compromised. If any changes were predicted between the batches then one has to go for clinical trials; we need to have CMC – chemistry, manufacturing and controls data for different batches, without it regulators will not

approve the product for marketing. Then he started to talk about the aluminum adjuvants, their characteristics and their application in vaccine formulations. He also spoke on the controlling the size of the particles, he told that it should be between 1 and 10 microns, if the size increases or the vaccine materials gets precipitated then the product efficiency will be poor. He also spoke about antigen binding to the adjuvants.

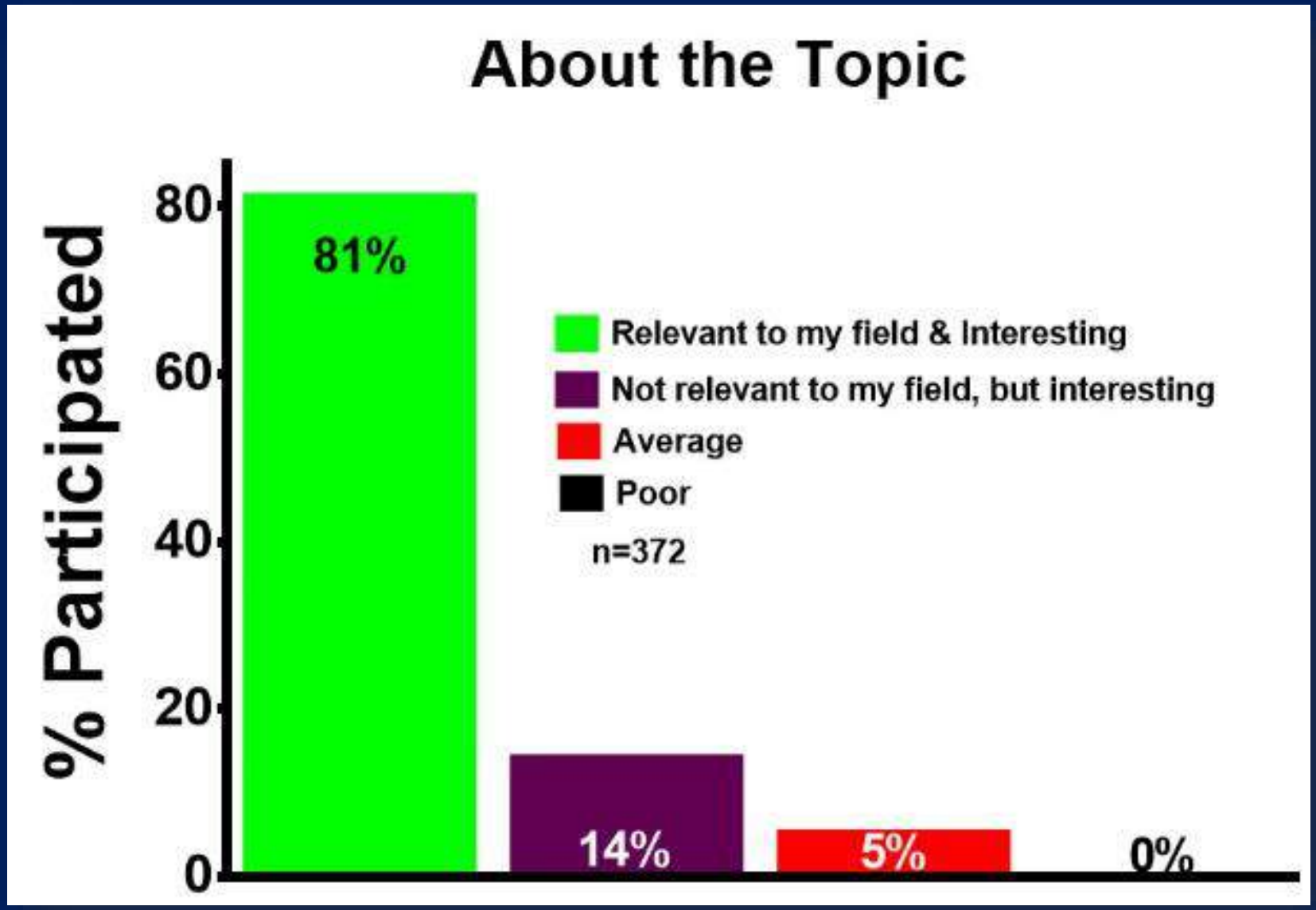
He compared the formulations with current- aluminum based adjuvants vs novel adjuvants which includes - particulate systems include microparticles, nanoparticles and Dendrimers etc., vs vesicular systems such as liposomes, niosomes. He explained how to control the release of antigens in each system mentioned here. He schematically shown the antigen delivery in nasal mucosa from PLGA based delivery system. He shown data including increase in IgG titers and relatively lower levels of inflammatory markers in people received aluminum based adjuvants than other systems. Then he moved on to talk about the cost-effective strategies in vaccine development. He explained using rota-virus vaccine as an example. To prevent degradation due to acidic environment in the stomach, it is co-administered with an antacid; some companies prepared two different vials

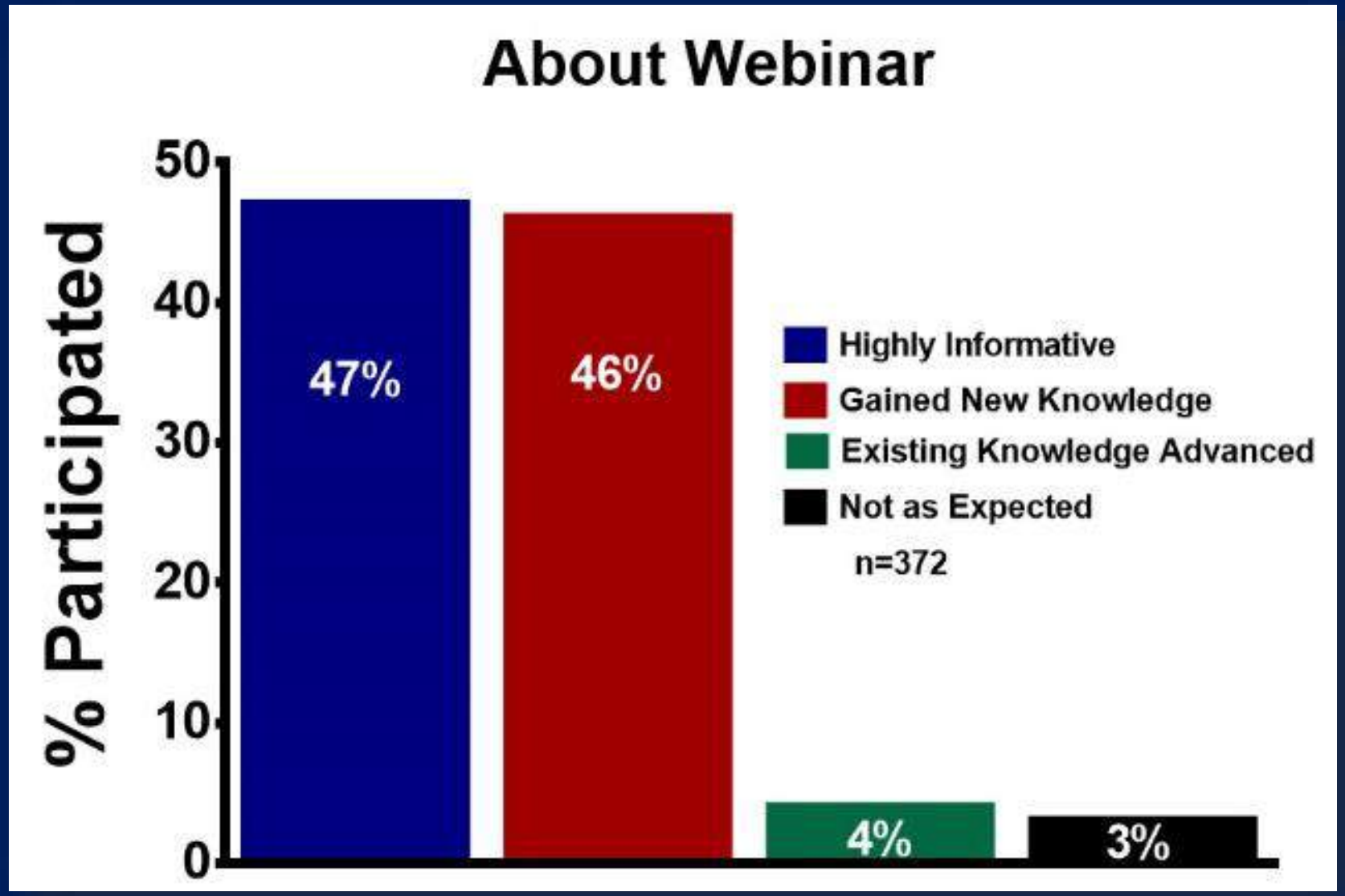
one containing antacid and another one the antigen; whereas some others prepared all-in-one formulation, which includes antacids. The he explained about the manufacturing challenges in the pharmaceutical aspects; 1. Formulation – simplified process vs. liquid vs lyophilized vs Excipients vs stability. 2. R & D Scale of production vs Pilot Scale vs Commercial scale vs Cost of Goods Manufactured (COGM). 3. Product equivalence vs safety & efficacy. Further he stated that the excipient selection is important, we prefer the excipients from non-animal sources and of vegetable grade to avoid post approval changes (PAC) and other complications. Then he explained the importance of mixing and homogenization of the vaccine, for example if we are preparing a 2,500-liter batch, the entire volume should be homogenously mixed and validated for uniformity and the amount of antigen adsorbed on the adjuvants. Then finally, post vaccine production; cleaning up of the production unit is important to ensure no ingredients from this vaccine product adulterates in to another vaccine product. He further told that in their facility, 25 different vaccine products are prepared, at the end of each product preparation, the cleaning validation will be done. A well written SOPs are available for all these things and are strictly followed. He told that all the process should be linked and closely monitored to avoid CMC changes. At last, he summarized all the

salient points about vaccine production, he thanked the organization – Narayana Medical College, Dean and the convener for the opportunity given.

Honorable Vice-Chancellor, Dr. S. Balasubramanian Thangavel, Chettinad Academy of Research and Education, Tamil Nadu joined as the panelist, he appreciated the speaker for a very nice talk and he asked him about the source of chitosan used in the novel drug delivery systems, whether it is natural or synthetic? Speaker replied to him stating that it is from natural source -crustaceans. Further he told that they purchase in bulk from commercial source. Vice-Chancellor of Chettinad Academy of Research and Education, thanked the host institution and the convener for arranging this talk. The speaker also thanked the professor. The webinar ended formally with a vote of thanks by the convener. The registrants were requested to take the poll survey; the results were as shown below.

Poll Survey


About the Topic
% Participated
80
60
40
20
0
81%
14%
5%
0%
Relevant to my field & Interesting
Not relevant to my field, but interesting
Average
Poor
n=372


About Webinar
% Participated
50
40
30
20
10
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47%
46%
4%
3%
Highly Informative
Gained New Knowledge
Existing Knowledge Advanced
Not as Expected
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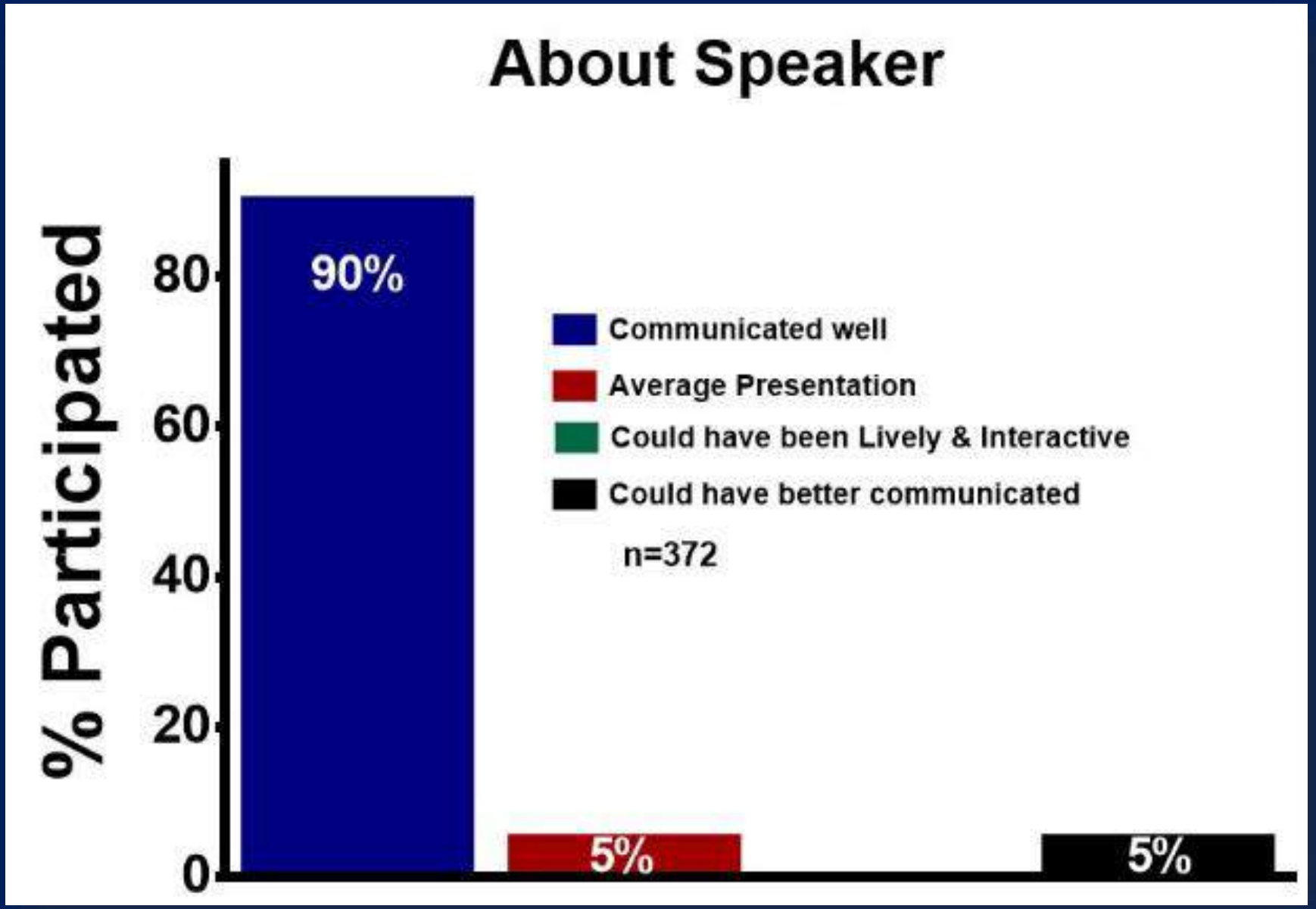
About Speaker
% Participated
80
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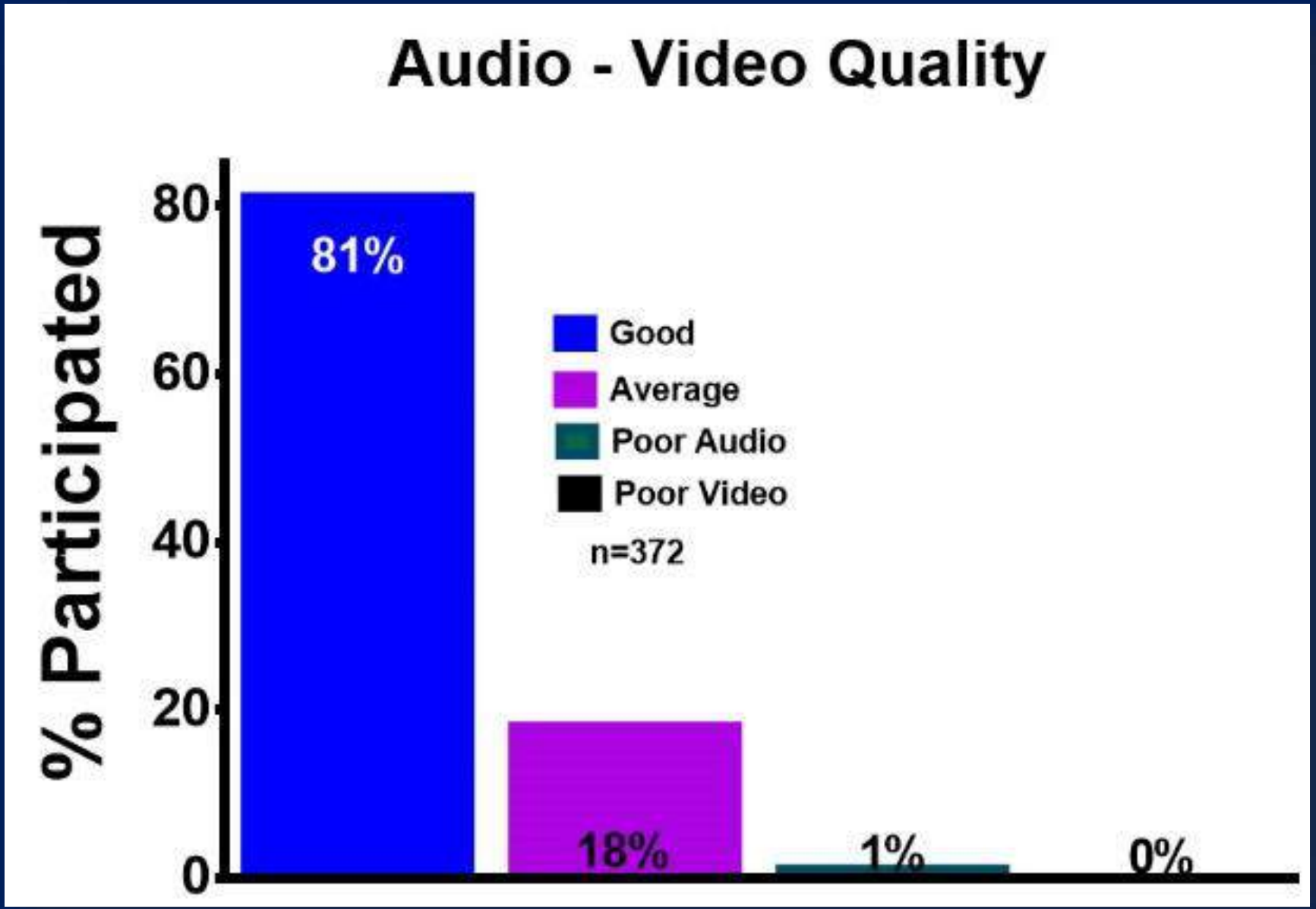
90%
5%
5%
Communicated well
Average Presentation
Could have been Lively & Interactive
Could have better communicated
n=372


Audio - Video Quality
% Participated
80
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20
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81%
18%
1%
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Good
Average
Poor Audio
Poor Video
n=372

Speaker's Presentation – Screen shot

Developing formulations for Game changing multivalent vaccines

by
Dr. Jaganathan KS
Dy. Director

02-Apr-2021

VACCINES

- Save Lives
- Preserve Good Health
- Maintain a high quality life

- Vaccination stands as one of the most successful public health measures in the last century
- Vaccines have provided some of the greatest success in the history of medicine
  - Eradication of Smallpox
  - Near Eradication of Polio
- Most cost effective, safe and powerful tool of medicine
- Prevents suffering, disability and death from infectious diseases

Pre- VACCINE Eg events

- **Birth defects caused by Rubella**
- **Children crippled by Polio**
- **Horrific sound of a baby struggling with Whooping cough**
- **Neonatal mortality by Tetanus**
- **Terrible scene of Hydrophobia**

Now,
"Every year, up to five million children's lives are saved by immunization"

Disease Case in US at 20th Century before advent of vaccine and after utilization of vaccine

S.No	Disease	Estimated prevaccine cases in 20th Century	Deaths in 2017
1	Smallpox	4.81 million	0
2	Poliomyelitis	1.63 million	0
3	Diphtheria	17.60 million	2
4	*Haemophilus Influenza*	2.00 million	22
5	Measles	5.03 million	36
6	Mumps	1.52 million	236
7	Pertussis	1.47 million	6632
8	Rubella	4.77 million	20
9	Tetanus	0.13 million	13

POLIO FACT SHEET - INDIA

S.No	Year	No of Polio cases Reported
1	1985	150000
2	1991	6028
3	2009	741
4	2010	42
5	2011	1
Last Case 13 January 2011		

- Last wild Poliovirus type1 - 13 Jan 2011, Howrah , West Bengal
- Last wild Poliovirus type2 - 10 Oct 1999, Aligarh, Uttarpradesh
- Last wild Poliovirus type3 - 22 Oct 2010, Pakur, Jharkhand

13 Jan 2012 - Major Milestone in the history of Polio Eradication

Polio Free World By 2023 (Tentatively)

HUMANITY AND VACCINATION

Recent times…

- **Despite our successes, we realize that the battle against disease will probably never end, since new challenges continuously appear**

Anthrax –

Bird Flu –

BSE/TSE

Chicken guinea

Dengue

SARS

Now COVID-19

VACCINE SCENARIO PAST

Drug Product: Formulation and its Challenges ???

- Conventional ? Aluminium adjuvants
- Lyophilized
- NDDS - ???
- Micro/Nanoparticulate Systems eg. Microparticles, Nanoparticles, Dentrimers, Soluble microneedle coated with nanoparticles etc
- Vesicular systems e.g Liposomes, Niosomes etc

Ideal requirements: Vaccine Formulations

- Stability: Liquid or lyophilized formulations???? COGM???
- Selection of excipients
- Easy operations : Process steps, duration / time??? Lean principles?
- Scale up challenges ? Additional characterization??? Safety, Stability, Efficacy? Further clinical trial??
- Analytical methods availability ??
- Shelf life??
- Regulatory requirements: Country specific
- Others: Market demand, competitors, IPR issues etc – Long term goal

Current Vaccine Delivery Platforms: Overview

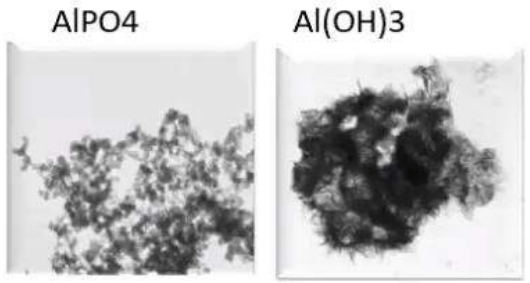
- Aluminium based adjuvants
  - Aluminium Hydroxide and Aluminium Phosphate
- NDDS based adjuvants
  - Particulate delivery systems
    - Microparticles and Nanoparticles
    - Dendrimers
  - Vesicular systems
    - Liposomes / Niosomes
  - Others:
    - Transdermal patches TLR agonist / MF-59 / ISCOM / QS-21 / MPL adjuvants

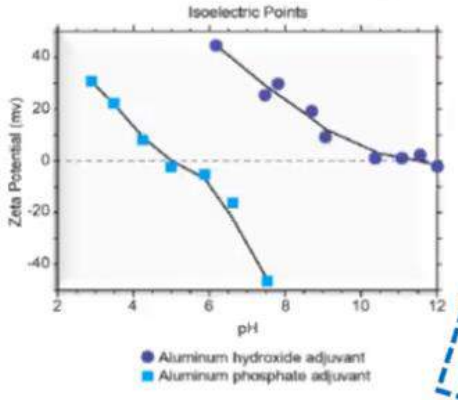
Pre-formed gel or in-situ precipitation

Case study : Microparticles and Liposome in-situ gelling system

Aluminium Based adjuvants: Contd...

- Aluminium Phosphate
  - Amorphous aluminum hydroxyphosphate
  - Negatively charged at phys. pH PZC ~5-7
  - Primary particles: Plate-like, 50 nm
- Aluminium Hydroxide
  - Crystalline aluminum oxyhydroxide
  - Positively charged at phys. pH, PZC=11
  - Primary particle: fibers, 4.5 x 2.2 x 10 nm
- Antigen-adjuvant adsorption ?
  - Electrostatic attraction
  - Ligand-exchange
  - Is percent adsorption important in vaccine??





Challenges in Combination vaccine development:
Adsorption mechanism & stability

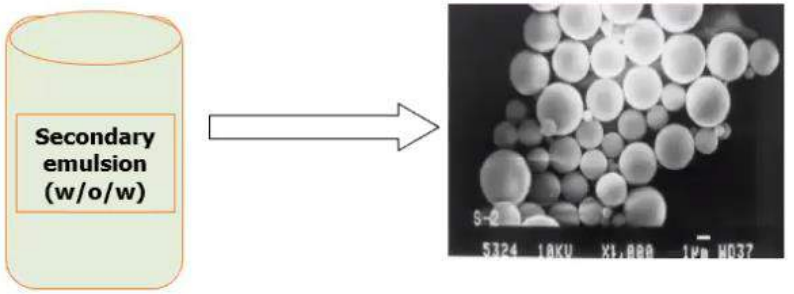
DD systems: Microparticles and In situ gelling system...

- **System(s):**
  - PLGA microspheres
  - Modified PLGA microspheres
  - Liposome in situ gelling system
- Antigen:
  - r-HBsAg
    - Issues:
      - Low Entrapment efficiency
      - Risk of altering antigen integrity
      - Acidic environment inside PLGA microspheres

- Stability of antigen in PLGA microspheres, modified PLGA microspheres (MPLGA) and Liposome *in-situ* gelling system(LIGS)
- Humoral Vs Cell mediated immune response or Both.
- To evaluate/compare its immune responses with control (Aluminium based vaccines)

Preparation of PLGA & MPLGA

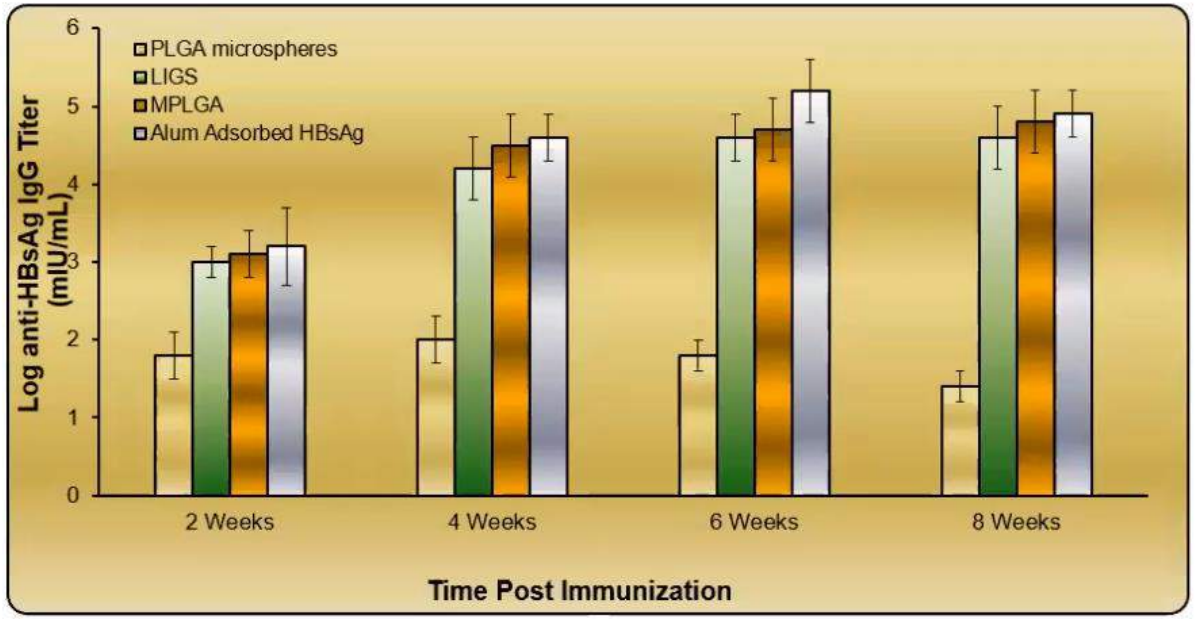
System with
Protein stabilizer
& Antacid



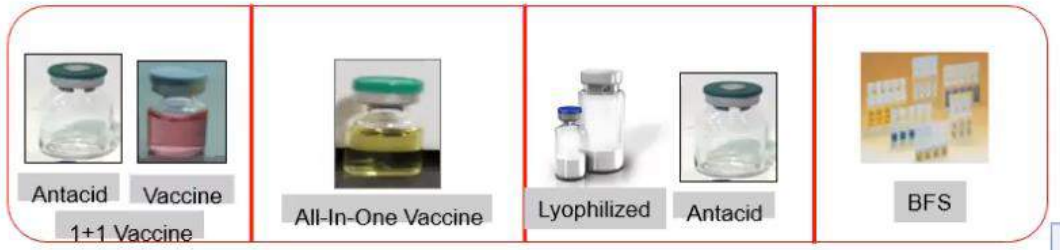
Chitosan Coated PLGA particles (MPLGA)

LIGS & Nasal Mucosa

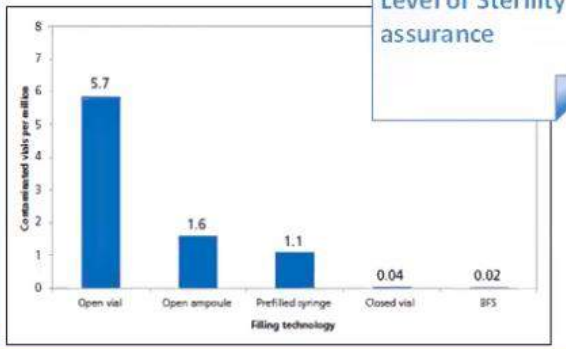
Serum IgG titer



Importance of Cost Effective Strategies : Vaccine Development



- Avoid process change and multiple clinical trials.
- Market demand Vs OEE Vs COGM Vs Quality requirements: Should have balance
- Process knowledge, Product equivalence and robustness are important factors for cost effective strategies.



Pharmaceutical Aspects: Manufacturing challenges

- Formulation:
  - Simplified process Vs Liquid Vs Lyophilized vs Excipients vs Stability
- Scale:
  - R&D scale Vs Pilot scale Vs Commercial scale Vs COGM
  - Product equivalence Vs safety & efficacy
- Process Validation: Process robustness
- Mixing and Homogeneity :
- Cleaning validation:
- Filling: Single dose vial Vs Multi-dose vial Vs PFS

Summary

- Importance of Formulation and manufacturing strategy in Vaccine industry:
  - ✓RFT
- Novel delivery systems : Important for upcoming vaccines and broad immune response
- Cost effective strategies : Development and commercial manufacturing
- Commercial manufacturing challenges:
  - ✓Trouble shooting and robust process are important
  - ✓Continues quality improvement and regulatory integration