Exbumin®, an EMA and FDA approved excipient, provides improved performance and stability in vaccine development and final formulations

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Introduction & Objectives

Human serum albumin (HSA) has been used in various parts of biopharmaceutical manufacturing for its well-known attributes and properties, including:

- Benefits stability and preservation
- Limits aggregation
- Prevents non-specific binding on surfaces
- Increases solubility
- Promotes transport and binding of molecules and ligands
- Protects from mechanical shear
- Enhances API homogeneity[1]

Of particular interest here is the stability and preservation effect that albumin has on viral vaccines. A key aspect of vaccine production is maintaining stability and function of the final product, including sustained potency and viral titer. Indeed, this knowledge has driven various preservation strategies, such as lyophilization, temperature control, and localized constitution for use. However, these are only partial solutions; these strategies introduce their own challenges to vaccine stability and potency. There are chemical stabilizers and excipients formulated for vaccines, but none have been shown to be as effective as those containing HSA in combination with other excipients (e.g., sugars). HSA's ability to serve as a preservative, protect biologics from both physical and chemical stresses, and the other advantages listed above remain unparalleled.

Recombinant HSA (rHSA), however, has additional benefits:

- Performance better than native HSA in most cases
- Eliminates safety concerns from blood-derived products, such as adventitious pathogenic agents and prions
- Reduces donor-to-donor variability of blood-derived products
- Removes dependence on blood supplies, which are at risk from Sars-COV-2 and similar supply disruptions.[2,3]

The objective of this poster is to demonstrate the performance and stability improvements that an rHSA, Exbumin®, has on viral vaccines. Furthermore, this FDA and EMA approved excipient should be preferred in future vaccine, cell therapy, and gene therapy formulations.

Exbumin rHSA

Exbumin is a recombinant human serum albumin (rHSA) that is completely animal- and blood-free. It was developed to improve stability for vaccines and cell & gene therapy.

- FDA and EMA approved excipient for injectables
- Scalable and reliable
- Made in the USA

Stability Performance Results

Previous studies by Wiggen et al. showed the stability benefits of rHSA against flavivirus vaccines for Dengue.[4] Reconstituted DEN-2 PDK-53 vaccine was evaluated for stability using various excipients, including common sugars, poloxamers, and Exbumin rHSA.

The results of various excipient combinations conclusively showed the "significant stabilizing effect of rHSA." Furthermore, the results showed the synergistic effect of combining rHSA with a sugar (trehalose) and a Pluronic® block copolymer (F127). Figure 1 shows that after 21 hours, there is no remaining viral titer in PBS solution. When 15% trehalose (T) and 2% F127 (F) are added, viral titer increases to 3% ± 1.7%. When Exbumin rHSA is added, the viral titer survival increases to 45.3% ± 2.3%.

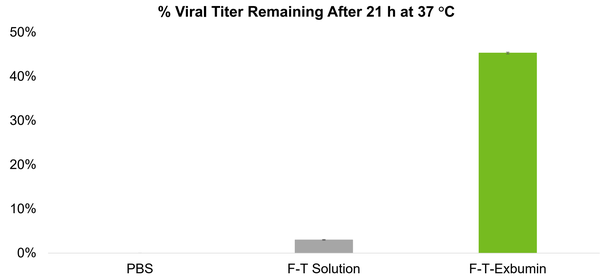

Figure 1. Exbumin® rHSA, when combined with F127 copolymer and trehalose, provides significant virus survival, particularly when compared to PBS, which showed no surviving virus after 21 hours.[4]

Similarly, the F-T-Exbumin rHSA formulation was also shown to preserve 100% of DEN-2 PDK-53 viral activity after undergoing two freeze-thaw cycles, compared to only 1.2% when PBS was used alone. Across several chimeric flaviviruses and at room temperature, 4 °C, and 37 °C, the F-T-Exbumin rHSA formulation provided the same level of stability, demonstrating its utility across a wide spectrum of flaviviridae.

These data show that albumin plays a critical role in stabilizing live virus against inactivation and protects lyophilized vaccine against physical collapse and from thermal stress from freeze-thaw cycles.

Alfano et al. complemented the data above by evaluating both stability and Vero cell-based virus productivity of four viruses:[5]

- Influenza
- Zika (ZIKV PRVABC59)
- Dengue (DENV-2 16681)
- Ebola (EbolaDVP30)

Infected Vero cells were expanded in 2D and 3D cultures using two contrasting media:

1. EMEM + 10% FBS (fetal bovine serum) to represent traditional media with native serum proteins.
2. Serum-free media formulated with Exbumin rHSA.

Figure 2 shows the relative production of the four viruses and demonstrate that Exbumin both produces and stabilizes the virus better than native serum proteins.

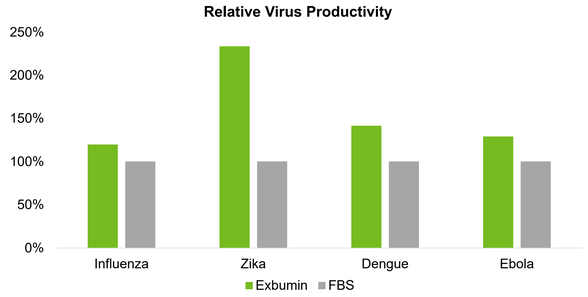

Figure 2. Relative virus production of Vero cells cultured in media with either Exbumin rHSA or FBS. Exbumin reduces degradation mechanisms and contributes to increased virus productivity. Data are normalized against titer from Vero cultured FBS.[5]

rHSA in Commercial Vaccines

While the above data demonstrate the effectiveness of Exbumin rHSA for both producing and stabilizing viruses, greater attention has recently been given to rHSA due to its benefits beyond performance. Addressing the supply chain fluctuations of human serum, especially due to the pandemic, and better compliance to regulatory demands due to enhanced quality and safety of removing blood- and serum-based components, the industry has been motivated to incorporate improved excipients in manufacturing and the final formulation.

Wiedmann et al. explored Merck's M-M-R® II vaccine (measles, mumps, and rubella) to evaluate replacing native HSA with an rHSA. This change was sought due to "regulatory requirements and limited suppliers of HSA suitable for human use."[6]

Figure 3 demonstrates improved viral titer in the formulation change from using HSA to rHSA.

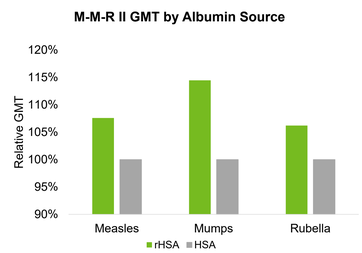

Figure 3. Comparison of M-M-R II by geometric mean titer (GMT) for measles, mumps, and rubella (data are normalized against the HSA data).[6]

The journey for rHSA to be included as an excipient in final formulation for an injectable drug product expanded as Exbumin was incorporated in Merck's ERVEBO® Ebola vaccine formulation:

- rHSA used as a final formulation excipient for the first time
- Chemistry, manufacturing and controls were submitted
- Exbumin® is made in the USA under cGMP standards
- Approved by both FDA and EMA[7,8]

"Excipient-grade product was collaboratively established to meet both the immediate and sustained needs of this medically-significant human vaccine program."[7]

Table 1. Composition of the ERVEBO Vaccine.[8]

Active Ingredients	Concentration	Function
Live attenuated rVSV expressing the glycoprotein of Zaire Ebola Virus	≥ 7.2 x 10^7 pfu/mL	Active
Inactive Ingredients	**Function**	
Tromentamol (Tris)	Buffer	
Recombinant Human Serum Albumin (rHSA)	Stabilizer	
Water for Injection	Quantity Solvent	

Table 1 is adapted from the EMA assessment report for ERVEBO. Hundreds of thousands of patients have benefitted from ERVEBO, stabilized with Exbumin rHSA.

Conclusions

- Albumin, among its many benefits, has a significant stabilizing effect on viruses, including from production to final use.
- rHSA is shown consistently to perform better than native forms of albumin and serum products and possesses numerous other supply chain reliability, regulatory, and safety benefits.
- Exbumin enables the realization of the benefits of albumin in production and formulation of vaccines without the variation, safety, and supply chain risks of serum-derived sources.
- Through close partnership, we were able to satisfy the requirements of both FDA and EMA for inclusion as the first rHSA excipient in a human-injectable vaccine.[8]
- Today, Merck serves the world with its unique ERVEBO Ebola vaccine that has shown remarkable safety and efficacy.

References

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