

HSI Symposium on Global Harmonization of Vaccine Testing Requirements.

Making the elimination of ATT and TABST a concrete global achievement – INDIAN SCENARIO



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Preamble

Vaccines are of biological origin and have the potential to vary from batch to batch. Consequently, vaccines are tested for batch-to-batch consistency and many of these tests involve animals i.e. it is at the expense of large numbers of animals that are used in quality control tests before vaccines are released onto the market.

The Principles of the 3Rs (Replacement, Reduction and Refinement) were developed over 50 years ago providing a framework for performing more humane animal research. Since then they have been embedded in national and international legislation and regulations on the use of animals in scientific procedures, as well as in the policies of organizations that fund or conduct animal research.

Abnormal Toxicity Test (ATT)) and Pharmacopoeial recommendations

- ▶ The Indian Pharmacopoeia (I.P.) required the abnormal toxicity test (ATT) using mice and guinea pigs as a non-specific safety test for vaccines and sera since long.
- ▶ But after the introduction of GMP and GLP principles in the manufacturing and testing of vaccines, the practice continued involving a huge animal number but with a common outcome that there was no significant outcome with respect to the positivity of the results i.e. the results always passed for ATT.
- ▶ Also, vaccines causing adverse reactions in the healthy subjects could not be identified by the abnormal toxicity test.

Abnormal Toxicity Test (ATT)) and Pharmacopoeial recommendations

- ▶ Indian Pharmacopoeia Commission (IPC) considers global pharmacopoeial harmonization while developing quality standard of drugs for Indian Pharmacopoeia. IPC has an expert committee on vaccines for human use which provides its recommendations for further consideration of the competent authority.
- ▶ IP has already provided option for use of any alternative methods under General notices and has taken proactive measures for the use of alternative tests in place of *in vivo* tests during the last few years.

Abnormal Toxicity Test (ATT)) and Pharmacopoeial recommendations

- ▶ As requirement of ATT causes unjustified use for a substantial number of animals without any benefit with regards to demonstrating product safety and that using live animals in ATT does not comply with animal welfare and the 3Rs principle because of lack of a sound scientific rationale and justification.
- ▶ Hence, based on above approach, Indian vaccine manufacturers approached Indian Pharmacopoeia Commission (IPC) during various collaborative meetings involving the vaccine manufacturers, National Regulatory Authority (NRA), National Control Laboratory (NCL) and Animal Welfare Bodies (All protagonists) like PETA to consider waiving of the ATT.

Abnormal Toxicity Test (ATT)) and Pharmacopoeial recommendations

- ▶ The issue was discussed at length and supportive evidences were provided. Based on the scientific reasoning and justification provided IPC finally published its recommendation for omission of ATT for routine lot release of vaccines as following:
- ▶ “The abnormal toxicity test may be omitted for routine lot release once the consistency of production has been well established to the satisfaction of NRA and Good Manufacturing Practices are in place. Each lot, if tested by the National Control Laboratory (NCL) should pass the test for abnormal toxicity.” (e.g. in case of AEFI Investigations).

Abnormal Toxicity Test (ATT)) and Pharmacopoeial recommendations

- ▶ In consonance with IPC's recommendation, most of the vaccine manufacturers then filed Post Approval Change (Variation) in accordance with Guidance For Industry with NRA for removal of abnormal toxicity test on vaccines and further also obtained approval from WHO (in case of WHO Prequalified Vaccines) and finally omitted ATT from routine testing for lot release.
- ▶ However, as a part of development of a new products ATT is still being performed until consistency of production is established to the satisfaction of NRA.

Scope for application of the 3Rs in ATT

Reducing animal use in Quality Control tests

- ▶ **Proposal:** The general monograph on Vaccines should provide a considerable scope for reduction by allowing the safety test to be waived for established vaccines under certain conditions: The number of consecutive batches to be tested depends on a number of factors such as the type of vaccine, the frequency of production of batches and experience with the vaccine during development safety testing and during application of the batch, testing of 10 consecutive batches is likely to be sufficient for most products.
- ▶ As ATT is still a requirement for product registration in different countries, there should be a globally harmonized approach to waiving of the safety test (ATT) through participation in the International Cooperation on Harmonization of Technical Requirements for Registration of vaccines.



Thank You

