Medicines & Healthcare products Regulatory Agency

NIBSC

Quality evaluation of clinical consistency lots of MenFive, a pentavalent (A,C,W,X,Y) meningococcal serogroup conjugate vaccine

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INTRODUCTION

Following success with MenAfriVac in protecting sub-Saharan populations from invasive group A- meningococcal disease, a multivalent vaccine was developed to protect against four additional circulating meningococcal serogroups (Fig. 1), where protection was feasible by a glycoconjugate approach. Three consistency batches of the pentavalent Meningococcal groups A, C, W, X and Y conjugate vaccine, MenFive, were manufactured by the Serum Institute of India Private Limited (SIIPL) for phase III clinical trials in West Africa and India. In addition to performing lot release testing at SIIPL, further independent evaluation was performed at the National Institute for Biological Standards and Control, U.K.

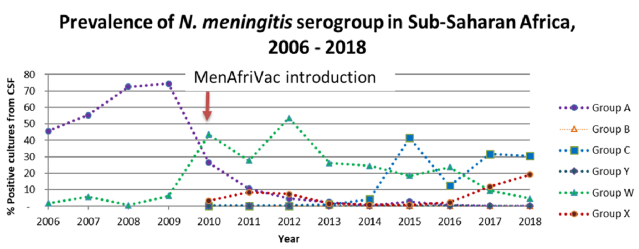


Figure 1: Seroepidemiology data acquired from lumbar punctures taken in sub-Saharan Africa reveal significant meningococcal disease due to serogroups C, W, and X following the elimination of group A strains. Data taken from Meningitis Weekly Bulletins, WHO, between 2006 and 2018.

MATERIALS AND METHODS

Analytical and ELISA-based methods were performed on purified polysaccharides (PS), conjugate bulk components as well as final product to confirm the structure, serological identity and safety. Testing carried out included O-Acetyl content, endotoxin content, Molecular size distribution, and Total and Free saccharide content, according to WHO recommendations for meningococcal polysaccharide (1976, 1980) and conjugate (2004, 2006) vaccines .

RESULTS

Polysaccharide Quality

Polysaccharide *O*-acetylation levels were on average, 85 % in group A, 72 % in group C; 35 % in group Y; and, 45 % in group W lots (Fig. 2), thus meeting WHO guidelines. The size of the PS's ranged Y > X > C > W > A, based on elution volume. Endotoxin (LAL) levels determined on the PS by kinetic turbidometric and gelation clot methods were < 10 IU/µg for groups C and Y; and < 45 IU/µg for groups A, W and X (Fig. 3).

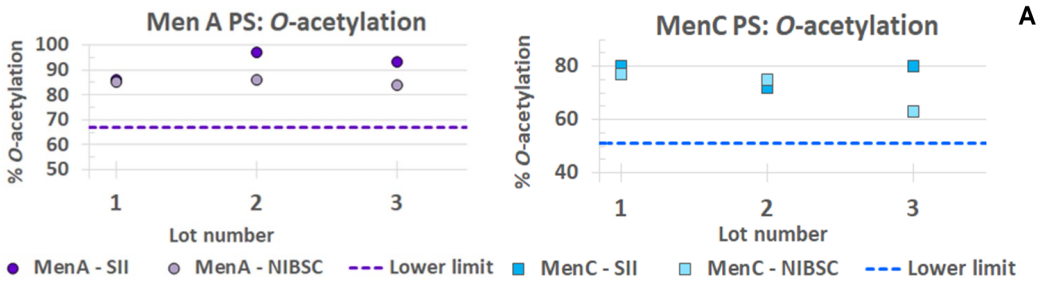
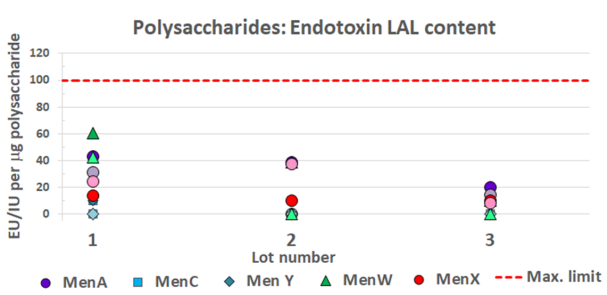


Figure 2: *O*-acetylation contents of phase III polysaccharides. Hestrin and ^{1}H-NMR methods were used at SII and NIBSC, respectively. The Hestrin values and lower limits were converted to % *O*-acetylation (mol *O*-acetyl per mol saccharide repeating unit) using formula weights of serogroup PS with typical *O*-acetylation.

Figure 3: Endotoxin content of purified polysaccharides. Kinetic turbidimetric and gel-clot assays were performed by SII (dark symbols) and NIBSC (pale shades), respectively for each of three phase III lots. The maximum limit indicated (≤ 100 IU/µg PS) was set for groups A, C and X, with a higher limit provisionally set for groups Y and W, although all lots were within the indicated limit.



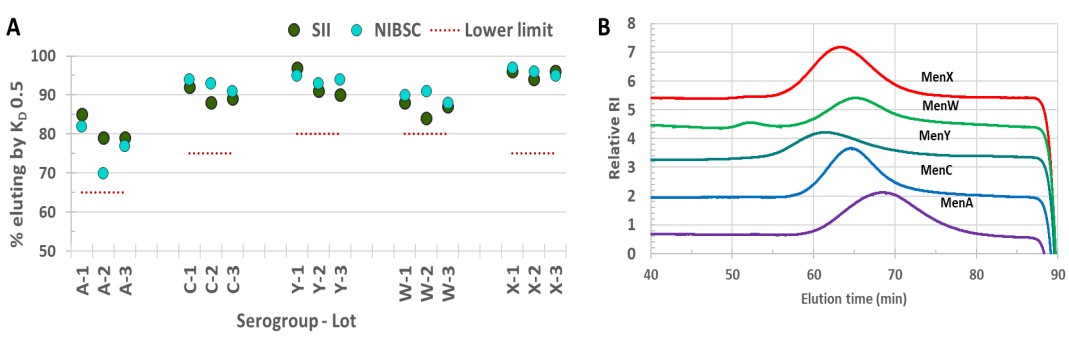


Figure 4 A & B: Molecular sizing of polysaccharides. Consistency data from SII and NIBSC (A) and chromatograms using a TSK 6000 + 5000 PWXL column series (B) are shown. Both laboratories used PBS 'A' eluent, and peaks were integrated using refractive index values.

Bulk conjugate characterisation

A sensitive measure of consistency, the sizing profiles of individual lots of the conjugated TT (to groups A and X) and rCRM197 (to groups C, Y and W) were generally superimposable, and free of measurable contaminants in 280 nm and RI traces. Size distributions were as expected for TT conjugates and rCRM197 conjugates (Fig. 5). Non-conjugated polysaccharide determined following separation by deoxycholate precipitation of the conjugated saccharide was < 25% for all groups (Fig. 6) and did not rise significantly during freeze-drying. PS/protein ratios showed consistency across the lots.

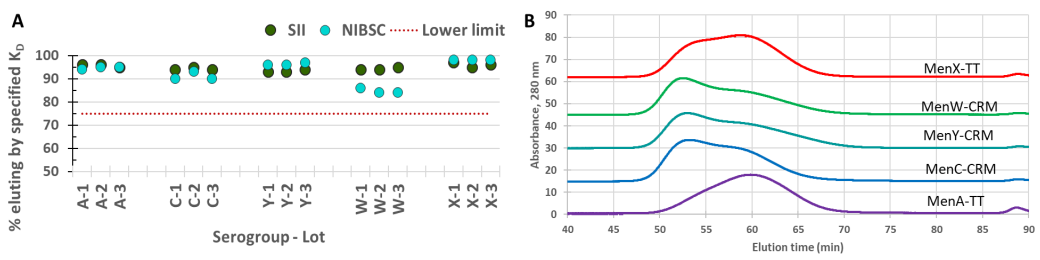


Figure 5 A & B: Molecular sizing of bulk conjugates. Consistency data (A) and chromatograms (B) are shown. Both laboratories used TSK 6000 + 5000 PWXL column series and PBS 'A' as eluent, and peaks were integrated using A280 nm signals. Each laboratory specified in-house KD values.

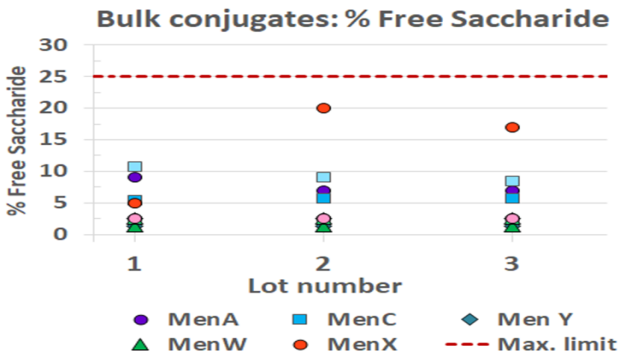


Figure 6: % Free Saccharide of bulk conjugates. Separation of unconjugated saccharide was performed by DOC-precipitation (SII, dark shades) or ultrafiltration (NIBSC, pale shades), while both laboratories used HPAEC-PAD for saccharide quantitation, using WHO International Standards for each PS serogroup (nibsc.org/products), or in-house PS standards with unitages established using the ISs.

Final vial consistency

The target dose of 5 µg/dose of each serogroup polysaccharide was confirmed by HPAEC-PAD using WHO International Standards (Fig. 7). Pyrogen content (Fig. 8) and sterility were confirmed according to WHO recommendations.

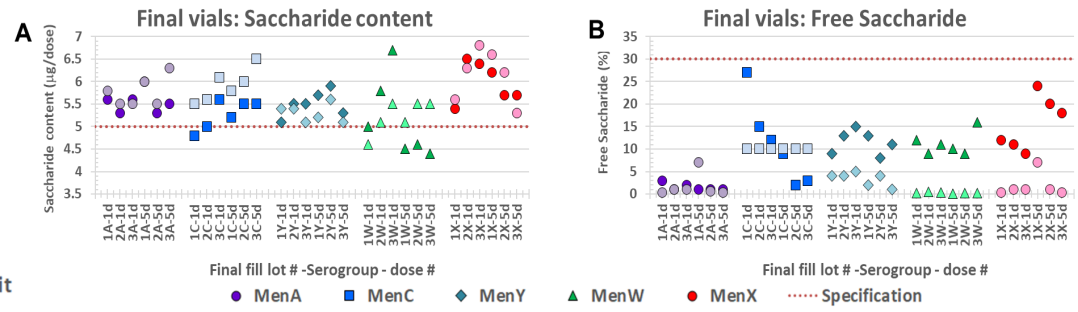


Figure 7 A & B: Saccharide contents (A) and % free saccharide (B). Saccharide contents were consistent between the manufacturer and independent control laboratory for 1-dose and 5-dose fills. All serogroup saccharides were ≥ 3.5 mg/dose (the acceptance criteria) using the HPAEC-PAD assay with polysaccharide standards described in Fig. 5 legend. Free saccharide contents (B) were assayed by different methods (see Fig 6) and all vials met the internal release criteria of < 30% free saccharide.

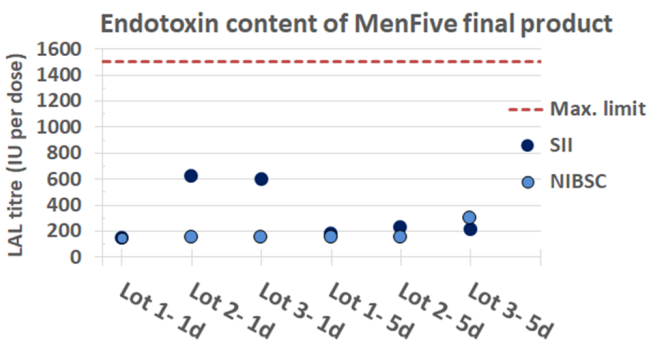


Figure 8: Endotoxin content of phase III lots of MenFive by two methods show consistent results for 1- and 5-dose formulations. Using *Limulus* amebocyte lysate, Kinetic Turbidimetric and Gel-clot assays were performed at SII and NIBSC, respectively, and values were lower than the provisional specification of 1500 IU/dose. Final vials were reconstituted in the product's diluent (saline) or water for injection.

CONCLUSIONS

The quality evaluation of this pentavalent vaccine developed by PATH and SIIPL has concluded. With the successful completion of ongoing clinical and stability evaluation, the vaccine is expected to progress to licensure and WHO Pre-qualification in 2021 for use on the African continent and globally to eliminate disease caused by five serogroups of meningococcus.

REFERENCES

Daugla et al.,*Lancet* 2014; 383:40. ; Chen *et al*., *Lancet Infect Dis 2018;* 18:1088. WHO. Meningococcal meningitis (Recommendations) https://www.who.int

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