NOVARTIS VACCINES AND DIAGNOSTICS	CONFIDENTIAL
Department: QCIM - ARC Laboratory: QC Bacterial Serology1 – ARC-AE1	Title: Qualification report of the Bexsero filled product (MNNZ_050) lot 126901 to be used as reference standard vaccine in the MDRP test.
SOP 305801-305566-305567	Protocol Number: **ATLAS No. 316288-03** **Legacy n°** N/A

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Report Number 316288-03
Legacy n° N/A

Title:
Qualification report of the Bexsero filled product (MNNZ_050) lot 126901 to be used as reference standard vaccine in the MDRP test.

PROTOCOL USED FOR QUALIFICATION: Atlas n°. 310656-01

1) Background and scope/Scopo

The purpose of the document is to define the potency value to assign to the new reference vaccine MNNZ 13.050 lot 126901 in the Multi Dilution Relative Potency (MDRP) testing for the Bexsero vaccine.

The Bexsero lot 126901 relative potency has been assessed with respect to the old reference standard, Bexsero lot 112801. The new reference lot 126901 will replace the current reference lot 112801.

The data used for the definition of the potency for the new reference were obtained from 12 immunization schemes according to the Qualification Protocol 310656.

Revision 02

Revision 02 of the document has been issued to report the assigned potency/conversion for each antigen of new reference vaccine lot 126901 with four decimal digits.

Statistical evaluation reported in Attachment 1 has also been updated to insert four decimal digits to the assigned potencies/conversion factors.

Revision 03

Revision 03 of the document has been issued to add numbers of Attachment pages.

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2) Qualification tests/Prove di Qualifica

In order to define the potency for the new reference lot 126901, twelve (12) immunization schemes were performed by Animal Experiment 1 laboratory, according to PLAS immunization procedure 305801, as reported in the Qualification Protocol No 310656. Packed lot 126901A was used for the immunizations. Each scheme was repeated twice (run 1 and run2), according to PLAS method, including 3 vaccine lots:

- Lot 1: 126901A (new reference)
- Lot 2: 112801-F (Gold reference, see qualification protocol No 310662)
- Lot 3: 112801 (current reference)

For each vaccine lot, 4 groups (four different doses) of 8 mice each (32 mice in total) were immunized two times at day 0 and day 21, bleeding at day 34-36 (SOP 305801).

The 32 sera for each vaccine lot were analyzed by QC Bacterial Serology 1 laboratory, performing an indirect ELISA test against every single antigen 287-953, 936-741, 961c and OMV according to PLAS method, respectively SOP 305566 and SOP 305567.

A statistical model (Parallel Line Assay as per Eur.Ph. 5.3) was used to estimate the Relative Potency (RP), selecting three vaccine doses combination for run, among the four used to immunize the mice. More details regarding the procedure used for the selection of the doses can be found in the TR Atlas number 305730.

3) Discussion of the results / discussione dei risultati

Out of twelve immunization schemes, twelve RP values were obtained for each antigen of the new reference lot 126901, with the exception of antigen 936-741 which provided eleven (11) valid results. The invalid result for the antigen 936-741, (immunization scheme B2) is due to the failure of the validity criterion related to significant regression of reference lot in both the runs. The above result was discarded from the analyses and no further immunizations were done to replace it, since at least 6 values are present (even after the Invalid deletion) for this antigen as per qualification strategy described in the protocol No 310656. RP results and the relative 95%CI of each single assay are reported in the table below (Table 1).

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Table 1: RP and relative 95%CI results for all the 4 antigens and the 12 schemes

	Nr. Immuniz. Scheme	ID Immuniz. Schema	287-953			936-741			961c			OMV			METHOD
			RP	LCL	UCL	RP	LCL	UCL	RP	LCL	UCL	RP	LCL	UCL	
126901A vs 112801	1	A1	1.0	0.7	1.5	1.7	0.7	4.8	1.1	0.8	1.6	0.8	0.6	1.2	PLAS
	2	A2	0.7	0.4	1.2	1.1	0.4	2.9	1.4	0.8	2.4	1.3	0.8	2.3	
	3	A3	1.3	0.8	2.2	1.1	0.5	2.2	1.6	1.0	2.7	1.1	0.6	1.9	
	4	B1	1.3	0.6	2.8	1.7	0.5	8.6	1.3	0.7	2.2	1.3	0.9	2.1	
	5	B2	0.6	0.3	1.3	invalid	invalid	invalid	1.3	0.8	2.2	1.3	0.8	2.1	
	6	B3	1.9	1.1	3.3	3.2	1.3	7.9	1.6	0.9	2.9	2.1	0.9	4.8	
	7	C1	0.7	0.4	1.2	1.0	0.4	2.0	1.1	0.7	1.8	1.3	0.8	2.2	
	8	C2	1.2	0.8	1.9	0.6	0.2	1.5	0.8	0.5	1.2	1.5	1.0	2.2	
	9	C3	0.9	0.5	1.8	1.9	0.9	4.1	0.8	0.5	1.2	1.1	0.8	1.7	
	10	D1	0.5	0.3	0.8	1.5	0.8	3.0	0.7	0.3	1.9	1.1	0.6	2.0	
	11	D2	1.1	0.8	1.6	0.9	0.3	2.5	1.2	0.8	1.8	0.9	0.5	1.6	
	12	D3	0.7	0.2	2.5	0.4	0.1	0.8	0.8	0.5	1.1	0.8	0.6	1.3	

Moreover, during the qualification tests, 1 OOS result for the antigen 936-741 and 1 OOS result for the antigen 287-953 were observed (OOS are outlined in red in above). The OOS were investigated (DR number 299401). Both the OOS results were confirmed and used in the statistical analyses. The statistical analyses started from doing the Dixon's test on all the usable RP values including the confirmed OOS results and excluding the invalid RP for the antigen 936-741. The Dixon's test did not pointed out any outliers for all the antigens. Due to this, the assigned potency has been calculated as combination of all the usable results listed above as per Eur.Ph. 5.3 paragraphs 6. Results are reported in the table below (Table 2) and details on the qualification strategy and the statistical analyses are given in the attachment 1.

Table 2: Results for the four antigens

Antigen	Method	LCL	Assigned potency	UCL	%LCL respect to RP	%LCL respect to RP	Desired precision
287-953	semi weighted	0.8171	**0.9693**	1.1500	84	119	Y
936-741	semi weighted	0.8908	**1.1885**	1.5857	75	133	Y
961c	weighted	0.9361	**1.0752**	1.2350	87	115	Y
OMV	weighted	0.9988	**1.1465**	1.3159	87	115	Y

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Acceptance criteria:

For all the antigens the precision must be in the range 69-146% of the RP.

For all the antigens the desired precision of 69-146% of the RP has been reached. As stated on the qualification protocol No 310656; no further immunizations were needed so the final assigned potencies were confirmed.

4) Conclusions and recommendations/ Conclusioni e raccomandazioni

The assigned potencies and the relative 95%CI were calculated as described above and more in detail in the attachment 1. For all the antigens the desired precision of 69-146% of the RP has been reached: the assigned potencies reported in the table below (Table 3) can be used as conversion factor for all the future MDRP tests which will use the new reference lot 126901.

Table3: Conversion factors for Relative Potency calculation

Antigen	Assigned potency/Conversion factor
287-953	0.9693
936-741	1.1885
961c	1.0752
OMV	1.1465

5) Stability/Stabilità

The lot MNNZ_050 126901 was produced in December 2012 and stored at a temperature of +2/8°C.

Considering that the shelf life of the current reference lot 112801 is 36 months as reported in the relevant Qualification Report 301437-03, the same shelf life can be applied to the lot under qualification. Therefore, lot 126901 can be used as reference for SOPs 305566 and 305567 until the end of November 2015.

However, any trend of the reference 126901 will be monitored every four months taking into considerations slope and relevant p-value of the linear trend and control chart violations as described in SOP 303007.

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6) Omogeneità delle aliquote (quando applicabile)

N/A

7) Enclosures / Allegati

Attachment 1: Statistical analyses for the qualification of the new reference lot 126901.pdf (updated with Rev 02), pages 10.

Attachment 2: 126901_qualification.xlsx, page 1.

Attachment 3: signed document of the raw-data double check.pdf, page 1.

Attachment 4: SAS routine for the statistical analysis.pdf, pages 3.

Attachment 5: SAS MACRO sub-routine for the Dixon's test.pdf, pages 2

Attachment 6: SAS MACRO sub-routine for the RPs combination, pages 2.

Attachment 7: raw data STD A1 immunization scheme, pages 465

Attachment 8: raw data STD A2 immunization scheme, pages 448

Attachment 9: raw data STD A3 immunization scheme, pages 410

Attachment 10: raw data STD B1 immunization scheme, for recombinant proteins, pages 304;

Attachment 10BIS: raw data STD B1 immunization scheme for OMV, pages 134

Attachment 11: raw data STD B2 immunization scheme, for recombinant proteins, pages 369;

Attachment 11BIS: raw data STD B1 immunization scheme for OMV, pages 122

Attachment 12: raw data STD B3 immunization scheme, pages 447

Attachment 13: raw data STD C1 immunization scheme, pages 455

Attachment 14: raw data STD C2 immunization scheme, pages 431

Attachment 15: raw data STD C3 immunization scheme, pages 440

Attachment 16: raw data STD D1 immunization scheme, pages 484

Attachment 17: raw data STD D2 immunization scheme, pages 439

Attachment 18: raw data STD D3 immunization scheme, pages 439

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