

9 Summary of product characteristics

Structure and other Characteristics

结构和其它性质

The 37th generation of varicella-zoster virus Oka strains is imported from US ATCC and approved by SMPA. It were separated from the chickenpox blister fluid of a Japanese boy with chickenpox and passed through original human embryonic lung cells, guinea pig embryo cells, human diploid cells (W138) and human diploid cells (MRC-5) with decreased toxicity. As the only strains for varicella vaccines production approved by WHO, they have been used for manufacturing Varicella Vaccine, Live.

第 37 代水痘-带状疱疹病毒 Oka 株由美国 ATCC 进口，经 SMPA 批准。它是从一名患水痘的日本男孩的水痘水泡液中分离出来的，并通过在初始人胚肺细胞，豚鼠胚胎细胞，人二倍体细胞（W138）和人二倍体细胞（MRC-5）中传代降低毒性。作为 WHO 批准生产水痘疫苗的唯一毒株，已用于生产水痘疫苗。

Seed banking systems

种子库系统

The strain used for production and quality control shall be sourced lawfully and be subject to the approval of the NRA. The viral strains/seeds shall be preserved, tested and distributed by the NCL or by the institutions designated by the NRA.

用于生产和质量控制的菌株应合法采购，并经 NRA 批准。病毒株/种子应由 NCL 或 NRA 指定的机构保存、检测和分发。

The production of biologics shall be based on a seed lot system. The history, source and biological characteristics of primary seed lot shall be verified. The master seed lot shall be prepared by passage and propagation of primary seed lot, and working seed lot shall be prepared by passage and propagation of master seed lot. The biological characteristics of the working seed lot shall be in conformity with that of primary seed lot. Each lot of master seed and working seed shall be preserved, tested and used respectively according to the requirements described in individual monographs. The limitation of passage number of each bacterial or viral seed lot at different levels shall be defined during the production and be subject to the approval of the NRA.

生物制品的生产应基于种子批系统。应验证原始种子批的历史、来源和生物学特性。主种子批应通过主种子批传代和繁殖制备，工作种子批应通过主种子批传代和繁殖制备。工作种子批的生物学特性应与原始种子批的生物学特性一致。根据各论中描述的要求分别保存、检测和使用每批主种子和工作种子。生产过程中，应确定不同水平的每个细菌或病毒种子批的传代次数限制，并应获得国家监管机构的批准。

Regarding the varicella vaccine, the master seed lot is 42nd generation and the working seed lot is 47th generation.

水痘疫苗主种子批为第 42 代，工作种子批为第 47 代。

The product were produced by inoculating seed viruses in human diploid cells (2BS strain), cultivating, bulk harvesting and freeze drying with proper stabilizers.

该产品是通过将毒种接种于人二倍体细胞（2BS 株），经培养、收获、加入适当的稳定剂冻干而成。

Structure

结构

Sample name 样品名称	Reference name 参考品名称	Reference size (bp)参 考品尺寸	Covered length (bp) 覆盖长度	Coverage (%) 覆盖率	Average depth 平均深度
Oka-vzv 47 generation	AB097932	125,078	125,076	99.9984	2,500
Oka-vzv 48 generation	AB097932	125,078	125,075	99.9976	1,200

This is the compare result between the VZV strain gene sequence tested by 47 generation and 48 generation and the standard sequence which sequence number is AB097932 in gene bank.

这是用 47 代和 48 代检测的 VZV 株基因序列与基因库中序列号为 AB097932 的标准序列的比较结果。

Stability

稳定性

Observe 3 batches of Varicella Vaccine, Live working seed lot SOka47-2018[5]-SOka47-2018[7] for 30 months. The virus titer declined slightly, the decline is 0.09 lg PFU/ml, 0.13 lg PFU/ml and 0.16 lg PFU/ml respectively. The results of stability observation test of working seed lot shows that the virus titer of working seed lot is very stable within observation period.

观察 3 批水痘疫苗工作种子批 SOka47-2018[5]- SOka47-2018[7], 持续 30 个月。病毒滴度略微下降, 下降幅度分别为 0.09 lg PFU/ml、0.13 lg PFU/ml、0.16 lg PFU/ml。工作种子批的稳定性观察试验结果表明, 工作种子批的病毒滴度在观察期内非常稳定。

The master seed lot and working seed lot should be test strictly before production, the test items include Identification test, Virus titration, Sterile test, Mycoplasma test, Virus adventitious agent test, Immunogenicity test and Monkey neurovirulence test. The master seed lot shall conduct all test items, the working seed lot shall conduct the identification test, virus titration, sterile test, mycoplasma test and virus adventitious agent test.

主种子批和工作种子批在生产前应进行严格的检测, 包括鉴别试验、病毒滴定、无菌试验、支原体试验、病毒外源因子试验、免疫原性试验和猴神经毒力试验。主种子批应进行所有项目的检测, 工作种子批应进行鉴别试验、病毒滴定、无菌试验、支原体试验、外源病毒因子检查。

Genome component analysis

基因组成分分析

Conduct the gene sequencing by Genemark to get the virus strain genomic situation. The reference genome is AB097932 (named vOka). The genome component analysis result is in following table:

由 GeneMark 进行基因测序, 获得病毒株基因组情况。参考基因组是 AB097932 (命名为 vOka)。基因组成分分析结果如下表所示:

Table 1. Sample Oka-vzv 47 generation and sample Oka-vzv 48 generation genome component analysis result

表 1. 样本 Oka-VZV 47 代和样本 Oka-VZV 48 代基因组成分分析结果

	Oka-vzv 47 generation	Oka-vzv 48 generation	vOka
Genome Size(bp)	125,078	125,078	125,078
GC Content (%)	46.13	46.11	46.10
Gene Number (#)	103	103	76
Total Length (bp)	116,034	116,262	110,130
Gene Average Length (bp)	1,127	1,129	1,449
Gene Length / Genome (%)	92.77	92.95	88.05
GC Content in Gene Region (%)	46.4	46.44	46.45
Intergenic Region Length (bp)	9,044	8,816	14,948
GC Content in Intergenic Region (%)	42.67	41.76	43.52
Intergenic Region Length / Genome (%)	7.23	7.05	11.95

Comparative genome analysis

比较基因组分析

Study the homology of test virus strain and reference genome, the more coverage means the more homology and it is easier to get the difference information by comparative genome analysis method.

研究供试病毒株与参考基因组的同源性，覆盖率越高，同源性越高，比较基因组分析方法越容易获得差异信息。

Table 2. Analysis depth and coverage

表 2. 分析深度和覆盖范围

Sample name 样品名称	Reference name 参考品名称	Reference size (bp) 参考品尺寸	Covered length (bp) 覆盖长度	Coverage (%) 覆盖率	Average depth 平均深度
Oka-vzv 47 generation	AB097932	125,078	125,076	99.9984	2,500
Oka-vzv 48 generation	AB097932	125,078	125,075	99.9976	1,200

Compared with reference genome AB097932 (vOka), the sample Oka-vzv 47 generation has 4 SNP (single nucleotide polymorphism) including 1 synonymous mutation and 0 nonsynonymous mutation. And sample Oka-vzv 48 generation has 3

SNP including 1 synonymous mutation and 0 nonsynonymous mutation.

与参考基因组 AB097932 (vOka) 相比, OKA-VZV 47 代样本具有 4 个单核苷酸多态性 (single nucleotide polymorphism, SNP), 包括 1 个同义突变和 0 个非同义突变。样本 OKA-VZV 48 代有 3 个 SNP, 包括 1 个同义突变和 0 个非同义突变。

SNP statistic result is in following table:

SNP 统计结果如下表所示:

Table 3. SNP statistic result

表 3. SNP 统计结果

Sample name	Region Type	CDS							Intergenic	Total	
		Start_syn	Stop_syn	Start_nonsyn	Stop_nonsyn	Premature_stop	Synonymous	Nonsynonymous			
Oka-vzv 47 generation	number	0	0	0	0	0	1	0	1	3	4
	rate(%)	0	0	0	0	0	25	0	25	75	--
Oka-vzv 48 generation	number	0	0	0	0	0	1	0	1	2	3
	rate(%)	0	0	0	0	0	33.3333	0	33.3333	66.6667	--

Note: Start_syn: initiation codon synonymous mutation, means after mutation, the initiation codon is also initiation codon;

Stop_syn: termination codon synonymous mutation;

Start_nonsyn: initiation codon nonsynonymous mutation, means after mutation, the initiation codon is not the initiation codon;

Stop_nonsyn: termination codon nonsynonymous mutation;

Premature_stop: nonsense mutation, the triplet codon change to termination codon;

Synonymous: synonymous mutation in genic region;

Nonsynonymous: synonymous mutation in intergenic region;

Intergenic: SNP in intergenic region;

Impurities

杂质

The medium with new born bovine serum albumin (NBS) is used in the cell preparation and virus culture process, and removed in the washing and virus harvesting process. The residual NBS is tested in the final product control test. The residual NBS content shall be not more than 50ng/dose by ELISA method.

含有新生牛血清白蛋白(NBS)的培养基用于细胞制备和病毒培养过程，并在洗涤和病毒收获过程中去除。在成品控制试验中检测残留新生牛血清。ELISA 法测定残留新生牛血清含量应不高于 50ng/剂。

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Date: June, 2022

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On behalf of Changchun Keygen Biological Products Co., Ltd.