

**Prequalification Team
WHO PUBLIC INSPECTION REPORT
Vaccine Manufacturer**

Part 1: General information

Name of Manufacturer	Sanofi Pasteur France
Unit number	Val de Reuil, Eure department in Normandy, France (VDR)
Production Blocks at Val de Reuil, Eure department in Normandy, France (VDR)	Building B16, B44, B8b, B33, B10, B12, B3 & B40
Physical address	Val de Reuil, Eure department in Normandy, France (VDR)
Contact address	As above
Date of inspection	03 - 05 June 2015
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Vaccines
WHO product numbers covered by the inspection	1. IPV (IMOVAX): Liquid for IM/SC injection 2. Yellow Fever (STAMARIL): Lyophilized + 0.9% Sodium Chloride in vial diluent: : IM/SC injection
Summary of the activities performed by the manufacturer	Production and quality control activities

Part 2: Summary

General information about the company and site

Sanofi Pasteur, the vaccines division of Sanofi, is considered one of the largest companies in the world devoted entirely to human vaccines. The company offers a broad range of vaccines providing protection against 20 bacterial and viral diseases (Yellow fever, Mumps, Poliomyelitis, Measles, Rubella, Influenza, Hepatitis A and B, Rabies, Japanese encephalitis, Chickenpox, Pertussis, Diphtheria, Haemophilus influenza type b infections, Meningococcal meningitis, Pneumococcal infections, Tetanus, Tuberculosis, Typhoid fever, Cholera).

Sanofi Pasteur distributes more than 1 billion doses of vaccine each year, contributing to vaccinate more than 500 million people across the globe. Sanofi Pasteur is considered one of the world's leading providers of Inactivated Polio Vaccine (IPV) and Rabies vaccine.

Val De Reuil site covers about 29 hectares. It is located in the Parc Industriel d'Incarville, just outside Louviers (Eure), in a major pharmaceutical area. The site is dedicated to Industrialization, Production and Control of vaccines, Formulation, Filling, visual inspection & Packaging and Distribution. Sanofi Pasteur is considered the site of reference for Flu antigens production and the first manufacturer in the world for seasonal and pandemic Flu production. Sanofi Pasteur (VDR site) is the world leader for Yellow Fever vaccine providing 75% of the global market and 35% of the world production of oral Polio antigens.

History of WHO and/or regulatory agency inspections

This was the 3rd inspection of the Sanofi Pasteur sites (MLE and VDR) by WHO-PQ. The first GMP inspection took place from 14 to 16 November 2005 and covered Imovax Polio, Inactivated Poliomyelitis Vaccine (IPV). The second GMP inspection took place from 26 to 30 November 2007 and covered DTP-Hib, MMR, measles and meningococcal vaccines.

Focus of the inspection

The present inspection focused on the production and control of Imovax Polio 10 D vials and Yellow Fever Vaccine 10 D vials manufactured in Val de Reuil (VDR) site. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises

- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 PHARMACEUTICAL QUALITY SYSTEM

a) **Pharmaceutical quality system:**

The organigrams of the Site Management, Quality and production Teams were presented and are available in the SMF. The mission of the Operational Quality Assurance as well as the Product Quality Assurance is considered adequately defined and sufficiently staffed.

b) **Change control:**

Change control was managed as per SOP. There was no risk categorisation of changes but these were categorised in 6 categories:

- i. Starting materials, Packaging components and consumables
- ii. Utilities/Facilities
- iii. Equipment/Computerised systems
- iv. Product and Process including seed lots
- v. Quality control testing
- vi. Quality system

The change control process was described from the initiation to the closure steps including the post implementation efficiency checks.

As spot checks, change controls were reviewed and found acceptable.

c) **Handling of deviations:**

The handling of deviations was performed as per SOP. An escalation process is in place as per the procedure dealing with the quality risk management.

The list of deviation was presented and found acceptable in general terms.

d) **Product quality review:**

The Annual Product Review (APR) was conducted as per SOP. It provided for review of APR either based on campaigns or annual anniversary based on first year of regulatory approval. The procedure provided that the APR completed within 90 days from the end of the review period. The review were designed to cover validation status, qualification of equipment and utilities, quality control data, changes, sub-contract for manufacturing and quality control, regulatory commitments, returns, complaints, recalls, regulatory inspections, pharmacovigilance and effectiveness of the previous CAPAs.

The APRs for AMARIL (Yellow Fever Vaccine) for the 2 campaigns for the bulk concentrate and final product in 2014 were reviewed.

The Annual Product Review for Imovax Polio covering the Polio Trivalent Concentrate, the final bulk and the finished products manufacturing from 02/07/13 to 01/07/14 were reviewed. Two lots were rejected. One lot was impacted by the use of defective rubber stoppers regarding the dimensional and aspect specifications. One lot was impacted by the use of the wrong volume (volume meant for 5D instead of 10D

vials) during the filling. Overall, the APR review was adequate and covered most of the requested sections.

2.2 GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were implemented. Necessary resources were generally provided, including qualified and trained personnel, premises, equipment and services, appropriate materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing steps were recorded in batch manufacturing and packaging records. Manufacturing processes were generally defined and reviewed. Instructions and procedures were generally written in clear and unambiguous language. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and records were made during manufacture.

2.3 SANITATION AND HYGIENE

Manufacturing areas are provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified and self-contained manufacturing areas are in place. Programs for cleaning of manufacturing areas and equipment are implemented and combined cleaning agent and disinfectants are used alternatively.

2.4 QUALIFICATION AND VALIDATION

Provisions for initial and follow up qualifications and validations are in place. Qualification and validation programs cover facilities, utilities and equipments as well as processes, analytical methods and their transfer and computerized systems.

Operational qualification report of the vials capping machine was reviewed. Detection of misplaced rubber stoppers was considered. At each vial format change, tests for the absence/presence and misplaced rubber stoppers are performed according to the SOP.

Validation report regarding the formulation of the Trivalent Polio Concentrate was reviewed. 3 batches were manufactured and the stability study was launched. The stability and the validation reports and results are considered conclusive by the company.

2.5 COMPLAINTS

Complaints dealt with in the Annual Product Review Imovax Polio were reviewed and found adequately addressed.

2.6 PRODUCT RECALLS

No recall was recorded since end of 2012 where a Typhim vaccine lot was recalled. A mock up recall is considered every two years by the company.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Provision for contract manufacturing and analysis was in place however, this was not covered during this inspection.

2.8 SELF INSPECTION AND QUALITY AUDIT

Provision for self-inspection was in place however, this was not covered during this inspection.

Suppliers 'audits and approval

Vendor audits were coordinated at the corporate level and had been reviewed during the inspection at MLE site carried out last week. These were not covered during the inspection of this site.

2.9 PERSONNEL

The site generally had adequate numbers of skilled staff to conduct the assigned responsibilities. Staff functional and reporting responsibilities were well outlined in organisation charts and job descriptions. The organisation and responsibilities supported the independence of the quality Unit even when quality officer were imbedded in various operational units.

2.10 TRAINING

Provision for recruitment, initial and periodic training are in place.

2.11 PERSONAL HYGIENE

The company had operating procedures as the basis for its approach to personal hygiene and sanitation in its production facility. The personnel entering the production area changed into clean garments according to established procedure. There were provisions for cleaning and sanitisation of hands Personnel entered and exited production areas through separate airlocks and these were also separate from those used for material entry and exit.

2.12 PREMISES

The Manufacturing buildings involved in the production of IPV (IMOVAX) and Yellow Fever at Val De Reuil (VDR) are in general terms considered suitable to the operations to be carried out.

The company has provided an acceptable Site Master File with relevant documentation regarding the manufacturing processes, buildings, utilities and maintenance plans.

Manufacturing areas, Rooms air classification, airflow patterns, flows of personnel, flows of materials, flows of working cells, working seeds, products and intermediates, flows of waste, flows of raw material are duly described in adequate provided plans.

2.13 EQUIPMENT

Overall, process equipment was installed and maintained in a way that minimizes risk of error, contamination and cross contamination.

A preventive maintenance program was in place and was followed.

2.14 MATERIALS

Provisions for incoming materials, intermediates and finished products are in place for reception, quarantine and release processes. Appropriate storage conditions are provided.

2.15 DOCUMENTATION

In general, documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken.

A documentation system was in place to guide production and control of products. These included Validation Master Plans (VMP); standard operating procedures (SOPs); Batch Manufacturing and Packaging Instructions and records (MIs, BMRs, BPRs); specifications of starting materials, packaging materials, packaging components and finished products; standard testing procedures, analytical records and certificates of analysis; qualification and validation protocols, schedules and reports; training schedules and records. There were corresponding records in form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

2.16 GOOD PRACTICES IN PRODUCTION

The finish of the floors, walls and ceilings confirm the SMF descriptions. Access to production areas was restricted to authorized personnel.

Production operations were done following clearly defined procedures. Batch Production Record was reviewed and found acceptable.

On spot checks Batch Production Records were reviewed and found acceptable.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The site had adequate facilities and procedures for the control of starting materials and intermediates, bulks and finished products. Quality operations were imbedded in various operational units to ensure the quality is built into the product but there were clear functional and reporting structures and responsibilities to support the independence for the quality unit. OOS methodology was reviewed and found acceptable.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, Sanofi Pasteur, Val de Reuil, Eure department in Normandy, France (VDR) with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.