

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

Part 1: General information

Name of Manufacturer	Sanofi Pasteur France
Unit number	Marcy-l'Etoile, Lyon, France (MLE)
Production Blocks at Marcy-l'Etoile, Lyon, France (MLE)	Building V4, V9, V10, V15, Abis Sud, Abis Nord, Building F, Building P and P' and Building I12, I14 and I15
Physical address	Marcy-l'Etoile, Lyon, France (MLE), 1541 avenue Marcel Mérieux, 69280 Marcy l'Etoile - France
Contact address	As above
Date of inspection	27 - 29 May 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. Typhoid (TYPHIM Vi): Liquid for IM injection
Summary of the activities performed by the manufacturer	Production and quality control of vaccines

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WHO Inspection Report
Sanofi Pasteur, Marcy-l'Etoile, Lyon, France
27-29 May 2015

Part 2: Summary

General information about the company and sites

Sanofi Pasteur, the vaccines division of Sanofi, is considered one of the largest company 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. These are manufactured at two sites in France: Marcy l'Etoile (MLE) and Val De Reuil (VDR).

The Campus Mérieux at Marcy l'Etoile includes about 90 buildings. It dates back to 1917 and now covers 34 hectares. The site is dedicated to Industrialization, Production and Control of vaccines, Formulation, Filling & Packaging. Vaccines against the following diseases are manufactured in this site:

Viral diseases:	Bacterial diseases:
Poliomyelitis	Pertussis
Measles	Diphtheria
Rubella	<i>Haemophilus influenza</i> type b infections
Hepatitis A	Pneumococcal infections
Rabies	Tetanus
	Typhoid Fever

MLE also purifies immunoglobulins.

History of WHO and/or regulatory agency inspections

The Sanofi Pasteur at Marcy-l'Etoile, Lyon site was licensed by the French Drug Regulatory Authorities. The site has been inspected by the WHO Pre-Qualification Team on regular basis.

Focus of the inspection

The present inspection focused on the production and control of vaccines. 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 management system
- Sanitization and hygiene
- Qualification and validation
- Complaints

- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control
- Packaging, transportation and VVM validation

2.1 PHARMACEUTICAL QUALITY SYSTEM

The company had a well-established quality system that was implemented and maintained.

The Annual Product Review (APR) is performed as per SOP for the purpose to:

- Assess, using all the data collected, the consistency of the manufacturing process,
- Evaluate the identified trends,
- Consider the need for changes (specifications, manufacturing procedures, controls),
- Evaluate the need to improve the product and/or process,
- Procure a communication aid for Production, Quality, Regulatory Affairs, Pharmacovigilance, etc. in order to enhance process quality and ensure regular updates for site management.

APR for vaccines of interest during the present inspection were presented and found acceptable in general terms.

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

- i. Equipment/Computer system
- ii. Facilities / Utilities
- iii. Product/Process
- iv. Quality system
- v. Raw Material / Package Material / Consumable
- vi. Testing

The main changes affecting vaccines of interest during this inspection were presented for review and found acceptable in general terms.

The policy for handling the deviations was presented and found adequate.

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 according to SOP. Combined cleaning agent and disinfectants are used alternatively. Bactericidal disinfectants and fungicidal are used alternatively as well as sporicidal disinfectants.

2.4 QUALIFICATION AND VALIDATION

Provision for validation and qualification was implemented.

As spot checks, qualification reports were reviewed and found acceptable in general terms.

HVAC and laminar air flow cabinets are controlled according to SOP.

The environmental monitoring (EM) at the filling/Lyophilization building in Abis Nord was reviewed and found acceptable.

Microbiological trend analysis of Abis Nord was reviewed and found acceptable.

WFI trend analysis for Abis Nord was reviewed and found acceptable.

2.5 COMPLAINTS

Processing customer complaints is implemented as per SOP.

There are 4 classes of complaint defined, the first three from severe to minor AEFIs and the 4th unrelated to AEFIs.

2.6 PRODUCT RECALLS

Recalls is dealt with as per procedure SOP.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Provision for Quality Agreement was implemented. The Quality Technical Agreement was considered covering most of the responsibilities between MLE and VDR sites except for the IPV 10 doses in vials. This was raised as an “other deficiency” and was satisfactorily addressed by the company.

2.8 SELF INSPECTION AND QUALITY AUDIT

a) Self-inspection

This aspect was not covered during this inspection.

b) Supplier qualification

The procedure for qualification of vendors for raw material (RM), packaging materials (PM), supplies, laboratory animals and services (e.g. cleaning, calibration, maintenance) was described in SOP.

The responsibility for vendor qualification lay with Quality Compliance group. Auditors were trained centrally by SANOFI Group based in Paris.

The procedure provided for evaluation using a questionnaire and site audit depending on criticality, one global supplier agreement for each supplier/site managed through TRACKWISE[®], a supplier quality document maintained in SAP, management of supplier complaints, management of changes made by the supplier, annual assessment of suppliers and regular supplier quality meetings. The frequency of audits was based on the material (*biological, sterile excipient, primary PM and secondary PM ≤ 2 years, gas/non-sterile ≤ 3 years, printed PM ≤ 4 years,*) but this was changing to base it on risk analysis. The schedule for 2015 was available and included 45 audits. The database for managing supplier was also being changed from TRACKWISE[®] to a Sanofi-wide system called PHENIX[®] and all legacy data had already been migrated. Data from PHENIX[®] will be extracted and processed in a risk analysis tool called SAFRAN[®]. There was no system of flagging the due date for auditing.

Addition of supplier was assessed through change control and may include analytical comparison, pilot trial or industrial scale trial.

All critical items are ordered via SAP based on specific material code and supplier. Review of selected examples of supplier qualification reports raised concerns on how materials from different supplier but managed with the same material code were controlled for regulatory compliance. It was clarified that this scenario was only possible with PM.

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

Personnel training was managed as per SOP. Training needs were identified by the departments and training plans and records were maintained.

2.11 PERSONAL HYGIENE

The company had a standard operating procedure 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 vaccines of interest during this inspection were 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. The site was supplied with drinking water from the city which was collected near R12. Deionised water and purified water was produced in each building generally with a local loop. This design was found adequate to avoid cross contamination. The water system was not inspected.

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.

The list of key starting material from animal sources used in the manufacturing process of vaccines of interest during this inspection was reviewed and found acceptable. These are supplied from approved suppliers and subject to internal release.

Alternative suppliers of key starting materials should be considered in order to prevent any risk of possible shortages.

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.

2.17 GOOD PRACTICES IN QUALITY CONTROL

QC laboratories are separated from production areas. In general terms, provisions are in place for sampling and testing of starting materials, packaging materials, intermediate products, bulk products and finished products as well as environmental monitoring, water systems and gases. Testing methods are validated and equipment are duly qualified and calibrated. OOS methodology reviewed and no issues arose. No comments.

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 France Marcy-l'Etoile, Lyon, France (MLE) 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.