SUBSTITUTION PLAN

Legal name of applicant(s):	Nuova Ompi S.r.l. unipersonale
Submitted by:	Nuova Ompi S.r.l. unipersonale
Substance:	4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues); (Octylphenolethoxylates, OPnEO).
Use title:	Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for one specific medicinal product of one pharmaceutical company.
Use number:	1

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INTRODUCTION

Nuova Ompi S.r.l. unipersonale (hereinafter referred to as 'Ompi') located in Piombino Dese, Italy, as part of the Pharmaceutical Systems division of Stevanato Group, offers the widest range of glass primary packaging, ranging from the traditional ones, such as vials and ampoules, to the high-value ones such as syringes and cartridges for auto-injectors and pen-injectors. Ompi is applying for an authorisation to continue the use of Octylphenolethoxylates (OPnEO) as emulsifier in the siliconisation of glass containers used as primary packaging for one specific medicinal product of one pharmaceutical company (F. Hoffmann-La Roche Ltd., hereinafter referred to as 'Roche') after the sunset date until complete substitution. Roche has outsourced part of the manufacturing of the medicinal product NeoRecormon® to the Contract Manufacturing Organisation (CMO) Vetter Pharma-Fertigung GmbH & Co. KG (hereinafter referred to as 'Vetter'). For the manufacturing of NeoRecormon®, Nuova Ompi provides Vetter with siliconised glass barrels which are filled with the medicinal product at Vetter's production sites.

In the Analysis of Alternatives (AoA), the function of OPnEO in the production of the affected medicinal products, the availability and hazards of the alternative as well as steps and time required for substitution was analysed. In the communication number AFA-C-2114486057-42-01/F, ECHA requested that a substitution plan is submitted to complete the information required by the SEAC for evaluation of the AfA. Ompi decided to submit a Substitution Plan as a separate document to provide the requested information.

The information required for Sections 1 and 2 of the Substitution Plan was already provided in the AoA. Reference to the relevant AoA sections is indicated in the corresponding sections of the Substitution Plan. Section 3 describes the structure in place at Ompi, Vetter and Roche to monitor the implementation of the substitution plan and ensure that the implementation of the selected alternative is successfully carried out.

1. FACTORS AFFECTING SUBSTITUTION

- Availability: An alternative silicone oil emulsion has been proposed by the manufacturer and is being tested. Please see AoA, Section 6.2.
- Details on the factors that can influence the substitution with an alternative silicone oil emulsion and the uncertainties for the timetables due to unforeseen technical and regulatory difficulties are explained in Section 7.1.2 of the AoA.
- Medicinal products are subject to extensive regulation by the health authorities all over the world. Change notifications of marketing authorisations have to be submitted to competent health authorities when any change is introduced in their production process. Please see a description on how regulatory factors affect the substitution in Section 5 of the AoA. The minimum standard that a medicines manufacturer must meet in their production processes is described in the current Good Manufacturing Practices (cGMP)[1].

[1] European Medicines Agency. Good Manufacturing Practices: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice

2. LIST OF ACTIONS AND TIMETABLE WITH MILESTONES

- Actions needed to complete the substitution: Multiple steps are required to replace the silicone oil emulsion used in the siliconisation by a new OPnEO-free emulsion. Please see Section 7.1.1 of the AoA for detailed description of the steps and estimated time needed for for the replacement of the silicone oil emulsion used in the siliconisation of primary packaging containers.
- Timetable for implementation of the changes and associated risks: For the estimated replacement timelines see AoA Section 7.1.2.
- Detailed description of the status of the substitution schedule and uncertainties can be found in Section 7.2 of the AoA.

3. MONITORING OF THE IMPLEMENTATION OF THE SUBSTITUTION PLAN

3.1 Management of the substitution projects at Ompi

At Nuova Ompi, the Customer Quality Management (CQM) has the leadership of the communication from/to the parties Roche and Vetter in order to give them the status of the project. Internally, the project is managed by a Project Leader (PL) with the task to collect data from the several departments involved and to then give the results of the elaboration to CQM and the other parties of the supply chain Nuova Ompi-Vetter-Roche (see Figure 1).

The monitoring of the substitution is strictly managed by Validation, including the execution of all validation activities and the subsequent communication of the results to the PL and the CQM.

The substitution of the silicone oil Dow Corning 365 35% Dimethicone NF Emulsion (DC365) with the alternative Dow Corning 366 35% Dimethicone NF Emulsion (DC366) has required the installation of a new equipment at Nuova Ompi's production site, which is strictly dedicated to the new silicone emulsion. This installation is ready to be used so that it is possible to switch to the alternative DC366 as soon as requested. Nuova Ompi is not directly involved in Vetter´s or Roche's substitution projects. The request to switch will be provided by Vetter based on approval from Roche as described below.

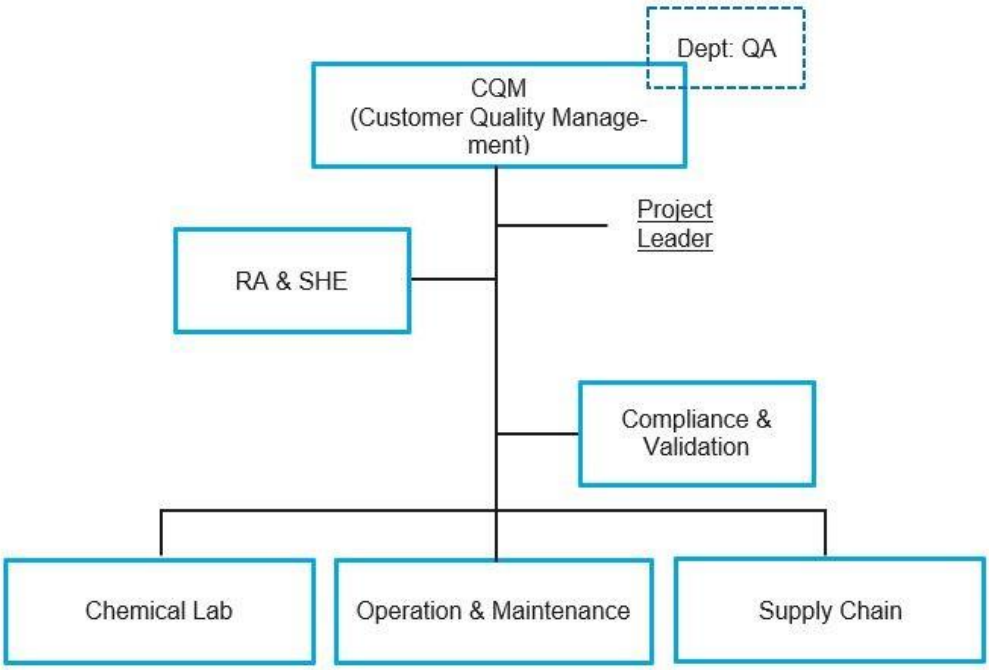

Figure 1. Organigram of Nuova Ompi's organisational structure for ensuring success of the substitution project.

Monitoring of the projects and implementation in collaboration with Vetter and Roche

As Roche is the marketing authorisation holder of the final medicinal product NeoRecormon®, Roche is responsible for ensuring that all regulatory requirements linked to the marketing authorization of the medicinal products are met and to obtain approval for any change in the manufacturing process including any changes at CMOs. Therefore, the approval to switch the silicone oil emulsion in the manufacturing process for NeoRecormon® is given from Roche to Vetter. Once Roche has provided approval, Vetter will order the DC366-siliconised syringes from Nuova Ompi for the manufacturing of the medicinal product.

Vetter and Roche have their own projects setup for substitution of DC365 with DC366. The change for NeoRecormon® with glass barrels siliconized by Ompi is also managed within these projects. The management of the projects is described below.

3.2 Management of the substitution project at Vetter

Vetter has a multidisciplinary team of experts working on the evaluation and substitution project of Dow Corning 365 35 % Dimethicone NF Emulsion (DC365) since 2017. The project team comprises relevant subject matter experts from line departments, such as Vetter Optimization System (VOS), Development Services, Production, Quality Assurance, Chemical Analytics, Microbiological Analytics, Alliance Management, Procurement and Environment, Health & Safety. The project leader is part of Vetter's VOS Operational Excellence team and reports directly to the Vice President of Development Services, who acts as project sponsor.

Additionally, the substitution project is embedded in the governance of Vetter's Operational Steering Committee (OSC) (see Figure 2). Members of the OSC are the Vice Presidents from

relevant line departments, such as Quality Assurance, Production, Supply Chain Management, Development Service, Marketing/Key Account Management, and Controlling.

The substitution project is reviewed on project/substitution progress and budget monthly by the OSC. Additionally, Senior Vice Presidents of the relevant line departments receive and review the monthly substitution project progress report, too. Constant monitoring of project progress is ensured via monthly meetings between the project leader and the project sponsor.

For more information about the monitoring of the project and the implementation at Vetter, please refer to the Substitution plan submitted by CMO Vetter for Use 1.

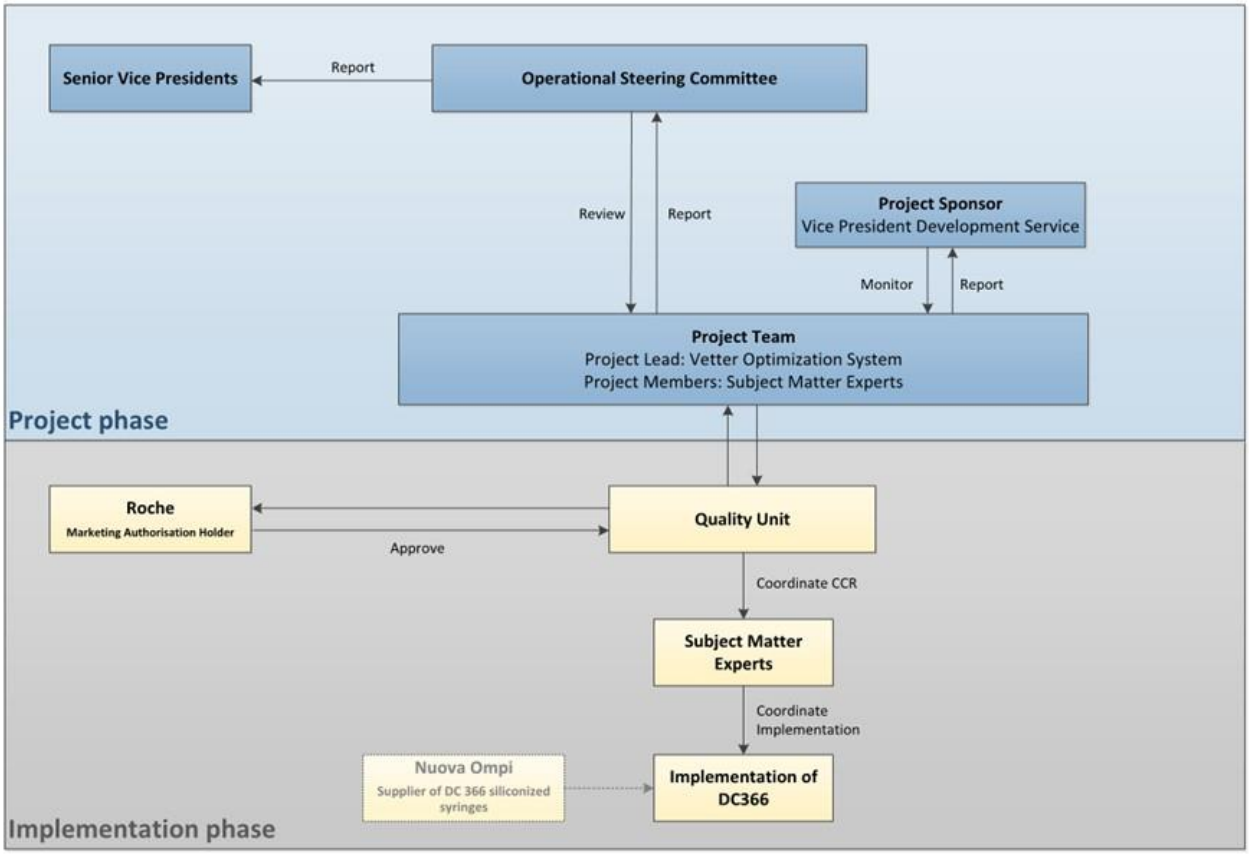

Figure 2. Organigram of Vetter's organizational structure for ensuring success of the substitution project.

3.3 Management of the substitution project at Roche

Roche as the holder of Marketing Authorisations (from health authorities) for the affected medicinal products must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of the senior management and requires the participation and commitment by staff in many different departments, as for instance Quality Assurance, Engineering, regulatory, etc. and at all levels within the company, by the company's suppliers and by its distributors. Consequently, a change request with global impact was authorised by the Global Change Commission at Roche. Under the sponsorship of the Head of Drug Product Manufacturing, a replacement project had been established, budgeted and approved.

For the management of the replacement project, a Project Manager has been assigned and has established a Steering Committee that meets monthly to ensure that the activities, as detailed in the project plan, are executed and delivered on time (see Figure 3). The Steering Committee is composed by a Sponsor, a Project Leader, a Chemical Legislation Representative, a Project Manager, a Drug Substance Manager, a Drug Product Manager, a Project Leader Pharma Technical Development, a Quality Control Manager, a Procurement Representative, a Supply Quality Manager, a Technical Product Manager and a Regulatory Manager.

For the overall monitoring of the project, a sub-Project Manager is reporting the status of the activities for the impacted medicinal products to the Steering Committee. The Drug Product Technical Lead (DPTL) of each impacted medicinal product is a member of the project team, is the owner of the child change requests, and incorporates the replacement plan into the strategy of the Product Team. The Roche Pharma Quality Management (PQS) contains procedures to ensure that outsourced processes and procedures are compliant with applicable regulations. A written contract between the Contract Giver (i.e. Roche) and the Contract Acceptor (i.e. the CMO Vetter) clearly establishes the roles and responsibilities of each party. Replacement projects for the Roche medicinal products produced at the CMO Vetter (partly with supply of pre-siliconised syringes by CMO Ompi) are managed in the same way as described for the products produced at Roche sites.

For more information about the PQS and the Good Documentation Practices (GDP) at Roche, please refer to the Substitution plan submitted by Roche for Use 1.

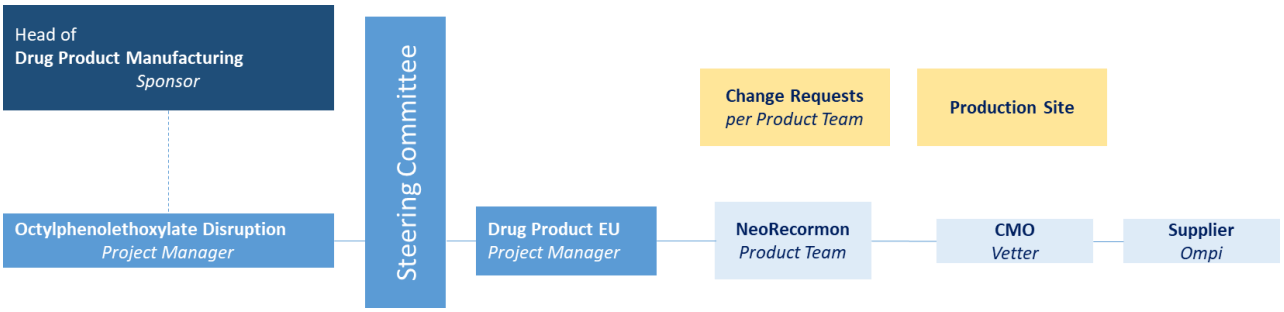

Figure 3. Organisational Set-up for the Replacement of Octylphenolethoxylates within Roche.

4. CONCLUSIONS

Stevanato Group aims to ensure the health and safety of its employees, customers, end users, suppliers, partners and visitors and to protect the environment. It operates its worldwide business under the principles of sustainability.

An alternative to replace the silicone oil emulsion containing OPnEO used in the siliconisation of glass containers used as primary packaging for medicinal products has been identified. The factors affecting the substitution and the list of actions needed to complete the substitution, as well as an estimated timetable, have already been thoroughly discussed in the AoA.

Ompi has implemented the structure required to oversee that the substitution is implemented according to the aforementioned substitution plan in a successful and timely manner. Vetter as CMO producing the affected medicinal product for Roche, has also a dedicated structure to oversee the implementation of the Substitution Plan. Finally, as Roche holds the marketing authorisation for

the affected medicinal products, Roche is responsible to obtain approval from competent health authorities for the substitution. Roche has likewise implemented a structure to oversee the Substitution Process. This structure is embedded in the Pharma quality management system (PQS).