## Synflorix

Procedural steps taken and scientific information after the authorisation

<table>
<thead>
<tr>
<th>Application number</th>
<th>Scope</th>
<th>Opinion/Notification ¹ issued on</th>
<th>Commission Decision Issued² / amended on</th>
<th>Product Information affected³</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB/0120</td>
<td>B.I.b.z - Change in control of the AS - Other variation</td>
<td>17/07/2017</td>
<td>n/a</td>
<td></td>
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<tr>
<td>PSUSA/9262/201612</td>
<td>Periodic Safety Update EU Single assessment - pneumococcal polysaccharide conjugate vaccine (adsorbed) - 10 valent</td>
<td>06/07/2017</td>
<td>n/a</td>
<td></td>
<td>PRAC Recommendation - maintenance</td>
</tr>
<tr>
<td>II/0116/G</td>
<td>This was an application for a group of variations.</td>
<td>22/06/2017</td>
<td>SmPC, Labelling and</td>
<td></td>
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</tr>
</tbody>
</table>

¹ Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.

² A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.

³ SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).
<table>
<thead>
<tr>
<th>Code</th>
<th>Change Description</th>
<th>Date</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.II.a.3.b.3</td>
<td>Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological product</td>
<td></td>
<td>PL</td>
</tr>
<tr>
<td>B.II.b.3.z</td>
<td>Change in the manufacturing process of the finished or intermediate product - Other variation</td>
<td></td>
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</tr>
<tr>
<td>B.II.d.1.c</td>
<td>Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.II.d.2.a</td>
<td>Change in test procedure for the finished product - Minor changes to an approved test procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.II.e.5.c</td>
<td>Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products</td>
<td></td>
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</tr>
<tr>
<td>B.II.e.5.a.1</td>
<td>Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</td>
<td></td>
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</tr>
<tr>
<td>IB/0118</td>
<td>B.II.z - Quality change - Finished product - Other variation</td>
<td>07/06/2017</td>
<td>n/a</td>
</tr>
<tr>
<td>II/0108</td>
<td>Update of sections 4.2 4.4, 4.8 and 5.1 of the SmPC</td>
<td>26/01/2017</td>
<td>SmPC and PL</td>
</tr>
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</table>

Study 10PN-PD-DIT-034 assessed the safety and...
in order to add information obtained from two clinical studies in subjects at risk for pneumococcal infections (study 10PN-PD-DIT-034 and study 10PN-PD-DIT-064). The package leaflet was amended accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to make consequential changes to the RMP and to change the final due date of a post-marketing surveillance study.

C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data

immunogenicity of Synflorix in children with increased risk for pneumococcal infections, i.e. Human Immunodeficiency Virus (HIV) infected or HIV exposed uninfected infants while study 10PN-PD-DIT-064 assessed the safety and immunogenicity of Synflorix in children with increased risk for pneumococcal infections, i.e. children with sickle cell disease (SCD).

Information including immunogenicity and safety results from both studies was added to the product information. The safety profile of Synflorix was considered acceptable in the studied high risk paediatric populations, suggesting that the benefit-risk profile of Synflorix is favourable in these populations. The benefit-risk profile of Synflorix is also considered favourable when administered in a 2+1 schedule beginning at 6 weeks of age. Administration of a booster dose (third or fourth dose) at 9 months of age does not adversely impact the safety profile and could provide additional benefit in terms of increased and prolonged protection.

The CHMP considered the proposed changes to the SmPC to be acceptable with some modifications.

<p>| IA/0114 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 24/01/2017 | n/a |
| II/0110 | B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product | 17/11/2016 | n/a |
| IG/0721 | A.7 - Administrative change - Deletion of | 10/10/2016 | n/a |
| IA/0112 | B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material | 22/09/2016 | n/a |
| IG/0719/G | This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information | 21/09/2016 | n/a |
| IB/0109 | B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol | 02/09/2016 | SmPC |</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB/0107</td>
<td>B.1.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)</td>
<td>26/07/2016</td>
<td>n/a</td>
</tr>
<tr>
<td>PSUSA/9262/201512</td>
<td>Periodic Safety Update EU Single assessment - pneumococcal polysaccharide conjugate vaccine (adsorbed) - 10 valent</td>
<td>07/07/2016</td>
<td>n/a</td>
</tr>
<tr>
<td>IG/0679</td>
<td>B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method</td>
<td>01/06/2016</td>
<td>n/a</td>
</tr>
<tr>
<td>IB/0105/G</td>
<td>This was an application for a group of variations.</td>
<td>11/05/2016</td>
<td>n/a</td>
</tr>
<tr>
<td>Application No.</td>
<td>Description</td>
<td>Date of Notification</td>
<td>Date of Decision</td>
</tr>
<tr>
<td>IA/0104</td>
<td>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits</td>
<td>23/03/2016</td>
<td>n/a</td>
</tr>
<tr>
<td>II/0100</td>
<td>B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol</td>
<td>10/12/2015</td>
<td>02/05/2016</td>
</tr>
<tr>
<td>N/0102</td>
<td>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)</td>
<td>16/11/2015</td>
<td>02/05/2016</td>
</tr>
<tr>
<td>II/0099</td>
<td>B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol</td>
<td>22/10/2015</td>
<td>n/a</td>
</tr>
<tr>
<td>IB/0101/G</td>
<td>This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</td>
<td>05/10/2015</td>
<td>n/a</td>
</tr>
<tr>
<td>II/0098</td>
<td>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</td>
<td>24/09/2015</td>
<td>n/a</td>
</tr>
<tr>
<td>WS/0748</td>
<td>This was an application for a variation following a worksharing procedure according to Article 20 of</td>
<td>30/07/2015</td>
<td>n/a</td>
</tr>
<tr>
<td>II/0096/G</td>
<td>This was an application for a group of variations. Update of section 5.1 of the SmPC with effectiveness data against pneumococcal vaccine serotypes and against vaccine related serotype 19A, and update of section 4.4 of the SmPC to include information on the immune response against serotype 19A observed in infants and children. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC, and to request extensions to the due dates for MEA 009: Study 10PN-PD-DIT-034 (111634) and MEA 018.5: Study 10PN-PD-DIT-064 (114056). A revised RMP version 13 was agreed during the procedure.</td>
<td>23/07/2015</td>
<td>02/05/2016</td>
</tr>
<tr>
<td>PSUSA/9262/201412</td>
<td>Periodic Safety Update EU Single assessment - pneumococcal polysaccharide conjugate vaccine</td>
<td>11/06/2015</td>
<td>n/a</td>
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<tr>
<td>Application ID</td>
<td>Description</td>
<td>Date</td>
<td>Approval Date</td>
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<tr>
<td>II/0092</td>
<td>Update of section 4.4 of the SmPC and corresponding section of the Package Leaflet with the information on effects of paracetamol and ibuprofen used prophylactically on fever and immune responses following primary vaccination and a booster dose of Synflorix. This submission fulfils the obligations with regards to Article 46 of Regulation (EC) No 1901/2006. Clinical data generated with ibuprofen suggest that its delayed use might reduce fever, while prophylactic use of ibuprofen showed a limited effect. Furthermore, the clinical data generated with paracetamol suggest that it might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known.</td>
<td>23/04/2015</td>
<td>02/05/2016</td>
</tr>
<tr>
<td>IB/0094/G</td>
<td>This was an application for a group of variations.</td>
<td>17/02/2015</td>
<td>n/a</td>
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</table>

- Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions.
- Clinical data generated with ibuprofen suggest that its delayed use might reduce fever, while prophylactic use of ibuprofen showed a limited effect. Furthermore, the clinical data generated with paracetamol suggest that it might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known.

<table>
<thead>
<tr>
<th>Application ID</th>
<th>Description</th>
<th>Date</th>
<th>Approval Date</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>IB/0093/G</td>
<td>This was an application for a group of variations.</td>
<td>23/12/2014</td>
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</table>

- B.1.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data
<table>
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<th>IB/0091/G</th>
<th>This was an application for a group of variations.</th>
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<td></td>
<td>B.I.a.1.a - Change in the manufacturer of AS or of a</td>
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<tr>
<td></td>
<td>starting material/reagent/intermediate for AS - The</td>
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<td></td>
<td>proposed manufacturer is part of the same</td>
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<td></td>
<td>pharmaceutical group as the currently approved</td>
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<td></td>
<td>manufacturer</td>
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<td></td>
<td>B.I.a.1.a - Change in the manufacturer of AS or of a</td>
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<tr>
<td></td>
<td>starting material/reagent/intermediate for AS - The</td>
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<tr>
<td></td>
<td>proposed manufacturer is part of the same</td>
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<td></td>
<td>pharmaceutical group as the currently approved</td>
</tr>
<tr>
<td></td>
<td>manufacturer</td>
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<td>23/12/2014</td>
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</tbody>
</table>

| IB/0089 | To delete a non-significant in-process test limit (the |
|         | upper limit of the diphtheria toxoid content range) at |
|         | the end of two ultrafiltration steps in the purification |
|         | process of the Diphteria Toxoid for the production |
|         | site in Gödöllő, Hungary. |
|         | B.I.a.4.z - Change to in-process tests or limits |
|         | applied during the manufacture of the AS - Other |
|         | variation |
|         | 17/12/2014 | n/a |

<p>| IB/0088 | B.I.b.2.e - Change in test procedure for AS or |
|         | starting material/reagent/intermediate - Other |
|         | 12/12/2014 | n/a |</p>
<table>
<thead>
<tr>
<th>Changes</th>
<th>Code</th>
<th>Details</th>
<th>Date</th>
<th>Status</th>
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<tbody>
<tr>
<td>Changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</td>
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<tr>
<td>IG/0498</td>
<td>B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised</td>
<td>21/11/2014</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>WS/0603</td>
<td></td>
<td>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</td>
<td>20/11/2014</td>
<td>n/a</td>
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<tr>
<td></td>
<td>B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation</td>
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<tr>
<td>WS/0591</td>
<td></td>
<td>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</td>
<td>20/11/2014</td>
<td>n/a</td>
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<tr>
<td></td>
<td></td>
<td>Submission of final study report of a post-approval clinical study to compare the current and the new plunger stoppers and tip caps in response to a CHMP recommendation.</td>
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<tr>
<td></td>
<td>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</td>
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</tr>
<tr>
<td>II/0078</td>
<td>Update of section 4.2 of the SmPC to delete the information related to a booster dose for children 12-23 months of age. Sections 4.4 and 5.1 are also updated following the results of new paediatric data</td>
<td>25/09/2014</td>
<td>27/10/2014</td>
<td>SmPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on the available data, the posology for unvaccinated infants and children ≥ 7 months of age and the related warning were updated as follows:</td>
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<tr>
<td></td>
<td></td>
<td>- Section 4.2: for unvaccinated infants and children ≥ 7</td>
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</tbody>
</table>
related to unvaccinated infants and children ≥ 7 months of age.

C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data

months of age, children aged 12 months - 5 years: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

- Section 4.4: Children younger than 2 years old should receive the appropriate-for-age Synflorix vaccination series (see section 4.2). The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines in children ≥ 2 years of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness, or those who are immunocompromised) placing them at higher risk for invasive disease due to Streptococcus pneumoniae. Whenever recommended, children at risk who are ≥ 24 months of age and already primed with Synflorix should receive 23-valent pneumococcal polysaccharide vaccine. In addition, the new paediatric data related to this population were also reflected in section 5.1 of the SmPC.

| II/0083 | Submission of a re-analysis of convulsions and swelling reactions reported following vaccination with Synflorix. As a consequence, an updated version of the Synflorix RMP (version 11.0) was submitted. | 25/09/2014 | n/a | The MAH comprehensively re-analysed the convulsions and swelling reactions reported following vaccination with Synflorix. The CHMP concluded that that the results of the updated review are in line with the information already reflected in Product Information. |
| II/0082 | Submission of the final study report of study 10PN-PD-DIT-041 Y4, designed to evaluate the long term persistence of antibody, approximately 48 months post-booster, in children who either received 4 doses of Synflorix or Prevenar or children who received 3 primary doses of Prevenar and a booster dose of Synflorix. | 25/09/2014 | n/a | The results of this study confirm the information already reflected in the Summary of Product Characteristics (SmPC). Persistence and immunological memory data have already been assessed, and are presented in the Product Information and the safety results were in agreement with what is previously known regarding the safety profile of Synflorix. It was, therefore, not considered necessary to |
### C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority

<table>
<thead>
<tr>
<th>Date</th>
<th>Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</th>
<th>SmPC and PL</th>
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<tbody>
<tr>
<td>20/08/2014</td>
<td>B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)</td>
<td>n/a</td>
</tr>
<tr>
<td>24/07/2014</td>
<td>C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure</td>
<td>27/10/2014</td>
</tr>
<tr>
<td>27/08/2014</td>
<td>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</td>
<td>n/a</td>
</tr>
<tr>
<td>22/08/2014</td>
<td>B.II.a.8.a. - Change to the in-process test or limits applied during the manufacture of the AS</td>
<td>n/a</td>
</tr>
<tr>
<td>27/09/2014</td>
<td>Update of section 5.1 of the SmPC to reflect the results of the phase III/IV clinical trial FinIP (Finnish Invasive Pneumococcal disease vaccine) to evaluate the effectiveness of Synflorix (against reduction of hospital-diagnosed pneumonia and impact on tympanostomy tube placements) to address a post-authorisation measure in the Risk Management Plan.</td>
<td>27/10/2014</td>
</tr>
<tr>
<td>25/09/2014</td>
<td>In the Finnish Invasive Pneumococcal disease vaccine study, the vaccine effectiveness in reducing hospital-diagnosed pneumonia cases (identified based on the International Classification of Diseases, ICD 10 codes for pneumonia) was 26.7% (95% CI: 4.9; 43.5) in the 3+1 infant schedule and 29.3% (95% CI: 7.5; 46.3) in the 2+1 infant schedule. For catch-up vaccination, vaccine effectiveness was 33.2% (95% CI: 3.0; 53.4) in the 7-11 month cohort and 22.4% (95% CI: -8.7; 44.8) in the 12-18 month cohort. Therefore, the results are similar between the different vaccination schedules and show the effectiveness of the vaccine in reducing hospital-diagnosed pneumonia cases. This study did not show significant results for the effectiveness of tympanostomy tube replacement.</td>
<td></td>
</tr>
<tr>
<td>25/08/2014</td>
<td>B.I.1.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</td>
<td>n/a</td>
</tr>
<tr>
<td>20/08/2014</td>
<td>B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)</td>
<td>n/a</td>
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</table>

**update the Product Information.**
<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Date</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSUV/0077</td>
<td>Periodic Safety Update</td>
<td>10/07/2014</td>
<td>n/a</td>
</tr>
<tr>
<td>IG/0446</td>
<td>C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location</td>
<td>24/06/2014</td>
<td>n/a</td>
</tr>
<tr>
<td>IB/0080</td>
<td>B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product</td>
<td>21/05/2014</td>
<td>n/a</td>
</tr>
<tr>
<td>WS/0494</td>
<td>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</td>
<td>25/04/2014</td>
<td>n/a</td>
</tr>
<tr>
<td>WS/0445/G</td>
<td>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. -Additional manufacturer of finished product. -Additional quality control testing manufacturer of the product. -Scale up of active substance of vaccine. -Introduction of alternative containers for the active</td>
<td>20/03/2014</td>
<td>n/a</td>
</tr>
</tbody>
</table>
substance.

B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes

B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place

B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)

B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs

| R/0068 | Renewal of the marketing authorisation. | 18/12/2013 | 21/02/2014 | SmPC, Annex II, Labelling and PL | Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Synflorix remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

- Identified risks including febrile convulsions, apnoea in premature infants, and hypotonic hyporesponsive episode (HHE) were observed with increasing rates. Emerging safety concerns, such as Kawasaki disease need further follow-up.
- Potential serotype replacement. |
Therefore, based upon the safety profile of Synflorix, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.

| II/0069 | Update of sections 4.4 and 5.1 of the SmPC with invasive pneumococcal disease (IPD) efficacy data, acute otitis media (AOM) efficacy data and carriage impact data coming from 2 large Phase III clinical studies. | 20/02/2014 | 27/10/2014 | SmPC | The MAH has presented new data regarding invasive pneumococcal disease (IPD), acute otitis media (AOM) and nasopharyngeal carriage from the COMPAS and the Finnish study 053. The data are considered relevant to include in the SmPC. The studies have partly been presented in other procedures e.g. variations applications EMEA/H/C/000973/II/0052 and II/0070, but the current evaluation was focussed on the data relevant to the proposed updates of the SmPC.

In conclusion the IPD data from the COMPAS study support the previously presented data. The protective efficacy/effectiveness against AOM in the COMPAS and 053 studies was lower than expected. Updated analyses of the studies were provided. The results for the catch-up vaccination schedules did not change substantially, but as discussed by the MAH, are not considered robust, especially due to the short follow-up period. The study was not designed to compare different vaccination schedules, and the confidence intervals are generally wide for the AOM endpoints. Therefore the results should not be presented in detail; however a brief summary should be included in the SmPC. The CHMP considered that risk benefit balance of Synflorix remains favourable in the approved indication. |
<p>| II/0070 | Update of section 4.8 of the SmPC to revise the safety information upon a safety pooled analysis from primary vaccination, booster and catch-up studies. The Package Leaflet was updated in accordance. | 23/01/2014 | 27/10/2014 | SmPC and PL | This variation summarizes the safety and reactogenicity data for Synflorix up to the data lock point (DLP) of December 10, 2012 and thus accounts for clinical studies completed since the first licensure of Synflorix in December 11, 2008. |</p>
<table>
<thead>
<tr>
<th>Application Number</th>
<th>Variation Description</th>
<th>Effective Date</th>
<th>End Date</th>
<th>File Details</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>II/0052</td>
<td>Extension of indication to include active immunisation against pneumonia for Synflorix. As a consequence, sections 4.1, 4.4 and 5.1 of the Summary of Product Characteristics have been updated with data from study10PN-PD-DIT-028 - Clinical Otitis Media and Pneumonia Study (COMPAS). The Package Leaflet was updated in accordance. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.</td>
<td>24/10/2013</td>
<td>25/11/2013</td>
<td>SmPC, Labelling and PL</td>
<td>Please refer to Assessment Report EMEA/H/C/000973/II/52.</td>
</tr>
<tr>
<td>II/0071</td>
<td>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</td>
<td>19/09/2013</td>
<td>25/11/2013</td>
<td>SmPC and PL</td>
<td></td>
</tr>
<tr>
<td>IA/0072/G</td>
<td>This was an application for a group of variations.</td>
<td>15/08/2013</td>
<td>n/a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data

The safety data from these clinical studies has significantly increased the safety database for Synflorix. The safety review supported the revisions of section 4.8 of the SmPC. The numbers of subjects exposed to Synflorix and the number of doses received in clinical trials was updated. In addition, the percentages of the most common local adverse reaction after primary vaccination observed in clinical trials was revised as well as the frequencies for crying abnormal, rash and urticaria. The revisions of section 4.8 of the SmPC do not affect the overall positive benefit / risk profile of Synflorix.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Value 1</th>
<th>Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB/0065/G</td>
<td>This was an application for a group of variations.</td>
<td>18/07/2013</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**B.I.b.1.b** - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits

**B.I.b.1.c** - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method

**B.I.b.2.e** - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate

**B.I.b.1.c** - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method

**B.I.b.2.e** - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate
<p>| B.I.b.1.c | Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent  - Addition of a new specification parameter to the specification and its corresponding test method |
| B.I.b.2.e | Change in test procedure for AS or starting material/intermediate/reagent - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate |</p>
<table>
<thead>
<tr>
<th>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</td>
<td></td>
</tr>
<tr>
<td>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</td>
<td></td>
</tr>
<tr>
<td>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</td>
<td></td>
</tr>
<tr>
<td>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</td>
<td></td>
</tr>
<tr>
<td>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</td>
<td></td>
</tr>
<tr>
<td>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</td>
<td></td>
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<tr>
<td>Changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</td>
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</tr>
<tr>
<td>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</td>
<td></td>
</tr>
<tr>
<td>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Application</th>
<th>Description</th>
<th>Date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA/0067/G</td>
<td>This was an application for a group of variations.</td>
<td>03/07/2013</td>
<td>n/a</td>
</tr>
</tbody>
</table>

B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test

B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test

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B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test
<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Date</th>
<th>Status</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WS/0383</td>
<td>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes on the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol.</td>
<td>27/06/2013</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>II/0057</td>
<td>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data.</td>
<td>27/06/2013</td>
<td>25/11/2013</td>
<td>SmPC, Labelling and PL</td>
</tr>
<tr>
<td>IG/0306</td>
<td>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation.</td>
<td>12/06/2013</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>IB/0063</td>
<td>B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time.</td>
<td>06/06/2013</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Data</td>
<td>Description</td>
<td>Date of Application</td>
<td>Date of Decision</td>
<td>SmPC, Labelling and PL</td>
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<tr>
<td>II/0051</td>
<td>Update of section 4.8 of the SmPC in order to update the safety information. The Package Leaflet is updated accordingly.</td>
<td>30/05/2013</td>
<td>25/11/2013</td>
<td>Synflorix SMPC, Labelling and PL Update of section 4.8 of the SmPC in order to update the safety information. The Package Leaflet is updated accordingly. This variation application provided safety and reactogenicity data for Synflorix up to the data lock point (DLP) of December 10, 2011. The safety database for Synflorix from clinical studies completed up to the DLP, consisted of 18 primary vaccination studies (including 7166 subjects in Total vaccinated cohort primed with Synflorix), 15 completed booster studies (5848 subjects in Booster Total vaccinated cohort receiving Synflorix) and five catch-up studies (883 subjects in Catch-up Total vaccinated cohort receiving Synflorix). In addition, post-marketing surveillance data in MAH worldwide safety database up to the DLP of April 2012 has been reviewed for spontaneous reports related to anaphylaxis and angioedema. Changes to the SmPC dealing with local and systemic events noted in primary, booster and catch up vaccination studies were proposed. The proposed additions/revisions to the SmPC were endorsed by the CHMP. The CHMP considered there was sufficient evidence of a causal relationship between Synflorix administration for anaphylaxis and angioedema to warrant an update of the relevant sections of the Product Information. Overall, the studies conducted with Synflorix and the post-marketing surveillance have demonstrated that the vaccine can be safely administered to infants and children up to 5 years of age together with other routinely administered paediatric vaccines.</td>
</tr>
<tr>
<td>IG/0304</td>
<td>A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS</td>
<td>17/05/2013</td>
<td>25/11/2013</td>
<td>Annex II</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
<td>Date</td>
<td>Approval</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IG/0297</td>
<td>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</td>
<td>19/04/2013</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>IB/0060</td>
<td>B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product</td>
<td>17/04/2013</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>IB/0058</td>
<td>B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product</td>
<td>05/02/2013</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>IG/0265/G</td>
<td>This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system</td>
<td>28/01/2013</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>WS/0336</td>
<td>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</td>
<td>17/01/2013</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>
To introduce a new method for monitoring homogeneity during filling.

### B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB/0056</td>
<td>B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product</td>
<td>04/01/2013</td>
<td>n/a</td>
</tr>
<tr>
<td>IB/0055</td>
<td>B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product</td>
<td>12/12/2012</td>
<td>n/a</td>
</tr>
<tr>
<td>IB/0054</td>
<td>B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product</td>
<td>19/11/2012</td>
<td>n/a</td>
</tr>
</tbody>
</table>
| II/0044   | Update of section 4.4 of the SmPC to add a warning related to psychogenic syncope. The package leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. | 20/09/2012 | 25/10/2012 SmPC and PL | The MAH provided a safety review to support an insertion of a warning statement regarding syncope associated with the injection of Synflorix. There has only been one possible report out of 63 million doses of Synflorix administered world-wide. The vast majority of doses were given to younger children, but some increase in the use in older children could be expected, as catch-up programs are introduced. It is therefore highly unlikely that insertion of a
of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data

warning will prevent any further injuries among the infants, but possibly among the older children.
In conclusion, the CHMP considered the inclusion of a warning in section 4.4 acceptable with the specification of the age range when these reactions could be expected. The update of contact details of local representatives was accepted.

<p>| IB/0050 | B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product | 26/09/2012 | n/a |
| IB/0048 | B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product | 12/09/2012 | n/a |
| IA/0049/G | This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) | 06/09/2012 | 25/10/2012 | SmPC and Labelling |
| IB/0047 | B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product | 06/07/2012 | n/a |
| IB/0046 | B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product | 12/06/2012 | n/a |
| IB/0045 | B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product | 29/05/2012 | n/a |
| WS/0239 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Registration of an additional site for QC sterility testing activities for pre-filled syringes, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The batch release site remains unchanged. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place | 19/04/2012 | n/a |
| WS/0237/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. | 19/04/2012 | n/a |</p>
<table>
<thead>
<tr>
<th>QC testing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.</td>
<td></td>
</tr>
<tr>
<td>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II/0040/G</th>
<th>This was an application for a group of variations.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Addition of a manufacturing site for the finished product. Change in immediate packaging of the finished product. Addition of a site where testing take place.</td>
</tr>
<tr>
<td></td>
<td>B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.</td>
</tr>
<tr>
<td></td>
<td>B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products</td>
</tr>
<tr>
<td></td>
<td>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place</td>
</tr>
<tr>
<td></td>
<td>B.II.b.1.a - Replacement or addition of a</td>
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<tr>
<td></td>
<td>15/03/2012</td>
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<tr>
<td></td>
<td>15/03/2012</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<td>------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>IB/0041</td>
<td>B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data</td>
</tr>
<tr>
<td>II/0029</td>
<td>Update of section 4.8 of the SmPC in order to update the safety information [addition of hypotonic-hyporesponsive episode in the undesirable effects Table]. The PL and Labelling are updated in accordance. In addition, the MAH took the opportunity to include information on paediatric development in section 5.1 of the SmPC, to make minor corrections to the SmPC in line with QRD template and to update Annex II in line with current CHMP recommendations. The list of local representatives in the PL was also updated.</td>
</tr>
<tr>
<td>WS/0201/G</td>
<td>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To propose new target fill volume controls. To align the volume specifications to be applied at release and during stability evaluation. To revise QC release procedures for final container</td>
</tr>
<tr>
<td>IG/0133</td>
<td>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system</td>
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<tr>
<td>---------</td>
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</tr>
<tr>
<td>WS/0166</td>
<td>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Registration of an additional facility for filling of finished product. The change relates to pre-filled syringes only. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.</td>
</tr>
<tr>
<td>Reference</td>
<td>B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS (20/10/2011)</td>
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<td>-----------</td>
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</tr>
<tr>
<td>IA/0028</td>
<td>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</td>
</tr>
<tr>
<td>IB/0027</td>
<td>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate (10/08/2011)</td>
</tr>
</tbody>
</table>
Annex II in order to reflect the latest approved RMP version 5.0.

C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one

<table>
<thead>
<tr>
<th>Reference</th>
<th>Change Description</th>
<th>Date of Notification</th>
<th>Date of Compliance</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB/0026</td>
<td>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</td>
<td>18/07/2011</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>IG/0081</td>
<td>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV</td>
<td>07/07/2011</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>II/0024/G</td>
<td>This was an application for a group of variations. To add a new manufacturing site for the finished product and to introduce some changes in the manufacturing process of the finished product.</td>
<td>19/05/2011</td>
<td>29/06/2011</td>
<td>SmPC, Labelling and PL</td>
</tr>
</tbody>
</table>

B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.
B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability.
B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological
<table>
<thead>
<tr>
<th>II/0023</th>
<th>Post-approval change management protocol for the addition of a new manufacturing site for the intermediates and active substances.</th>
<th>19/05/2011</th>
<th>19/05/2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>IG/0064/G</th>
<th>This was an application for a group of variations. Update of section 4.8 of the SmPC to include immediate injection site pain, stinging and burning sensation. The PL is updated in accordance. The MAH has also taken the opportunity to align section 4.6 of the prefilled syringe presentation with the vial presentation. Furthermore, the Labelling is updated to specify the container 'prefilled syringe'. In addition, the MAH has taken the opportunity to update the list of local representatives in the PL.</th>
<th>04/05/2011</th>
<th>n/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure</td>
<td></td>
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</tr>
</tbody>
</table>

Following clusters of spontaneous reports of immediate onset injection site pain reported in certain batches of the preservative-free formulation of Twinrix Adult, immediate pain, stinging and burning at the injection site has been reflected in section 4.8 of the SmPC and section 4 of the package leaflet. The MAH’s investigation report revealed no specific root cause for the clusters of reports of immediate injection site pain. The injection site reactions were non-serious and self-limited in all cases. The benefit-risk of Twinrix Adult remains positive.
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Date</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.II.e.3.c</td>
<td>Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised</td>
<td>27/04/2011</td>
<td>Annex II</td>
</tr>
<tr>
<td>B.II.e.6.b</td>
<td>Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>B.II.e.7.a</td>
<td>Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier</td>
<td>18/03/2011</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**IG/0062/G**

This was an application for a group of variations.

- C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD
- C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system

**IG/0052/G**

This was an application for a group of variations.

- B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits
- B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification

27/04/2011  n/a      Annex II

18/03/2011  n/a
<table>
<thead>
<tr>
<th>Parameter to the specification with its corresponding test method</th>
<th>B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>II/0021</th>
<th>Post-approval change management protocol for the addition of a Quality Control activities site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II/0016</th>
<th>The MAH seeks to update section 4.2, 4.8 and 5.1 of the SmPC to include information on preterm infants based on the data provided in response to FUM 005 and FUM 006 that have been assessed by the Rapporteur and reviewed by the CHMP.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</td>
</tr>
</tbody>
</table>

| | The current SmPC of 10Pn-PD-DiT in Europe has no recommendation with respect to the posology for vaccination of preterm infants and no description of the immunogenicity and safety of vaccination in preterm infants. The MAH has received requests from immunisation experts and healthcare professionals from several European Member States to have clarification of vaccination status for preterm infants and inclusion of the data in the SmPC for 10Pn-PD-DiT. |
| | The update of SmPC section 4.2, 4.8 and 5.1 of the SmPC to include information on preterm infants is based on data of two studies (primary and booster studies) that evaluate the safety, reactogenicity and immunogenicity of 10Pn-PD-DiT when co-administered with DTPa-HBV-IPV/Hib vaccine in preterm infants (born after a gestation period of 27-36 weeks) as a 3-dose primary immunisation course during the first 6 months of life and then a booster dose at the age of 12-15 months. |
Having assessed these data the CHMP supports the inclusion of information on preterm infants in the SmPC (sections 4.2, 4.8 and 5.1) to give clear guidance to prescribers how to use the 10Pn-PD-DiT vaccine in this vulnerable group.

| II/0014 | Update of section 4.2 of the SmPC with a recommendation for use of Synflorix with 2+1 schedule in routine infant immunisation programmes and to add paragraphs in section 5.1 to reflect immunogenicity data on the 2-dose primary vaccination schedule. | 16/12/2010 | 24/01/2011 | SmPC and PL | The immunogenicity of Synflorix following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in studies 10PN-PD-DIT-002 and -011. The recent study 10PN-PD-DIT-046 assessed the persistence and immunological memory following 2+1 and 3+1 vaccination. The product information has been updated accordingly.

The immunogenicity of Synflorix following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in studies 10PN-PD-DIT-002 and -011. The recent study 10PN-PD-DIT-046 assessed the persistence and immunological memory following 2+1 and 3+1 vaccination.

Amendment to section 4.4 with a statement that vaccination in high risk groups should be considered on an individual basis, with a cross-reference to section 4.2.

To ensure the safe and proper administration of Synflorix using a pre-filled syringe, the MAH took the opportunity to update section 6.6 of the SmPC to include further instructions for the use of the pre-filled syringe (with illustration).
Some further minor amendments have been made in the SmPC to comply with the latest version of the QRD template.

Finally the details of the MAH's local representatives in EU countries have been updated in the PL.

C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data

<table>
<thead>
<tr>
<th>IB/0019</th>
<th>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</th>
<th>18/01/2011</th>
<th>n/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>II/0015</td>
<td>Changes to a test procedure for polysaccharide content for the finished product release.</td>
<td>16/12/2010</td>
<td>12/01/2011</td>
</tr>
<tr>
<td></td>
<td>B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/immunological/immunochemical test method or a method using a biological reagent</td>
<td></td>
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</tr>
<tr>
<td>IB/0022</td>
<td>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</td>
<td>07/01/2011</td>
<td>n/a</td>
</tr>
<tr>
<td>IB/0018</td>
<td>B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data</td>
<td>07/01/2011</td>
<td>n/a</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
<td>Date of Application</td>
<td>Date of Decision</td>
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<tr>
<td>IB/0013</td>
<td>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</td>
<td>28/06/2010</td>
<td>n/a</td>
</tr>
<tr>
<td>WS/0001</td>
<td>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To register an additional building for formulation activities. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.</td>
<td>22/04/2010</td>
<td>22/04/2010</td>
</tr>
<tr>
<td>II/0011</td>
<td>Changes to the manufacturing process of the drug substance Change(s) to the manufacturing process for the active substance</td>
<td>18/02/2010</td>
<td>03/03/2010</td>
</tr>
<tr>
<td>II/0010</td>
<td>Changes to manufacture and control of the drug substance Change(s) to the manufacturing process for the active substance</td>
<td>18/02/2010</td>
<td>03/03/2010</td>
</tr>
<tr>
<td>II/0009</td>
<td>Changes of shelf life</td>
<td>18/02/2010</td>
<td>03/03/2010</td>
</tr>
<tr>
<td>Change(s) to shelf-life or storage conditions</td>
<td>Change(s) to the test method(s) and/or specifications for the active substance</td>
<td>Date</td>
<td>Date</td>
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<tr>
<td>II/0006 Changes to the specifications for the active substance</td>
<td></td>
<td>18/02/2010</td>
<td>03/03/2010</td>
</tr>
<tr>
<td>Change(s) to the test method(s) and/or specifications for the active substance</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Change(s) to the specifications for the active substance</th>
<th>Change(s) to the test method(s) and/or specifications for the active substance</th>
<th>Date</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB/0012 B.1.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)</td>
<td></td>
<td>26/02/2010</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change(s) to the control of the drug product</th>
<th>Change(s) to the test method(s) and/or specifications for the finished product</th>
<th>Date</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Change(s) to the control of the drug product</th>
<th>Change(s) to the test method(s) and/or specifications for the finished product</th>
<th>Date</th>
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</tr>
</thead>
<tbody>
<tr>
<td>IA/0005 IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.</td>
<td></td>
<td>31/07/2009</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change(s) to the manufacturing process for the finished product</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>II/0003 Change to the primary pack stopper and tip cap for pre-filled syringes.</td>
<td></td>
<td>25/06/2009</td>
<td>13/07/2009</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change(s) to the test method(s) and/or specifications for the finished product</th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>II/0004 Optional release program intended for National Control Laboratories in International countries that require independent laboratory testing for lot release purpose of Synflorix drug product.</td>
<td></td>
<td>29/05/2009</td>
<td>08/06/2009</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
<td>Date</td>
<td>Date</td>
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</tr>
<tr>
<td>IB/0001</td>
<td>IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size</td>
<td>07/05/2009</td>
<td>07/05/2009</td>
</tr>
<tr>
<td>IA/0002</td>
<td>IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site</td>
<td>17/04/2009</td>
<td>n/a</td>
</tr>
</tbody>
</table>