Name of medicine (INN):	**Pneumococcal Polysaccharide and Non-typeable H.influenzae (NTHi) Protein D Conjugate vaccine (PCV 10), 0.5 mL suspension for IM injection**
Indication:	Active immunization of infants and children from 6 weeks up to 5 years of age against disease caused by Streptococcus pneumoniae serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (including sepsis, meningitis, pneumonia, bacteraemia and acute otitis media) and against acute otitis media caused by Non-Typeable Haemophilus influenzae.
Date/s of deliberation:	14 January 2015 04 March 2015 05 June 2015
Recommendation:	**DISAPPROVAL**
Clinical evidence:	Two PCVs are currently registered by the Philippine FDA, a 10-valent PCV (Synflorix®), which covers 10 of approximately 90 *S. pneumoniae* serotypes, and a 13-valent PCV (Prevnar®), which covers 3 additional serotypes. Both vaccines have been proven safe and effective to prevent diseases caused by *S. pneumonia,* including sepsis, meningitis, pneumonia, bacteremia and AOM in children less than 5 years old. For a 3+1 schedule of the pre-existing PCV7, a meta-analysis of randomized controlled trials (RCTs) showed a vaccine efficacy (VE) against vaccine-type invasive pneumococcal disease (IPD) of 89% (Pavia et al., 2009). To date, no published RCT data showing the impact on the final clinical endpoints are available for PCV13. However, immunogenicity trials of PCV13 demonstrated non-inferiority compared to PCV7 for the common serotypes and PCV13 effectiveness data has been reported in various settings such as the UK and the US, where IPD infections decreased from 42% to 75% (Kaplan et al., 2013; Moore, 2014; Andrews et al., 2014). Two randomized controlled trials (RCTs) have been conducted for PCV10. The 'Clinical Otitis Media & Pneumonia Study' (COMPAS) (Tregnaghi et al., 2014) using a 3+1 schedule, and the Finnish Invasive Pneumococcal disease trial (FinIP) (Palmu et al., 2013) using 3+1 and 2+1 schedules. Data on the clinical efficacy against IPD was based on the FinIP trial, which reported a VE of 92% in reducing vaccine-type IPD for the 2+1 schedule. This value was adjusted by accounting for the Philippine serotype coverage (Table 1). The VE against all-cause pneumonia and AOM was set at 8.7% and 19%, respectively, based on the COMPAS results. Overall VE against pneumonia and AOM was adjusted to a 2+1 dosing schedule and assumed to increase proportionally with the increase in vaccine serotype IPD coverage in the Philippines (Table 2).

The Formulary Executive Council (FEC) stated that it is reasonable to assume in the model that both PCV10 and PCV13 efficacy could be extrapolated from PCV10 since this is the most direct evidence for a vaccine which could protect against at least 10 serotypes. It should be noted that prior to available direct evidence for PCV10, both PCV10 and PCV13 efficacy data were extrapolated from PCV7. Further, the overall vaccine efficacy against clinical AOM as shown in the COMPAS could only be ascribed to protection against the pneumococcal serotypes contained in the vaccine, as there was no statistically significant evidence that AOM efficacy was partially due to NTHi.

Table 2. Vaccine efficacy by syndrome adjusted by 2+1 schedule and local serotype distribution.

Health conditions	Adjusted overall VE using Philippine serotype coverage	
	PCV 10	PCV13
IPD all serotypes	46.49%[a]	64.30%[b]
Clinical pneumonia	8.42%[c]	11.64[d]
Clinical AOM	18.38%[c]	25.43[d]

a- $PCV10_{2+1}$ against vaccine-type IPD x local vaccine serotype IPD coverage of PCV 10
b- $PCV10_{2+1}$ against vaccine-type IPD x local vaccine serotype IPD coverage of PCV 13
c- $PCV10_{3+1}$ x (1-0.0324)
d- $PCV10_{3+1}$ x (1-0.0324) x (local vaccine serotype IPD coverage of PCV 13 / local vaccine serotype IPD coverage of PCV 10)

Cost data:

A cost-utility analysis of pneumococcal conjugate vaccines in the Philippines was recently conducted by the DOH Philippines in collaboration with UK NICE International, WHO and Thailand HITAP. This was done to update the previous WHO analysis in 2012 which showed Incremental Cost Effectiveness Ratios (ICERs) of Php 111,858and Php 95,014 per DALY prevented for PCV10 and PCV13, respectively (WHO, 2012).

A Markov simulation model was used to examine the comparative cost-effectiveness of PCV10 and PCV13 against the current scenario of no vaccination. A health system perspective was employed to explore different funding schemes, which include full or partial vaccination coverage subsidized by the government. A ceiling threshold of one per capita gross domestic product or Php 120,000 per QALY gained was used to determine the cost-effectiveness of each intervention as recommended by the FEC.

One of the key findings of the study was that the current list price of the manufacturer to the government, with a cost per vaccinated child of Php 1,872 for PCV10 and Php2,100 for PCV13, introducing **partial or universal PCV vaccination for both vaccines is cost-effective in the Philippines compared to no vaccination**

(Table 4).

Table 4. Incremental outcomes of introducing PCV10 and PCV13 compared to 'no vaccination'.

	PCV 10 vs. no vaccination			PCV 13 vs. no vaccination			PCV 13 vs. PCV 10		
	Increm. Cost	Increm. QALYs	ICER/ QALY (Php)	Increm. Cost	Increm. QALYs	ICER/ QALY (Php)	Increm. Cost	Increm. QALYs	ICER/ QALY (Php)
With herd protection Scenario 1 (Universal coverage)	1491	0.02186	**68182**	1613	0.029584	**54510**	122	0.007724	**15,795**
Without herd protection Scenario 2 (25/0)	440	0.003906	**112640**	483	0.00571	**84654**	43	0.001804	**23,836**

QALY- Quality adjusted life year

Scenario 1: Cases averted with universal coverage (one time vaccination)
Assumption that Philippine government will vaccinate the entire birth cohort with PCV13 at Php 4.34 Billion compared to PCV10 at 3.87 Billion (vaccine cost only):

Universal Vaccination	PCV-10 vs nothing	PCV-13 vs nothing	Difference between PCV-13 and PCV-10
Cases of IPD averted	1,479	1,858	379
Cases of all-cause pneumonia averted	26,096	34,140	8,044
Cases of AOM averted	140,107	194,782	54,675
Deaths averted	1,904	2,399	495

Scenario 2: Cases averted with partial vaccination (one time vaccination)
Assume that the PHL government will vaccinate a quintile of the birth cohort with PCV13 at Php 1.09 Billion compared to PCV10 at 970 million.

Partial Vaccination (25% of birth cohort)	PCV-10 vs nothing	PCV-13 vs nothing	Difference between PCV-13 and PCV-10
Cases of IPD averted	84	164	80
Cases of all-cause pneumonia averted	4,478	6,223	1,745
Cases of all-cause AOM averted	35,027	48,695	13,668
Deaths averted	149	225	76

The study confirms that universal vaccination is a more preferable option concerning the greater value of money. In this scenario, indirect effects (herd protection) are realized since a significant portion of the eligible population is vaccinated (≥80%), preventing the disease in unvaccinated populations. Furthermore, introducing the slightly more expensive PCV13 into the Expanded Program of Immunization will have more clinical benefits in averting severe diseases

	than PCV10. The main reason for this is that the 3 additional strains covered by PCV13 but not PCV10 are common in Filipino children below 5 years of age (~20% among the age group infected with *Streptococcus pneumoniae*). As a result, a higher proportion of invasive and non-invasive pneumococcal diseases, which cause the most child deaths in the Philippines, are prevented by PCV13. Hence, PCV13 would have, at least, equal value for money compared to that of PCV10, and should be a better choice in the Philippines. In addition, it has been observed in countries implementing the first PCV7 vaccine that serotypes not included in the vaccines tend to replace the serotypes included in the vaccines (Miller et al., 2011; Weinberger et al., 2011). Serotype replacement was experienced in the US, UK and Spain, particularly for the virulent and multidrug resistant serotype 19A (Weinberger et al., 2011), which is only covered by PCV13. As a consequence, many Western countries replaced the earlier version of PCV7 with PCV13 in their national immunization programs due to the rapid rise of this serotype in invasive pneumococcal isolates. Serotype 19A was also one of the more commonly isolated serotypes in Filipino children under 5 years of age (Capeding, 2012). Partial vaccination coverage may also generate indirect effects provided that the entire birth cohort of selected high-risk regions is vaccinated and migration is contained. This would lead to herd protection among the unvaccinated population in the high-risk regions only. The FEC noted that this approach may have some issues on equity principles, however, given the limited resources of the government, it might be considered as a potential option. In terms of budget impact, vaccinating 25% of the birth cohort with PCV10 will require an annual budget of Php 970 M, whereas partial vaccination coverage with PCV13 will have a budget impact of Php 1.09 B. Expanding PCV to the total birth cohort of 2.2 M infants will require substantial financial resources of Php 2.67 B and 3.14 B for PCV10 and PCV13, respectively.
Review of appeal:	The Formulary Executive Council appreciates the evidence put forth in the appeal of GlaxoSmithKline Philippines for reconsideration for inclusion of the pneumococcal conjugate vaccine in the Philippine formulary. The main points are summarized below: 1. The proponent claims there is “strong evidence that Synflorix® also provides protection against serotypes not included in the vaccine (6A and 19A) and that the protection of the recently listed PCV13 against serotype 3 disease is, so far, unconvincing.” *With regard to the evidence on cross-protection of Synflorix® against serotype 6A and 19A, the FEC has cross-checked the approved indications of use by the Philippine FDA and other regulatory agencies such as the*

European Medicines Agency (EMA). Both agencies have not included protection beyond the serotypes covered in the vaccine. So far, evidence on cross-protection is insufficient to make a claim on the effectiveness of serotypes not contained in the vaccine. We recommend that GSK submits to the FEC the final recommendation of the EMA on cross-protection once it is available.

In a recent study by Moore et al. [1], which was submitted to the Pharmaceutical Division by GSK, the authors were unable to identify a reduction in IPD caused by serotype 3 (included in PCV13) in the USA. The same study also notes that "findings from another publication suggests that there was a reduction in serotype 3 IPD cases in eight paediatric hospitals (in the USA) [2], whereas data from a large, national surveillance programme in England and Wales suggested no evidence of effectiveness of PCV13 against serotype 3 [3]". The authors concluded that "definitive evidence of effectiveness of PCV13 against serotype 3 colonization and IPD needs more study".

2. The proponent further points out that "by listing only one pneumococcal conjugate vaccine in the PNF, the FEC could open itself to a claim that it had given an 'unwarranted benefit, preference or advantage' to the listed vaccine supplier."

   We confirm that the government procurement process is bound by RA 9184 which puts competitive bidding as the default mode of procurement. However, competitive bidding can only be performed for similar products, which is not the case for both pneumococcal conjugate vaccines. The additional serotypes included only in PCV13 accounted for 19% of all confirmed invasive pneumococcal isolates in Filipino children below 5 years of age [4]. Under the assumption that serotype 3 is excluded, additional serotypes (6A and 19A) accounted for 14% of confirmed isolates in children below 5. PCV 10 and 13 are not equal in terms of efficacy thus in the model previously done by the DOH, the parity price at which PCV 10 will be equally cost-effective to PCV 13 was calculated at Php 526.00.

Remarks:

After considering the documents submitted for reconsideration, the Secretary of Health, upon the recommendation of the Formulary Executive Council (FEC), has officially disapproved the said request.