FACT-FINDING INVESTIGATION IC50 – VACCINES FOR HUMAN USE
EXECUTIVE SUMMARY

Opening of the investigation

1. On 5 May 2015 the Italian Competition Authority (Autorità Garante della Concorrenza e del Mercato, hereinafter Authority or AGCM) opened a fact-finding investigation into the principal markets for vaccines for human use administered through the Italian National Health Service (Sistema Sanitario Nazionale, hereinafter SSN). The investigation – which did not include flu vaccines since their production and commercial cycles are highly seasonal – was prompted by the perception that a number of competition problems have arisen both from broader global industry trends and from some more typically domestic characteristics of pharmaceutical public procurement policies. The investigation, which ended in May 2016, confirmed that problems do indeed exist and revealed a number of issues specific to the sector. These are summarised below.

Main findings of the investigation and the Authority's recommendations

Industry background

2. Vaccines are a key public health acquisition. However, vaccines have traditionally been viewed as a segment of the pharmaceutical industry that lacked any major commercial potential and was characterised by relatively low-cost products. This situation has changed radically over the last 20 years with the introduction of "innovative" vaccines (the term "innovative" referring here to the frequent use of advanced biotechnologies in their development). The prices for these are much higher than for "classic" vaccines, for example those originally envisaged by the World Health Organisation (WHO) in its *Expanded Programme on Immunization*. The new vaccines – most notably the current pneumococcal conjugate vaccines (PCV), papillomavirus vaccines (HPV vaccines) and some multivalent vaccines – are exhibiting strong commercial expansion. At least some of them have gained a steady presence in the limited category of "blockbuster" medicines, i.e. those with global annual sales of over one billion dollars.

3. Overall, vaccine industry sales are showing strong and steady growth and, compared with 23 billion euro globally in 2014, could, according to recent estimates, exceed 35 billion euro by the end of 2016. Profitability too is high, even higher than for the pharmaceutical sector on average. At present, this trend is almost entirely due to prophylactic vaccines: those intended to prevent disease. At the same time, numerous "therapeutic" vaccines, designed to *treat* illnesses, including some that are very widespread among the world's population, are at an advanced stage of development.

4. The significant change of scenario described above does not seem to have been adequately absorbed and conveyed in information terms; the result is a lack of awareness among purchasers and the principal public decision-makers. This situation of "perceptive asymmetry" regarding the significance and importance of the sector has been accompanied by, and to some degree might even have contributed to, the progressive consolidation of significant market power in the hands of the principal vaccine producers.

5. The technological development of the sector and the progressive reduction of the public presence in (not so much research as) manufacturing activities has led to **the establishment of an oligopoly of large private companies, highly concentrated at the global level, in which the four leading operators – GlaxoSmithKline (GSK), Merck Sharp & Dohme (MSD), Sanofi Pasteur (SP) and Pfizer – account for over 80% of the global market in terms of value.** Within the European Union (EU), MSD and SP operate through a joint venture (MSDSP) which, it has been announced, is soon to be dissolved. This oligopoly, at least in the short term, looks set to continue, even though competitive pressure is growing from new operators of Asian origin – most notably a number of Indian and Chinese companies – which are showing an autonomous capacity to develop innovative vaccines and are adopting different price policies.

Patent-related barriers, pharmacological equivalence/commercial substitutability of vaccines and the impact of competition on product competition

6. As regards product competition, as things stand at present **it is extremely difficult to find equivalent alternatives to innovative vaccines**. These difficulties **can be explained by the technological investment needed to develop the products** (both in terms of formulating the antigens and of developing them in combined formulae, e.g. for multivalent vaccines) and **the high degree of patent protection they enjoy** (relating to a number of additional components to the active substance, e.g. adjuvants or routes of administration).

7. Vaccines are, to all intents and purposes, pharmaceuticals with a biotechnological basis. However, it does not seem that effective pathways to develop generic versions can be applied to them by following the "biosimilar pathway" model – designed to cut the time required for copy versions to enter the market – that already exists in some systems. This question clearly requires a solution at the supra-national level. Staying within the EU, this consideration is borne out by the fact that vaccines are among the pharmaceutical products subject to the centralised authorisation procedures for marketing that are managed by the European Medicines Agency (EMA). On this point, **the Authority hopes that the competent actors at the supra-national level will actively consider the question of the pathways to be put in place for the production of generic vaccines,**

following the model already adopted both for chemical-based and biotechnological medicines, with a view to developing effective product competition.

8. Even when several vaccine products exist for the same disease, it is not a given that effective product competition will develop, because of the particularly advanced product differentiation processes that are found in the sector. Indeed, any two vaccines designed to prevent the same disease may not be considered interchangeable in the eyes of consumers (public demand) on the basis of their different serotype coverage, i.e. the number of strains/serotypes of the disease that they act upon.

9. From the point of view of defining the relevant product markets from an antitrust perspective this means that, in principle, **vaccines designed to prevent the same disease but with different serotype coverage could belong to different relevant markets**. This conclusion implies that, in assessing vaccine markets, we are very often faced with supply-side monopoly situations that, with a view to achieving an appropriate balance in procurement negotiations, can only sometimes correspond to a concentration of public demand in the form of one or more contracting authorities.

10. In the light of this supply differentiation process, the Authority:

- considers that **the preventive/therapeutic product equivalence on which possible direct competition of two vaccines designed to treat the same disease is based, requires evaluations and stances to be adopted by competent and independent health authorities** to ensure that purchasers' decision-making is based on genuinely scientific considerations;
- calls for **this decision-making process to be established and followed at the international level** (on this, for the Italian context, see paragraph 32).

Principal price policies and informational asymmetries between demand and supply

11. As regards pricing policies in the vaccine sector, the investigation found that **operators who are part of the global oligopoly referred to above adopt a tiered pricing commercial policy on a global level.** This entails a grouping together of different countries – and consequently of their public and private purchasers – in distinct tiers of financial resources, which results in the application of differentiated prices. The grouping is based on parameters which, although never declared in detail, appear to be related essentially to economic factors (e.g. GDP) with a view to estimating individual purchasers' ability/willingness to pay.

12. The effects of this strategy are without a doubt positive for the supply side of vaccine products, which can thus make price distinctions to extract the greatest possible surplus from each transaction. On the demand side too, we can say that there might be advantages, mainly with regard to maximising purchasers'

spending capacity, where the reference tier is applied correctly. For this to happen, however, any informational asymmetry that might undermine the balanced negotiating position that should be a primary pre-condition in achieving total welfare goals must be avoided.

13. The opacity of the criteria applied in tiered pricing strategies, first and foremost with respect to the inclusion of a State/purchaser in a given tier, is combined with a high degree of difficulty in obtaining reliable and well organised information regarding the prices applied to different buyers for the same product. These difficulties often stem from the confidential nature of the price information that sellers impose on buyers, primarily through bilateral agreements drawn up as pre-conditions of supply. The informational imbalance to the detriment of the demand side for vaccines is worsened by the complex question, which we might describe as "preliminary" (and which applies to the entire pharmaceutical sector), of the opacity surrounding the costs of medicines. On this point, with specific reference to the Italian market, see the considerations in paragraph 37.

14 Overall, the resulting informational imbalances can prevent the demand side from carrying out the comparability analyses and cost/opportunity evaluations on which, from the consumers' perspective, any efficient procurement policy should be based. The Authority therefore hopes that:

- **the possibility of balanced negotiations between the demand side and the supply side for vaccines is guaranteed in the most effective way possible**;
- **the demand side for vaccines is allowed access to the broadest possible range of information on a global basis** to make appropriate decisions on its purchases;
- taking the possible advantages that would also arise for the demand side into account, **the legitimacy of any confidentiality agreements is rigorously assessed on a case-by-case basis**.

Vaccine strategies, product availability and product procurement policies in Italy

15. In Italy, since 1999, public demand for vaccines on the part of the SSN has been based on National Vaccine-based Prevention Plans (**Piani Nazionali di Prevenzione Vaccinale**, hereinafter **PNPV**). Each new plan is jointly approved by central government bodies and local administrations. Approval usually leads to **the inclusion of the vaccinations envisaged in the plans in the Essential Treatment Levels (Livelli Essenziali di Assistenza**, hereinafter **LEA**) **which the SSN is required to provide in a uniform manner throughout the country**.

16. Given these organisational criteria for vaccine prevention strategies, the investigation found that, with the exception of a minimum core of vaccines that are absolutely necessary in terms of basic epidemiological safety throughout the country, the important factor for the success of a vaccine product is precisely the

definition of said vaccine as "essential" as a result of its inclusion in the PNPV/LEA.

The Authority therefore recommends that:

- **the Parliament and the Government,** each within its sphere of competence, **take action to amend and simplify the legislation governing vaccines, in particular to highlight the central role played by the definition of vaccines included in the PNPV/LEA as "essential"**;
- the competent institutions – such as, first and foremost, the **Ministry of Health, along with the regional government bodies** responsible for deciding on vaccine supply within their region – **clarify how the preventive use of vaccines has evolved for the persons they are intended for,** the aim being to increase awareness of vaccine products among consumers. This clarification could be achieved through **specific communications plans**.

17. As regards the supply of vaccine products, **the inclusion and subsequent retention of a vaccine in the list of those deemed essential under the PNPV/LEA bring a notable competitive advantage**, which in many cases corresponds to a sort of guarantee of purchase by the SSN. Taking into account the factors influencing demand and the economic-commercial impact they give rise to, the Authority therefore recommends that:

- **decisions to include a vaccine product in a public prevention programme and/or to categorise it as essential should always be based on the maximum guarantees of scientific rigour, transparency and independence;**
- **the inclusion of a vaccine should be based, in an explicit and verifiable manner, on widely available instruments for technical-economic analysis, especially as regards the cost-effectiveness profiles of the different vaccine products** (e.g. Health Technology Assessment methods), in the light of the recommendations and best practice at the international level.

18. As confirmation of the importance, from an economic and competition perspective, of this key element in the decision-making process, when this investigation ended the new PNPV for 2016-18 had not yet been formally approved. This was because of the need – raised by the Ministry of the Economy and Finance – to conduct a more detailed analysis of the economic sustainability of extending vaccine availability compared with the current situation, with an increase from 300 to over 600 million euro in total expenditure on the part of the SSN[*].

[*] On the basis of the latest formally approved PNPV and the current LEA, the essential vaccines that can be administered to the population on Italian territory are the following: (1) diphtheria vaccine; (2) tetanus vaccine; (3) polio vaccine; (4) hepatitis B vaccine; (5) pertussis vaccine; (6) measles vaccine; (7) rubella vaccine; (8) parotitis (mumps) vaccine; (9) Hib vaccine; (10) HPV vaccine; (11) Pneumococcal conjugate vaccine (PCV); (12) meningococcal C vaccine; (13) varicella vaccine. Under the new PNPV awaiting formal approval, in addition to the administration of the HPV vaccine and PCV to groups of the population at present excluded, the following

19. With reference to these recently introduced developments in public procurement and in the light of our earlier considerations regarding possible informational asymmetries emerging during vaccine purchase negotiations, it should be noted that **the Italian system is distinctive at the international level since it has to date envisaged a significant degree of administrative transparency and transparency of public procurement data**. This experience, which admittedly has ample margins for improvement, should be preserved, from the perspective of positive increments in competition and the attainment of the above-mentioned harmonious balance between the opposing claims of the demand and the supply sides in procurement transactions.

20. Therefore, also taking into account the historic opportunity opened up by the very recent introduction of a new legislative framework for procurement (see Legislative Decree No 50 of 18 April 2016), the Authority recommends that:

- **the competent government offices and bodies should put in place reliable, uniform, open and constantly up-dated information instruments** in order to enable:
    - public demand to define its contractual position in an appropriate manner in the purchase of pharmaceutical products/vaccines;
    - the supply side to operate with the necessary guarantees of administrative transparency and plan its operational activities to best effect.

This could be achieved, for example, through a standardisation of the data relating to tenders and the availability of such data within sources that are open and easy to find and process.

21. The structure of public demand for vaccines on the part of the SSN has traditionally been characterised by a marked fragmentation on the purchasing side. In accordance with recent legislative provisions, an important process of reducing the number of contracting authorities is under way with a view to establishing a limited number of procurement centres. In this respect, the Authority takes positive note of the aggregation process currently under way at the national level. At the same time, it should be underscored that **the mere aggregation of demand is not in itself an absolute guarantee of obtaining greater operational efficiencies**. For such efficiencies actually to be achieved, the Authority therefore feels that **the first and fundamental condition for efficient purchasing policies is to put in place suitable instruments to obtain constant and targeted market intelligence with a view to dynamically benchmarking supply** – which again places the focus on the question of data availability – and **establishing good management practices agreed by those in charge of public procurement**.

---

vaccines will also be classed as essential: (14) herpes zoster vaccine; (15) rotavirus vaccine; (16) meningococcal vaccine.

22. Again with respect to current developments in demand at the national level, some key actors on the production side have expressed their concerns to the Authority over the possible effects of excessive concentration of purchases. In the light of the investigation just closed, **the Authority considers that as things stand at present demand-side aggregation processes do not pose particular problems**. More specifically, it does not feel that aggregation is likely to lead to the establishment of a public monopoly with the ability to exert overwhelming purchasing power over the supply side and thus depress its profitability to levels that could discourage investment and innovation. On the contrary, the process currently under way appears to stem from the consolidation of a timely countervailing buyer power with respect to a supply side that is objectively very concentrated and has ample market power. Positive operational effects for the supply side can also be expected from the aggregation of demand, e.g. in terms of more efficient planning of production activities and economic-financial flows.

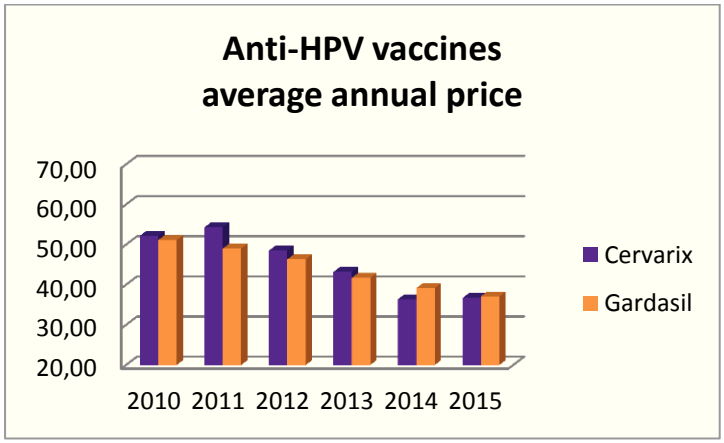
Key trends in purchases of vaccines for the SSN in 2010-15

23. The investigation considered purchases of vaccines for the SSN in 2010-15, which correspond, to date, to average total annual expenditure of about 300 million euro. Of this, a limited number of products account for the largest shares, most notably (according to the figures for 2014):

- **PCV (84 million euro);**
- **hexavalent vaccines (75 million euro);**
- **HPV vaccines (23 million euro)**.

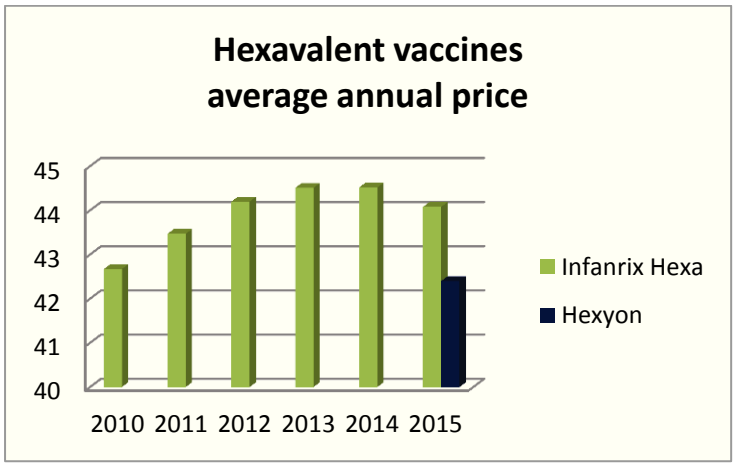
24. The analyses conducted during the investigation on trends in SSN expenditure allow us to state that, overall, **the development of effective price competition between vaccines for the prevention of a given disease produces significant effects in terms of reducing the average contract award price, even when the tender involves original products in the absence of generics**.

25. HPV vaccines (which protect against papillomavirus infection) are a case in point. During the period under examination, average award prices fell by nearly 30%, to the current approximately 36 euro per dose for both the available products. These are Cervarix (a bivalent vaccine, i.e. which protects against 2 types of papillomavirus, produced by GSK) and Gardasil (a quadrivalent vaccine produced by MSDSP and offering the same cancer prevention cover as Cervarix, as well as cover against other conditions caused by two different strains of the same virus). The following chart shows the downwards trend in average prices that occurred during the continuous and direct competition between these products – with Gardasil accounting for about 65% of supply and Cervarix the remaining 35% – in tenders or individual lots to supply the SSN.



Source: AGCM database, using data from companies and contracting authorities

26. In the case of hexavalent vaccines too (designed to prevent diphtheria, tetanus, hepatitis B, poliovirus, acellular pertussis and *Haemophilus influenzae* type B), direct competition between products translated into price competition. This is true even though both competitors – as in the case of the HPV vaccines – were branded and had similar published prices that were far different from those we might expect for generic versions. In more detail, after a long period of monopoly enjoyed by GSK's Infanrix Hexa, in 2015 a new competitor – MSDSP's Hexyon – became available. The newcomer's entry to the market – limited as it was – was immediately followed by a downwards adjustment in average contract award prices. While between 2010 and 2014 the average price per dose of Infanrix Hexa increased by about 4%, from around 42.6 to around 44.5 euro per dose, after Hexyon entered the market the price fell to 44.1 euro per dose, with particularly significant dips for certain tenders. The average price per dose of Hexyon in the tenders won in 2015 was 42.4 euro per dose.



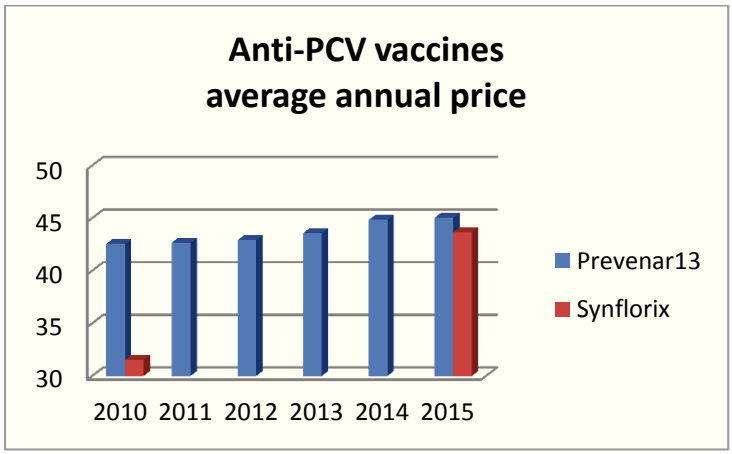
Source: AGCM database, using data from companies and contracting authorities

27. Again in terms of competition analysis it should be underscored that, **in the case of both HPV and hexavalent vaccines, competitive pressure was able to be exerted since the contracting authorities did not adopt product differentiation**

criteria – in terms of the bacteria or virus strains affected by the treatment – that would have prevented the inclusion of several vaccines in a single lot or tender.

28. In the case of pneumococcal conjugate vaccines (PCV)** (used to prevent pneumococcal infections), the play of competition between the two products available on the Italian market has not, to date, been possible, for reasons of serotype differentiation. More specifically, GSK produces a vaccine product, Synflorix, which offers cover against 11 strains of bacteria. However, supply to the SSN has essentially been monopolised by Synflorix's rival product, Pfizer's Prevenar13, which provides cover against 13 strains. As regards, specifically, commercial trends witnessed in Italy, between 2010 and 2015 Prevenar13 came to hold over 95% of the market by value, with average award prices rising from 42.6 to 45 euro per dose, an overall percentage increase of around 6%.

29. A closer reading of these price trends also leads to the consideration that, in the case of Prevenar13, a fairly clear case of penetration strategy occurred: the gradual increase of prices once a product has obtained an "essential to health" status. As confirmation of just how important it is for vaccines in Italy to be included in the PNPV/LEA, Prevenar13 had been recommended since the 2012-14 PNPV/LEA and in 2013 its average price reached over 43 euro per dose. The other possible competitor product, GSK's 11-valent Synflorix, won a very small number of tenders and essentially disappeared from the market from 2011 to 2014. Even so, its average price rose from about 31.5 to 43.6 euro per dose, which seems to suggest a purely parasitical strategy of following the market leader's price.



Source: AGCM database, using data from companies and contracting authorities

** Although several PCVs are available, under the current PNPV only "conjugate" vaccines can be administered to infants, the main population group treated to date with this vaccine. Conjugate vaccines are composed of different micro-organisms which, once combined, develop new immunogenic attributes. This provision therefore limits potential competition to those vaccines that are composed in this way. In general, with respect to PCV, the scientific literature has recorded about 90 strains of Streptococcus pneumoniae bacteria, 20 of which are responsible for over 70% of the invasive diseases caused by infections.

30. To conclude our discussion of the commercial trends in the supply of PCV to the SSN, we should consider that Prevenar13's absolute predominance can be ascribed to the fact that, as mentioned earlier, it offers greater vaccination coverage than Synflorix (13 strains of bacteria, compared with 11). Even with the general recommendation in the PNPV 2012-2014 (as well as the latest available version of the PNPV 2016-2018) of a pneumococcal conjugate vaccine, Italian health facilities therefore tend to prefer a product that offers broader coverage in terms of the number of strains of bacteria covered. When procuring supplies of 13-valent PCV, they often end up issuing calls to tender that merely formalise their demand for a single, clearly defined product.

31. Evaluations of the equivalence/substitutability of different vaccine products designed to prevent or treat the same condition must, as we have seen, be conducted in an unambiguous, authoritative and independent manner. In this light, and considering that what occurred in the case of PCV is a prime example of the above-mentioned product differentiation that is so widespread in the sector, with consequences that are bound to be repeated for other types of vaccine, the Authority recommends that:

- **the question of possible direct competition for a number of vaccines providing different forms or degrees of serotype cover should be managed and resolved by the leading medical-health authorities at the national level, while pursuing the highest possible prophylactic vaccination objectives consistent with the epidemiological characteristics of the region under consideration.**

32. In concrete terms, therefore, **the serotype coverage needed to ensure that the national medical-epidemiological objectives are met should be defined officially by the leading medical and scientific authorities, with a view to achieving the best possible interests of health. When possible, the contracting authorities responsible for meeting SSN demand should be able to exploit any benefits deriving from direct competition between different products.** In this respect, the model of existing national competencies used by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) when assessing the therapeutic equivalence of medicines with different active substances in accordance with Decree Law No 158 of 13 September 2012, as modified by Law No 189 of 8 November 2012, is worthy of note. **Any other gain in serotype coverage (with resulting additional health benefits) could therefore be considered and rewarded in the context of the evaluation process to determine the most cost-effective supply,** a process that has recently been strengthened by the new provisions governing public tenders.

33. In the broader perspective, the need is to limit as far as possible any scope for abuse by setting unfair prices. This would have immediate repercussions on SSN spending and, in effect, improve its economic sustainability. In this respect,

the Authority notes that, in the case of both Prevenar13 PCV and the hexavalent Infanrix Hexa, the price increases introduced in Italy under *de facto* monopoly conditions occurred for mature products – both are among the vaccines that for years have been generating the highest sales at the global level – following the recognition of their essential nature under the PNPV/LEA, which translates into a substantial guarantee of large-scale public purchases. The commercial trend for these products in Italy, therefore, does not seem to have followed the common experience, where prices fall as the amounts sold increase.

Registration of vaccines in reimbursement bands and price negotiations

34. Still on the subject of commercial policies for vaccine products, **the investigation revealed that, with the sole exception of HPV vaccines** (classed as band H medicines)**, in Italy all vaccines are classed as band C medicines, the published price of which is freely set by companies**. This classification seems odd, given that many of these products are in the great majority of cases intended to meet public demand from SSN facilities, the costs of which are entirely covered by the State. We would therefore expect price negotiations at what might be described as the "entry level" to the public health system (something that indeed happens for pharmaceutical products in reimbursement categories A and H).

35. On this point, we should also consider that the substantial freedom to set reference prices for vaccines concerns products that, by reasons of the industry trends we examined earlier, are often marketed under monopoly conditions, without any real alternatives on the market. On the basis of a complex set of regulatory provisions, the Italian system "compensates" for this pricing freedom for vaccines by allowing for mandatory minimum discounts for public contracting authorities. Taking these discounts as a starting point, even better offers may emerge as a result of procurement procedures. Nonetheless, this mechanism hardly seems efficient, since it can lead to a serious lack of informational transparency and in any case cannot be applied to private demand. This, although of minor significance in universal healthcare systems like the Italian one, does still exist, and so should be adequately protected.

36. Moreover, as far as we have been able to ascertain through comparisons with neighbouring and sufficiently similar systems (e.g. by size of population, organisation of health system, and size and characteristics of the economy), such as France, **the prices applied to the SSN for the main vaccines are in effect aligned with, if not higher than, the published prices envisaged in those systems. This is true even after the complex discount system in Italy has been taken into account.** The prices for Infanrix Hexa and Hexyon, for example, are 39.4 and 38.2 euro per dose respectively. This situation confirms that the national discount system currently in force is hardly efficient and at most brings public procurement prices closer to published prices abroad. It also seems to demonstrate **the existence of reference/reserve prices established at the international level by parent**

companies, evidently in the context of those tiered pricing policies which, even though they need to take into account the specific features and regulatory complexities of individual systems, manufacturers manage in any case to impose.

37. The Authority therefore recommends that:

- **Vaccines in the PNPV/LEA should be subject to supply price negotiation mechanisms based on criteria of efficiency and transparency applicable throughout the country**. This would be a marked change from the current opaque criteria of discounts applied to the published prices applied freely by companies.
- Taking into account what is essentially a guarantee of sales to the SSN resulting from the recognition of a vaccine's "essential" status, the Authority's recommendations could be implemented, for example, **by transferring vaccines, once they have been included in the PNPV/LEA, to reimbursement categories that envisage negotiations on reference prices by companies and appropriately qualified institutional actors**. This is what currently happens with the AIFA for class A and H medicines (for which companies are already required to provide information and clarification regarding their cost structures). These reference prices would thus establish an agreed minimum level that would act as a basis for the competent contracting authorities to obtain further discounts in a manner correctly proportionate to: the effects of direct competition – when it exists – between products, the quantities being purchased, and other conditions of supply.
- When the reference prices are being set, **the same qualified institutional actor** could also conduct **a prior assessment of the highly relevant question of product equivalence/substitutability between vaccines designed to treat/prevent the same disease, but which do not entirely overlap in terms of serotype coverage**.

Rome, 11 May 2016