CONFIDENTIAL

Ms Caron Ryalls

9th March 2012

Freedom of Information (FOI) Request: FOI 12/075

Dear Ms Ryalls,

Re: Freedom of Information (FOI) Request - Human papilloma virus (HPV) vaccine

Thank you for your Freedom of Information (FOI) request dated 11th February 2012 requesting information on the Medicines and Healthcare products Regulatory Agency's (MHRA's) policy and methodology on investigating Adverse Drug Reaction (ADR) reports highlighted by the Yellow Card Scheme in relation to the Human papilloma virus (HPV) vaccine.

Underpinning vaccine and medicines pharmacovigilance in the UK is the Yellow Card Scheme, which has been in operation since 1964. This is a voluntary reporting system through which any healthcare professional or member of the public can report a suspected ADR to any vaccine or medicine on the UK market. A Yellow Card report is not proof of a side effect occurring, but merely a suspicion by the reporter that the vaccine or medicine may have caused the side effect. Yellow Card reports may therefore relate to true side effects or they may be coincidental. More information on the Scheme can be found at www.yellowcard.gov.uk.

All reports of serious ADRs are individually reviewed, and followed up with reporters if necessary to obtain further clinical details. As well as using clinical judgement to detect new safety signals from such data, we use specialised IT software and statistical approaches, including disproportionality analyses, to systematically generate safety 'signals' from the Yellow Card data. In carrying out our work, teams of scientists and physicians with responsibility for portfolios of vaccines and medicines continually assess the emerging safety data and re-evaluate the balance of risks and benefits. As well as Yellow Card data, we routinely evaluate all sources of safety data including clinical and epidemiological studies, published medical literature, and information from other regulatory authorities as well as pharmaceutical companies. We also have access to electronic data sources and record linkage databases such as the General Practice Research Database (GPRD) and, if necessary, will conduct *ad hoc* evaluation and research using such data. We may also implement active safety surveillance and/or commission research on a case by case basis.

For HPV vaccine, key aspects of our strategy were to encourage ADR reporting (via letters and other communication material) and conduct real-time 'observed vs expected' (O/E) analysis. The O/E approach uses statistical methodology to compare, on a near real-time and ongoing basis, the number of reported cases of ADRs against the normal rates of such illnesses that are expected to occur by chance amongst the number of girls immunised at each point in time. These analyses adjust for various levels of possible under-reporting through the Yellow Card Scheme. More details of the HPV strategy and our two year safety analysis can be found at www.mhra.gov.uk/HPVvaccine.

The MHRA receives around 25,000 Yellow Card reports from within the UK every year. For HPV vaccine, following administration of at least 5 million doses across the UK since September 2008, we have received more than 6,000 Yellow Card reports since 2008. In relation to your question regarding under-reporting, this is likely to be highly variable depending on many factors with serious events more likely to be reported. The level of ADR reporting may also fluctuate between given years due to a variety of reasons such as a medicine/vaccines being new (reporting rates are generally higher when a product is first introduced), stimulated interest/publicity and variations in exposure to the medicine/vaccine.

I can confirm that as of 9th March 2012, the MHRA has received a total of 6,106 reports of suspected ADRs associated with the use of Cervarix vaccine (including, reports where brand is unspecified), in the United Kingdom, involving 13,857 suspected adverse reactions.

Table 1 below details the number of ADR reports submitted from industry (GlaxoSmithKline), healthcare professionals and patients, and total number of reports, received for each year of the immunisation programme, respectively.

Year	Number of Reports		Total Number of Reports
	GlaxoSmithKline	Healthcare Professionals & Patients	
2008	36	1256	1292
2009	70	1842	1912
2010	48	1746	1794
2011	25	1040	1065
2012	1	37	38

Table 1

Please note that all ADR reports regardless of source are analysed and assessed in the same way. It is important to be aware that a report of a suspected side effect to the MHRA does not necessarily mean that it has been caused by the vaccine only that the reporter had a suspicion that it may have. Many factors have to be taken into account in assessing the relationship between a vaccine and a suspected side effect such as the possible role of underlying or undiagnosed illness or infection. The number of reports received should not be used as a basis for determining incidence of a reaction as neither the total number of reactions occurring nor the exact number of patients using the vaccine is known.

In terms of decision-making, MHRA has in place processes to obtain independent expert advice on the balance of risks and benefits from the Commission on Human Medicines (CHM) and its sub-committees. As we also work within a European regulatory framework and as many new vaccines (such as HPV vaccines) have a single EU-wide marketing authorisation, we work very closely with other EU Member States and the European Medicines Agency in vaccine pharmacovigilance and regulatory decision making. When considering balance of benefits and risks, all relevant available data is taken into consideration.

Please be assured that the number and nature of suspected ADRs received following HPV vaccine so far is very much in line with what the MHRA expected to receive at this time and no serious new risks have been identified. CHM has advised that the balance of risks and benefits of HPV vaccine remains positive.

As with all vaccines and medicines, the MHRA will continue to closely monitoring the safety of HPV vaccine.

I hope this information is useful to you.

Kind Regards,

Miss Saira Mahmood
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