15th March, 2018

FOOD AND DRUGS AUTHORITY
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16 MAR 2018
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THE CHIEF EXECUTIVE OFFICER,
FOOD AND DRUGS AUTHORITY
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ACCRA -GHANA

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Dear Madam,

DHCPL - EMA COMMUNICATION REGARDING CCT LEAKAGES FOR A NUMBER OF GSK VACCINES OK

Beginning in July 2015, GSK identified an increase in the reporting rate of leakages in ceramic coated tip (CCT) syringes at the connection of the syringe tip and the needle hub during vaccine preparation and administration in some markets in the EU.

The Vaccines in scope are Tedivax, Encepur (adult and children), Tetanol Pur, Td-pur, Twinrix (adult and paediatric), Ambirix, Boostrix, Boostrix IPV, Infanrix, Infanrix IPV, Infanrix IPV+Hib, Infanrix hexa, Varilrix, Priorix, Priorix-Tetra, Havrix, Engerix, Typherix, Hepatyrix, Fendrix, Menjugate KIT Lyo and Menitorix **of which Varilrix, Priorix, Havrix and Engerix are registered in our market.**

In Europe the corresponding rate is 2.6 per 100,000 doses distributed with a range of 2 to10 per 100,000 doses for the 5 highest reporting countries, though the precise frequency of leakage is not known and may be higher. The leakage does not pose a concern for sterility assurance.

The potential risk associated with leakage of vaccine from the syringe is that it could, in theory, result in under-dosing, leaving patients inadequately protected from disease after immunization.

However, review of GSK's pharmacovigilance data as of December 14, 2017 shows no evidence that the observed leakage has resulted in vaccination failure (lack of efficacy) or any other patient safety concern.

A DHCP Letter (attached) has been agreed with EMA for proactive communication with relevant Authorities.

We request your advice and guidance on the need for a DHCPL to be communicated.

We look forward to your response.

Yours Sincerely,

Dr. Louisa Preko

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16/03/2018

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Direct Healthcare Professional Communication

23 February 2018

Leaking syringes for a number of GSK vaccines

Tedivax, Encepur (adult and children), Tetanol Pur, Td-pur, Twinrix (adult and paediatric), Ambirix, Boostrix, Boostrix IPV, Infanrix, Infanrix IPV, Infanrix IPV+Hib, Infanrix hexa, Varilrix, Priorix, Priorix-Tetra, Havrix, Engerix, Typherix, Hepatyrix, Fendrix, Menjugate KIT Lyo and Menitorix.

Dear Healthcare Professional,

GlaxoSmithKline Biologicals SA (GSK) in agreement with the European Medicines Agency and the Food and Drugs Authority would like to inform you of the following:

Summary

- Leakages from syringes for several vaccines have occurred during vaccine preparation or administration (see Figure 1).
- In Europe the corresponding rate is 2.6 per 100,000 doses distributed with a range of 2 to10 per 100,000 doses for the 5 highest reporting countries, though the precise frequency of leakage is not known and may be higher.
- The leakage does not pose a concern for sterility assurance.
- The potential risk associated with leakage of vaccine from the syringe is that it could, in theory, result in under-dosing, leaving patients inadequately protected from disease after immunization.

  However, review of GSK's pharmacovigilance data as of December 14, 2017 shows no evidence that the observed leakage has resulted in vaccination failure (lack of efficacy) or any other patient safety concern.
- **<u>If the leakage occurs during reconstitution</u> of lyophilized vaccines, the impacted syringe should be discarded.**
- **<u>If the leakage occurs during vaccine injection</u>, the healthcare professional can decide whether to revaccinate individuals who have been given less than the standard dose. Healthcare professionals should take into account the potential benefit of increasing protection by administering a repeated full dose, the potential risk of adverse events from a repeated dose, and the potential risk of decreased protection if the patient is not re-vaccinated.**

TVA BE 0440 872 918
RPM Nivelles 0440 872 918
Deutsche Bank AG 826-0006444-59

- Healthcare professionals should follow local recommendations on how to handle potential vaccine under-dosing.
- Healthcare professionals are encouraged to report complaints about product quality, medication errors and suspected adverse reactions (see "Call for reporting").

Background on the leaking syringes incident

Beginning in July 2015, GSK identified an increase in the reporting rate of leakages in ceramic coated tip (CCT) syringes at the connection of the syringe tip and the needle hub during vaccine preparation and administration.

The leakages occurred at the interface of the needle and the syringe at the time of usage (see Figure 1) and are not due to compromised integrity of the syringe before usage.

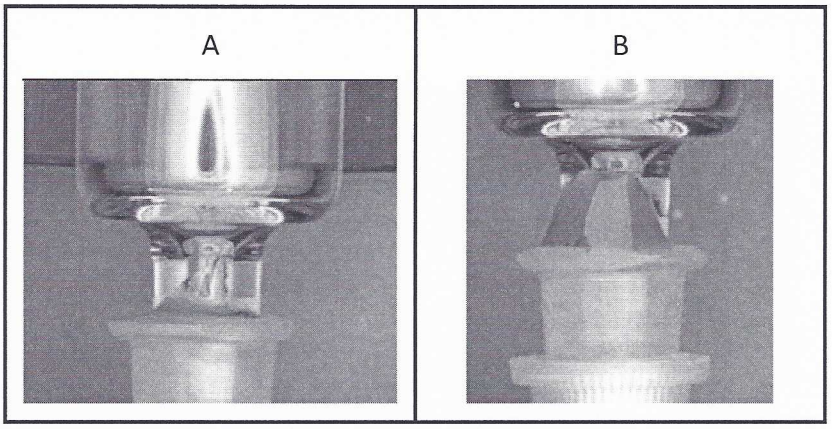

Figure 1: Examples of different volume losses (blue area)

Based on data from literature, syringe supplier investigation and practical testing, volume loss can range approximately from 10 µl (Picture A) to 50 µl (Picture B).

An extreme case with a falling droplet would potentially lead to a volume loss of 100 µl or higher.

GSK has implemented corrective actions with its syringe suppliers and has introduced improved syringes in its filling operations as of January 2018. Both the improved and current syringes will be on the market until the end of 2019, with the proportion of potentially affected syringes progressively decreasing towards the end of 2019 by when the current syringes are expected to have been used up.

Information on potential under-dosing

Relevant data on administration of lower antigen content are available for Havrix, Engerix and Fendrix (1-2). Available data suggest that the administration of half the required antigen dose of Engerix or Havrix will not affect seroprotection or seropositivity. As probability of a leakage resulting in patients receiving half the required dose is very low, a leakage is not expected to impact seroprotection/seropositivity following vaccination.

It is not possible to assess the potential impact of reduced antigen content for Fendrix in end stage renal disease (ESRD) vaccine recipients as a dose-range study was not conducted in this population.

For Twinrix/Ambirix, although no dose-range studies are available, the immune response to the two antigens in the Twinrix vaccine was demonstrated to be at least as good as the one observed after vaccination with the monovalent vaccines Havrix and Engerix (3) for which data on administration of lower antigen content are available.

For the other vaccines potentially impacted by leakages, it is not possible to assess the likely impact of under-dosing on seroprotection/seropositivity. However, for vaccines given in a multi-dose schedule (2-3 priming doses plus booster), it is highly unlikely that each dose will be administered with a leaking syringe.

Additional information on recommendations in the event of under-dosing

In case no local recommendations are in place, the following US Centers for Disease Control and Prevention (CDC), the UK Public Health England (PHE) and the World Health Organization (WHO) recommendations may be considered.

- According to the CDC guidelines, it is recommended that "Any vaccination using less than the standard dose should not be counted, and the person should be revaccinated according to age unless serologic testing indicates that an adequate response has developed. If a partial dose of a parenteral vaccine is administered because of syringe or needle leakage, the dose should be repeated." (12)
- According to United Kingdom Public Health England, it is recommended that "Where vaccines are administered to patients at less than the recommended dose, vaccination will need to be repeated because the doses that patients received may not be sufficient to evoke a full immune response. Vaccination should ideally be repeated on the same day. If it is not possible to repeat the vaccine on the same day, live vaccines should be repeated following a minimum interval of four weeks since the incorrect dose. Inactivated vaccines should be repeated as soon as possible"(13).

According to WHO in its 2015 recommendations for interrupted or delayed schedules it is advised for DTP combination, Measles, Rabies, Mumps and Varicella vaccines "to resume the schedule without repeating the previous dose, however the booster dose should always be given"(14).

Information on potential over-dosing

Regarding the potential risk of overdosing in case of revaccination, according to available data for vaccines after over-dosage with vaccines including Infanrix, Infanrix-IPV and Infanrix-IPV+Hib, Boostrix, Boostrix Polio, Twinrix/Ambirix and Priorix (4-11), the reported adverse events were similar to those reported with the standard dose administration.

Call for reporting

GSK would like to emphasize the importance of reporting any product complaints, including leakage, as an important element of the safety follow-up of vaccines.

HCPs are therefore encouraged to report complaints about product quality, medication errors, and suspected adverse reactions to

- GSK Ghana Representative office or
- the Safety Monitoring Department
  Food and Drugs Authority
  P. O. Box CT 2783
  Cantonments, Accra
  Email: drug.safety@fdaghana.gov.gh

Company contact point

QPPV, GSK Ghana Representative office,
5th Floor GNAT Heights
No. 30 Independence Ave
Ridge, Accra
Email: infomed-fwca@gsk.com
Tel: 0800010038, 0302 221 5555

References:

(1) DoFs 2016N286147_00, 2016N286148_00 and 2016N286149_00 GSK data on file.
(2) Innis B, Snitbhan R, Kunasol P et al., J. Protection Against Hepatitis A by an Inactivated Vaccine JAMA. 1994;271(17):1328-1334.
(3) Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine, Expert Rev.
(4) GDS Infanrix™-IPV+Hib version 012.
(5) GDS Infanrix™ HB-IPV + Hib version 015
(6) (https://www.medicines.org.uk/emc/medicine/14555)
(7) GDS Boostrix™ Version 009.
(8) Boostrix-IPV SmPC- https://www.medicines.org.uk/emc/medicine/28679
(9) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000129/WC500044248.pdf Twinrix European SPC, Last accessed 06/Feb/2017
(10) Priorix™ GDS version 013

(11) https://www.medicines.org.uk/emc/medicine/9787
(12) CDC, accessible at: http://www.cdc.gov/vaccines/pubs/pinkbook/vac-admin.html#nonstandard Last accessed: 06/Feb/2017.
(13) UK Public Health England: Vaccine incident guidance : Actions to take in response to vaccine errors. March 2012 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/326417/Vaccine_Incident_Guidance.pdf Last accessed: 06/Feb/2017.
(14) WHO recommendations for interrupted or delayed immunization schedules – summary of WHO position papers, update 27 February 2015 accessible: http://www.who.int/immunization/policy/Immunization_routine_table3.pdf?ua=1 Last accessed: 06/Feb/2017

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Tedivax, Encepur (adult and children), Tetanol Pur, Td-pur, Twinrix (adult and paediatric), Ambirix, Boostrix, Boostrix IPV, Infanrix, Infanrix IPV, Infanrix IPV+Hib, Infanrix hexa, Varilrix, Priorix, Priorix-Tetra, Havrix, Engerix, Typherix, Hepatyrix, Fendrix, Menjugate KIT Lyo, Menitorix
Marketing authorisation holder(s)	GlaxoSmithKline Biological SA
Safety concern and purpose of the communication	Leaking syringes incident for a number of GSK vaccines
DHPC recipients	GSK EU local operating companies will define the final list of recipients with their national competent authorities.
Member States where the DHPC will be distributed	It is up to the national competent authority in each Member State to decide on whether there is a need for the distribution of the DHPC on their territory and on whether additional details are required for their specific market.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	na
DHPC and communication plan (in English) agreed by CHMP/CMDh	23 Feb. 2018
Submission of translated DHPCs to the national competent authorities for review	9. Mar. 2018
Agreement of translations by national competent authorities	23 Mar. 2018
Dissemination of DHPC	Starting 30 Mar. 2018