アレパンリックス（H1N1）筋注における黒色微粒子に関するまとめ

2009 年 12 月 17 日

黒色微粒子について

カナダで流通している Arepanrix H1N1 について、バイアル中に黒色の微粒子が混入していると医療機関から 4 件報告がありました。このうち 1 件について原因を調査いたしましたので以下に示します。なお、他の 1 件についてはロット番号が不明であるため調査できず、その他の 2 件（ロット番号：A80CA003A および A80CA011A）については現在調査中ですが、まもなく結果が得られる予定です。［11 月 12 日付の照会（カナダ死亡例に関する照会）4 に対する回答］。一方、カナダにおいてアナフィラキシー反応の問題から調査が完了するまで使用せず保管しておくように当局に要請した A80CA007A のロットに関しては黒色の微粒子は認められておりません。

1. 黒色微粒子の調査

Arepanrix H1N1（ロット番号：A80CA009A（AFLPA319BB））について、接種後にアナフィラキシー反応および ORS（Ocular Respiratory Syndrome）の発現が顕著であり、その接種したワクチンにおいて抗原製剤とアジュバント製剤の混合後のいくつかのバイアル内に黒色の微粒子を認めた、と医療機関から報告を受けたことから、その返送サンプルおよび保管検体ならびに製造記録書等の文書について、製造元であるケベック工場にて調査を実施した。なお、その医療機関では調製後のワクチンの分注に 20G の注射針を使用していた。科学的な検討の結果、ワクチンの混合には 23G および接種には 23～25G の注射針が推奨されており、さらに、冷蔵保存により減少したストッパーの弾性を回復させるために、混合時および接種時における注射針のストッパーへの穿刺の前は、少なくとも 15 分間はバイアルを室温で放置することが推奨されている。

各種文書から、ワクチン製品および使用したストッパーは規格に適合し、製造工程において逸脱がなかったことを確認した。また、製造元の保管検体には黒色の微粒子が存在しないことを確認した。さらに、返送サンプルに残っていた黒色の微粒子を FT-IR により測定したところ、ポリシロキサン様の微粒子であることがわかった。

以上のことから、検体中の黒色の微粒子はコアリングで生じたものであることを確認した。なお、当該ロットがアナフィラキシー反応および ORS の発現が顕著であったとされることの原因については確証が得られなかった。

［平成 21 年 11 月 24 日提出　報告書“Plainte Technique #1500028133, # du lot: A80CA009A (AFLPA319BB) Particulate matter”］、［12 月 11 日付の照会に対する回答］および
［平成 21 年 12 月 15 日提出　報告書“Presence of coring particles in the vial after reconstitution of Pandemrix”］

2. ストッパーの組成

Arepanrix H1N1 の抗原製剤およびアジュバント製剤のバイアルに使用するストッパーは、いずれも塩素化ブチルゴムを主成分としており、天然ゴムは含有していない［11 月 18 日付の照会 7 に対する回答］。また、ストッパーは欧州薬局方（3.2.9. Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders）に適合している［11 月 18 日付の照会 6 に対する回答］。

3. 提出資料一覧（黒色微粒子について）

2.1　黒色微粒子に関するまとめ（本資料）

2.2　Presence of coring particles in the vial after reconstitution of Pandemrix™

別添

“Plainte Technique #1500028133, # du lot: A80CA009A (AFLPA319BB) Particulate matter”和文

不溶性微粒子報告書

Technical Complaint No.1500028133
ロット番号：A80CA009A（AFLPA319BB）

製造場所：Ste-Foy 工場、ケベック、カナダ（GSK Biologicals 社）
苦情受理日：2009 年 11 月 10 日
検体受領日：2009 年 11 月 13 日

1. 苦情内容：

Arepanrix の A80CA009A のロットを接種した後の、アナフィラキシー反応および ORS（Ocular Respiratory Syndrome）の発現が顕著であった。また、同ロットの抗原製剤について、ワクチン調製後のいくつかのバイアル中に、黒色の微粒子を認めた（20G の注射針を使用）。

2. 返送された検体の目視検査

合計 7 バイアルが 2009 年 11 月 13 日に返送された（カートン、添付文書およびフリップオフキャップはなかった）。7 バイアルすべてのストッパーは少なくとも 1 回穿刺されており、バイアルの破損は認められなかった。バイアル中の残量は、1.5～5mL であった。また、どの検体もアジュバント製剤と混合済みであった。7 バイアルのうち 6 バイアルで、浮遊した黒色の微粒子が認められた。

3. ドキュメントのレビュー

品質保証部門により以下の書類を確認した。

3.1. 逸脱管理文書

逸脱はない（英仏版レポートの 7～10 ページ）。

3.2. 規格外試験結果（OOS）の調査

OOS はない（英仏版レポートの 7～10 ページ）。

3.3. 警報およびアクションレポート

製造工程において警報基準値を超えた報告はない（英仏版レポートの 7～10 ページ）。

3.4. 単価抗原バルク（原液）の製造記録書

以下の製造記録書を確認したところ、原液の製造工程において、今回の調査に関わる問題はなかった（英仏版レポートの 72～79 ページ（原液～製剤））。

	抗原製剤	単価抗原バルク（ろ過後）	単価抗原バルク
ロット番号	AFLPA319	1B9377CL	1M9096CL

3.5. 抗原製剤の製造記録書

以下の製造記録書を確認したところ、製剤化および二次／三次包装の工程において、今回の調査に関わる問題はなかった（英仏版レポートの 72～79 ページ（原液～製剤））。
充てん工程においては、104 バイアルが排除された（限界値は 73 バイアル）のでアクションレポートが作成された（英仏版レポートの 80～87 ページ（原液～製剤））。

	三次包装品	二次包装品	充てん品	抗原製剤
ロット番号	A80CA009A	AFLPA319BB	AFLPA319B	AFLPA319

3.6. AQLの検証

ロット番号 AFLPA319B について AQL の検証を行った結果、微粒子の存在は認められなかった。

3.7. ストッパー

ストッパー（ロット番号：C000003976）は、品質管理部門から規格のとおりに出荷された（英仏版レポートの 58～70 ページ）。

3.8. 品質試験

3.8.1. 保有サンプル

目視検査を実施したところ、92 バイアル中 91 バイアルに微粒子は認められなかったが、1 バイアルに 1 個の微粒子を認めた。セルロース様の微粒子であることを確認した。このような微粒子の由来は既知であり、安全性についての重大な懸念はない（英仏版レポートの 49～57 ページ）。

3.8.2. 返送された検体

微粒子をストッパーの内側および製剤から認めた。微粒子とストッパーの FT-IR スペクトルを比較した結果、この微粒子はストッパーに由来することが判明した（英仏版レポートの 12～48 ページ）。

3.9. 技術的な苦情に関するデータベース

ロット番号 AFLPA319B についての苦情が 1 件、他に 3 件がデータベースに登録されている。

3.10. 輸送

Arepanrix の A80CA009A のロットはケベックやブリティッシュコロンビアに出荷されており、GSK Biologicals 社の Ste-Foy 工場にバイアルの在庫はない（英仏版レポートの 89 ページ）。

4. 結論

Arepanrix の A80CA009A のロットに関するすべての書類について再調査し、規格および SOP に準拠していることを確認した。小分製品の保有サンプルは、品質試験規格に適合した。また、AQL にも適合した。
返送されたバイアルの微粒子は、注射針でストッパーが削られるコアリングにより生じたものであり、FT-IR の結果からポリシロキサン様の微粒子であることが分かった。ポリシロキ

サンはストッパーの重要な成分である。また、ストッパーはゲージの大きい注射針により穴が開けられていた。
GSK Biologicals 社の Ste-Foy 工場は、本検討の結果、検体中の微粒子がコアリングで生じたものであることを確認した。コアリングにより、バイアル中に微粒子を発生させるもっとも可能性の高い原因は、アジュバント製剤と抗原の混合時や接種時に大きい注射針を使用することであると考えられる。
　今回の調査の結果、黒い微粒子については GSK Biologicals 社の Ste-Foy 工場内の管理に起因する問題ではないことが明らかになったが、Arepanrix の A80CA009A のロットを接種した後の、アナフィラキシー反応および ORS（Ocular Respiratory Syndrome）の発現が顕著であったことの原因については確証が得られなかった。

その他
製品情報シート（英仏版レポートの 95～120 ページ）

Arepanrix H1N1
AS03 アジュバント含有パンデミックインフルエンザワクチン（H1N1）

バージョン 1 （2009 年 10 月 21 日承認）

2009 年 10 月 13 日付けの仮命令により、カナダ保健省はヒトでの限定的な臨床試験結果に基づいて、Arepanrix H1N1 ワクチンの販売を承認した。本承認は、ワクチンに関して公表された品質、接種可能性、免疫原性をカナダ保健省が評価した結果に基づくものである。現在のパンデミックの脅威や人への健康リスクを考慮し、Arepanrix H1N1 ワクチンのリスク・ベネフィットの分析結果は、公式にパンデミックが宣言された状況下において、2009 年の H1N1 インフルエンザ株に対する能動免疫法を許容するものであると判断した。
Arepanrix H1N1 ワクチンの販売に関して、カナダ保健省はワクチン販売後のすべてのコミットメントについて了承するようスポンサーに依頼した。カナダ保健省とカナダ公衆衛生局は継続して、これらのコミットメントの進捗、品質、非臨床や臨床データの更新情報を監視していく。
製品情報シートは必要に応じて更新する予定である。
本製品に関する最新情報については、以下のカナダ保健省のウェブサイトを参照。
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/index-eng.php
カナダ保健省のすべての勧告を考慮すること。

目次

上記の情報については以下のカナダ保健省のウェブサイトを参照。
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/prodinfo-vaccin-eng.php

MEDICAL BACKGROUNDER
Proposed intended use: Internal Use
FOR VERBAL REACTIVE RESPONSE TO ENQUIRIES ONLY
NOT FOR EXTERNAL DISTRIBUTION

Presence of coring particles in the vial after reconstitution of *Pandemrix*™

November 27, 2009

1. Background

Pandemrix™ consists of two containers:
- 1 multidose vial (type I glass) of at least 2.5 ml containing the antigen (a minimum of 10 x 0.25 ml doses) with a stopper (butyl rubber).
- 1 multidose vial (type I glass) of at least 2.5 ml containing the adjuvant (a minimum of 10 x 0.25 ml doses) with a stopper (butyl rubber).

The vaccine is mixed by withdrawing the content of the vial containing the adjuvant by means of a syringe and by adding it to the vial containing the antigen

GSK Biologicals has received complaints describing the presence of particles or coring from the rubber stopper after reconstitution of the vaccine.

2. Manufacturing Investigation

Based on the information currently available to GSK Biologicals, it appears that the observed particles are due to the coring of the rubber stoppers, i.e., small pieces of stopper material are shearing off as a result of the repeated needle insertions through the stopper.

The multidose stoppers used by GSK Biologicals fulfill the requirements of the fragmentation test set forth in monograph 3.2.9. of the current European Pharmacopoeia edition. The test specification incorporates some tolerance for the generation of fragments recognizing that, under normal conditions, some level of stopper coring may be observed even with stoppers that fully meet the compendial requirements.

The complaints received by GSK Biologicals suggest however that the number of fragments observed might be larger than expected and investigations at the manufacturing site have been launched in an effort to identify the root cause of this possible discrepancy.

After investigation, it appears that abnormal level of stopper coring may be due to the piercing of cold stoppers and/or the usage of needles with larger borings.

Because of the effect of temperature on the elasticity of the rubber closure material, coring is more likely to occur when reconstitution is performed immediately after removal of the vaccine from the refrigerator when the stoppers are still cold. It is therefore recommended that the vaccine is kept at room temperature for at least 15 minutes before reconstituting the vaccine.

The incidence of stopper coring may increase in case of usage of needs with larger borings or inadequate needle insertion technique. GSK Biologicals provide under section 4 below an updated recommendation on the needles to be used for the reconstitution of *Pandemrix*™ vaccine.

GlaxoSmithKline Biologicals investigated and results are now available (see document in appendix below)

3. Impact Assessment

Both the adjuvant and antigen rubber closure systems are made of elastomeric materials that have been determined to be safe for the immediate packaging of injections according to the specific requirements of the FDA guidance "Container Closure Systems for Packaging Human Drugs and Biologics" issued in May 1999.

For each stopper, a comprehensive safety evaluation was carried out including the characterization tests on elastomers according to USP <381>, biological reactivity tests according to USP <87> or <88>, extractable and leachable study with, where appropriate, a toxicological evaluation of the safety of extracted substances.

In addition, all elastomeric materials are certified TSE/BSE free and are also free of natural rubber latex known to have the potential to cause allergic reactions in predisposed individuals.

A review of the MSDS (Material Safety Data Sheet) for butyl rubber addresses toxicities associated with inhalation, ingestion, skin or eye exposure, but does not address toxicities associated with intramuscular injection.

A review of the literature was performed and limited information was found to describe the impact of intramuscular injection of rubber stopper material.

A study performed in 1950 in animals found that plugs of neoprene or synthetic rubber produced a relatively mild reaction when injected into guinea pigs. Injections were given intramuscularly, and in guinea pig, the fragments of polymer migrated into popliteal space after being injected into the gluteal muscle.[1] The authors reporting the results indicate it unlikely that such plugs would produce much damage unless one were injected directly into blood vessel, or unless one became the nidus for an infection.

Intramuscular injection of particulate foreign material such as may occur with coring of a rubber stopper would be expected to result in development of a granulomatous inflammatory process at the injection site. GSK has not received any adverse event reports of granulomatous inflammation associated with lots reported to contain black or gray particles.

Based on currently available data, GlaxoSmithKline has not identified any safety-related events related to the presence of the particles.

4. Recommendation regarding needles and syringes required. Instruction for mixing and administration of the vaccine to the patient?

Per 10 doses of vaccine

- 1 syringe (5mL) + 1 needle 23G (32mm) to transfer the adjuvant into the antigen vial
- 10 syringes (1 ml) + 10 needle(s) 23G to 25G (32mm) to withdraw the 0.5mL dose or 10 syringes (1 ml) + 1 needle 23G to 25G (32mm) in case of multiple syringes being prepared consecutively and one needle used for withdrawal.
- 10 needles 23 G or 25G (32mm) for vaccine injection in patients.

GlaxoSmithKline Biologicals is currently proposing an update of the SmPC Section 6.6 "Special precautions for disposal and other handling" to stress the importance of allowing vials to reach room temperature before mixing.

Instruction for mixing and administration of the vaccine

1) Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should **be allowed to reach room temperature; each vial should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.**

2) The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a syringe and by adding it to the vial containing the antigen.

3) After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish emulsion. In the event of other variation being observed, discard the vaccine.

4) The volume of the *Pandemrix*™ vial after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section 4.2).

5) The vial should be shaken prior to each administration.

6) Each vaccine dose of 0.5 ml (full dose) or 0.25 ml (half dose) is withdrawn into a syringe for injection and administered intramuscularly.

7) After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2°C - 8°C) or at room temperature not exceeding 25°C. **If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature before each withdrawal.**

Any unused product or waste material should be disposed of in accordance with local requirements.

5. Conclusion

Based on all the above elements and investigation available in appendix, the following recommendations can be suggested to minimize the risk of coring

1) The usage of needles with large borings (i.e. larger than 20 G) should be avoided. An in-use study showed that needles of 23G/32mm are suitable for the reconstitution of the vaccine and the drawing-up of vaccine doses. Accordingly, GSK recommends

   - The use of a 5-mL syringe equipped with a 23G needle for the withdrawal of the adjuvant and the subsequent addition into the vial containing the antigen. The vial containing the adjuvant should be maintained in downright position to facilitate the withdrawal of the full content.

   - The use of 1-mL syringes equipped with a needle gauge not larger than 23G for the withdrawal of the vaccine doses.

2) Careful insertion technique as described in the paper of Roth referenced below has been reported to help reduce the incidence of coring.[2]

3) In case of multiple syringes being prepared consecutively over a short period of time, one single needle can be used for the consecutive withdrawals.

4) Although the influence of temperature was not clearly shown in the study, it is a best practice to ensure vial closures are brought back to room temperature before needle insertion so that they are at their full elasticity. This can be done by keeping the vials at room temperature for at least 15 minutes before reconstituting the vaccine.

[1] Maghat T.B. and J. T. McClellan. 1950. Reaction to accidentally injected rubber plugs. *Amer. J. Clin. Pathol.* 20:829-833

[2]Roth, J.V. How to Enter a Medication Vial without Coring. *Anesth.Analg.* 2007;104:1615.

[3]Nicol, G. Preventing rubber stopper coring. *Anaesthasia,* 2002; 57:207.

APPENDIX:
Rubber coring particles after reconstitution: investigation report (27 Nov 2009 - 5 pages)

In vitro Quality Control
Physico – Chemical

GlaxoSmithKline

Analytical report **Date: 27/11/2009**

Rubber coring particles after reconstitution: investigation report.

1. Introduction

This investigation was prompted by complaints relating to the observation of presence of cores of closure material in the reconstituted H1N1 flu pandemic vaccine. Coring is reported to occur because small pieces of stopper material are sheared off as a result of the repeated needle insertions through the stopper.

The purpose of this investigation was threefold

1. Assess if the test routinely performed at GSK Biologicals on incoming lots of vial rubber stoppers is meaningful for the prediction of coring.
2. Evaluate the extent of coring under various experimental setups designed to mimic real situations.
3. Identify possible ways to minimize the risk of coring.

2. Fragmentation test

2.a. Principle

The rubber stoppers used by GSK Biologicals fulfil the requirements of the fragmentation test set forth in monograph 3.2.9 of the current European Pharmacopoeia edition. This test defines the maximum level of coring acceptable for closures intended to be pierced by a hypodermic needle. In this test, 12 units per stopper lot are each pierced four times, each time at a different site, with a 0.8 mm (21G) hypodermic needle. The test is passed if the total number of fragments visible to the naked eye does not exceed 5. The full description of the test can be found below.

> **Fragmentation**. For closures intended to be pierced by a hypodermic needle, carry out the following test. If the closures are to be used for aqueous preparations, place in 12 clean vials a volume of *water R* corresponding to the nominal volume minus 4 ml, close the vials with the closures to be examined, secure with a cap and allow to stand for 16 h. If the closures are to be used with dry preparations, close 12 clean vials with the closures to be examined. Using a lubricated long-bevel(1) (bevel angle 12 ± 2°) hypodermic needle with an external diameter of 0.8 mm fitted to a clean syringe, inject into the vial 1 ml of *water R* and remove 1 ml of air; carry out this operation 4 times for each closure, piercing each time at a different site. Use a new needle for each closure and check that the needle is not blunted during the test. Pass the liquid in the vials through a filter having approximately 0.5 µm pores. Count the fragments of rubber visible to the naked eye. The total number of fragments does not exceed 5. This limit is based on the assumption that fragments with a diameter equal to or greater than 50 µm are visible to the naked eye; in cases of doubt or dispute, the fragments are examined with a microscope to verify their nature and size.

2.b. Historical data

The table below summarizes the fragmentation test results obtained for the lots of rubber stopper used both for the AS03 adjuvant vial (West PH21/50 grey 12-mm stopper) and the H1N1 antigen vial (Stelmi 6340GS grey 19-mm stopper).

As it can be seen from the table, all the lots of closure used complied with the requirements of PE 3.2.9.

EP 3.2.9 Fragmentation test results	
Lot #	# visible fragments
Stopper 12mm West PH21/50 Grey	
6330950201	2
6330950301	0
6346100101	2
6355920101	0
6355920201	0
6355920301	0
6418890101	0
6418890201	0
6451871801	0
6451871901	1
6480750501	0
6505160101	0
6505160201	0
6543150101	0
6543150201	0
1000007385	0
Stopper 19mm Stelmi 6340GS Grey	
6346090201	0
6355900201	0
6388010201	0
6543140101	0
6543140102	1
6580250101	0
1000000883	0
1000000887	0
1000007508	0
1000008492	0
1000009434	0
1000009096	0
1000009434	0
1000009839	0

2.c. Influence of temperature and of needle bevel

Because of the effect of temperature on the elasticity of the rubber closure material, coring is known to be more likely to occur when the needle is inserted in a cold stopper.

According to the needle supplier (Terumo, Belgium), the risk of coring can be reduced by using needles with a shorter bevel.

To assess the possible influence of these two parameters, the PE 3.2.9.fragmentation test was repeated on one lot of each closure type under the following setups:

- at room temperature (RT) and immediately after removal from the refrigerator (4°C)
- using 21G needles with regular bevel (21G/R, 12° angle) and short bevel (21G/S, 18.5° angle)

The results are summarized in the table below. As it can be seen from the table, the level of fragmentation remained comparable and within specifications in all setups suggesting that temperature and needle bevel length may not always have a clear influence on the risk of coring

Rubber stopper formulation	Temperature	# visible fragments	
		21G/R	21G/S
Stopper 12mm West PH21/50 Grey	4°C	0	2
	Room Temp.	0	0
Stopper 19mm Stelmi 6340GS Grey	4°C	2	1
	Room Temp.	0	0

3. In-use study

It is recognized that the use of the reconstituted H1N1 vaccine requires a larger number of closure punctures than what is simulated in the PE 3.2.9.fragmentation test since up to 20 needle insertions can be performed in case of administration of 0.25 mL paediatric doses (21 insertions taking into account the initial puncture for vaccine reconstitution).

Another difference with the PE 3.2.9.fragmentation test is that, under real-world circumstances, a new needle is used for each puncture. Finally, puncturing may be performed with needles with different borings than 21G. Larger gauge needles may increase the risk of coring.

To assess the influence of all these differentiating factors on the risk of coring, an in-use study was performed to mimic the administration setting of adult (0.5 mL) and paediatric (0.25 mL) doses of reconstituted vaccine using 1-mL syringes equipped with different gauge needles. In each setting, five different vials of reconstituted vaccine were tested and initial reconstitution was performed with 5-mL syringes attached to 21G needles. The results are shown in the table hereafter.

As can be seen from the table, all the settings gave comparable results with only very low levels of coring suggesting that multiple punctures with gauge needles in the range 25G to 20G should not notably increase the risk of coring the 19mm Stelmi 6340GS stopper.
In addition, the number of fragments observed in this in-use study was similar to what was noted with the PE 3.2.9. fragmentation test indicating that the compendial test provides a good predictive model for the real situation of coring.

Needle gauge	# punctures per vial	Volume per withdrawal	Vial ID	# visible fragments
20G/38mm/S	1(21G) + 10	0.5ml	1	None
			2	None
			3	1
			4	None
			5	None
21G/38mm/S	1(21G) + 10	0.5ml	1	None
			2	None
			3	None
			4	1
			5	None
23G/32mm/R	1(21G) + 10	0.5ml	1	None
			2	None
			3	None
			4	None
			5	None
25G/25mm/R	1(21G) + 10	0.5ml	1	None
			2	None
			3	None
			4	None
			5	1
23G/32mm/R	1(21G) + 20	0.25ml	1	None
			2	None
			3	None
			4	None
			5	None
25G/25mm/R	1(21G) + 20	0.25ml	1	None
			2	None
			3	None
			4	None
			5	None

R = regular bevel (angle 12°) / S = short bevel (angle 18.5°)

4. Conclusion and recommendations

The stoppers used by GSK Biologicals fulfil the requirements of the fragmentation test set forth in monograph 3.2.9. of the current European Pharmacopoeia edition. The test specification incorporates some tolerance for the generation of fragments recognizing that, under normal conditions, some level of stopper coring may be observed even with stoppers that fully meet the compendial requirements.

The data discussed in this report suggest that

1. Coring may happen in real situations but is most likely a low-frequency event
2. The following factors may have only limited effect on the risk of coring: the temperature of the stopper at the time of insertion, the length of the needle bevel and the gauge of the needle as long as it remains in the range 25G to 20G.
3. The PE 3.2.9. fragmentation test appears to provide a realistic predictive model for the situation of coring.

In addition to the laboratory investigation, a review of the literature was performed and retrieved the following additional information:

1. Smaller gauge needles may reduce the risk of coring ("How to Enter a Medication Vial without Coring" by J.V. Roth, Anesth.Analg. 2007, 104, 1615).
2. There is a longstanding recommended technique of needle insertion into a medication vial that reduces the risk of coring ("How to Enter a Medication Vial without Coring" by J.V. Roth, Anesth.Analg. 2007, 104, 1615).
3. Stopper coring can be prevented by the use of "vial access cannula" replacing needles for withdrawing medication from vials. ("Preventing rubber stopper coring" by G.Nicol, Anaesthasia, 2002, 57, 207).

Based on all the above elements, the following recommendations can be suggested to minimize the risk of coring

1. The usage of needles with large borings (i.e. larger than 20 G) should be avoided. An in-use study showed that needles of 23G/32mm are suitable for the reconstitution of the vaccine and the drawing-up of vaccine doses. Accordingly, GSK recommends
   - The use of a 5-mL syringe equipped with a 23G needle for the withdrawal of the adjuvant and the subsequent addition into the vial containing the antigen. The vial containing the adjuvant should be maintained in downright position to facilitate the withdrawal of the full content.
   - The use of 1-mL syringes equipped with a needle gauge not larger than 23G for the withdrawal of the vaccine doses.
2. Careful insertion technique as described in the paper of Roth referenced above has been reported to help reduce the incidence of coring.
3. In case of multiple syringes being prepared consecutively over a short period of time, one single needle can be used for the consecutive withdrawals.
4. Although the influence of temperature was not clearly shown in the study, it is a best practice to ensure vial closures are brought back to room temperature before needle insertion so that they are at their full elasticity. This can be done by keeping the vials at room temperature for at least 15 minutes before reconstituting the vaccine.