別紙様式第2－1

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日 2009年10月22日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	別紙のとおり		研究報告の公表状況	新型インフルエンザに関する報道発表資料（農林水産省、2009年10月21日）	公表国 日本	
販売名（企業名）	別紙のとおり					

研究報告の概要	使用上の注意記載状況・その他参考事項等
問題点：新型インフルエンザに感染した豚が国内で初めて確認された。 1.経緯 大阪府の養豚農場で分離されたインフルエンザウイルスについて、(独)農研機構動物衛生研究所が、H 亜型検査（遺伝子解析）及びN亜型検査（遺伝子解析）を実施した結果、本ウイルスは、H1N1亜型であり、現在国内で流行している新型インフルエンザウイルスと同一であることが本日確認されました。 2.対応 大阪府において、当該農場に対して、臨床検査、遺伝子検査（PCR検査法）により異常がないことが確認されるまで、飼養豚の移動を自粛するよう要請しました。 なお、当該農場からと畜場へは、検査で陰性を確認した豚のみを出荷することとしています。	記載なし

報告企業の意見	今後の対応
別紙のとおり	今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。

MedDRA/J ver.12.0

163

26

別紙

一般的名称	①人血清アルブミン、②人血清アルブミン、③人血清アルブミン*、④人免疫グロブリン、⑤人免疫グロブリン、⑥人免疫グロブリン、⑦乾燥ペプシン処理人免疫グロブリン、⑧乾燥ペプシン処理人免疫グロブリン、⑨乾燥スルホ化人免疫グロブリン、⑩乾燥スルホ化人免疫グロブリン、⑪乾燥スルホ化人免疫グロブリン、⑫乾燥スルホ化人免疫グロブリン、⑬乾燥スルホ化人免疫グロブリン、⑭乾燥スルホ化人免疫グロブリン*、⑮乾燥濃縮人活性化プロテインC、⑯乾燥濃縮人血液凝固第Ⅷ因子、⑰乾燥濃縮人血液凝固第Ⅷ因子、⑱乾燥濃縮人血液凝固第Ⅷ因子、⑲乾燥濃縮人血液凝固第Ⅷ因子、⑳乾燥濃縮人血液凝固第Ⅸ因子、㉑乾燥濃縮人血液凝固第Ⅸ因子、㉒乾燥濃縮人血液凝固第Ⅸ因子、㉓乾燥濃縮人血液凝固第Ⅸ因子、㉔乾燥抗破傷風人免疫グロブリン、㉕乾燥抗破傷風人免疫グロブリン、㉖抗HBs人免疫グロブリン、㉗抗HBs人免疫グロブリン、㉘トロンビン、㉙フィブリノゲン加第ⅩⅢ因子、㉚フィブリノゲン加第ⅩⅢ因子、㉛乾燥濃縮人アンチトロンビンⅢ、㉜乾燥濃縮人アンチトロンビンⅢ、㉝ヒスタミン加人免疫グロブリン製剤、㉞ヒスタミン加人免疫グロブリン製剤、㉟人血清アルブミン*、㊱人血清アルブミン*、㊲乾燥ペプシン処理人免疫グロブリン*、㊳乾燥人血液凝固第Ⅸ因子複合体*、㊴乾燥濃縮人アンチトロンビンⅢ
販売名(企業名)	①献血アルブミン20“化血研”、②献血アルブミン25“化血研”、③人血清アルブミン“化血研”*、④“化血研”ガンマーグロブリン、⑤ガンマーグロブリン筋注450mg/3mL「化血研」、⑥ガンマーグロブリン筋注1500mg/10mL「化血研」、⑦献血静注グロブリン“化血研”、⑧献血グロブリン注射用2500mg「化血研」、⑨献血ベニロンーⅠ、⑩献血ベニロンーⅠ静注用500mg、⑪献血ベニロンーⅠ静注用1000mg、⑫献血ベニロンーⅠ静注用2500mg、⑬献血ベニロンーⅠ静注用5000mg、⑭ベニロン*、⑮注射用アナクトC2,500単位、⑯コンファクトF、⑰コンファクトF注射用250、⑱コンファクトF注射用500、⑲コンファクトF注射用1000、⑳ノバクトM、㉑ノバクトM注射用250、㉒ノバクトM注射用500、㉓ノバクトM注射用1000、㉔テタノセーラ、㉕テタノセーラ筋注用250単位、㉖ヘパトセーラ、㉗ヘパトセーラ筋注200単位/mL、㉘トロンビン“化血研”、㉙ボルヒール、㉚ボルヒール組織接着用、㉛アンスロビンP、㉜アンスロビンP500注射用、㉝ヒスタグロビン、㉞ヒスタグロビン皮下注用、㉟アルブミン20%化血研*、㊱アルブミン5%化血研*、㊲静注グロブリン*、㊳ノバクトF*、㊴アンスロビンP1500注射用
報告企業の意見	インフルエンザウイルス粒子は70～120nmの球形または多形性で、8本の分節状マイナス一本鎖RNAを核酸として有する。エンベロープの表面に赤血球凝集素(HA)とノイラミダーゼ(NA)のスパイクを持ち、その抗原性により16種類のHA亜型および9種類のNA亜型に分類される。 今回の新型インフルエンザの原因ウイルスは、1930年代以降に発見された米国由来のブタインフルエンザウイルス、ヒトインフルエンザウイルス（H3N2）、鳥インフルエンザウイルスの3つのウイルスの遺伝子がブタインフルエンザとして再集合してできたウイルスに、さらにユーラシア大陸由来のブタインフルエンザウイルスの遺伝子の一部の分節が再集合して加わったものであると推察されている。新型インフルエンザは、これまでのところ限られた知見しか得られていないが、そのヒトからヒトへの感染伝播経路は従来の季節性インフルエンザに準ずると考えられている。すなわち、感染・発病者の咳やくしゃみとともに口から発せられる飛沫による飛沫感染が主な感染経路であり、患者との直接、間接の接触による接触感染も感染経路としての可能性がある。臨床症状であるが、これまでのところ、この新型インフルエンザのヒトへの病原性は、高病原性鳥インフルエンザウイルスA/H5N1のヒト感染例とは異なって、ヒトに対する病原性はそれほど高くはないと考えられている。 (http://idsc.nih.go.jp/idwr/douko/2009d/17douko.html) 弊所の血漿分画製剤の製造工程には、冷エタノール分画工程、ウイルス除去膜ろ過工程あるいは加熱工程等の原理の異なるウイルス除去及び不活化工程が存在しているので、ウイルスクリアランスが期待される。各製造工程のウイルス除去・不活化効果は、「血漿分画製剤のウイルスに対する安全性確保に関するガイドライン（医薬発第1047号、平成11年8月30日）」に従い、ウシウイルス性下痢ウイルス（BVDV）、仮性狂犬病ウイルス（PRV）、ブタパルボウイルス（PPV）、A型肝炎ウイルス（HAV）または脳心筋炎ウイルス（EMCV）をモデルウイルスとして、ウイルスプロセスバリデーションを実施し、評価を行っている。今回報告したインフルエンザウイルスは、エンベロープの有無、核酸の種類等からモデルウイルスとしてはBVDVが該当すると考えられるが、上記バリデーションの結果から、弊所の血漿分画製剤の製造工程がBVDVの除去・不活化効果を有することを確認している。また、これまでに当該製剤によるインフルエンザの報告例は無い。 以上の点から、当該製剤はインフルエンザウイルスに対する安全性を確保していると考える。

*現在製造を行っていない

164

INF2009-005

農林水産省

プレスリリース

平成21年10月21日
農林水産省

大阪府における豚への新型インフルエンザの感染事例について

本日、大阪府の養豚農場の豚から分離されたウイルスは現在国内で流行している新型インフルエンザウイルスであることが確認されました。
当該農場に対して、臨床検査、遺伝子検査により異常がないことが確認されるまで、飼養豚の移動を自粛するよう要請しました。
なお、世界保健機関(WHO)等の国際機関によれば、適切に処理された豚肉を人が食べてインフルエンザに感染することはありません。

1.経緯

大阪府の養豚農場で分離されたインフルエンザウイルスについて、(独)農研機構動物衛生研究所が、H亜型検査(遺伝子解析)及びN亜型検査(遺伝子解析)を実施した結果、本ウイルスは、H1N1亜型であり、現在国内で流行している新型インフルエンザウイルスと同一であることが本日確認されました。

2.対応

大阪府において、当該農場に対して、臨床検査、遺伝子検査(PCR検査法)により異常がないことが確認されるまで、飼養豚の移動を自粛するよう要請しました。
なお、当該農場からと畜場へは、検査で陰性を確認した豚のみを出荷することとしています。

■ 報道機関へのお願い

1. 現場での取材は、本病の豚への感染を引き起こすおそれもあることから、厳に慎むようお願いします。
2. 今後とも、本病に関する情報提供に努めますので、生産者等の関係者や消費者が根拠のない噂などにより混乱することがないよう、ご協力をお願いします。

世界保健機関(WHO)等の国際機関によれば、適切に処理された豚肉を人が食べてインフルエンザに感染することはありません。

―― お問い合わせ先 ――
消費・安全局動物衛生課
担当者:伏見、嶋崎
代表:03-3502-8111(内線4582)
ダイヤルイン:03-3502-8292
FAX:03-3502-3385

ページトップへ

〒100−8950 東京都千代田区霞が関1−2−1 電話:03-3502-8111(代表)
農林水産省

別紙様式第2-1　　No. 17

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分		総合機構処理欄
				2009. 7. 21	該当なし		
一般的名称	人血清アルブミン				公表国		使用上の注意記載状況・その他参考事項等
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)		研究報告の公表状況	CDC. Available from: http://www.cdc.gov/travel/content/outbreak-notice/chikungunya-fever.aspx	米国		赤十字アルブミン20 赤十字アルブミン25 赤十字アルブミン20%静注4g/20mL 赤十字アルブミン20%静注10g/50mL 赤十字アルブミン25%静注12.5g/50mL 血液を原料とすることに由来する感染症伝播等

研究報告の概要

○米国疾病対策センター(CDC)によるアウトブレイク情報　アジアにおけるチクングニヤ熱

現状:2009年1月以降、チクングニヤ熱症例数の増加がタイ、マレーシア、インドを含むアジアの一部地域で報告されている。チクングニヤ熱は蚊の媒介でヒトに感染が広がるウイルス感染症である。症状には、急な発熱、関節痛(腫脹を伴うこともある)、悪寒、頭痛、吐き気、嘔吐、腰痛、紅斑などがある。流行地域は主にアフリカとアジアだが、2007年にはイタリアでの限定的な伝播が見られた。

タイでは、2009年7月22日時点で、プーケットなどの観光地を含むタイ南部で大規模なアウトブレイクが発生している。タイ保健省によると50の県で34,200例が記録されたが、死亡例はなかった。マレーシアでは、7月18日時点で2,900例以上のチクングニヤ熱症例が主に北部地域から報告された。インドでは、4月29日時点で2,700例以上の症例が主に南部地域から報告されたが、死亡例はなかった。報告数の増加に伴い、アジアの他の国々では監視を強化している。

渡航者向け勧告:流行地への渡航者は蚊に刺されないよう、朝晩に戸外に出る場合は虫除けを使用すること。罹患した場合は医師の診察を受けること。また、他人への感染拡大を防ぐため、蚊に刺されないよう注意すること。

チクングニヤ熱の潜伏期間は通常3〜7日である。症状は数日〜2週間持続するが、数週間にわたって疲労感を感じる患者もいる。ほとんどの患者が関節痛や関節炎を報告しており、数週間〜数ヶ月続くこともある。症状はデング熱によく似ているが、出血やショック症状は通常見られず、ほとんどは入院を必要としない。患者は自然治癒し、死亡に至ることは滅多にない。チクングニヤ熱の治療薬はないため、治療は対症療法が中心となる。

報告企業の意見	今後の対応
タイ、マレーシア、インドにおいてチクングニヤ熱のアウトブレイクが発生し、米国疾病対策センターが渡航者向けに蚊に刺されないよう注意喚起する情報を発表したとの報告である。 チクングニヤウイルスは脂質膜を持つRNAウイルスである。これまで、本製剤によるチクングニヤウイルス感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本製剤の安全性は確保されていると考える。	念のため今後も情報収集に努める。なお、日本赤十字社では帰国(入国)後4週間は献血不適とし、輸入感染症の防止に努めている。

(27)

Centers for Disease Control and Prevention
Your Online Source for Credible Health Information

Outbreak Notice
Chikungunya Fever in Asia
This information is current as of today, August 17, 2009 at 00:28 EDT

Updated: July 29, 2009

Situation Information

Since January 2009, a growing number of cases of chikungunya fever has been reported in parts of Asia, including Thailand, Malaysia, and India. Chikungunya fever is a disease caused by a virus that is spread to people through the bite of infected mosquitoes. Symptoms can include sudden fever, joint pain with or without swelling, chills, headache, nausea, vomiting, lower back pain, and a rash. Chikungunya mainly occurs in areas of Africa and Asia. In 2007, limited transmission of Chikungunya virus occurred in Italy (/travel/destinations/Italy.aspx).

Thailand

As of July 22, 2009, a large outbreak of chikungunya fever has affected the southern region of Thailand (/travel/destinations/Thailand.aspx) including some tourist destinations, such as Phuket. According to the Ministry of Public Health in Thailand, over 34,200 cases have been documented this year in 50 provinces, with no deaths reported. The most affected areas are the southern provinces of Songula, Narathiwat, Pattani, and Yala.

Recent reports show that Chikungunya virus has now from the southern provinces to all other regions of the country.

Malaysia

As of July 18, 2009, the Ministry of Health in Malaysia (/travel/destinations/Malaysia.aspx) has reported over 2,900 cases of chikungunya fever. The most affected areas are the northern provinces of Kedah, followed by Selangor, Kelantan, Perak and Sarawak.

India

As of April 29, 2009, the Directorate of National Vector Borne Disease Control Programme in India (/travel/destinations/India.aspx) has reported over 2,700 suspected cases of chikungunya fever, with no deaths reported. The most affected areas are the Karnataka, followed by Andhra, Goa, and Kerala states.

In response to the growing number of reports, other countries in Asia have increased surveillance for chikungunya fever.

Advice for Travelers

No medications or vaccines are available to prevent a person from getting sick with chikungunya fever. CDC recommends that people traveling to areas where chikungunya fever has been reported take the following steps to protect themselves from mosquito bites.

- The best way to avoid Chikungunya fever is to avoid mosquito bites. When outdoors during the day and at night, use insect repellent (http://www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm#proper) on exposed skin.
  - Look for a repellent that contains one of the following active ingredients: DEET, picaridin (KBR 3023), Oil of Lemon Eucalyptus/PMD, or IR3535. Always follow the instructions on the label when you use the repellent.
  - In general, repellents protect longer against mosquito bites when they have a higher concentration (%) of any of these active ingredients. However, concentrations above 50% do not offer a distinct increase in protection time. Products with less than 10% of an active ingredient may offer only limited protection, often from 1-2 hours.
  - The American Academy of Pediatrics (/travel/forward.aspx?t=aHR0cDovL3d3dy5hYXAub3JnL3B1YmxpY2VkL0JSX1JlcGVsbGVudHMuaHRt-QBZtvSqqfw%3d) approves the use of repellents with up to 30% DEET on children over 2 months of age.

If you get sick with a fever and think you may have chikungunya fever, you should seek medical care. Although there is no specific treatment for the disease, a doctor may be able to help treat your symptoms. Avoid getting any other mosquito bites, because you could transmit the disease to other people through mosquitoes.

For more travel health information, see the destinations (/travel/destinations/list.aspx) section and search for the country you are planning to visit.

More Information

The incubation period for chikungunya (time from infection to illness) can be 2-12 days, but is usually 3-7 days. Chikungunya fever typically lasts a few days to 2 weeks, but some patients feel fatigue lasting several weeks. Most patients have reported severe joint pain or arthritis, which may last for weeks or months. The symptoms are similar to those of dengue fever, but, unlike dengue, people who have chikungunya fever do not usually experience hemorrhage (bleeding) or go into shock. People with chikungunya fever generally get better on their own and rarely die from the disease.

There is no specific drug treatment for chikungunya fever, and medical care is usually focused on treating the symptoms of the disease. Bed rest, fluids, and mild pain medications such as ibuprofen, naproxen, or acetaminophen (paracetamol) may relieve symptoms of fever and aching, provided there are no medical contraindications for using these medications. Most people are not sick enough to need to stay in the hospital. All people who become sick with chikungunya fever should be protected against additional mosquito bites to reduce the risk of further transmission of the virus.

For more information, see—

- Chikungunya (http://www.cdc.gov/ncidod/dvbid/Chikungunya/CH_FactSheet.html) (CDC Fact Sheet)
- Traveling with Children: Resources (http://wwwn.cdc.gov/travel/contentChildTravel.aspx) (CDC Travelers' Health website)

Other Mosquito-Related Diseases

In many of the areas where chikungunya is present, there are other diseases spread by mosquito bites, such as dengue (/travel/yellowbook/2010/chapter-5/dengue-fever-dengue-hemorrhagic-fever.aspx), malaria (/travel/yellowbook/2010/chapter-2/malaria.aspx), Japanese encephalitis (/travel/yellowbook/2010/chapter-2/japanese-encephalitis.aspx), and yellow fever (/travel/yellowbook/2010/chapter-2/yellow-fever.aspx). If you are traveling to any tropical and subtropical areas of the world, you should take steps to avoid mosquito bites.

- Page last reviewed: July 29, 2009
- Page last updated: July 29, 2009
- Page created: August 21, 2008
- Content source:
  Division of Global Migration and Quarantine
  National Center for Preparedness, Detection, and Control of Infectious Diseases

USA.gov Government Made Easy

Centers for Disease Control and Prevention 1600 Clifton Rd. Atlanta, GA 30333, USA
800-CDC-INFO (800-232-4636) TTY: (888) 232-6348, 24 Hours/Every Day - cdcinfo@cdc.gov

別紙様式第2-1
番号17

医薬品
医薬部外品　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2009年7月30日	新医薬品等の区分	厚生労働省処理欄
一般的名称	①ポリエチレングリコール処理人免疫グロブリン ②人免疫グロブリン	研究報告の公表状況	Transfusion (Malden) 2009; 49(7): 1488-1492	公表国 アメリカ		
販売名（企業名）	①献血ヴェノグロブリン-IH ヨシトミ（ベネシス） ②グロブリン-Wf（ベネシス）					

研究報告の概要

米国における新しいパルボウイルスB19遺伝子型3の発見と分析

背景：パルボウイルスB19（B19V）は、核酸検出でヒト血漿においてしばしば同定される病原体である。3つのB19V遺伝子型は、全体のDNA配列で10%を超える相違のある分離株に基づいて定義された。B19V遺伝子型3は、主にガーナで、散発的にブラジルおよびフランスから報告されてきたが、過去に北アメリカでの報告はなかった。

研究設計と方法：B19Vを広い特異性で検出するためのPCR測定系が開発された。この測定法の性能は、81,000人以上のドナー由来の約440,000の臨床的サンプルを検査することによって評価された。B19Vタイター、DNA配列と抗体濃度の判定は、重要なサンプルで実施された。

結果：この評価の結果、DNA配列分析によってB19遺伝子型3に感染していると確認された米国の1人のドナーから28日の間に8回の血漿ドネーションを行っていることが確認された。この一連のドネーションのB19Vタイターは、ピークにおいて10^{11}IU/mLを超えるウイルス力価に達した。ウイルス力価は、免疫グロブリンM（IgM）抗体価の増加に合わせてその後数回のドネーションにおいて減少した。IgG濃度も増加したが、IgM濃度より約7日遅れた。

結論：これは、米国における血漿ドナーから検出されたB19V遺伝子型3の最初の報告である。我々のデータはこの遺伝子型の低い発生率を示唆している最近の報告と合致しているにも関わらず、それは血液及び血漿ドナーとの関連性が増していることを示している。

報告企業の意見	今後の対応
米国において血漿ドナーからB19V遺伝子型3が検出された最初の報告である。 献血ヴェノグロブリン-IHについては、万一本剤の原料血漿にB19が混入したとしても、CPVをモデルウイルスとしたウイルスバリデーション試験成績及びB19を用いた不活化・除去試験の結果から、本剤の製造工程において十分に不活化・除去されると考えている。 グロブリン-Wfについては、血漿分画製剤の製造工程での十分な不活化・除去が困難であり、本ウイルスの伝播リスクを完全に否定することはできないため、1996年11月より、使用上の注意にパルボウイルスB19についての記載を行い注意喚起を図っている。なお、一変承認後に製造されたロットについては、献血ヴェノグロブリン-IHと同様に、製造工程において不活化/除去されると考えている。	本報告は本剤の安全性に影響を与えるものではないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

代表として献血ヴェノグロブリン-IH ヨシトミの記載を示す。

1. 慎重投与

(5) 溶血性・失血性貧血の患者〔ヒトパルボウイルスB19の感染を起こす可能性を否定できない。感染した場合には、発熱と急激な貧血を伴う重篤な全身症状を起こすことがある。〕

(6) 免疫不全患者・免疫抑制状態の患者〔ヒトパルボウイルスB19の感染を起こす可能性を否定できない。感染した場合には、持続性の貧血を起こすことがある。〕

2. 重要な基本的注意

(1) 略

1) 血漿分画製剤の現在の製造工程では、ヒトパルボウイルスB19等のウイルスを完全に不活化・除去することが困難であるため、本剤の投与によりその感染の可能性を否定できないので、投与後の経過を十分に観察すること。

6. 妊婦、産婦、授乳婦等への投与

妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。〔妊娠中の投与に関する安全性は確立していない。本剤の投与によりヒトパルボウイルスB19の感染の可能性を否定できない。感染した場合には胎児への障害（流産、胎児水腫、胎児死亡）が起こる可能性がある。〕

169

TRANSFUSION COMPLICATIONS

Discovery and analysis of a novel parvovirus B19 Genotype 3 isolate in the United States

Lori A. Rinckel, Brett R. Buno, Todd M. Gierman, and Douglas C. Lee

BACKGROUND: Parvovirus B19 (B19V) is a pathogen frequently identified in human plasma donations through the detection of nucleic acids. Three B19V genotypes have been defined based on isolates having greater than 10% divergence in overall DNA sequence. B19V Genotype 3 is a rarely occurring genotype that has been detected primarily in Ghana with sporadic reports in Brazil and France but has not been previously reported in North America.

STUDY DESIGN AND METHODS: A polymerase chain reaction assay was developed with broad specificity for B19V detection. The performance of this assay was assessed by testing approximately 440,000 clinical samples representing more than 81,000 individual donors. Determinations of B19V titer, DNA sequence, and antibody concentrations were performed on samples of interest.

RESULTS: This assessment identified a series of eight plasma donations spanning 28 days from a single donor in the United States infected with B19V Genotype 3 as confirmed by DNA sequence analysis. The B19V titer of this series of donations showed virus titers that peaked at greater than 10^{11} IU/mL. The virus titer decreased significantly over the next several donations coinciding with an increase in immunoglobulin M (IgM) levels. The immunoglobulin G levels also increased but lagged approximately 7 days behind the IgM levels.

CONCLUSION: This is the first report of a B19V Genotype 3 detected from a plasma donor located in the United States. Although our data are consistent with recent reports suggesting low incidence for this genotype, they indicate its increasing relevance among blood and plasma donors.

Human parvovirus B19 (B19V) is a commo human pathogen that possesses a mutatio rate that is uncharacteristically high for DNA virus.[1,2] B19V DNA sequence homolog is used to classify B19V into three genotypes.[3] The gene types are defined as having approximately 10% divergenc in overall DNA sequence. Genotype 1 is the most prevale B19V currently circulating in North America and Europ and is represented by the prototype strain Au (GenBan Accession Number M13178).[4] Genotype 2 also circulate in North America and Europe but with lower frequenc than Genotype 1 and is represented by the prototyp strain A6 (GenBank Accession Number AY064475).[5] Genc type 3 is endemic to Ghana but has also been foun in Brazil and France.[6] Genotype 3 is represented by tw prototype strains, V9 and D91.1 (GenBank Accessio Numbers AX003421 and AY083234, respectively).[3] Numei ous genetic variants of B19V exist within each of thes three genotypes. By definition, these variants differ by les than 10% in their DNA sequence when compared to th genotypic prototype.

These three genotypes were shown to constitute on single serotype through various functional, structural, an immunologic studies;[7] current evidence suggests that a variants of B19V induce similar pathologies.[8] A primar interest and concern with the wide assortment of B19 genotypes and variants is diagnostic. Polymerase chai reaction (PCR) assays developed around specific referenc standards frequently fail to detect accurately specifi B19V genotypes and variants.[5,9-11] Therefore, developers o molecular diagnostics and the biologics industry have al

ABBREVIATION: B19V = parvovirus B19.

From the Department of Pathogen Safety, Talecris Biotherapeutics, Raleigh Test Laboratory, Raleigh, North Carolina.

Address correspondence to: Lori Rinckel, Raleigh Test Laboratory, Talecris Biotherapeutics, 1200 New Hope Road, Raleigh, NC 27610; e-mail: lori.rinckel@talecris.com.

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170

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increased interest in the prevalence of emerging B19V variants.

Here, we report a unique isolate of B19V. This isolate was discovered in a series of human plasma donations from a single donor located in the United States. Analysis indicated that this isolate exhibits strong DNA sequence homology to B19V Genotype 3. Analysis of the series of donations from this donor demonstrated the expected clinical pattern of antibody response to this B19V Genotype 3 infection. This is the first report of the discovery and characterization of B19V Genotype 3 among US plasma donors.

MATERIALS AND METHODS

A quantitative real-time PCR assay was developed with a target region within the NS1 coding sequence of the B19V genome utilizing oligonucleotide primers and probes purchased from Integrated DNA Technologies (IDT, Coralville, IA). The assay used two detection probes for the B19V target. One detection probe contained the DNA sequence of the B19V Au Genotype 1 prototype strain; the second probe contained a DNA sequence that is a consensus derived from the B19V A6 Genotype 2 prototype strain and the V9 and D91.1 Genotype 3 prototype strains. Both probes were labeled with the same fluorophore. The assay also incorporated a third detection probe for a competitive internal control that was labeled with a different fluorophore than that of the two B19V target probes. Test results indicating a PCR signal for the internal control, B19V target, or both were deemed valid; results indicating no PCR signal for both the internal control and the B19V target were deemed invalid. The quantitation standards used in the real-time PCR assay were dilutions of plasmid pYT104-C, which contains a B19V Genotype 1 strain (Au) genome.[12] A quantitative standard curve was used to assign values (copies/mL) to test samples. The results expressed as copies/mL were converted to IU/mL using a correlation factor of 2.9 copies/IU, determined by comparing the potency of the First WHO International Standard for B19V DNA nucleic acid test assays (99/800) to the potency of the dilution of pYT104-C used to create the quantitation standards.[13]

The performance of the B19V assay was assessed against a qualitative B19V assay that served as the test of record using a study sample of approximately 440,000 donor samples corresponding to roughly 81,000 individual donors. Both assays were designed to detect all three B19V genotypes; neither assay was designed to discriminate among the three genotypes. Donation samples were tested initially in pools of 384 or 480 samples to increase testing efficiency. Additional testing of B19V-reactive samples was performed using a B19V PCR assay (artus RealArt, Parvo B19 PCR assay, Qiagen, Hilden, Germany). Antibody detection was performed on test samples in duplicate using the B19V immunoglobulin M (IgM) and immunoglobulin G (IgG) enzyme immunoassay (EIA) kits (Biotrin, Dublin, Ireland).

DNA sequencing was performed on PCR amplicons generated using primers containing B19V consensus DNA sequences. The purified PCR amplicons were sequenced by primer walking performed at Lark Technologies (Houston, TX). The contiguous DNA sequences were assembled using sequence analysis cloning software (Vector NTI, Invitrogen Corp., Carlsbad, CA). DNA sequence alignments were performed with Vector NTI and with the GenBank database using BLAST.[14]

RESULTS

The performance of a new B19V assay was assessed using a study sample set consisting of approximately 440,000 donor samples, representing roughly 81,000 individual donors. The performance of the B19V assay was benchmarked against results obtained using an earlier version assay. During the course of the study, 1 in 2400 donor samples tested reactive for B19V. Review of results discordant between the two assays identified several samples for follow-up analysis. This investigation identified two reactive donations that were ultimately linked to a series originating from a single donor resident in the United States. Using a lookback process coupled with follow-up testing, a series comprising eight donations, designated P0 through P7, was identified and these units were pulled from the inventory for continued research. The two plasma samples with the highest titer from this series, P1 and P2, were used to characterize the B19V isolate. Additional testing using the Qiagen artus RealArt Parvo B19 PCR assay yielded negative results for neat and diluted samples (neat and 1:480).

DNA sequencing of B19V amplicons generated from P1 and P2 using our assay showed that both donations contained identical DNA target sequences. This preliminary sequence information also suggested that nucleic acid isolates from P1 and P2 have higher DNA sequence homology to B19V Genotype 3 than to Genotypes 1 and 2. The preliminary DNA sequence information was used to design and synthesize a new detection probe (P1 probe) containing 100% DNA sequence homology to the P1 and P2 isolates. This new detection probe was used to quantitate sample viral loads at 8×10^{11} IU/mL for P1 and 3×10^{10} IU/mL for P2 (Fig. 1).

The DNA sequence was determined for 4846 nucleotides of the P1 B19V genome (GenBank Accession Number FJ265736). Analysis of the DNA sequence from P1 (Fig. 2) shows that this B19V isolate has the highest DNA sequence homology to representative isolates of B19V Genotype 3. This sequence exhibited 97% homology to B19V strain V9 and 96% homology to B19V strain D91.1, suggesting that the P1 isolate belongs to Genotype 3

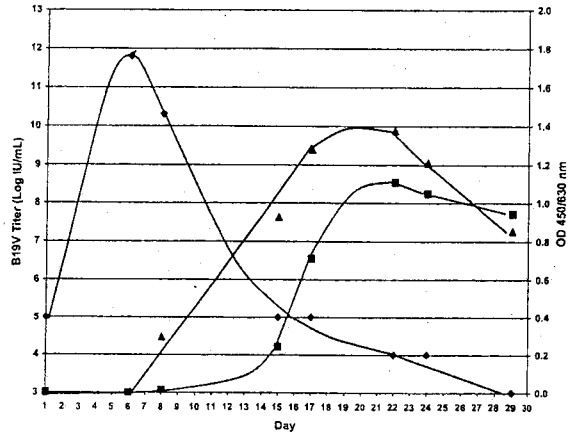
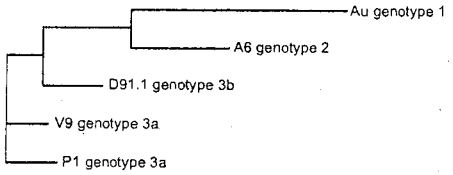


Fig. 1. B19V titer (◆) and IgM (▲) and IgG (■) levels for the series of Genotype 3 donations. The B19V titer is expressed in IU/mL.

A



B

	Genotype 1 Au	Genotype 2 A6	Genotype 3b D91.1	Genotype 3a V9	P1
Genotype 1 Au	100	91	90	89	89
Genotype 2 A6		100	93	93	92
Genotype 3b D91.1			100	98	96
Genotype 3a V9				100	97
P1					100

Fig. 2. Global DNA sequence alignment of B19V strain P1 with the prototype strains for B19V Genotype 1, Au; Genotype 2, A6; Genotype 3b, D91.1; and Genotype 3a, V9. (A) Phylogenetic tree. (B) Numerical comparison of DNA sequence homologies. This analysis shows that P1 is a member of B19V Genotype 3a.

Subtype B19/3a.[15] The P1 isolate is significantly less homologous to B19V Genotypes 1 and 2 with 89% homology to B19V Genotype 1 prototype strain Au and 92% homology to B19V Genotype 2 prototype strain A6.

When tested using the P1 probe, the B19V titers of this series of donations show the expected pattern for a B19V infection. B19V titers increased rapidly, peaking within several days after infection and then decreased gradually for several weeks (Fig. 1).

In addition, IgM and IgG B19V antibody levels were detected in this series of plasma donations using EIA methods (Fig. 1). For reference, the day of the P0 donation is referred to as Day 1. The IgM response was first detected on Day 8 (P3), peaked on Day 22 (P5), and decreased thereafter. The IgG antibody response was first detected on Day 15 (P3), peaked on Day 22 (P5), and gradually decreased through Day 29 (P7). The B19V antibody levels detected in these plasma donations displayed an increase in IgM level concurrent with the decrease in B19V titer (Fig. 1).

DISCUSSION

This is the first report of a B19V Genotype 3 detected in a blood or plasma donation in the United States. Previously, B19V Genotype 3 had been reported to occur primarily in the African country of Ghana, with less frequent reports in Brazil and France. The frequency of B19V Genotype 3 in Ghana was reported to be approximately 100% of the strains identified.[16] The frequency of B19V Genotype 3 in Brazil was approximately 50% and in France was approximately 11% of the strains identified.[3,6] Not only is the identification of a B19V Genotype 3 in the United States noteworthy, but also our characterization of this B19V Genotype 3 infection in this donation series has demonstrated that isolates of this genotype can achieve the high virus titers typically associated with acute B19V Genotype 1 infections. In contrast, previous reports concerning B19V Genotype 3 have suggested that high-titer infections involving this genotype occur infrequently.[3,16,17] The titers of the isolates described in these prior reports, however, may reflect late or persistent infections which would exhibit lower titers than an initial infection. The B19V titers of the series of donations in this report show the expected pattern for an acute infection where virus titers increase rapidly, peak within several days after infection, and then decrease gradually over a period of several weeks.

The B19V isolate described in this report, designated P1, was found to exhibit strong DNA sequence homology with B19V Genotype 3. Alignment to V9 and D91.1, both Genotype 3 isolates, demonstrated significantly higher DNA sequence homology (at least 94%) than to representative isolates for Genotypes 1 and 2. More specifically, P1

appears to belong to Genotype 3 Subtype B19/3a.[15] Subtype B19/3a was reported to be prevalent in Ghana whereas Subtype B19/3b appears to be more prevalent in Western Europe and Brazil.[15]

The B19V titers in these donations increased rapidly and peaked at a titer of approximately 8×10^{11} IU/mL. Our results also show that the decrease in B19V titer was concurrent with an increase in IgM antibodies. The increase in IgM antibodies was followed by an increase in the levels of IgG antibodies. These results concur with published works that suggest that the Genotype 1 antigens present in the Biotrin EIA kit are effective for the detection of Genotype 3 antibodies.[18] These results are also consistent with the suggestion that a single serotype may exist for the different B19V genotypes.[7]

Recent discussion concerning the incidence of the B19V Genotype 3 infection among blood and source plasma donors has suggested that the prevalence of this genotype in the United States is low or absent.[2] The comparison of the performance of two B19V assays in this limited, high-throughput sample set (approx. 440,000 donations) identified B19V at a frequency of 1:2400 donations. This detection frequency is typical for the time of year at which the study was conducted (based on data from nearly 8 years of high-throughput testing). When the study results were analyzed by donor, B19V-reactive donations were associated with 117 individual donors among 81,000 total donors (approx. 1:700). In contrast, the putative detection frequencies for samples and donors reactive for B19V Genotype 3 appear significantly lower. Samples containing high-titer B19V Genotype 3 (i.e., $>10^6$ IU/mL) were detected at the rate of 1:220,000 and were contributed by a single donor among the 81,000 donors comprising the sample set (1:81,000). Whether these frequencies accurately reflect the incidence of Genotype 3 within the source plasma donor population remains unclear, because the assays used in this study were not designed to differentiate among the three genotypes. Moreover, this study was designed to evaluate assay performance, rather than B19V epidemiology. Nevertheless, the fact that this study resulted in the identification and interdiction of 8 plasma units from a single donor, 2 of which contained sufficient B19V to exceed the prescribed limits for plasma fractionation pools, underscores the increasing relevance of assays that can detect B19V Genotype 3.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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No. 18

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 7. 21	該当なし	

一般的名称	人血清アルブミン	研究報告の公表状況	FDA, CBER. Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm071592.htm.	公表国 米国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)			

研究報告の概要

○血漿分画製剤によりヒトパルボウイルスB19が伝播する危険性を低減するための核酸検査(NAT)にかかる業界向けガイダンス
米国食品医薬品局(FDA)は、血漿分画製剤製造に使用される原料血漿および回収血漿の工程内検査として、ヒトパルボウイルスB19核酸増幅検査(NAT)の実施を製造業者に対し勧告するガイダンスを発表した。これは2008年7月付ガイダンス案の最終決定版である。
B19は脂質膜を持たない一本鎖DNAウイルスで、熱処理やS/D処理等の一般的な不活化法に抵抗性があり、小型であるため除去も困難である。輸血用血液製剤や血漿分画製剤の投与によりウイルス感染が起こり、妊婦や血液疾患、免疫不全の患者等、影響を受けやすい患者が感染すると死亡(または胎児水腫、流産、死産等)する可能性も否定できない。輸血用血液による感染はまれだが、B19急性感染期で無症候の献血者から採血した最高10^{13}IU/mL程度のウイルスを含む血液が血漿分画製剤の原料として用いられた場合には、多数の血漿をプールして製造することから感染リスクが高くなる。しかし、ウイルス血症期の献血者血液中には、長期にわたり低濃度のウイルスと中和抗体としてのB19抗体が共存しており、低濃度のウイルスを保有する献血者を排除することは、プール血漿中のB19抗体レベルを下げることになるため、望ましくない。
FDAは、血漿分画製剤の製造業者に対し、B19 DNAを検出するため、以下の手順を導入することを勧告する。
1. 全ての血漿分画製剤の製造に際し、製造工程中の品質管理としてB19 DNAのNATを実施し、製造原料となる血漿プール中のB19 DNA濃度が10^{4}IU/mLを超えないことを保証する。
2. 血漿分画製剤の製造原料となる血漿製剤に対し、B19のミニプールNATを実施する。B19のNATに用いるプライマーやプローブは、現在判明している全ての遺伝子型を検出できるものであること。
3. 血漿製剤がB19陽性であることが判明し、使用により血漿プール中のウイルス力価が10^{4}IU/mLを超える可能性がある場合には、その血漿を血漿分画製剤の製造原料として用いてはならない。
製造業者は、原料血漿及び回収血漿中のB19 DNA検出に用いるNATのバリデーションを行い、血漿プール中のB19 DNAが10^{4}IU/mLを超えないことを実証すること。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
米国食品医薬品局が、血漿分画製剤製造に使用される原料血漿および回収血漿の工程内検査として、ヒトパルボウイルスB19核酸増幅検査(NAT)の実施を製造業者に対し勧告するガイダンスの最終版を発表したとの報告である。 ヒトパルボウイルスB19(B19V)は脂質膜のないDNAウイルスである。これまで、本剤によるB19V感染の報告はない。B19は耐熱性とされていたが最近、液状加熱で容易に不活化できることが明らかにされた。本製剤の製造工程には、当該工程が含まれている。また最終製品についてB19-NAT陰性であることを確認していることから、本製剤の安全性は確保されている。	念のため今後も情報収集に努める。なお、日本赤十字社では、以前よりRHA法によるB19抗原検査を導入しウイルス量の多い血液を排除してきた。2008年からさらに感度の高い化学発光酵素免疫測定法(CLEIA)を導入し、10^{6}IU/mL以上のB19を含む血液を陽性と判定し排除するものであることから、現在は原料血漿プール中のウイルス濃度が10^{4}IU/mL以下となっている。今後も輸血用血液及び血漿分画製剤の安全性向上のために努力する。

(29)

JRC2009T-037

Guidance for Industry

Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-Derived Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Table of Contents

I. INTRODUCTION 1
II. BACKGROUND 1
III. RECOMMENDATIONS 3
IV. REFERENCES 4

Guidance for Industry

Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-Derived Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are issuing this guidance to provide you, manufacturers of plasma-derived products, with recommendations for performing nucleic acid testing (NAT) for human parvovirus B19 as an in-process test for Source Plasma and recovered plasma used in the further manufacturing of plasma-derived products. Such testing will identify and help to prevent the use of plasma units containing high levels of parvovirus B19. This guidance also recommends how to report to FDA implementation of parvovirus B19 NAT.

We recognize that in the current business practice for parvovirus B19 NAT in-process testing, several weeks can elapse between collection of the units of Source Plasma or recovered plasma and identification of B19 NAT-positive pools or units. We encourage manufacturers of plasma-derived products to employ practices that will reduce the time between product collection and in-process testing to allow for the meaningful notification of blood and plasma collection establishments of positive test results within the dating period of any blood components intended for use in transfusion.

This guidance finalizes the draft guidance of the same title, dated July 2008.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Human parvovirus B19 is a small, non-enveloped single stranded DNA virus. Virus clearance studies, using non-human parvoviruses as models for parvovirus B19, have indicated that this virus is highly resistant to all commonly used inactivation methods, including heat and

solvent/detergent (S/D) treatment, and is also difficult to remove by filtration because of its small size. More recent studies have demonstrated that human parvovirus B19 may be more readily cleared than certain model animal parvoviruses (Refs. 1, 2, 3 and 4). The parvovirus B19 can be transmitted by blood components and certain plasma derivatives, and may cause morbidity to susceptible recipients such as pregnant women (and their fetuses exposed in utero), persons with underlying hemolytic disorders, and immune compromised individuals (Refs. 5 and 6). The disease transmission by transfusion of blood components is rare. However, extremely high levels of parvovirus B19, up to 10^{12} IU/mL, in plasma of acutely infected but asymptomatic donors may present a greater risk in plasma derivatives due to pooling of large numbers of plasma units in the manufacture of these products. The virus can be detected by NAT in plasma pools when there are high levels of parvovirus B19 DNA in viremic donations. For example, the parvovirus B19 DNA can be detected in various plasma-derived products, particularly in coagulation factors (Refs. 7 and 8). There have been a few reports of parvovirus B19 infection associated with the administration of coagulation factors (Refs. 9 and 10) and S/D Treated Pooled Plasma (Refs. 5 and 11). Parvovirus B19 DNA is less frequently detected in albumin and immunoglobulin products and, when detected, the levels are usually low. There are no confirmed reports that albumin and immunoglobulin products have transmitted parvovirus B19 infection.

We have held or participated in several meetings to discuss the potential risk of parvovirus B19 infection by plasma-derived products, and the strategy for reducing such risk. The meetings included FDA-sponsored NAT workshops in 1999 and 2001 (Refs. 12 and 13), Blood Products Advisory Committee (BPAC) meetings in 1999 and 2002 (Refs. 14, 15, and 16), the National Heart, Lung, and Blood Institute-sponsored Parvovirus B19 workshop in 1999 (Ref. 5), and an ad hoc Public Health Service (PHS) panel in 2002 (discussed at the 2002 BPAC meeting (Ref. 16)). In these meetings, it was recognized that viral inactivation/removal steps that are routinely used in the manufacturing process of plasma-derived products do not alone appear to be sufficient to completely clear the virus if high viral load is present in the starting material. Therefore, in these meetings, a common recommendation for mitigating the risk of parvovirus B19 transmission by plasma derivatives has been to limit the virus load in the manufacturing plasma pool by testing the plasma donations for high titer parvovirus B19 DNA, using a minipool format. This viral load reduction strategy combined with the ability of the manufacturing process to clear the residual virus could greatly reduce the risk of parvovirus B19 infection by plasma-derived products.

The recommended limit in this guidance for viral load of parvovirus B19 DNA in the manufacturing plasma pool (i.e., not to exceed 10^4 IU/mL) was primarily derived from studies that were conducted on the transmission of parvovirus B19 associated with S/D Treated Pooled Plasma (Refs. 5, 11, and 14). In principle, testing in a minipool format to measure the viral load for parvovirus B19 DNA in a manufacturing plasma pool is acceptable in order to exclude only the high-titer plasma donations, thereby avoiding too great a loss of plasma for further manufacturing. Furthermore, during the viremic period for parvovirus B19 infected donors, which can be very lengthy, low levels of parvovirus B19 coexist with parvovirus B19 antibodies

(potentially complexing with and neutralizing the virus). Therefore, it is undesirable to remove plasma units with low levels of B19 DNA, because it would diminish the parvovirus B19 antibody levels in plasma pools and in some of the resulting plasma-derived products (Refs. 17 and 18).

III. RECOMMENDATIONS

We recommend that you implement the following procedures to detect the presence of parvovirus B19 DNA:

- For all plasma-derived products, you should perform parvovirus B19 NAT as an in-process test to ensure that the viral load of parvovirus B19 DNA in the manufacturing pools does not exceed 10^4 IU/mL.
- Use parvovirus B19 NAT on minipool samples to screen plasma units intended for further manufacturing into plasma-derived products. Primers and probes selected for parvovirus B19 NAT should detect all known genotypes of the virus (Ref. 19).
- When identified, you should not use individual plasma units, intended for further manufacturing into plasma-derived products, when such units are found to have a titer of parvovirus B19 DNA that might result in plasma manufacturing pools exceeding a parvovirus B19 DNA titer of 10^4 IU/mL.

You should assess validation data demonstrating the accuracy, sensitivity, specificity, reproducibility, and other performance characteristics of the parvovirus B19 NAT assay used for the detection of parvovirus B19 DNA in the Source Plasma and recovered plasma, and for demonstrating that the viral load of parvovirus B19 DNA in the manufacturing pool does not exceed 10^4 IU/mL.

If the above recommendations are implemented, you must inform FDA, as required under 21 CFR 601.12(a). You may submit these changes as a "Supplement-Changes Being Effected" supplement (CBE supplement), under 21 CFR 601.12(c)(5).

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