

Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

Draft Guidance for Industry

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

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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**Bacterial Risk Control Strategies for Blood Collection
Establishments and Transfusion Services to Enhance the Safety and
Availability of Platelets for Transfusion**

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are issuing this guidance document to provide you, blood collection establishments and transfusion services, with recommendations to control the risk of bacterial contamination of room temperature stored platelets intended for transfusion. The recommendations in this guidance apply to all platelet products, including platelets manufactured by automated methods (apheresis platelets), whole blood derived (WBD) platelets, pooled platelets (pre-storage and post-storage) and platelets stored in additive solutions.

Additionally, this guidance provides licensed blood establishments with recommendations on how to report implementation of manufacturing and labeling changes under 21 CFR 601.12. This draft guidance replaces the draft guidance of the same title dated March 2016.

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

Room temperature stored platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component. The risk of bacterial contamination of platelets is a leading risk of infection from blood transfusion. Bacterial residual risk per transfused unit on the day of transfusion is 1/2300 (Ref. 1), and fatal transfusion reactions from undetected

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43 contaminated platelet collections continue to occur (Ref. 2). This risk has persisted despite
44 numerous interventions, including the widely used method of primary culture to test platelets
45 prior to transfusion (Refs. 3, 4, 5, 6).
46

47 The reported rates of septic transfusion reactions from platelets vary from 1/100,000 by passive
48 surveillance to 1/10,000 by active surveillance when testing with primary culture alone (Refs. 1,
49 7). Surveillance data on platelets stored up to 5 days have shown that 95-100% of platelet
50 transfusion-related septic reactions (Refs. 3, 4, 8) and 100% of associated fatalities have occurred
51 with transfusion of day 4 and day 5 stored platelets (Ref. 8).
52

53 FDA has established regulations to address the control of bacterial contamination of platelets.
54 Under 21 CFR 606.145(a), blood establishments and transfusion services must assure that the
55 risk of bacterial contamination of platelets is adequately controlled using FDA approved or
56 cleared devices, or other adequate and appropriate methods found acceptable for this purpose by
57 FDA.
58

59 Currently, this risk can be controlled by bacterial testing or pathogen reduction methods.
60 Bacterial testing includes the use of culture-based or rapid detection tests.¹ While primary testing
61 is typically performed by culture and within 24 hours of collection, secondary testing is
62 performed at later times of storage prior to transfusion. Pathogen reduction is performed shortly
63 after platelet collection.
64

65 Under 21 CFR 610.53(b), the dating period for platelets with a storage temperature between 20
66 and 24 degrees Celsius is 5 days from the date of collection, unless a different dating period is
67 specified in the instructions for use by the blood collection, processing and storage system
68 approved or cleared for such use by FDA. Accordingly, implementation of the recommendations
69 in this guidance on extension of platelet dating beyond day 5 is contingent on the use of cleared
70 or approved and suitably labeled platelet storage containers, bacterial detection tests and
71 pathogen reduction devices.² The current maximum dating period (expiration date) for platelets
72 in the United States (U.S.) is up to 7 days in the cleared storage containers.
73

74 Most recently, FDA convened a Blood Products Advisory Committee (BPAC) meeting in July
75 2018 (Ref. 9) to discuss bacterial contamination of platelets and strategies to control the risk. At
76 this meeting, BPAC considered the scientific evidence and operational considerations of all
77 available strategies to control the risk of bacterial contamination of platelets with 5-day and 7-
78 day dating, including bacterial testing strategies using culture-based devices, rapid bacterial
79

¹ Bacterial tests are labeled as a “safety measure” when clinical studies have shown benefit for detection of bacterial contamination not revealed by previous bacterial testing or have analytical sensitivity at least equivalent to a previously cleared “safety measure” device or qualify by other methods found acceptable to FDA.

² Currently, storage systems that ensure platelet efficacy past 5 days of storage, and up to 7 days of storage, of platelets treated by pathogen reduction technology (PRT) are not available. Extended dating past 5 days based on pathogen reduction of apheresis platelets may not be implemented until such technologies are approved for use in this blood component (21 CFR 606.65(e)).

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80 detection devices, and the implementation of pathogen reduction technology. The data presented
81 and BPAC’s discussion at the July 2018 meeting provided the foundation for the
82 recommendations in this guidance.

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85 **III. RECOMMENDATIONS FOR THE CONTROL OF BACTERIAL** 86 **CONTAMINATION OF PLATELETS**

87

88 Table 1 summarizes recommended strategies for 5-day platelet storage and 7-day platelet
89 storage.

90

91 **Table 1. Summary Table of FDA’s Recommendations**

92

Recommendations to control the risk of bacterial contamination in platelets		
Dating	Method	Applicable components
5-day storage	Primary culture + secondary culture (no earlier than Day 3)	<ul style="list-style-type: none">• Apheresis• Pre-storage pools
	Primary culture + secondary rapid testing	<ul style="list-style-type: none">• Apheresis• Pre-storage pools
	Pathogen Reduction Technology	<ul style="list-style-type: none">• Apheresis³
7-day storage	Primary culture + secondary culture (no earlier than Day 4)	<ul style="list-style-type: none">• Apheresis
	Primary culture + secondary rapid testing	<ul style="list-style-type: none">• Apheresis
	Large volume delayed sampling ⁴	<ul style="list-style-type: none">• Apheresis

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A. General Considerations

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1. Use FDA-cleared or approved bacterial detection tests, pathogen reduction devices, and platelet storage containers.

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2. Bacterial detection testing, pathogen reduction, and the use of platelet storage containers must be performed consistent with the instructions for use of the device (21 CFR 606.65(e)).

100

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103

³ This strategy could apply to other platelet products in the future if appropriately labeled devices become available.

⁴ The instructions for use of the culture-based device currently labeled as a “safety measure” require a primary culture and secondary test to extend dating of platelets. Therefore, the large volume, delayed sampling strategy cannot be implemented until appropriately labeled devices are available.

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- 104 3. Blood collection establishments and transfusion services should have in place
105 measures to promptly alert the collection establishment or transfusion service
106 if a distributed platelet product is subsequently identified as positive for
107 bacterial contamination.
108

B. Primary Culture Testing

109 This section provides general information pertaining to recommendations for primary
110 culture testing. Primary culture testing is used as one of several strategies discussed in
111 this guidance.
112
113

114 Culture-based primary testing should be performed no sooner than 24 hours after
115 collection. Testing should include methods to identify both aerobic and anaerobic
116 organisms. To maximize the sensitivity of the culture, we recommend use of the upper
117 limit of the sample volume range permitted by the device’s instructions for each of the
118 aerobic and anaerobic cultures. If you opt to sample a volume larger than the upper
119 limit of the volume range described in the device’s instructions for use for one culture,
120 we recommend that the amount of the sample that is in excess of the upper limit volume
121 recommended for use be inoculated into additional culture.
122

123 If the instructions for use of the bacterial detection device specify a minimum incubation
124 period, you should release platelet products consistent with the incubation period
125 specified. If the instructions for use of the bacterial detection device do not specify a
126 minimum incubation period, we recommend a minimum incubation period of 12 hours.
127
128

C. 5-Day Platelet Storage

129 The following strategies apply to platelets with 5-day storage:
130

1. Primary culture followed by secondary culture performed no earlier 131 than Day 3

132 This strategy applies to apheresis platelets and pre-storage pools and includes the
133 following steps:
134

- 135 • Initial primary culture (see section III.B of this guidance).
- 136 • Secondary culture on Day 3 or Day 4.

137 *Secondary culture:*
138

139 To maximize the sensitivity of the culture, we recommend use of the upper limit
140 of the sample volume range permitted by the device’s instructions for use, taken
141 from the main collection, and inoculating the sample into an aerobic media. Use
142 of an anaerobic culture, in addition to the aerobic culture, should be considered.
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149 If the instructions for use of the bacterial detection device specify a minimum
150 incubation period, you should release platelet products consistent with the
151 incubation period specified. If the instructions for use of the bacterial detection
152 device do not specify a minimum incubation period, we recommend that you
153 establish a minimum incubation time period in your Standard Operating
154 Procedures (SOPs).

2. Primary culture, followed by secondary rapid testing

155
156 This strategy applies to apheresis platelets and pre-storage pools, and includes
157 the following steps:

- 158 • Initial primary culture (see section III.B. of this guidance).
- 159 • Secondary testing with a rapid test.

3. Pathogen reduction

160
161 This strategy applies to apheresis platelets.^{5,6} Platelets that have been treated by
162 pathogen reduction need no further measures because pathogen reduction
163 technology adequately controls the risk of bacterial contamination of platelets
164

D. 7-Day Platelet Storage

165
166 Storage may be extended beyond 5 days if:

- 167 • The platelets are stored in a container cleared or approved by FDA for 7-day
168 storage, and
- 169 • Individual platelet units are subsequently tested for bacterial detection using a
170 bacterial detection device cleared by FDA and labeled for use as a “safety
171 measure.”⁷

172 The following strategies are recommended for storage of platelets of up to 7 days:

1. Primary culture, followed by a secondary culture with a device labeled as a “safety measure” performed no earlier than Day 4

173
174 This strategy applies to apheresis platelets, and includes the following steps:
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⁵ This strategy could apply to other platelet products in the future if appropriately labeled pathogen reduction devices and storage systems become available.

⁶ See footnote 2.

⁷ See footnote 1.

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- 188
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- Initial primary culture (see section III.B. of this guidance).
 - Secondary culture no earlier than Day 4, using a device labeled as a “safety measure.”

Secondary culture:

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194 To maximize the sensitivity of the culture, we recommend use of the upper limit

195 of the sample volume range permitted by the device’s instructions for use,

196 inoculated into both an aerobic culture and an anaerobic culture.

197

198 If the instructions for use of the bacterial detection device specify a minimum

199 incubation period, you should release platelet products consistent with the

200 incubation period specified. If the instructions for use of the bacterial detection

201 device do not specify a minimum incubation period, we recommend a minimum

202 incubation period of 12 hours.

2. Primary culture, followed by a secondary rapid test labeled as a “safety measure”

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206

207 This strategy applies to apheresis platelets, and includes the following steps:

- 208
- Initial primary culture (see section III.B of this guidance).
 - Secondary testing with a rapid test labeled as a “safety measure.”

3. Large volume delayed sampling ⁸

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214 This strategy applies to apheresis platelets, and includes the following steps:

- 215
- A single culture performed using a culture-based bacterial detection device no sooner than 48 hours after collection with a sampling volume of at least 16 mL, inoculated evenly into an aerobic culture and an anaerobic culture.
 - Each apheresis unit should be sampled for culture. If the apheresis product is split, each split product should be sampled.
 - If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend a minimum incubation period of 12 hours.
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⁸ The instructions for use of the culture-based device currently labeled as a “safety measure” require a primary culture and secondary test to extend dating. Therefore, the large volume, delayed sampling strategy cannot be implemented until appropriately labeled devices are available.

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229 **E. Post-Storage Pooled Platelets**

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231 Transfusion services should perform a rapid bacterial detection test prior to transfusion
232 on pools of WBD platelets if the constituent single units were not previously tested.

233 Post-storage pooled platelets expire 4 hours from the time of preparation

234 (21 CFR 606.122(1)(2)).

235

236 **F. Single Units of WBD Platelets**

237

238 Single units of WBD platelets may be stored for 5 days. For single units of WBD
239 platelets that have not been previously tested and are not intended for pooling, testing
240 should be performed according to either or both of the following strategies:

241

242 1. Sample no sooner than 24 hours after collection, the largest practical
243 volume within the range permitted by the device's instructions for use and
244 inoculate into a culture. Use of an aerobic and an anaerobic culture may be
245 considered; and/or

246

247 2. Perform testing with a rapid test.

248

249 **G. Labeling**

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251 1. Labels on the Container

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253 a. The container labels must comply with 21 CFR 606.121 and
254 21 CFR 610.60. Blood collection establishments and transfusion services,
255 as appropriate, must also follow the general requirements for labeling
256 operations described in 21 CFR 606.120.

257

258 b. The container labels must include the expiration date and time, if
259 applicable, of the product based on bacterial detection testing (21 CFR
260 606.121(c)(4)(i)).

261

262 c. If secondary testing of platelets is performed consistent with this guidance,
263 and the expiration date is extended to 6 or 7 days based on the bacterial
264 testing performed, the blood establishment or transfusion service that
265 performed the secondary testing must update the container label to reflect
266 the new expiration date (21 CFR 606.121(c)(4)(i)).

267

268 2. Circular of Information

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270 You must update your Circular of Information to include appropriate
271 statements regarding bacterial detection testing or pathogen reduction (21 CFR
272 606.122).

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274 **IV. REPORTING IMPLEMENTATION OF MANUFACTURING AND LABELING** 275 **CHANGES**

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277 An establishment that distributes platelet products in interstate commerce must have an approved
278 BLA, in accordance with section 351 of the Public Health Service Act.

279
280 Licensed establishments must report changes to their approved biologics license applications
281 (BLA) in accordance with 21 CFR 601.12. The information below is intended to assist you in
282 determining which reporting mechanism is appropriate for a change to your approved BLA, as it
283 applies to the bacterial testing of platelet products and the manufacture of apheresis platelets
284 with a 6 or 7-day dating period.⁹ You should prominently label each submission with the
285 reporting category under which you are reporting your change, for example, “Prior Approval
286 Supplement,” or “Annual Report.”
287

288 **A. Prior Approval Supplement (PAS)**

- 289
290 1. Changes requiring supplement submission and approval prior to
291 distribution of the product made using the change (21 CFR 601.12(b)).
292

293 Under 21 CFR 601.12(b), changes that have a substantial potential to have an
294 adverse effect on the identity, strength, quality, purity, or potency of the product
295 as they may relate to the safety or effectiveness of the product must be reported
296 to FDA in a Prior Approval Supplement (PAS). You must not distribute in
297 interstate commerce blood components made using a new or changed
298 manufacturing process requiring a PAS until you have received our approval of
299 your PAS (21 CFR 601.12(b)(3)).
300

301 We believe a PAS submission is appropriate in the following situations:

- 302
303 a. You are currently licensed to manufacture apheresis platelets with a 5-
304 day expiration date and you choose to extend the storage time to a 6-day
305 or 7-day expiration date and distribute these products in interstate
306 commerce.
307
308 2. To comply with the requirements in 21 CFR 601.12(b)(3), you must
309 include the following minimum information in your PAS submission:
310
311

⁹ FDA’s recommendations for the implementation of pathogen reduction are addressed in the guidance document titled, “Implementation of Pathogen Reduction Technology in the Manufacture of Blood Components in Blood Establishments: Questions and Answers; Draft Guidance for Industry,” dated December 2017. The draft guidance, when finalized, will represent FDA’s current thinking on this topic.

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- 312 a. Form FDA 356h, “Application to Market a New or Abbreviated New
313 Drug or Biologic for Human Use.”
314
315 b. List of the platelet products involved.
316
317 c. Address and registration number of the manufacturing facility/facilities.
318
319 d. A detailed description of the manufacturing process. We recommend
320 the submission of written standard operating procedures (SOPs) that
321 include:
322
323 i. Component manufacturing (if these SOPs were previously
324 approved by FDA, include the reference number under which
325 they were reviewed).
326 ii. Bacterial detection testing, including the name of the device(s)
327 used for bacterial detection, when the platelet product is sampled
328 and when the product will be released.
329 iii. How to label the platelet product based on the results of the
330 bacterial detection testing and the timeframe after which the
331 negative results are no longer valid.
332 iv. Measures to alert the consignee that a distributed platelet product
333 has tested positive for bacterial contamination.
334 v. Quarantine and disposition of unsuitable products.
335 vi. Investigation of units with positive test results.
336 vii. A communication plan to notify your consignees the type of
337 storage container the platelets are stored in, for example, a
338 storage container approved for 5-day storage or for 7-day
339 storage and when the bacterial detection testing was performed.
340
341 e. The name, address and registration number, if available, of any
342 contractors who are performing bacterial detection testing of platelet
343 products for you.
344
345 f. Validation plan for the bacterial detection testing method and a
346 summary of the validation data.
347
348 g. Two consecutive months of quality control data for the pH at
349 expiration or on the date the product is issued for each platelet product
350 type that will have the expiration date extended based on bacterial
351 detection testing.
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353 h. Labeling – include the following in your supplement:
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- i. Container Labels: A container label for each platelet product, unless previously approved by FDA, that includes the expiration date and time, if applicable, of the platelet product based on bacterial detection testing.
 - ii. Circular of Information.
3. You may also consider submitting a Comparability Protocol as a PAS under 21 CFR 601.12(e). A Comparability Protocol is not required, but an approved Comparability Protocol may justify a reduced reporting category for manufacturing apheresis platelets with a 6-day or 7-day expiration date in multiple locations. In addition to the content listed in section IV.A. of the guidance, Comparability Protocol (21 CFR 601.12(e)) submissions must also include the plan for implementing the bacterial detection testing at multiple manufacturing sites. The plan should include a description of how you will validate the new procedures.

B. Annual Report

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Under 21 CFR 601.12(d), changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be documented in an annual report submitted each year within 60 days of the anniversary date of approval of the BLA.

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We believe the following changes may be submitted in an Annual Report¹⁰ noting the date the process was implemented:

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1. Implementation of bacterial detection testing as described in this guidance without modification and the expiration date of apheresis, single units of WBD platelets, and pre-storage pooled WBD platelets remains at 5 days.
 2. You or your contractor change from one type of FDA cleared bacterial detection device to another type of FDA-cleared bacterial detection device.

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NOTE: For assistance in reporting your changes, see FDA’s “Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture; Guidance for Industry” dated December 2014.

¹⁰ See 21 CFR 601.12(a)(3).

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398 The December 2014 guidance represents FDA’s current thinking on this topic and can be
399 found on FDA’s website at:
400 <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm/Guidances/Blood/ucm354559.htm>.
401
402

403 404 **V. TRANSFUSION SERVICES—REGISTRATION AND BLOOD PRODUCT** 405 **LISTING** 406

407 Except as provided in 21 CFR 607.65, all owners and operators of blood establishments that
408 engage in the manufacture of blood products must register with FDA and list the blood
409 products they manufacture, pursuant to section 510 of the Federal Food, Drug, and Cosmetic
410 Act and the implementing regulations under 21 CFR 607.7. The implementation of a bacterial
411 detection device that is used to re-label a platelet product with a 6 or 7-day expiration date,
412 thereby extending the dating of the platelet product, is a manufacturing procedure requiring
413 registration and blood product listing, as described in 21 CFR 607.3(d). Transfusion services
414 that implement secondary testing on platelets with a 5-day expiration date are not required to
415 register and list because they are not extending the dating period of platelets.
416

417 If you are a transfusion service that is currently exempt from registration and blood product
418 listing under the provisions of 21 CFR 607.65(f), and you implement a bacterial detection test
419 to determine the suitability of platelet products to be released on day 6 or day 7 after
420 collection, you are no longer considered exempt because you are engaging in blood product
421 manufacturing under 21 CFR 607.3(d). You must therefore register your blood establishment
422 with FDA and list the blood products you manufacture, pursuant to 21 CFR 607.7. Indicate
423 that you are performing bacterial detection testing on platelet products by selecting “Bacterial
424 Testing” as a process for the platelet products.
425

426 Instructions on how to register electronically with FDA can be found on FDA’s website at:
427 [https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Est
428 ablishmentRegistration/BloodEstablishmentRegistration/default.htm](https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/BloodEstablishmentRegistration/default.htm).
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431 **VI. IMPLEMENTATION** 432

433 We recommend that you implement the recommendations contained in this guidance within 12
434 months after the final guidance is issued.
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438 VII. REFERENCES

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471 <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesand>
472 [OtherBiologics/BloodProductsAdvisoryCommittee/ucm597841.htm](https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesand)
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