

Proposed changes to Draft Leukocyte Reduction Guidance - Validation and Quality Control

Issue	Current Draft Guidance	Proposed Change	Comments
Validation and QC of incomplete filtration rate	Not included	Incomplete filtration rate should be $\leq 0.5\%$ (excluding incomplete filtration due to identified donor factors)	a.
Post-filtration WBC content	1×10^6 residual WBC	5×10^6 residual WBC	
Validation of WBC content	95% of products have $\leq 1 \times 10^6$ residual WBC with 95% confidence (0 failures/SOP @N=60 consecutive counts)	95% of products have $\leq 5 \times 10^6$ residual WBC with 95% confidence (0 failures/individual SOP @n=60)	b.
Elements of process variations defined by individual SOP	Time after collection, filtration temperature, elapsed filtration time, filter type, (lot #)	To be updated based on new filter performance data	c.
Recommended QC procedure for residual WBC content	5 WBC counts @ week/3 months	1% of total process (≈ 5 counts/week for each SOP used during that week.) For each 12 weeks of individual SOP use, 95% of products should meet 5×10^6 residual WBC standard @ 95% confidence.	
Rationale and references for validation, QC recommendations	Not detailed	To be incorporated	b.
Process failure definition and corrective action	Investigation of failure followed by corrective action and re-validation of process.	With observed process failure (SOP specific), initiate failure investigation and begin counting consecutive n=60. If no further failure, QC resumes after corrective action. If further failure observed during consecutive counting, process is out of control. Donor-specific variation ¹ process failure	d.
Identification and follow-up of donor-specific factors that cause incomplete filtration or $\geq 5 \times 10^6$ residual WBC	Not detailed	Donor record should be flagged. Upon second occurrence of incomplete filtration or inadequate WBC removal, donor not eligible for WB donation.	
Consignee notification	Not detailed	Out of control process only.	Defined by Center SOP
Options for alternate QC	Not specified	Alternate validation/QC approaches to reach 95%/95% standard allowed. Submit to FDA as PAS.	

Comments (Validation and Quality Control):

- a. Rates of incomplete filtration and post-filtration residual WBC content are to be considered as two distinct outcomes for purposes of validation and quality control. Guidance will recommend the use of validated blood mixing devices or manual procedures to reduce rates of incomplete filtration due to clotting.
- b. Counting recommendations and results indicated provide 95% confidence that 95% of products meet defined standard. This is based on exact binomial distribution. Exact binomial distribution is used for dichotomous outcome (pass/fail) where failures for period of evaluation expected to be $< n=5$. Counting can be simplified by only determining when a count exceeds 5×10^6 residual WBC (vs. actual enumeration).
- c. Guidance will recommend bounds of these process conditions that should have separate validation. Filter lot validation is the responsibility of the filter manufacturer, however users have experienced lot-related failures. Guidance will discuss and indicate that centers experiencing lot variations should notify filter manufacturer and FDA Division of Hematology.
- d. Incomplete filtration or poor WBC removal due to defined donor factors does not constitute a process failure, since donor factors are currently not predictable. However, donors contributing to incomplete filtration or poor WBC removal should be flagged for investigation. After a second occurrence, these donors should be considered ineligible for further donation of filtered products unless a validated procedure is used to prevent such failure.

Proposed changes to Draft Leukocyte Reduction Guidance - Non-QC Issues

<p>Use of leukocyte-reduced blood products for patients for which CMV may be harmful.</p>	<p>Count residual WBC in all leukocyte-reduced blood products used for CMV-susceptible patients.</p>	<p>Remove recommendation for counting residual WBC in blood products used for CMV-susceptible patients. Encourage centers to maintain validated inventory where feasible. Discuss advantages of supporting susceptible patients with leukoreduced products that are also CMV seronegative.</p>	<p>Dual inventory may not be logistically feasible at all sites. Product COI specifies that leukoreduced product "may reduce risk of CMV transmission by transfusion"; Non-validated products to be used at physician's discretion.</p>
<p>HbS screening of donors</p>	<p>Recommended</p>	<p>No recommendation. However discussion of process control will include HbS screening as one way to reduce failures.</p>	<p>BPAC unanimously failed to endorse HbS screening recommendation</p>
<p>Use of validated mechanical mixing device or validated manual mixing procedure during collection.</p>	<p>Not specified</p>	<p>Recommended</p>	<p>Inadequate mixing during collection is a source of small clots which block filter</p>