Evaluation of traceability in various TB&NK workflows to assess stages of errors proneness and auditability

Lori Apoll,[1] Nicolas Bailly,[2] Maureen Martin[3]
[1]Becton Dickinson and Company, Canada; [2]Becton Dickinson and Company, Belgium; [3]Becton Dickinson and Company, U.S.

Introduction

Specimen and reagent traceability is integral to Good Laboratory Practice (GLP). Current staffing challenges and increased workloads demand high traceability. Various flow cytometry workflows employ specimen and reagent barcodes and audit trails throughout the process for both GLP and enhancing workloads: (1) manual methods with visual confirmation or logs; (2) semi-automation enables increased auto-traceability; and (3) fully integrated automation systems have high auto-traceability.

TB&NK kits are widely available in flow cytometry as IVD(R). These include robust documentation from the manufacturer to support standardized processing of specimens, which enables an objective assessment of traceability and auditability. Assessment methods, applied to these workflows for traceability evaluation, can inform automation selections to enhance GLP.

Materials and Samples

The scoring system will be completed using the available information in the relevant IFU's and experienced BD Applications Specialist inputs with verification in publicly available BD documentation (instructions for use, user guides, etc.). No samples or systems were run.

Method

The three workflows assessed were paired with three representative configurations for which documentation was available and are utilized in the clinical laboratory for performing TB&NK enumeration *(Table 1)*. The reagent used in this simulation was the BD Multitest™ 6-Color TBNK Reagent with BD Trucount™ Tubes technology.

Assumptions included all possible features for traceability and auditability by the respective workflows being utilized and all workflows utilized middleware to transfer results to the LIS (no manual entry).

Table 1: Workflow and representative configurations used

Flow cytometry workflow	Configuration used for assessment
(1) manual methods with visual confirmation or logs;	Manual to BD FACSLyric™ Flow Cytometry System
(2) semi-automation enables increased auto-traceability	BD FACS™ Sample Prep Assistant (SPA) III to BD FACSCanto™ II Clinical Flow Cytometry System
(3) fully integrated automation systems have high auto-traceability	BD FACSDuet™ Sample Preparation System to BD FACSLyric™ Flow Cytometry System

Table 2: Workflow and substages

Workflow Components	Examples of Sub-Steps (non exhaustive list)
(a) preparation	• Reagent lot and expiry • Specimen information • BD Trucount™ lot and expiry • Lysing reagent lot and expiry • Dispensing of samples and reagents
(b) middleware involvement (BD FACSLink™ Software or Workflow Manager)	• Creating worklists • Exporting of worklist from sample prep to flow cytometer • Transfer of results to LIS
(c) acquisition/ analysis)	• Specimen tube to position logged • Secondary tube positions logged per specimen • Report with operator information • Approval of results

Six Sigma attributes methodology was utilized to score the TB&NK workflow stages of (a) preparation (b) middleware involvement (utilized throughout the process) and (c) acquisition/analysis. These were then further sub-staged (*Table 2*) using manufacturer product-specific instructions for use (IFU), product inserts, user guides (UG) and other available documentation (e.g., website quick reference guides (QRG).

The various components of specimen and reagent traceability were scored as follows:

1. A score of "0" was assigned with visual confirmation only being used
2. Score of "1" with a manual entry into software or paper log; and
3. Finally a score of "2" for barcode enabled auto-entry

Each stage was then classified as auditable and/or error prone.

Analysis and Results

A total of 51 distinct substages, or individual opportunities for traceability and audit trail development, were identified across the three methods, which were assigned an attribute score. The (1) manual preparation to BD FACSLyric™ Flow Cytometry System method had a total of 24 substages, the (2) semi-automated BD FACS™ Sample Prep Assistant (SPA) III to BD FACSCanto™ II Clinical Flow Cytometry System had 36 substages, and the (1) fully integrated and automated BD FACSDuet™ Sample Preparation System to BD FACSLyric™ Flow Cytometry System had 31 substages.

- The (1) manual method had the highest percentage of workflow traceability, 45.8%, employing visual checks by the operator occurring primarily in the sample preparation stage, resulting in a over all score of 0.76/2.00. Visual checks would include verifying the sample ID checking the lot number of reagent and the BD Trucount™ Tubes used. Once the specimen moved to the acquisition and analysis stage where the traceability by the flow cytometer enabled increased scoring. Of note, this second phase of the workflow relies on the integrity of the first phase sample preparation workflow. Traceability increase with (2) semi-automation and is greatly increased with fully-automated systems (*Table 4)*.
- Automation, whether semi or full, increases traceability and the auditability of each of the substages. This is achieved either through the use of electronic logs into which data can have manual/semi-automated software logged entries (score of 1) or fully automated barcoded entries (score of 2). The instance of auditable stages is lowest for the (1) manual method (41.7%) and highest for the (3) fully automated system (80.6%). Examples of auditability were worklists and reports that contained specimen and reagent components used in the processing of the TB&NK workflow. Examples of non-auditable stages in the fully automated were relating to reagent recall, or stages not requiring an audit (removal of samples from the system) and may not result in lack of information in the audit trial or error prone stages.
- Due to the nature of the (1) manual method, it had the highest number of error prone stages in relation to traceability of the three methods assessed at 75.0% error prone. The least error prone method was the (3) fully-automated process.

FREQUENCY TABLES:

The frequencies of these could be quantified and represented in various forms, all which provide information on the relative differences between the methods. A frequency table (*Table 3*) provides a snapshot on the various metrics achieved from which statements can be derived for decision making.

Table 3: Frequency of scoring

Method	1	2	3
Frequency Score	Manual to BD FACSLyric™ Flow Cytometry System	BD FACS™ Sample Prep Assistant (SPA) III to BD FACSCanto™ II Clinical Flow Cytometry System)	BD FACSDuet™ Sample Preparation System to BD FACSLyric™ Flow Cytometry System
0	11	7	0
1	7	20	2
2	6	9	29
Total	24	36	31

Almost half, or 48.0%, of traceable stages in the (1) Manual Process involve a visual check only (score of 0). Whereas in the (2) Semi-automated process it was 19.4% which is a 41.7% improvement over the manual method. The (3) Fully Integrated process has 100% traceability of its workflow being traceable (score of 1 and 2) with 93.5% of traceability that is automated using barcodes, middleware and worklist functionality.

MAPPING TRACEABILITY SCORES: These data can also be visualized to demonstrate the workflow substages where the traceability scores were applied as depicted in *Figure 1.*

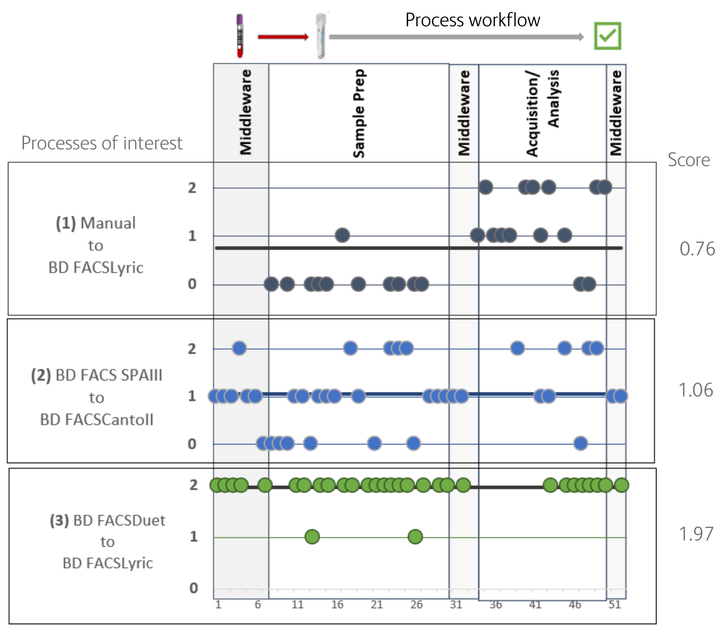

Figure 1: Traceability detailed score mapping

Automated systems, whether (2) semi-automated or (3) fully automated, utilized LIS capabilities from the start of the process through to the end of the results verification stage. This increases the number of substages relative to the manual method (manual to BD FACSLyric™ Flow Cytometry System method) of 24 substages, the semi-automated (BD FACS™ Sample Prep Assistant (SPA) III to BD FACSCanto™ II Clinical Flow Cytometry System) with 36 substages, and the fully-automated (BD FACSDuet™ Sample Preparation System to BD FACSLyric™ Flow Cytometry System) with 31.

The reduction in substage from (2) semi-automated to (3) fully automated was in part to the automated worklist generation, with partial countering by increased use of bar codes capability for both sample and reagents across the process.

This data visualization *(Figure 1)* demonstrates a clear picture of the substages category assignment and can be represented horizontally for further assessment *(Figure 2)*.

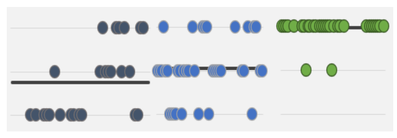

Figure 2: Horizontal score mapping comparison

In the (1) fully automated workflow for TB&NK, there were only two data points that scored as 1. The first was attributed to the entry of the BD Trucount™ Tubes into the BD FACSDuet™ Sample Preparation System where the lot number, expiry and bead counts could be scanned in using the barcode on the pouch, but the operator would verify the lot in use upon starting a worklist. The system has secondary tube barcode scanning, BD Trucount™ Tubes do not have lot barcodes on their label for verfiication by automation. The second was the ability of the BD FACS™ Lyse Wash Assistant Solution lot number and expiry date to be entered into the BD FACSDuet™ Sample Preparation System, with the dilution of the 10X solution would have to be verified and made up every 30 days. The BD FACSDuet™ Sample Preparation System lysing container location, not barcoded, and contents are not limited to BD FACS™ Lyse Wash Assistant used in the TB&NK processing, thus the operator would need to verify upon launching a worklist.

CUMULATIVE ERROR PRONE AND AUDITABLE STAGES:

Graphic display of the progression of steps in relation to error proneness and auditability across the workflow provides a visual comparison of the three TB&NK representative configurations. The (1) manual workflow display shows the error prone nature of the sample preparation stages (grey bars meeting the task line) which is slightly improved upon moving to the flow cytometer along with increased auditability. In contrast, the (3) fully automated has good correlation of auditability for each task while having minimal error proneness.

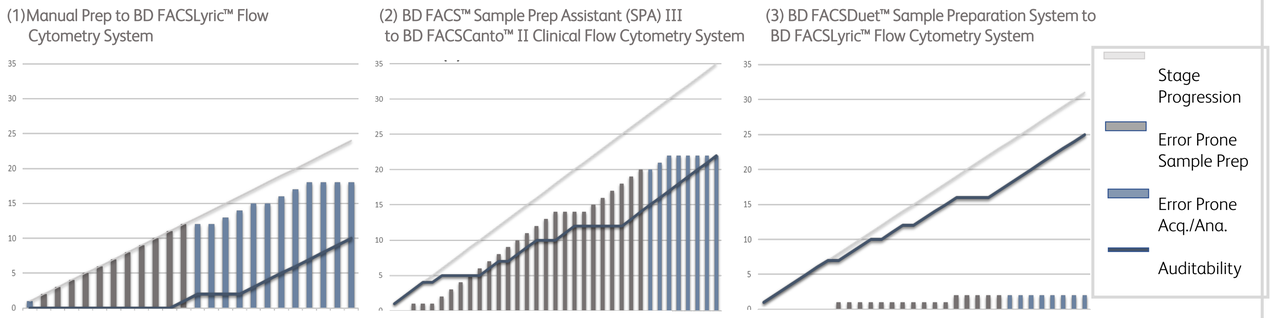

Figure 2: Horizontal score mapping comparison

As displayed in the (2) semi-automated graph, an increased number of stages for traceability using preparation device software tools and worklist creation, have been further developed and streamlined into automatic barcode reading and auto-transfer of worklist information in (3) automated workflow stages.

Table 4: Final results

Score	Manual to BD FACSLyric™ Flow Cytometry System	BD FACS™ (SPA) III to BD FACSCanto™ II Flow Cytometer	BD FACSDuet™ Sample Preparation System to BD FACSLyric™ Flow Cytometer
Traceability	0.76/2.00	1.06/2.00	1.97/2.00
Auditability	41.7%	62.9%	80.6%
Error Prone	75.0%	62.9%	6.5%

Conclusion

Using this objective method, the (3) fully integrated automation system running TB&NK testing provided the highest traceability score (1.97/2.00) and employs automatic barcodes reading with audit trails to ensure consistency in practice and documentation. The tools in this methodology are simple to apply when evaluating next generation systems to adhere to Good Laboratory Practice.