Current Good Manufacturing Practices (cGMP) for the UWMC Transfusion Service Laboratory

Good Manufacturing Practices (GMP)

- GMP
  - Part of QUALITY assurance
  - Ensures that blood products are consistently manufactured
  - Ensures that blood products are controlled to maintain:
    - Safety
    - Potency
    - Purity
    - Efficacy appropriate to their intended use

What is cGMP?

- cGMP stands for current Good Manufacturing Practices
- The reason “current” is used as part of the term is to emphasize that these regulations are dynamic and always changing
- They are not static. Systems and equipment used to prevent contamination, mix-ups, and errors, which may have been "top-of-the-line" 20 years ago, may be less than adequate by today's standards.

Oversight of cGMP

- cGMP are regulations enforced by the US Food and Drug Administration (FDA)
  - FDA Title 21 Food and Drugs
    - Chapter I – Food and Drug Administration Dept. Of Health and Human Services
      - Subchapter F – Biologics
        - Part 606 – Current Good Manufacturing Practice for Blood and Blood Components
- The FDA is responsible for oversight of blood collection and for manufacturing of blood products. This includes:
  - Transfusable components of whole blood
  - Pharmaceuticals derived from blood cells or plasma
  - Related medical devices

cGMP

- These regulations, which have the force of law, require that manufacturers and processors of blood take proactive steps to ensure that their products are safe, pure, and effective.
- GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix-ups, and errors.
- This protects the consumer from a product which is not effective or even dangerous. Failure to comply with GMP regulations can result in very serious consequences including recall, seizure, fines, and jail time.

Enforcing Compliance

- The FDA inspects blood establishments for compliance to these cGMP regulations
- The FDA also monitors:
  - Reports of errors
  - Accidents
  - Adverse clinical events

Benefits of cGMP

- cGMP regulations are designed to ensure the following for all aspects of manufacturing processes and facilities where it is performed
  - Proper design
  - Monitoring
  - Control
  - Quality
- By requiring that manufacturers of blood products and derivatives adequately control all phases of the manufacturing process the following are assured:
  - Identity
  - Strength
  - Quality
  - Safety
  - Purity of blood and blood components

Aspects of manufacturing GMP covers:

- Collection
- Transportation
- Labeling of products
- Testing of donor and recipient (quality control of reagents, acceptability of specimens)
- Quality control
- Medical devices: Laboratory information system (Sunquest, blood warmers)
- Storage of products (temperature, equipment
- Secondary processing of the products (irradiation, volume reduction)
- Delivery of the finished product
- Administration of the blood component
- Follow-up of adverse events (transfusion reactions, post-donation information, lookbacks)
- Training of transfusion service lab staff

Quality Assurance

- **Quality is everyone's responsibility**
  - Not management alone or those in a specific quality or compliance role in the organization
  - Don't just make the product or do your job and leave it up to Quality Assurance to fix the problems

QUALITY
starts with
YOU

cGMPS are the minimum requirements that must be met

cGMPS include the following:

- CFR 21 Part 606
  - Subpart A General Provisions
  - Subpart B Organization and Personnel
  - Subpart C Plant and Facilities
  - Subpart D Equipment
  - Subpart F Production and Process Controls
  - Subpart G Finished Product Control
  - Subpart H Laboratory Controls
  - Subpart I Records and Reports

Subpart A: General Provisions

DEFINITIONS:

- *Blood* means a product that is a fluid containing dissolved and suspended elements which was collected from the vascular system of a human
- *Facilities* means any area used for the collection, processing, compatibility testing, storage or distribution of blood and blood components

Subpart A: General Provisions

DEFINITIONS:

- *Compatibility testing* means the procedures performed to establish the matching of a donor's blood or blood components with that of a potential recipient
- *Control* means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices

Subpart B: Organization and Personnel

- There are competent and appropriately qualified personnel in sufficient numbers to ensure service provision
- Staff are **authorized** to carry out processes and procedures only after appropriate, documented training
- There is a quality control unit with responsibility to reject and approval all material, procedures and specifications

Subpart B: Organization and Personnel

- All personnel receive initial and continuing training relevant to their needs
- Training is:
  - Structured
  - Continuous
- Training records based on SOPs are maintained as evidence staff have been trained and found competent to perform process and procedures as specified

Subpart B: Organization and Personnel

- Competency Assessments are performed periodically (at a minimum meeting CLIA requirements) to:
  - Verify staff continued compliance with process and procedures
  - Identify unintended drift from established policies and procedures

Subpart B: Organization and Personnel

- Personnel:
  - Wear clean clothing
  - Wear protective apparel to prevent contamination
  - Practice good sanitation

Subpart C: Plant and Facilities

- The premises and equipment must be located, designed, constructed, validated and maintained to suit the intended operations
- Lay out, design and operation must be designed so as to minimize the risk of errors and permit effective cleaning and maintenance
- There is adequate and safe provision of lighting, heating, ventilation, power gases water and drainage

Subpart C: Plant and Facilities

- Sewage and trash will be stored and disposed of in a safe and sanitary manner
- Adequate washing and toilet facilities are available
- There should be defined storage areas for quarantine, released, rejected and recalled materials

Subpart C: Plant and Facilities

- Reagents and other materials that must be quality controlled prior to use, should be stored in a manner to prevent accidental use until tested
- Where specific storage conditions are required these should be provided, checked, and monitored for compliance
- Storage areas should be secure; restricted to authorized person access

Subpart D: Equipment

All equipment shall:

- Be evaluated to meet specifications prior to purchase
- Be validated before being put into use (IQ; OQ; PQ). Written instructions should specify when equipment must be revalidated
- Have a unique, original identifier (serial number)
- Be calibrated, cleaned, and maintained according to written instructions and schedule
- Be cleaned with only approved cleaning agents

Subpart D: Equipment

- Maintenance, cleaning and fault logs should be maintained for each piece of equipment.
- There should be written instructions for removing equipment from use when it is found to be defective, or does not meet specifications
- Defective equipment is labeled clearly as out of service to prevent unintended use and removed from the area when appropriate

Subpart D: Equipment

- Any corrective action to repair equipment must be documented with clear explanation of repair by the person who preforms the repair
- Repaired or moved equipment must be qualified prior to placing into use and be approved in writing by management or quality personnel. Qualification may include revalidation, calibration, quality control as applicable to the repair

Subpart F: Production and Process Controls

- There should be written policies and procedures that control all processes.
  - This includes:
    - Receipt of reagents, blood components, and essential supplies (i.e. transfer packs)
    - Investigation of errors and adverse events
    - Sample labeling and maintaining the identity of the patient through the entire process of testing and blood product release

Subpart F: Production and Process Controls

- There should be a document proving that errors are corrected and procedures are consistently followed for each step of the manufacturing process each and every time
  - Quality Improvement form documents:
    - The error
    - The immediate action to gain control
    - The investigation into the root cause of the problem
    - The corrective action based on the result of the investigation

Subpart G: Finished Product Control

- Labeling operations shall be separated physically or spatially from other operations in a manner adequate to prevent mix-ups
- All necessary checks in labeling procedures shall be utilized to prevent errors in translating test results to container labels
- All labeling shall be clear and legible

Subpart H: Laboratory Controls

- The establishment of scientifically sound and appropriate specifications, standards and test procedures to assure that blood and blood components are safe, pure, potent and effective
- Adequate provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments

Subpart H: Laboratory Controls

- Adequate identification and handling of all test samples so that they are accurately related to the specific unit of product being tested, or to its donor or specific recipient, where applicable

Subpart I: Records and Reports

- Records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage and distribution of each unit of blood and blood components so that all steps can be clearly traced.

Subpart I: Records and Reports

- Records should be maintained for:
  - Receipt, storage and disposal of all blood components
  - Receipt, storage, quality control and use of all reagents and applicable supplies
  - Testing
  - Additional processing or manipulation of any blood component
  - Investigations
  - Training
  - Validation, calibration and maintenance of all equipment
  - Errors and error corrections
  - Cleaning
  - Almost everything!

Subpart I: Records and Reports

- All records shall:
  - Be legible and indelible
  - Identify the person performing the work
  - Include dates of the various entries
  - Show test results as well as the interpretation of the results
  - Show the expiration date assigned to specific products
  - Be as detailed as necessary to provide a complete history of the work performed

Subpart I: Records and Reports

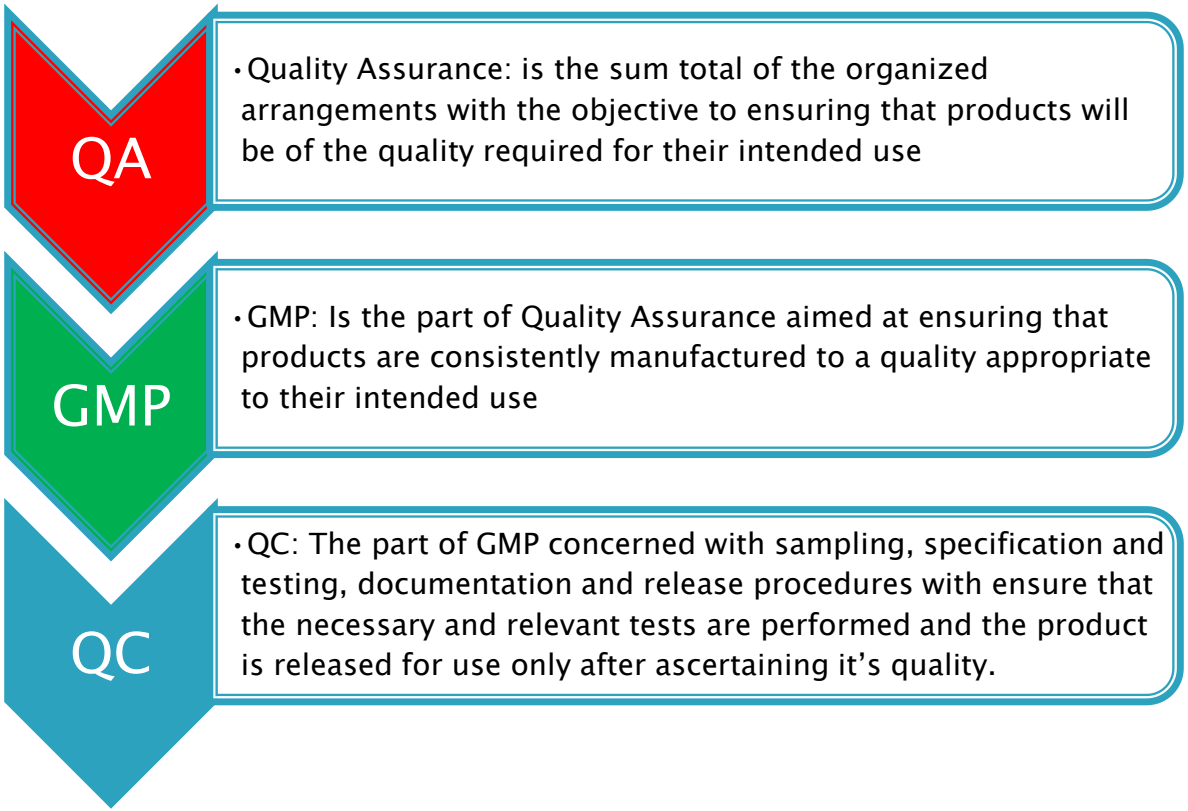
- Only official original should be used. If a copy is made, it should be clearly marked as a copy.
- Records should be completed in blue or black ink. Colored ink is not acceptable.
- Required documentation on a record must not be added as a post-it note.
- Any alteration to a record should be signed and dated with the original entry still visible
- Changes to official documents should be avoided, where absolutely necessary they must be signed by an authorized person.

Records and Reports Cont.

- Error correction on records are made by drawing a single line through the error so that the original entry remains visible and the correction is initialed and dated by the person making the correction.
  - Never use white out
  - Never use scrap paper or post it notes for official documentation
  - Use only black or blue ink on records (colored ink is not acceptable)
- Sign only what you perform or verify
- Documentation must be recorded at the time it occurred (no back dating – unless you are documenting from an alternate official record such as the downtime logs used for documentation of issuing, testing or component prep)

cGMP provides a quality framework

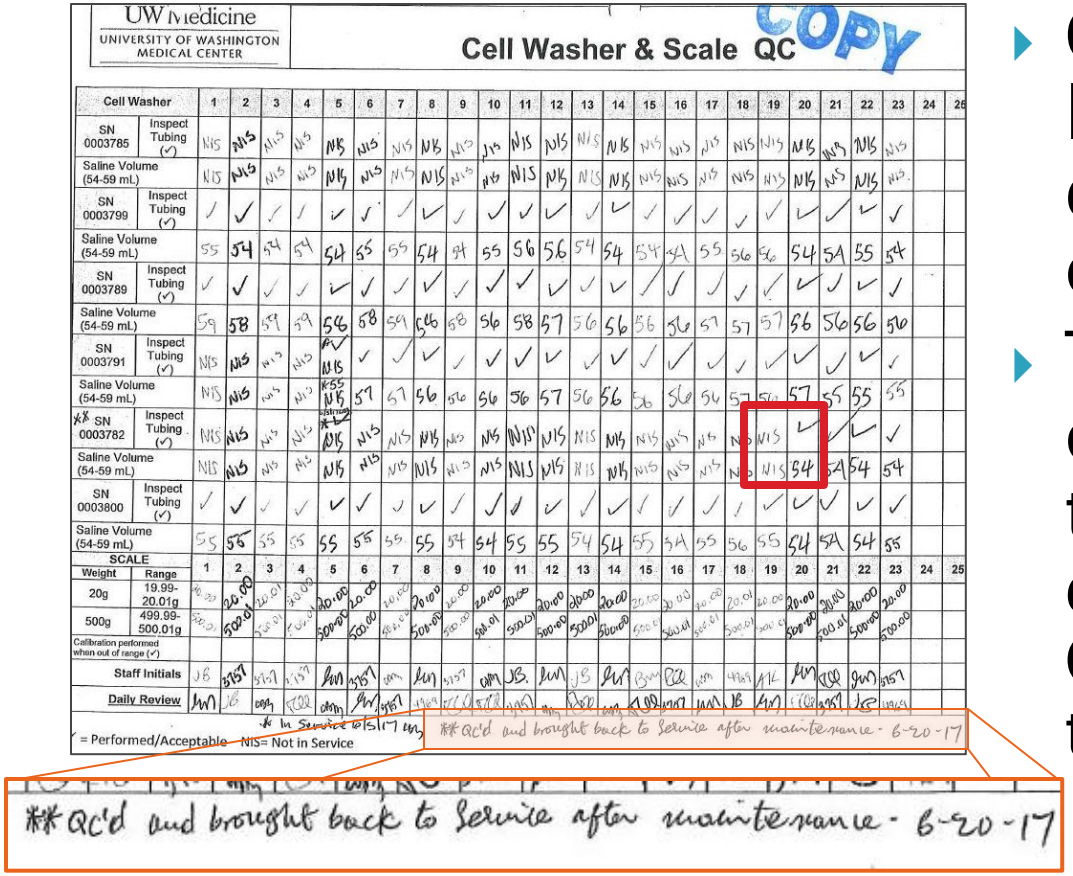
As Professor Basvaraj Nanjwade outlines:



Case Studies

- Learning from mistakes made over the last year

Example of Improper return to Service


UW Medicine
UNIVERSITY OF WASHINGTON MEDICAL CENTER

Cell Washer & Scale QC

COPY

Cell Washer		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
SN 0003785	Inspect Tubing (✓)	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS		
Saline Volume (54-59 mL)		NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS		
SN 0003799	Inspect Tubing (✓)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Saline Volume (54-59 mL)		55	54	54	54	54	55	55	54	54	55	56	56	54	54	54	54	55	56	56	54	54	55	54		
SN 0003789	Inspect Tubing (✓)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Saline Volume (54-59 mL)		59	58	59	59	56	58	59	56	58	56	58	57	56	56	56	56	57	57	57	56	56	56	56		
SN 0003791	Inspect Tubing (✓)	NIS	NIS	NIS	NIS	✓ NIS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Saline Volume (54-59 mL)		NIS	NIS	NIS	NIS	K55 NIS	57	57	56	56	56	56	57	56	56	56	56	56	57	57	57	55	55	55		
** SN 0003782	Inspect Tubing (✓)	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	✓	✓	✓	✓		
Saline Volume (54-59 mL)		NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	NIS	54	54	54	54		
SN 0003800	Inspect Tubing (✓)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Saline Volume (54-59 mL)		55	55	55	55	55	55	55	55	54	54	55	55	54	54	55	54	55	56	55	54	54	54	55		
SCALE		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Weight	Range																									
20g	19.99-20.01g																									
500g	499.99-500.01g																									
Calibration performed when out of range (✓)																										
Staff Initials		JB																								
Daily Review																										

✓ = Performed/Acceptable NIS= Not in Service

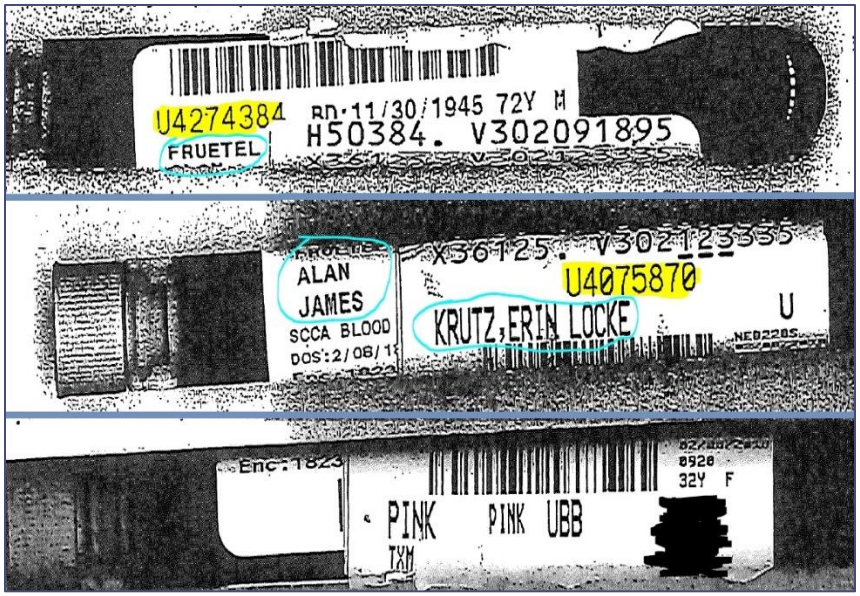
** QC'd and brought back to Service after maintenance - 6-20-17

- Cell washer was being repaired during shift change on the 19th
- The tech discovered on the 20th that there was no documentation that QC was performed on the 19th
  - The cell washer was used by the two previous shifts

What Should Have Been Done?

- Prior to returning equipment to service:
  - Consult with Compliance Analyst or Laboratory Manager to determine what maintenance and QC is required
  - Perform and document required QC

Example of Improper Sample Identification



The incorrect sample was pulled from the HOLD rack. The tech signed that they matched the new label information to the original label. The sample was run on the Tango and then tested manually. Test results were reported on the incorrect patient.

What Should Have Been Done?

- There were three opportunities to catch the error:
  - Labeling tech missed the mislabel
  - Tango tech missed that the label did not match when they put it on the Tango
  - Manual testing tech missed that the label did not match when performing the manual testing
- Verify that the base label and subsequent labels are consistent whenever handling a sample

Sample Identification

- The requisitions were switched for two samples
  - Testing was performed by two different techs
- Techs labeled their tubes based on the sample
- Techs both scanned the MRN into BOP from the requisition
- Both techs entered results of the tube testing under the incorrect patient

What Should Have Been Done?

- Scan the CID from the Patient tube into BOP
  - The same is required for resulting testing from the Tango
- Verify that the patient identifier on the test tube matches the patient order in Sunquest prior to entering results

Order Identification

- A Blood Product Release Form was received and was matched to an incorrect Requisition
- The issuing tech scanned the MRN from the Requisition
- Blood was sent that was labeled for another patient

What Should Have Been Done?

- Scan the MRN from the Blood Product Release form when issuing product
- Clerical check that the issued unit matches the Blood Product Release Form for:
  - Patient
  - Type of product (Platelet, RBC, etc.)

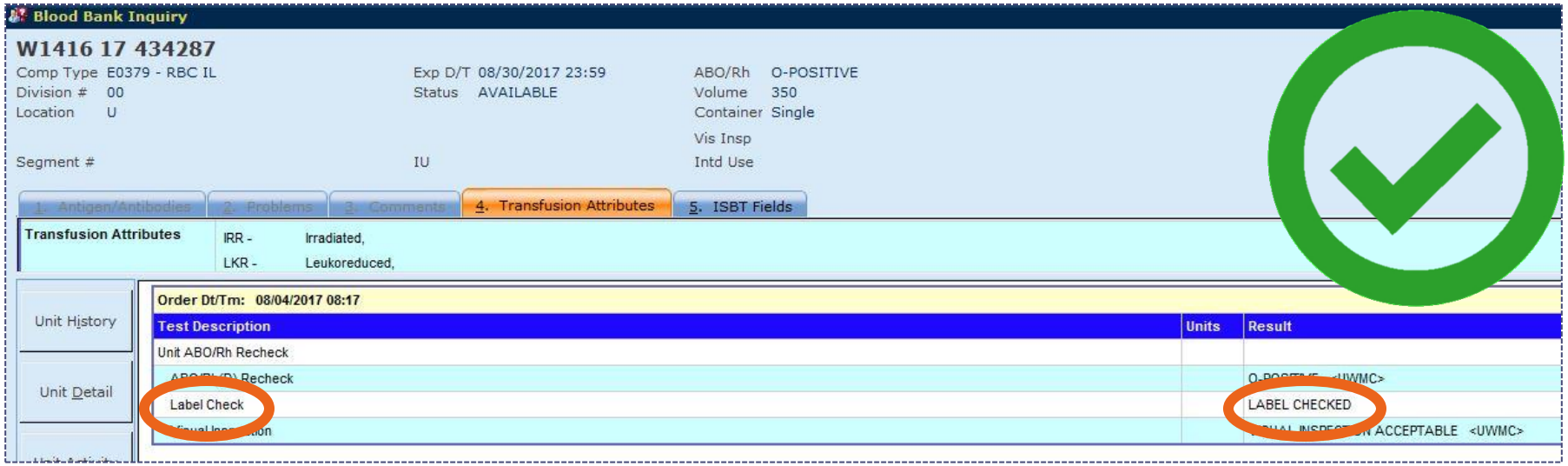
Performance of Label Check

- Tech performed Label check on only a select number of units processed
- FDA reportable error for over 300 units issued without being label checked

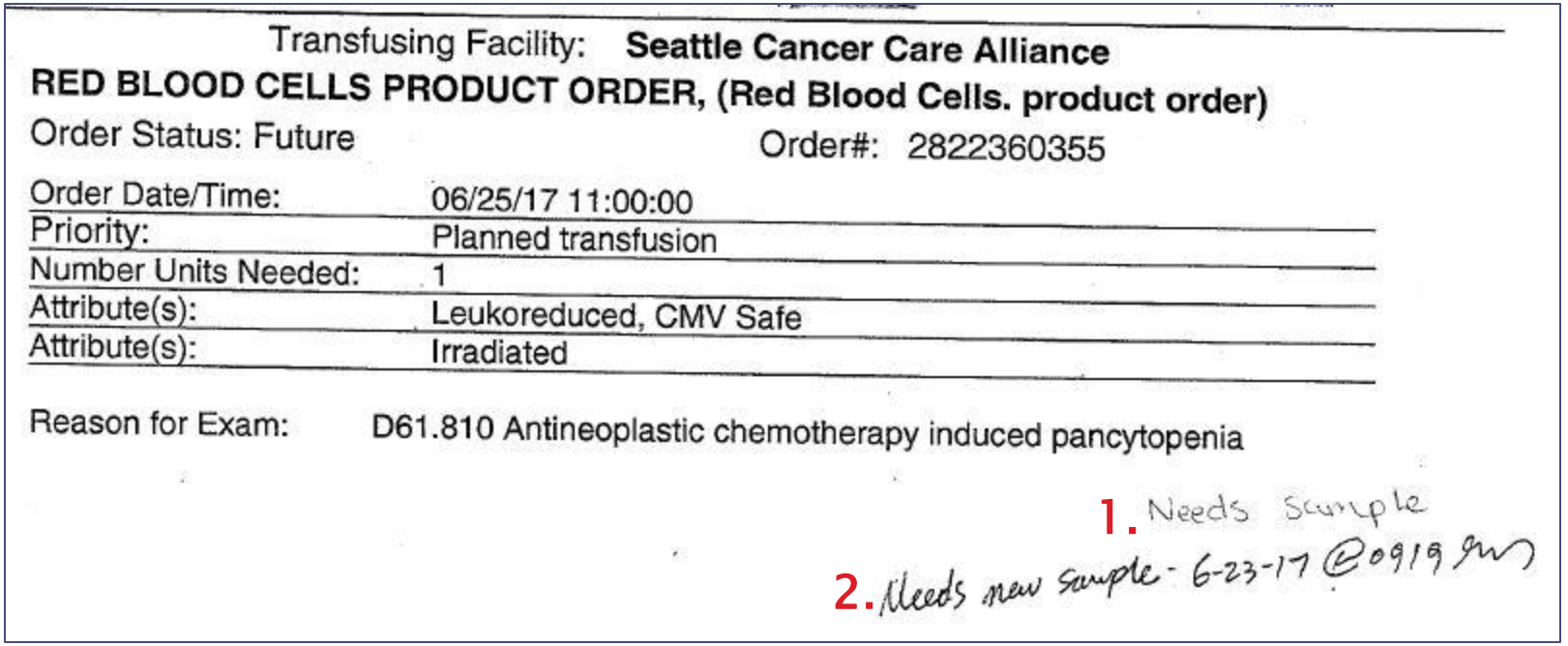
What Should Have Been Done?

- Blood Label Check **MUST** be performed after processing a unit
  - Every unit
  - Every process
  - Every time
- Label check can be verified in BB Inquiry under the Product Testing tab

How to verify Label Check was performed



Incomplete Documentation Led to Re-work



Transfusing Facility: **Seattle Cancer Care Alliance**

RED BLOOD CELLS PRODUCT ORDER, (Red Blood Cells. product order)

Order Status: Future Order#: 2822360355

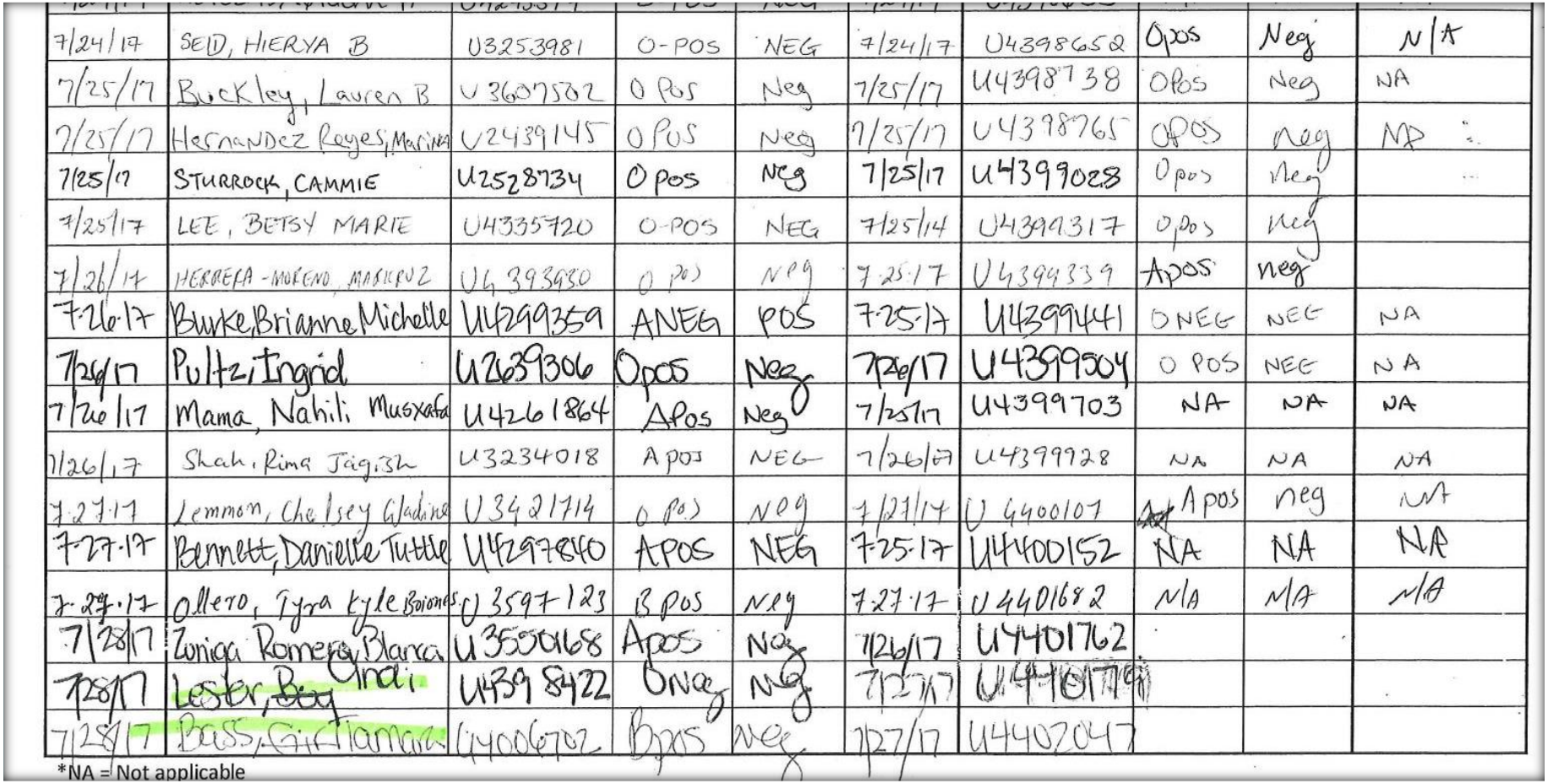
Order Date/Time:	06/25/17 11:00:00
Priority:	Planned transfusion
Number Units Needed:	1
Attribute(s):	Leukoreduced, CMV Safe
Attribute(s):	Irradiated

Reason for Exam: D61.810 Antineoplastic chemotherapy induced pancytopenia

1. Needs Sample

2. Needs new sample - 6-23-17 @0919 JM

- Entry 1 is missing who checked for a sample and when it was done. The tech remembered and went back to complete the entry and found that Entry 2 was made less than an hour after theirs.

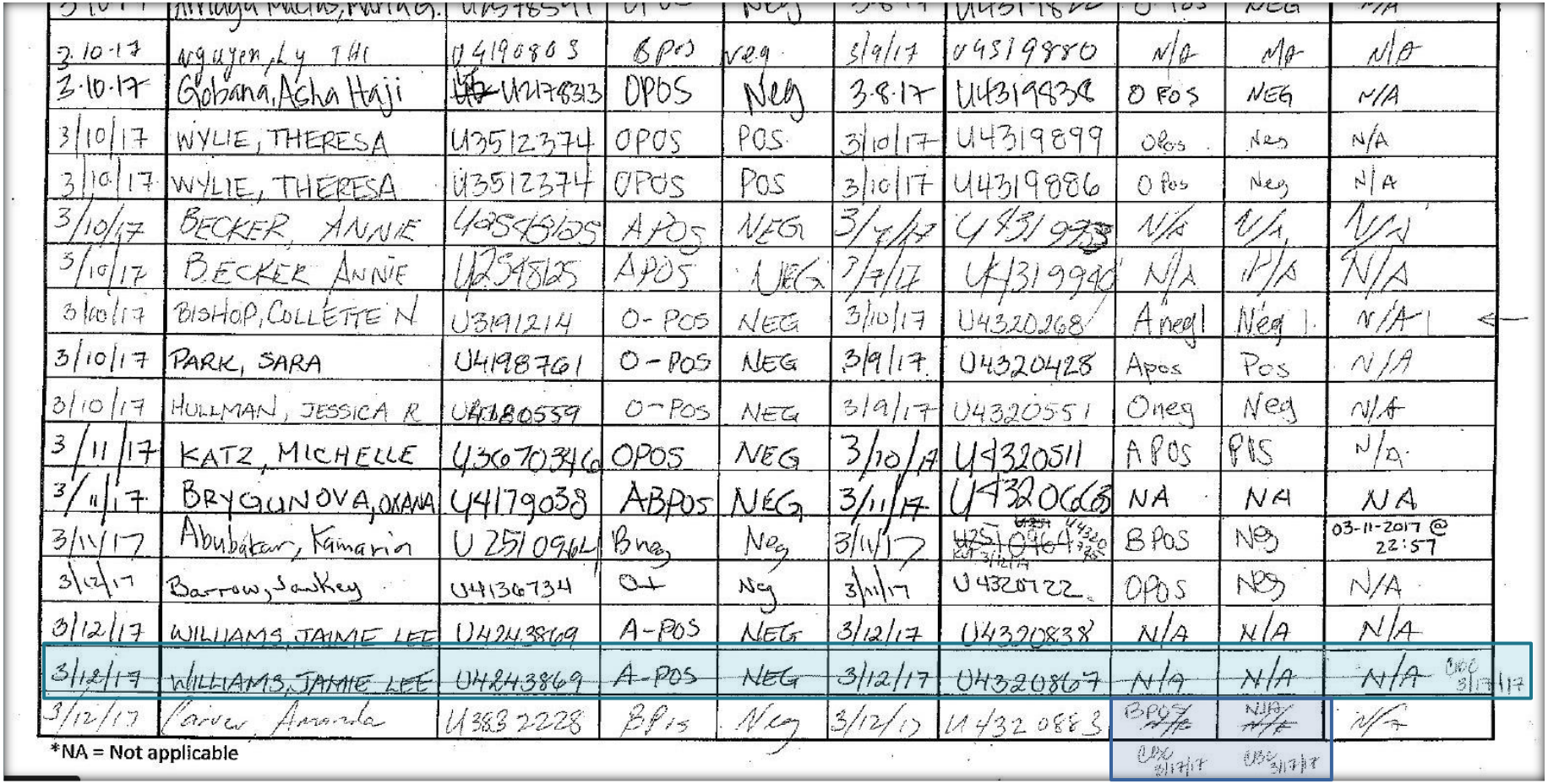


7/24/17	SEID, HIERYA B	U3253981	O-POS	NEG	7/24/17	U4398652	Opos	Neg	N/A
7/25/17	Buckley, Lauren B	U3607502	O Pos	Neg	7/25/17	U4398738	OPos	Neg	NA
7/25/17	Hernandez Reyes, Marina	U2439145	O Pos	Neg	7/25/17	U4398765	OPOS	Neg	NA
7/25/17	STURROCK, CAMMIE	U2528734	O pos	Neg	7/25/17	U4399028	Opos	Neg	
7/25/17	LEE, BETSY MARIE	U4335720	O-POS	NEG	7/25/14	U4399317	Opos	Neg	
7/26/17	HERRERA-MORENO, MARIBEL	U4393930	O Pos	Neg	7-25-17	U4399339	Apos	neg	
7-26-17	Burke, Brianne Michelle	U4299359	ANEG	POS	7-25-17	U4399441	ONEG	NEG	NA
7/26/17	Pultz, Ingrid	U2639306	Opos	Neg	7/26/17	U4399504	O POS	NEG	NA
7/26/17	Mama, Nahili Musxafa	U4261864	APos	Neg	7/25/17	U4399703	NA	NA	NA
7/26/17	Shah, Rima Jagish	U3234018	A Pos	NEG	7/26/17	U4399928	NA	NA	NA
7-27-17	Lemmon, Chelsey Gladine	U3421714	O Pos	Neg	7/27/17	U 4400107	APos	neg	NA
7-27-17	Bennett, Danielle Tuttle	U4297840	APOS	NEG	7-25-17	U4400152	NA	NA	NA
7-27-17	Allero, Tyra Kyle Boiones	U3597123	B Pos	Neg	7-27-17	U4401682	N/A	N/A	N/A
7/28/17	Zuniga Romero, Blanca	U3500168	APOS	Neg	7/26/17	U4401762			
7/28/17	Lester, Beq Gina	U4398422	ONeg	Neg	7/27/17	U4401794			
7/28/17	Bass, Christiana	U4006702	Bpos	neg	7/27/17	U4402047			

*NA = Not applicable

Incorrect Error Correction

The person that made the error did not Tech ID and date the mark through

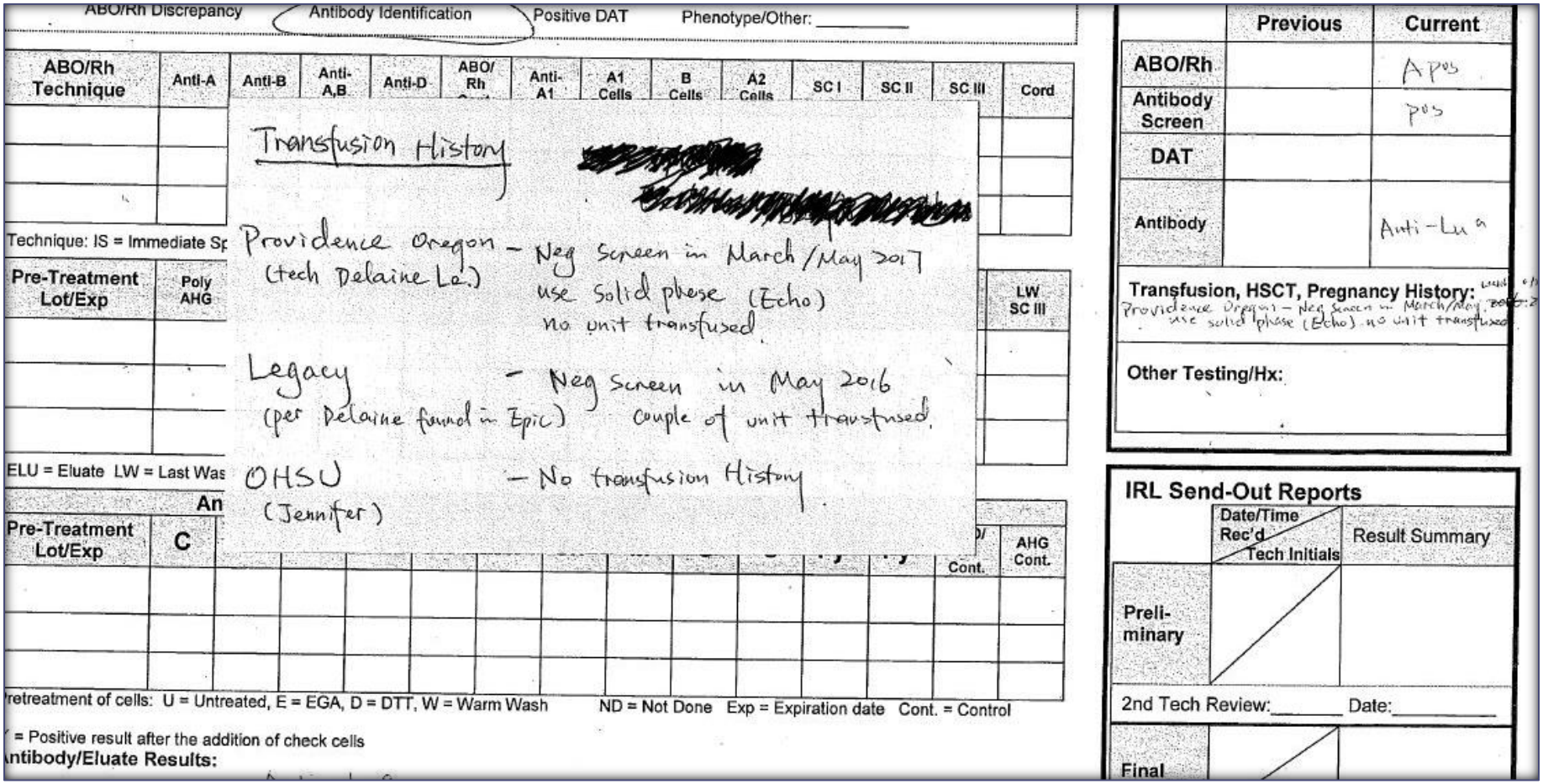


3.10.17	Nguyen, Ly THI	U419080 S	BPos	neg	3/9/17	U4319880	N/A	NA	N/A
3.10.17	Gobana, Acha Haji	~~U~~ U417833	OPOS	Neg	3.8.17	U4319838	O POS	NEG	N/A
3/10/17	WYLIE, THERESA	U35123774	OPOS	POS	3/10/17	U4319899	OPos	Neg	N/A
3/10/17	WYLIE, THERESA	U35123774	OPOS	POS	3/10/17	U4319886	O Pos	Neg	N/A
3/10/17	BECKER, ANNIE	U25498625	APOS	NEG	3/7/17	U4319933	N/A	N/A	N/A
3/10/17	BECKER, ANNIE	U25498625	APOS	NEG	3/7/17	U4319946	N/A	N/A	N/A
3/10/17	BISHOP, COLLETTE N	U3191214	O-POS	NEG	3/10/17	U4320268	A neg	Neg	N/A
3/10/17	PARK, SARA	U4198761	O-POS	NEG	3/9/17	U4320428	Apos	Pos	N/A
3/10/17	HULLMAN, JESSICA R	U4180559	O-POS	NEG	3/9/17	U4320551	Oneg	Neg	N/A
3/11/17	KATZ, MICHELLE	U36703416	OPOS	NEG	3/10/17	U4320511	A POS	POS	N/A
3/11/17	BRYGUNOVA, OKANA	U4179038	ABPOS	NEG	3/11/17	U4320668	NA	NA	NA
3/11/17	Abubakar, Kamaria	U25109641	Bneg	Neg	3/11/17	~~U25109641~~ U4320	B POS	NEG	03-11-2017 @ 22:57
3/12/17	Barrow, JaKey	U41367341	O+	Neg	3/11/17	U4320722	OPOS	NEG	N/A
3/12/17	WILLIAMS, JAIME LEE	U4243869	A-POS	NEG	3/12/17	U4320838	N/A	N/A	N/A
3/12/17	WILLIAMS, JAIME LEE	U4243869	A-POS	NEG	3/12/17	U4320867	N/A	N/A	N/A
3/12/17	Carver, Amanda	U3832228	BPos	Neg	3/12/17	U4320883	BPOS	NEG	N/A

*NA = Not applicable

Examples of Correct Error Correction

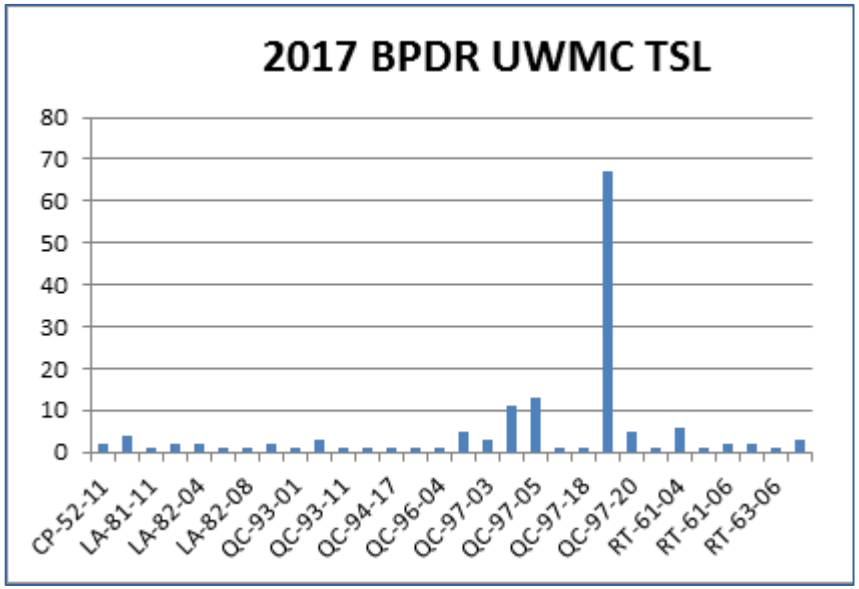
Line through so that the original entry is still visible and Tech ID and Date



Documentation on a Post it Note »

This information is a part of the tech's investigation and needs to be on the Extended Work-up Form. Write it on the back and write "See back" if there isn't enough room

2017 Blood Product Deviation Report for UWMC TSL



NOTE: QC-97 BPDR descriptions begin with "Distribution procedure not performed in accordance with blood bank transfusion service's specifications"

- QC-97-02: Product not irradiated as required (5 incidences)
- QC-97-04 Improper product selected for patient (11 incidences)
- QC-97-05 Improper ABO or Rh type selected for patient (13 incidences)
- QC-97-19 Product not documented or incorrectly documented as issued in the computer (67 incidences)
- QC-97-20 Product not volume reduced as required (5 incidences)
- RT-61-04Testing performed, interpreted, or documented incorrectly for ABO and/or Rh (6 incidences)

Quality is the responsibility of all of us!

- Follow all SOPs
  - They keep you and our patients safe
- Ensure the blood component is not issued to a patient when something goes wrong or the safety, purity, potency or efficacy of a blood component has been compromised
- Notify a lead, manager or quality representative when you suspect a process or procedure is not being followed as written
- Document all deviations and errors

cGMP gives us confidence and the framework that as a team…

…we will provide our patients the most safe and effective blood component possible!