Establishment of an Unrelated Cord Blood Bank Qualification Program a Transplant Center/Cell Therapy Manufacturing Perspective

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Objectives of Presentation

- The importance of a strong cord blood bank qualification program
- Quality versus regulatory qualification criteria
- Retrospective versus Prospective qualification
- Advantages and limitations with the qualification system

Abbreviations/Terminology in This Presentation

Unrelated Umbilical Cord Blood Bank, also synonymous with the frequently used term Public Cord Blood Bank = CBB

Unrelated Umbilical Cord Blood Unit = CBU

Driving Forces of Qualification Program

- May, 2005 US Food and Drug Administration (FDA) regulation of unrelated cord blood manufacture - 21 CFR Part 1271
- October, 2011 FDA regulatory requirement: Cord Blood Bank must have IND or License to manufacture and distribute
- Provides systematic process to evaluate the quality of cord blood banks necessary prior to the need for a CBU arises

Limitations of CBB Qualification

The qualification process is not fool-proof.

Therefore, monitoring of quality indices related to CBUs received and transplanted is critical as a supplement to the vendor qualification process.

Cord Blood Bank Qualification Possibilities

- In person audit
  - Yikes

- Remote audit review of paper-work
- Rely on professional accreditations
- Rely on government licensure or (non-US) government endorsement
- Rely on past CBU experience (quality indices)
- Combination or hybrid of above

Our CBB Vendor Qualification Experience

- Implemented a hybrid approach
- Developed an algorithm to define our process:
  - Retrospective qualification
  - Prospective qualification

Basis of Our Algorithm

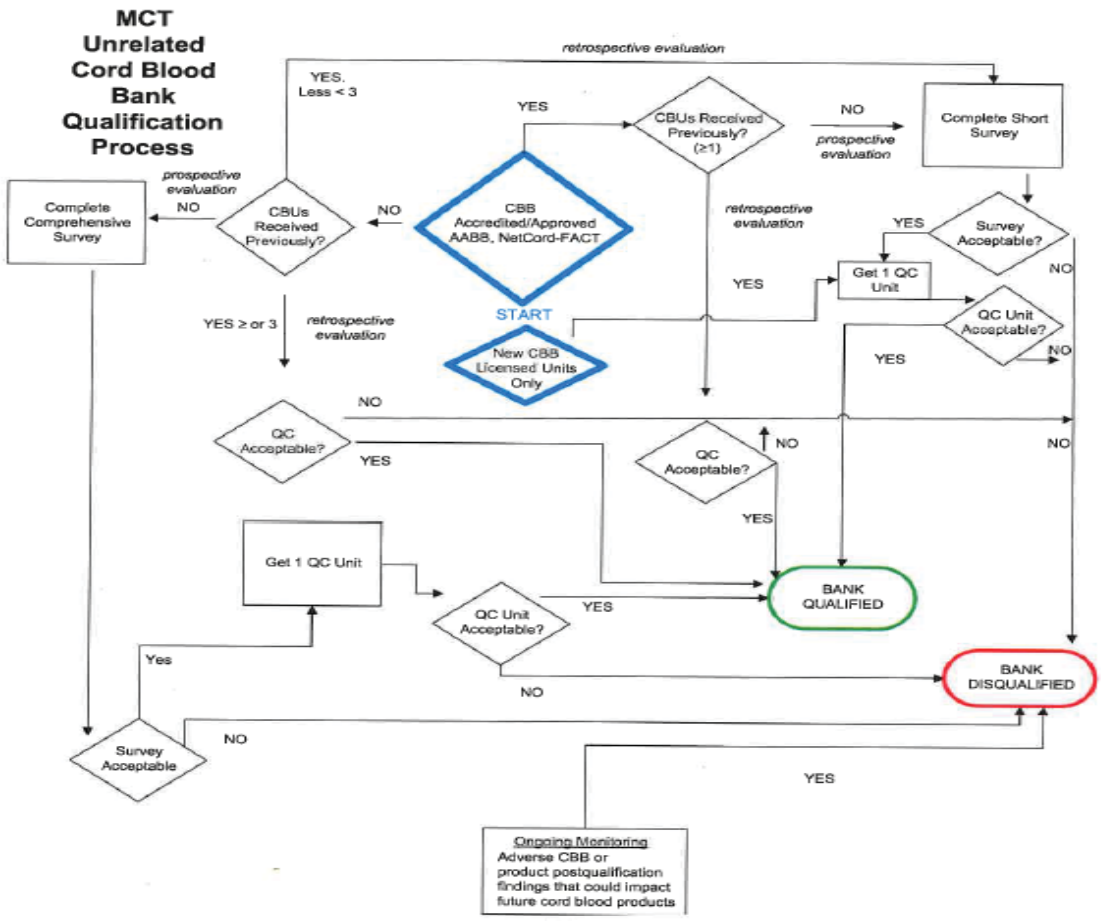
Risk based approach intended to capture the elements that we consider **critical** related to the cord blood bank:

- Ensure FDA requirements, 21 CFR 1271, 210 and 211 are met (US CBBs)
- Ensure adequate approach to donor screening and testing to eliminate/reduce disease transmission risk (US and Non-US CBBs Banks)
- Quality systems in place to ensure consistent quality practices (US and Non-US CBBs)
- Demonstrated product quality (US and Non-US CBBs)

Basis of Our Algorithm

Includes all of the following components

- Review of QC indices from previously received CBUs (retrospective qualification only)
- Review of QC indices from newly ordered CBUs (prospective qualification only)
- Review to ensure US FDA regulatory compliance (US CBB only)
- Review to ensure infectious disease transmission donor screening/testing is performed (Non-US CBB)
- Review of standard QA systems
- Confirming US FDA registered establishment
- Review and of professional accreditation
- FDA 481s and Warning Letters



RETROSPECTIVE QUALIFICATION

Cord Blood Banks that had been used as a source for cord blood for a short period or a number of years before a qualification process was developed, were retrospectively qualified.

Retrospective Qualification Evaluation Tools

Consideration of a Combination of Criteria:

1) FDA Establishment Registration (*FDA Form 3356*): Must be registered
2) The number of CBUs received during period of evaluation: Must have received at least 1
3) Results of historical post-thaw cell count(s): Must meet our internal requirement
4) The professional accreditation status of the Cord Blood Bank: AABB or NetCord-FACT
5) Short survey

Short Survey

The Short Survey is only used in cases where the Cord Blood Bank has accreditation from:

- NetCord Foundation for the Accreditation of Cellular Therapy (NetCord-FACT)

  Or

- AABB

The assumption is that the quality systems have been evaluated by the professional accrediting group; therefore the Short Survey looks at non-quality system criteria

Short Survey Content- Major Components

Quality/Regulatory Administrative

Collection Program

Donor Qualification

Product processing and testing

Retrospective Qualification of the Cord Blood Bank University of Minnesota, MCT Algorithm

Previously Received CBUs from the CBB	QC Result(s)	CBB Accredited?	Short Survey	Comp-rehensive Survey	Qualification Result
1 or 2 CBUs	Failed	STOP	STOP	N/A	**FAILED**
1 or 2 CBUs	Yes-OK	Yes	N/A	N/A	**PASS**
1 or 2 CBUs	Yes-OK	No	N/A	Yes-OK	**PASS**
1 or 2 CBUs	Yes-OK	No	Yes-Failed	N/A	**FAILED**
≥3 CBUs	Failed	STOP	STOP	N/A	**FAILED**
≥3 CBUs	Yes-OK	N/A	N/A	N/A	**PASS**

Retrospective Qualification Results

1172 CBUs were evaluated

- Represented 41 CBB
  - US CBBs = 19 (46%)
  - Non-US CBBs = 22 (54%)
  - The 2 primary US CBB = 26% and 21% of total

7 CBBs were disqualified based on QC results

- US CBBs = 4 (57%)
- Non-US = 3 (43%)

8 CBBs moved to the prospective category

Unique Category

Retrospective qualification found 8 CBBs where we had only received 1 unit.

The 8 CBBs were not accredited.

We chose not to proceed with retrospective qualification (did not ask them to complete short survey)

These CBBs could be prospectively qualified.

Prospective Qualification

New Cord Blood Banks that have never been used by the transplant center/manufacturing facility are qualified prospectively.

Prospection Qualification "Tools"

- FDA Establishment Registration
- Accreditation status (NetCord-FACT or AABB)
- Short or Comprehensive Survey
- CBU requested QC result

Survey Category Comparison

Comprehensive Survey Major Categories

- Quality/Regulatory and Administrative
- Staff
- Equipment
- Collection Program
- Donor Qualification
- Product Processing, Storage and Testing

Short Survey Major Categories

- Quality/Regulatory and Administrative
- Collection Program
- Donor Qualification
- Product Processing, Storage and Testing

Prospective Qualification of the Cord Blood Bank University of Minnesota Algorithm

Received CBUs From the CBB	Accredited	Short Survey	Comp-rehensive Survey	QC Result	CBB Qualification
0	Yes	Yes-OK	N/A	Yes-OK	PASS
0	Yes	Yes-Failed	N/A	STOP	FAILED
0	Yes	Yes-OK	N/A	Yes-Failed	FAILED
0	No	N/A	Yes-OK	Yes-OK	PASS
0	No	N/A	Yes-Failed	STOP	FAILED
0	No	N/A	Yes-OK	Yes-Failed	FAILED
0-licensed	N/A	N/A	N/A	Yes-OK	Pass
0 -licensed	N/A	N/A	N/A	Yes-Failed	FAILED

Prospective Qualification Results

Qualified

3 US CBBs

1 Non-US CBB

Failed

1 CBB did not pass due to poor QC unit results

1 CBB failed due to survey results

Disqualification (after qualification)

A qualified CBB can be disqualified as an approved vendor at any time. Disqualification may be a result of, but not limited to:

- Failure of QC results or engraftment of a CBU
- Removal of accreditation by FACT-NetCord or AABB
- Voluntary or involuntary (FDA initiated) recalls
- FDA (or other government for non-US CBBs) actions such as FDA 483s, warning letters or other actions
- Other quality/regulatory issues associated with the CBB
- Patient adverse events
- Other

Additional Cautions and Considerations

Varied levels of approval:

1-2 banks have passed the approval process but not all subsequent CBUs received were of optimal quality.

- Bank remains on qualified list, but a notation is made that the bank is only utilized if an alternate “better” unit from a different qualified bank can not be sourced.

Challenges Faced in the Process

- Retrospective qualification: The CBBs practices have evolved over time. We may pick a "starting date" for CBUs we will accept.
- Prospective qualification:
  - The CBBs practices have evolved over time
  - Low compliance rate with participation of international centers when requests for survey completion
  - Some CBBs not thrilled with assuming expense of providing and shipping a CBU for testing

Summary

The qualification of unrelated CBBs by the user is an important and necessary process.

A center that has been in operation for some time may use both a retrospective and prospective qualification process.

The prospective qualification process should include the consideration of donor screening and testing, manufacturing and other criteria.

The CBB vendor qualification process should be supplemented by on-going monitoring of CBU quality indices and transplant events and outcomes.

References

Code of federal regulations. Federal Register, Volume 70, No. 100/Wednesday, May 25, 2005. Washington, DC:US Government Printing Office

Rabe F, McKenna DH, Kadidlo DM. Establishment of an unrelated umbilical cord blood bank qualification program: Transfusion.

Questions ????

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