

OPENBIOME

When is a Fecal Transplantation Preparation Ready for Use?

Health Monitoring and Material Release
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Abstract

Stool banking is a complex, multi-step process that includes screening and monitoring donor health as well as manufacturing fecal microbiota transplantation (FMT) preparations from donated stool. To help ensure that FMT preparations meet the stool bank's quality and safety standards, a Quality Department reviews all information associated with an FMT preparation and its donor to verify that it is suitable for patient treatment. This paper outlines and discusses basic quality checks that FMT material should pass before it is released for clinical use.

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Overview of Quality Department

A stool bank's Quality Department is responsible for ensuring that investigational Fecal Microbiota Transplant (FMT) products meet the stool bank's quality and safety standards. This mission comprises three main responsibilities:

- 1. Monitoring donor health in real time.** Stool donors undergo multiple health evaluations, including two bookend clinical assessments that involve a battery of laboratory screens, periodic health checks throughout the donation window, and health checks before each donation. The Quality Department reviews all health data generated from a donor and tracks their eligibility to donate in real time.
- 2. Monitoring FMT product manufacturing in real time.** The manufacture of an FMT unit generates records describing the quality of the stool, the manufacturing process that was followed to process the stool into an FMT preparation, and tracking information. The Quality Department stores and reviews all data generated from manufacturing an FMT unit and tracks the unit's location and status in real time.
- 3. Retrospectively reviewing all information associated with an FMT unit and its donor before making a final decision to release the unit for patient use.** After its manufacture, an FMT preparation is stored in quarantine. To become eligible for release and clinical use, the Quality Department reviews all data related to the FMT preparation's manufacture, quality control testing, and the health of its donor. This data is collected into a unit release packet and a final disposition decision is made.

Each of these three responsibilities will be discussed in further detail in subsequent sections of this white paper.

Personnel

The size and organization of the Quality Department may vary depending on the size and needs of the stool bank. OpenBiome, a large stool bank, has a Quality Department with three teams:

Quality Assurance (QA): This team is responsible for ensuring that all FMT units are manufactured in a way that maintains Safety, Integrity, Strength, Purity and Quality (SISPQ) standards. The QA team oversees the release of units for clinical use, as well as managing procedures and procedure review, investigations, trainings, audits, and supplier qualification processes.

Quality Systems (QS): This team supports QA by keeping track of and organizing physical and digital records as well as overseeing quality management and biobanking software systems.

Quality Control (QC): This team tests FMT material, reviews and approves associated data, and creates certificates of analysis to support release of FMT material. Testing includes evaluating the potency of each FMT lot in terms of viable bacteria per mL and overseeing the stability program to support the expiration date associated with FMT product. Safety testing is done by external laboratories.

The Head of Quality at OpenBiome is accountable to the Executive Director for the direct oversight of these functions. The Head of Quality has the authority to monitor, report, and act on the internal and external status of product, process quality and the Quality Management System.

During the data generation and review process, the Quality Department interacts with several other teams, including:

1. **The Donor Operations Team**, made up of clinical staff and donation coordinators, who evaluate donor health and manage the process of receiving stool donations.
2. **The Biomanufacturing Team**, made up of laboratory technicians who process stool donations into FMT preparations and generate associated paperwork.

Additional Resources

Quality review touches upon many aspects of stool banking that are beyond the scope of this white paper. Although not necessary, it may be useful to refer to the following papers for additional information:

1. [Clinical Consideration for Donor Screening](#)
2. The Logistics of Donor Screening
3. [From Stool Donation to FMT Preparation: The Logistics of FMT Manufacturing](#)
4. [Tracking Patient Outcomes and Adverse Events](#)

Key Takeaway

Quality Assurance is an integral part of a stool bank's Quality and Safety program alongside Donor Assessment, Manufacturing, and Pharmacovigilance (Figure 1). A stool bank's Quality Department should review and organize all data generated from donor health evaluations and FMT manufacturing in real time, and perform a final retrospective data review before releasing units for clinical use.

Monitoring Donor Health

Evaluation of donor health is crucial for preventing the transmission of pathogens or potentially microbiome-mediated health conditions from a stool donor to FMT recipient. This section uses OpenBiome, a large stool bank, as an example of how a Quality Department is involved with monitoring donor health.

At OpenBiome, donors provide stool several times per week during a 60-day donation window. Donor health data is collected at the following time points (Figure 2).

1. Initial donor qualification (Day 0)
 - Before donating stool, donors must complete the first bookend screening made up of an in-depth health questionnaire, an in-person clinical assessment, and a battery of laboratory testing. Less than 3% of prospective donors qualify to donate stool. More information on how donors are screened can be found in the papers titled “Clinical Considerations for Donor Screening” and “The Logistics of Donor Screening.”
2. Ongoing health monitoring during the donation process (Day 1-59)
 - Donors must report any travel or change in health status while they are eligible to donate stool. Changes in health may result in a temporary deferral or permanent exclusion from the stool donor program.
 - Donors undergo periodic, in-person clinical assessments while they are eligible to donate stool.
 - Before each stool donation, donors complete a **short health questionnaire (SHQ)** (Figure 3A)
3. Bookend testing after donation window is complete (Day 60)
 - Donors repeat the complete set of clinical and laboratory assessments they underwent during the initial qualification process. These health evaluations “bookend” the 60-day collection period.
 - FMT preparations manufactured from stool collected within the 60-day donation window are stored in quarantine until a donor passes the second bookend testing (Figure 3A).

Key Takeaway: OpenBiome does not screen every stool donation. Instead, bookend assessments of a donor’s health at the beginning and end of the 60-day donation window as well as additional health checks during that time, are taken as sufficient evidence that intervening donations meet OpenBiome’s quality and safety standards.

As donor health data is generated from the clinical assessments described above, the Quality Assurance Team (QA) reviews records and modifies donor status if needed.

Maintaining donor health records

All donor health data—including in-person clinical assessments and laboratory testing results—are compiled into a **Donor Review Packet** (Figure 2B). The Donor Review Packet is later used during the final unit review process (Figure 3B) to determine whether the donor met OpenBiome’s quality and safety standards throughout their donation window.

Modifying Donor Status

Donors are assigned one of two statuses: ACTIVE (eligible to donate stool) or INACTIVE (ineligible to donate stool). Monitoring donor health and status helps ensure that only eligible donors provide stool that is manufactured into FMT units.

- Clinicians on the **Donor Operations Team**, who perform health assessments, are responsible for changing a donor’s status from ACTIVE to INACTIVE.
- Quality Assurance (QA), who is responsible for reviewing health data, are responsible for changing a donor’s status from INACTIVE to ACTIVE.

Figure 2A and 2B maps out how donor status may change during the donation window

- Day 0: A prospective donor undergoes the first bookend screening
 - If the donor passes, QA enters the donor as ACTIVE in the donor database.
 - If the donor fails the screening, they are permanently excluded from the stool banking program.
 - A donor with a temporary health condition (such as a transient illness or travel to a country with a high prevalence of infectious disease) may be deferred and rescreened at a later time.
- Day 1-59: A donor undergoes periodic health checks and completes a **short health questionnaire (SHQ)** before each donation.
 - If the donor passes, QA maintains the donor status as ACTIVE
 - If the donor fails, the Clinical Team changes the donor status to INACTIVE and the donor is removed from the stool banking program.
 - A donor may also be deferred if they have a temporary health condition. The Clinical Team changes the donor status to INACTIVE.
 - After an appropriate time, the donor repeats the health check. They may either pass and be reactivated by QA, fail and be removed from the program, or be deferred again.

- Day 60: Donor completes second bookend testing
 - If the donor passes, QA maintains the donor status as ACTIVE
 - If the donor fails, the Clinical Team changes the donor status to INACTIVE and the donor is removed from the stool banking program.
 - A donor may also be deferred if they have a temporary health condition. The Clinical Team changes the donor status to INACTIVE.
 - After an appropriate time, the donor repeats the bookend testing. They may either pass and be reactivated by QA, fail and be removed from the program, or be deferred again.
 - In practice, the second bookend screen typically occurs between Day 30 and Day 60 to account for donor scheduling constraints.

Summary: Clinical staff from the Donor Operations Team and Quality Assurance work together to collect, review, and monitor donor health data and update donor status in real time.

Key Documents

- **Short Health Questionnaire (SHQ)**
 - A list of health-related questions that donors complete before they provide stool
 - Description of the SHQ is provided in [Appendix 1](#)
- **Donor Review Packet**
 - A compilation of all donor health data not including the SHQ.
 - Includes clinical assessments and laboratory screens from bookend testing as well as donor health data from periodic health checks between bookends.
 - Any comments from clinicians are included in the donor review packet.

Monitoring Manufacturing

During the manufacturing process, Quality Assurance (QA) and the Biomanufacturing team work together to generate and collect data describing the manufacture of an FMT unit and its status. This section uses OpenBiome, a large stool bank, as an example of how a Quality Department is involved with monitoring manufacturing.

Figure 3A maps out information generated during the manufacturing process.

1. Before providing stool, the donor completes a **Short Health Questionnaire (SHQ)**. Donor stool is weighed, assessed using the Bristol stool scale, and visually inspected for signs of pathology. Results of this analysis are recorded in the **Stool Donation Form**.

- a. If the donor or donated stool fail the premanufacturing assessments described above, the stool is destroyed. If both the donor and donated stool pass the premanufacturing assessments, the Biomanufacturing team begins the manufacturing process.
 - b. QA collects the SHQ from the Donor Operations team and the stool donation form from the Biomanufacturing team.
2. During the manufacturing process, the Biomanufacturing team processes the stool into an FMT preparation based on instructions or **Batch Record** provided by QA.
 - a. After manufacturing, QA collects the **Batch Record** back from the Biomanufacturing team, which has signed and dated the paperwork indicating that the manufacturing process was completed as instructed.
3. During the manufacturing process, safety aliquots are retained by the Biomanufacturing team to be stored in case they are needed for retrospective testing, and samples of FMT material are taken by the Quality Control (QC) team for potency analysis.
 - a. OpenBiome performs potency testing by counting the number of viable bacteria per mL of FMT material. Potency testing results are recorded in **Certificates of Analysis (CoA)**.
4. After manufacturing, FMT preparations are placed in a quarantine freezer separate from units that have been reviewed by QA and set for release.
 - a. The Biomanufacturing team and QA give each FMT unit and associated safety aliquots unique identifiers and barcodes for tracking purposes.
 - b. The location and status of each FMT unit is recorded by QA using an appropriate electronic database system.

Summary: During the manufacturing process, QA, QC, Donor Operations, and the Biomanufacturing team work together to record information describing the donor's health status at the time of their donation, the quality of the donated stool, and the processing of stool into FMT preparations. Newly manufactured FMT units are stored in quarantine and tracked with a unique identifier in a database.

Key Documents

- **Short Health Questionnaire (SHQ)**
 - List of health-related questions, donors complete before they provide stool
 - Description of the SHQ is provided in [Appendix 1](#)
- **Stool Donation Form**

- Record of weight of stool donation, Bristol stool scale score, and results of visual inspection for pathology
- **Batch Record**
 - Instructions for manufacturing an FMT preparation. This document is prepared by QA, given to the Biomanufacturing team, and returned with dates and signatures to QA after manufacturing is complete.
- **Certificate of Analysis**
 - Paperwork documenting the result of potency testing in the form of number of viable bacteria per FMT preparation dose.

Unit Release

Overview: After its manufacture, each FMT unit is stored in quarantine and undergoes a Quality review. During this review an FMT unit may have one of six statuses:

In the best-case scenario, units go through three statuses after their manufacture: Quarantine, Released, and Shipped.

1. **Quarantine:** After its manufacture, a unit is isolated physically or by other effective means pending a decision on its subsequent approval or rejections. Unit may not be used until it is reviewed and released by QA.
2. **Released:** After review, QA determines that unit meets acceptance criteria specifications and cGMP requirements. Unit is ready to be shipped to hospitals for clinical use.
3. **Shipped:** Unit has been shipped to a healthcare facility for clinical use and is no longer in the stool bank's inventory.

In some cases, FMT material may have manufacturing- or safety- related concerns that require more investigation. Such units are placed on hold and, depending on the results of the investigation, may go through a destruction process or be released.

4. **Hold:** Unit has a condition barring release (such as a deviations in manufacturing process or an irregular test result) that requires further investigation. Units on hold are held until the condition has been resolved.
5. **Pending Destruction:** Unit has met criteria that makes it un-releasable.
6. **Destroyed:** Unit has been removed from inventory and physically destroyed.

Units in quarantine or hold are stored in separate freezers from units that are released. When a unit changes status to set for release, QA oversees the transfer of the FMT preparation between freezers.

Logistics of Unit Release: The unit release process begins after the stool donor completes their second bookend screening. Working together, Donor Operations and QA compile the totality of a donor's health data into the **Donor Review Packet** (Figure 3B). This section uses OpenBiome, a large stool bank, as an example of how a Quality Department is involved with unit release.

During the unit release process, QA follows the steps listed below to review all data associated with an FMT unit and its donor to make a final disposition decision (Figure 3B)

1. Determine stool collection window
 - The stool collection window is defined by bookend testing. To be eligible for release, FMT units must have been produced within the 60-day donation window bookended by clinical assessments and laboratory testing.
 - The stool collection window calculation also accounts for extended seroconversion time.
 - Individuals exposed to pathogens (such as HIV), may not test positive until days or weeks after their initial infection.
 - Of the pathogens tested, HIV has the longest seroconversion time (21 days). To account for this extended seroconversion time, FMT preparations produced from stool donated less than 21 days before the final bookend blood draw remain in quarantine and are only released if the donor passes another bookend assessment at the end of the next 60-day collection window.
2. Generate list of units within stool collection window
 - Once a stool collection window is determined, QA uses appropriate database systems to identify all FMT units derived from the donor within the collection window
3. Review documentation associated with each FMT unit including:
 - Donor Review Packet (Compilation of all donor health data from bookend health assessments and periodic health checks during 60-day donation window)
 - Batch Record
 - Certificate of Analysis, stool donation form, and short health questionnaire (which are included as an attachment to the Batch Record)

During the review process, QA verifies that:

- No donor health data was overwritten or altered
 - The clinical team has signed off on donor health information and that clinical recommendations are consistent with screening results and any new health information
 - The Donor Review Packet is the next consecutive stool collection window to be released.
 - Units are released chronologically from earliest to latest manufacturing date as health or safety concerns in an earlier stool collection window may affect material in subsequent windows.
4. Compile associated documentation into a unit release packet
- All documentation regarding the FMT units is compiled together in a **Unit Release Packet** for record keeping.
5. Make a final disposition decision
- QA makes a final decision on whether to release the units. This decision is recorded in a **Quality Assurance Unit Disposition Form**, which is included in the unit release packet.

Once units are released, QA communicates the decision to the rest of the organization, updates the status of units to “Released” in the database, and witnesses the movement of the units from the quarantine freezer to release freezer.

Placing units on hold: If Quality finds abnormalities in the donor or FMT unit records—such as potentially abnormal laboratory test results, donor screening windows that are too wide (exceed 60 days), deviation in the manufacturing process, or other concerns—the unit is placed on hold.

Holds can be placed on units that were previously in quarantine (Hold, previously quarantined) or had been released (Hold, previously released) before the condition was discovered. As an example, after receiving reports of a safety event potentially related to FMT material, a stool bank may place all released units from the donor associated with the event on hold.

Holds are resolved through investigations into abnormalities identified by the Quality team. More complex investigations may require convening a **Material Review Board**, comprising members of the Quality, Manufacturing, Pharmacovigilance, and Clinical teams, to discuss the disposition.

Depending on the conclusion of the investigation, units in question will either be destroyed or released. Units undergoing destruction will have their units changed to “pending destruction” and “destroyed”. A memo detailing the decision-making process of the Material Review Board is added to the **Unit Release Packet**.

Summary: During the Unit Release process, QA reviews and compiles all data associated with FMT units and donors, including the final disposition decision, into a **Unit Release Packet**. Potential abnormalities with the data are resolved with an investigation that may require convening a **Material Review Board**.

Key Documents and Groups

- **Unit Release Packet**
 - Record compiling all data associated with FMT units and associated donors analyzed during the unit release process as well as paperwork documenting decision making processes. Unit release packet includes the Quality Assurance Unit Disposition Form and any memos resulting from Material Review Board meetings.
- **Quality Assurance Unit Disposition Form**
 - A form and checklist that QA completes to ensure that they have followed the unit release protocol and documented the disposition decision for the release window.
- **Material Review Board**
 - Group comprising members of the Clinical and Quality Assurance team that meet to discuss and resolve potential irregularities uncovered during the unit release process.

Figure 1

Overview of OpenBiome's Quality and Safety Program including its Quality Assurance process

Donor Assessment	Manufacturing	Quality Assurance	Pharmacovigilance
<p>Clinical Assessment Prospective candidates undergo clinical evaluation that includes medical histories, behavioral risks, and current health status</p> <p>Laboratory Screening Prospective candidates are screened through a clinical examination and a panel of 30+ stool, nasal, and serological tests. Less than 3% qualify to become donors.</p>	<p>Standardized Stool Examinations Lab technicians evaluate every stool sample based on Bristol type and stool pathology</p> <p>Processing Controls All stool processing occurs under a Class II biosafety cabinet that is UV-sterilized and cleaned with a sporicidal agent. All equipment is sterilized and/or disposable.</p> <p>Storage and Shipping Controls All samples are stored in a glycerol buffer at -80°C, sealed with tamper-evident bands, and transported on dry ice with temperature verification.</p>	<p>Continuous Donor Requalification Donors are under medical monitoring throughout the entire donation window and fully rescreened every 60 days.</p> <p>Quarantine Procedure Prior to release, donated material is quarantined for 60 days in between two full panel screens.</p> <p>Safety Aliquots Multiple samples of all material are preserved for a minimum of 24 months, enabling retesting as needed.</p>	<p>Material Tracking Clinical partners complete Material Tracking Logs to evaluate unit-specific inventory regularly, enabling response coordination, and proactive system-wide recalls if necessary.</p> <p>Efficacy Monitoring Partners complete FMT Follow-Up Forms for each patient treated with OpenBiome material, reporting de-identified patient outcome data.</p> <p>Adverse Event Reporting All adverse events are reported to OpenBiome and evaluated using a standardized consensus-based decision-making algorithm.</p>

Figure 2

A stool bank's Quality Department monitors donor health and updates donor status in real time throughout the donation window.

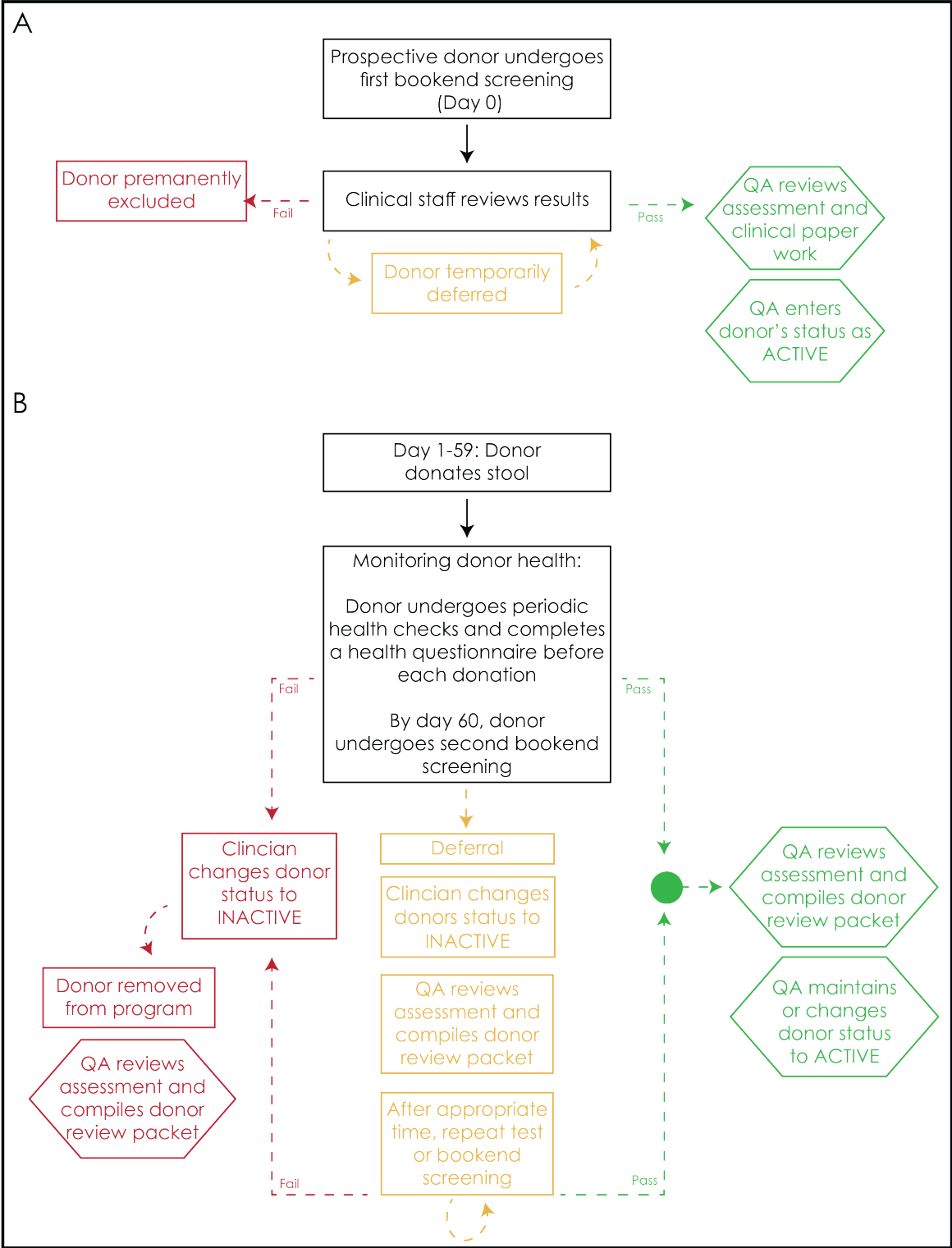
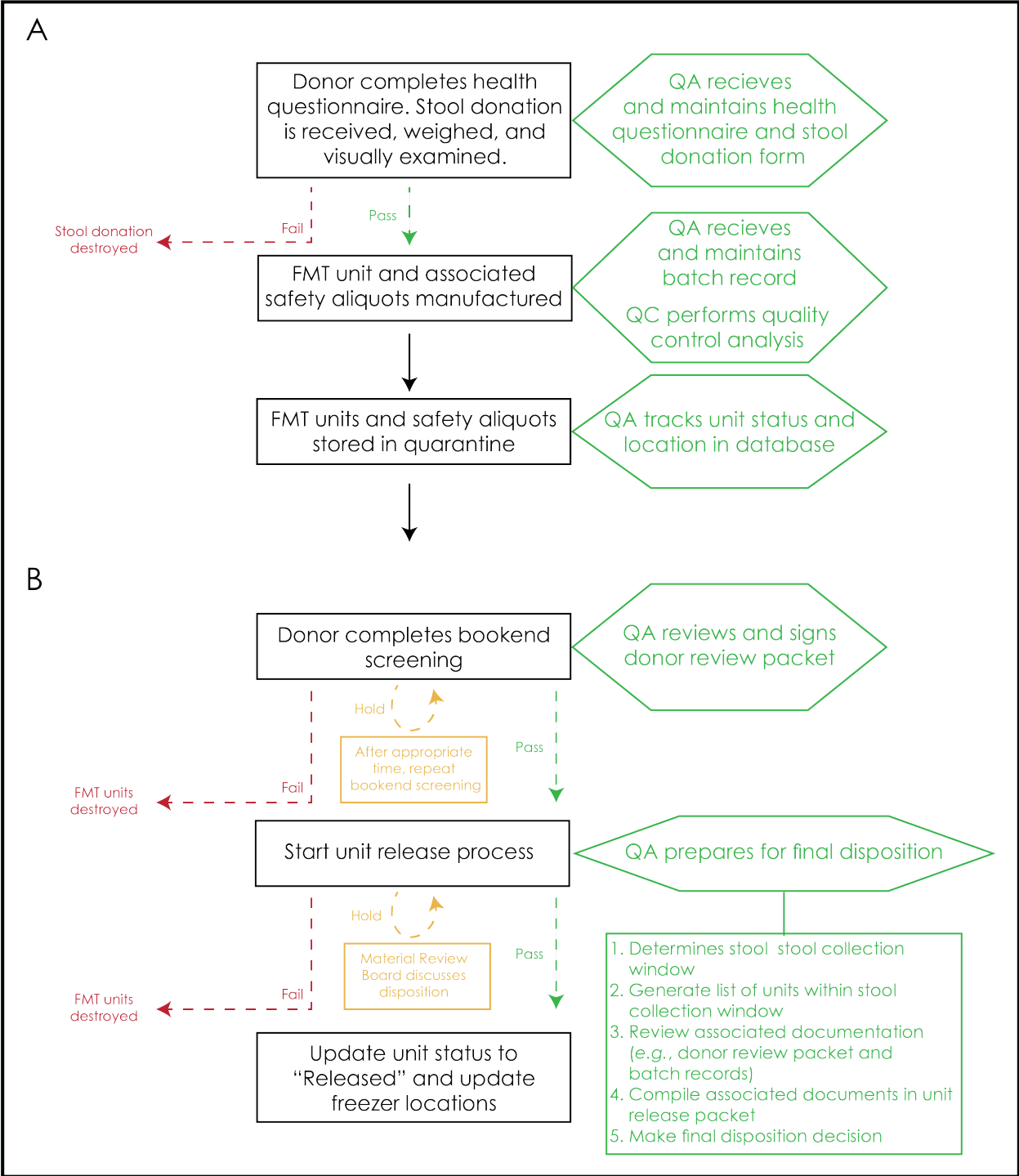


Figure 3

A stool bank's Quality Department monitors the manufacturing process (A) and begins the unit release process after the donor completes their second bookend screening (B).



Appendix 1

Description of OpenBiome Short Health Questionnaire (SHQ) that is completed by donors before each stool donation.

The SHQ aims to capture any changes in donor health or exposures that could impact the potential for new infectious or non-infectious disease risk factors. The SHQ covers;

- Recent sickness
- Changes in diet
- Changes in bowel consistency or frequency
- Travel
- Medical visits
- Antibiotic, antifungal or antiviral exposure
- Other new medications or over the counter supplements
- Other risk factors for multi-drug (e.g. hospital admission, medical tourism)
- Contacts or symptoms of SARS-CoV-2 (e.g. fever, cough, shortness of breath)

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