Meeting Report

First meeting of the working group convened for the NIAID-funded grant:

Microbiota Transplantation: Recommendations for a Regulatory Framework

December 3-4, 2015

Investigators

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- Dr. Frank Palumbo, Center on Drugs and Public Policy, University of Maryland School of Pharmacy
- Dr. Jacques Ravel, Institute for Genome Sciences, University of Maryland School of Medicine
- Dr. Mary-Claire Roghmann, Department of Epidemiology and Public Health, University of Maryland School of Medicine
- Dr. Erik von Rosenvinge, Division of Gastroenterology, University of Maryland School of Medicine and Veterans Affairs Maryland Health Care System
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Background

In June 2015, Diane Hoffmann and co-investigators from the University of Maryland Baltimore were awarded a grant from the National Institute for Allergy and Infectious Diseases (NIAID) to study the legal and regulatory aspects of a cutting edge medical treatment called microbiota transplantation (MT). The two-year grant is facilitating a project to study regulatory options for fecal microbiota transplantation and other emerging MT options including vaginal, skin, anterior nares, oral, and whole body microbiome transplants.

Advances in DNA sequencing technologies have created the field of metagenomics that allows analysis of genetic material harvested directly from microbial communities. Human Microbiome Project (HMP) scientists are using metagenomics and genetic analyses of available reference microbial strains to understand the complexity of human-associated microbial communities and how the microbiome and human host interact to support health or to trigger disease. One of the most significant outgrowths of the HMP is advanced research into probiotics - or live microorganisms which when administered in adequate amounts confer a health benefit on the host. In addition to the development of probiotic therapies, advances in our understanding of the human microbiome are also likely to make MT –transplantation of communities of microorganisms from one individual to another – increasingly common. At present, there is much interest and increasing evidence-based support for one type of MT: fecal microbiota transplantation (FMT). FMT involves the transplantation of fecal material obtained from a
healthy individual into the gastrointestinal tract of a patient recipient to treat disease. Interest in FMT is growing as strong evidence is emerging that FMT is highly effective in treating Clostridium difficile infection (CDI) and may also be effective in treating other conditions.

Although FMT is the focus of much attention, emerging microbiota transplantation options include vaginal, skin, oral, and anterior nares transplantations. Use of these other microbiota transplantation options is still in its infancy and there has been little, if any, discussion in the literature as to their appropriate regulation.

The Project

Under the grant, the co-investigators established a working group of approximately 30 expert stakeholders including scientists, clinicians, patient and professional association advocates, bioethicists, academics, lawyers, and individuals from the biotechnology industries who have an interest in microbiota transplantation or expertise relevant to the project. In addition, representatives of FDA and NIH are participating as observers. The full working group list is attached as Appendix A.

In their proposal, the researchers stated that the working group members will meet three times over the course of the two-year grant period to study how microbiota transplantation should be regulated by considering how other related types of products and procedures are regulated in the US. Regulatory frameworks that may be appropriate in whole or in part for microbiota transplantation include the regulatory frameworks for biological products, blood and blood products, vascularized organs, human cells, tissues and cellular products.

The working group is to evaluate whether each potential regulatory framework for MT meets the following specific criteria of an effective regulatory scheme: 1) ensures the safety of the substance/procedure; 2) ensures the effectiveness of the substance/procedure; 3) provides reliable information to recipients about the safety and effectiveness of the substance/procedure; 4) ensures that patients who need them have appropriate access to the substance/procedure; 5) ensures that the regulations do not unnecessarily discourage research on microbial transplants; and 6) supports public health objectives relating to MT, including its potential to mitigate hospital acquired-infection and to discourage unsafe home use of microbiota transplantation. The working group will also consider whether a hybrid or new regulatory scheme is best to ensure the safety, effectiveness, and accessibility of the procedures. As a follow-up to the meetings, the co-investigators will prepare a paper or series of papers with the help of participants that contain regulatory policy options and the pros and cons of each.

The Working Group met for the first time on December 3-4, 2015 at the University of Maryland Carey School of Law. The agenda for the first meeting is attached as Appendix B. The meeting was designed to provide a snapshot of the current science and clinical use of all forms of MT from a research and clinical perspective and, then, discuss three potential frameworks for regulation of FMT, specifically the frameworks for: 1) biological products (as FMT is currently regulated); 2) human cells, tissues and cellular and tissue-based products; and 3) blood and blood transfusion.
The First Meeting

Introductory Discussion of the Human Microbiome and Specific Microbiome Areas

The meeting started with an overview of the Human Microbiome Project (HMP) provided by Dr. Clifford McDonald, Senior Adviser for Science and Integrity in the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention (CDC). Dr. McDonald explained that there are $10^{14}$ bacteria in the gut alone, which is about ten times the number of cells in the human body. Adding to the complexity of the bacterial communities that live in different sites on the same human body, there are vast differences in the composition and structure of the microbiota from person to person. Humans and their microbial communities have evolved over millions of years and the human microbiome is thought to be critical for immune system maturation and homeostasis, bile acid metabolism (affecting lipid metabolism, fat-soluble vitamins, and intestinal barrier function), regulation of hepatic metabolizing enzymes, important endocrine functions, defense against infections, and immune stimulation among other things.

In his talk, Dr. McDonald noted that there has been an exponential growth in microbiome science over the last 10 years, with new science linking imbalances in the microbiome with disease causation. Growth in microbiome science is in large part the result of major public funding initiatives, most notably NIH’s HMP and the European Union’s MetaHit project, and now, although microbiome biotechnology is still in early phases, there is increasing research and development investment by the pharmaceutical, biotechnology, and food industries in this area. In turn, public interest in the promise of microbiome science is growing, as seen by the dramatic growth of the pre- and probiotics industry.

A new generation of DNA sequencing technologies is now allowing for characterization of bacterial communities that contain unculturable organisms. 16S rRNA gene amplicon sequencing can determine which bacteria are present at a site or in a sample, metagenomic sequencing can provide insights into the metabolic pathways present in microbial communities, and metatranscriptomics can determine which of these pathways are active under specific conditions and what the bacteria are actually doing. However, Dr. McDonald noted the computational analysis necessary for biological interpretation of this incredible amount of data is an ongoing and complex challenge.

As a CDC scientist, Dr. McDonald described his study of the role of the microbiome in infection control for multidrug-resistant bacteria. Colonization by multidrug-resistant bacteria takes place at body sites normally inhabited by a complex and diverse human microbiota. The key premise of research in this area is that the intact human microbiome is a primary host defense for preventing colonization, dominance, and infection with pathobionts (organisms potentially pathogenic, which under normal conditions act as symbionts). The CDC is developing Microbiome Disruption Indices that monitor patients before, during, and after antibiotic therapy as well as creating an alert when disruption reaches a critical level or if colonization or dominance is detected. Microbiome restoration can take place via “rebiosis” or competitive exclusion and controls of pathobionts, a process used successfully in the poultry industry since
the 1970s. Dr. McDonald asserted that rebiosis will be a major priority in human health maintenance and treatment of disease in the future.

Dr. McDonald’s introductory talk was followed by specific MT overviews as follows:

- Gastrointestinal Tract (Dr. Alexander Khoruts, Department of Gastroenterology, University of Minnesota)
- Vaginal Tract (Dr. Richard Cone, Thomas C. Jenkins Department of Biophysics, Johns Hopkins University)
- Skin (Dr. Elizabeth Grice, Penn Institute for Immunology, Perelman School of Medicine, University of Pennsylvania)
- Oral Cavity (Dr. Floyd Dewhirst, Department of Microbiology, Forsyth Institute and Harvard School of Dentistry)
- Nares (Dr. Katherine Lemon, Department of Microbiology, Forsyth Institute and Harvard Medical School)

All of the speakers were asked to address the following information with regard to their focus area: a description of microbiota communities that reside in that area; what diseases might be caused by abnormal microbiota; current treatment for those conditions; what conditions or diseases might be treated by microbiota transplant; the status and gaps in research about microbiota transplantation; and any risk, safety concerns, or adverse events that have or may be associated with microbiota transplantation in their focus area.

Dr. Khoruts described how FMT is used in the treatment of CDI. Current research indicates that FMT results in restoration of gut microbial diversity in CDI patients and elimination of *C. difficile* infection. How this cures CDI, i.e. the mechanism of action, is not yet fully understood but scientists believe FMT may act through effects on bile acids, short chain fatty acids, the innate and adaptive immune system, and by blocking the following essential functions of *C. difficile*:

- Sporulation
- Spore germination
- Vegetative growth
- Adhesion to epithelial cells
- Toxin production

Dr. Khoruts noted that using **FMT to treat CDI** is going after the “low-hanging fruit.” According to a 2013 meta-analysis of FMT research studies, eleven studies with a total of 273 CDI patients treated with FMT were identified; two-hundred and forty-five out of 273 patients experienced clinical resolution. The authors of the meta-analysis concluded that “FMT holds

1 The presentations by the speakers are available at this link http://www.law.umaryland.edu/programs/health/events/microbiota/.
considerable promise as a therapy for recurrent CDI . . .”
What is less clear is the role FMT might play to treat other conditions caused by dysbiosis, or microbial imbalance, particularly dysbiosis relating to antibiotic usage. Dr. Khoruts described mouse studies done in the 1970s that show that the guts of healthy mice can resist colonization by pathogens (e.g., *E. coli*). Antibiotics can lower colonization resistance by eliminating key elements of the microbiota and weakening the microbial network. Further, Dr. Khoruts described how overuse of antibiotics in the last half-century has dramatically reduced the numbers of bacteria in the human microbiome. Mouse and human studies have shown that recolonization with anaerobic microflora can restore both microbial balance and colonization resistance. As such, Dr. Khoruts described the need to conduct research regarding the value of FMT beyond the narrow CDI context, claiming like Dr. McDonald, that microbiota transplantation has a strong role in reversing the damage of antibiotic overuse.

In terms of the FMT procedure itself, Khoruts described the main challenges as determining what bacteria are required for a successful transplant, how to best conduct donor selection, how to best prepare the recipient for the transplant, and what is the most appropriate timing for the procedure.

Dr. Cone, of Johns Hopkins University, discussed the vaginal microbiome and potential for vaginal microbiota transplants. According to Dr. Cone, ‘normal’ vaginal microbiota is dominated by *Lactobacillus* bacteria. However, only 38% of women have *Lactobacillus*-dominated vaginal microbiota, while 33% are classified as having an “intermediate” level of *Lactobacillus* bacteria, and 29% as having microbiota that is low in *Lactobacillus* and high in other types of bacteria that are less protective of vaginal health. Women in this latter group are considered as having bacterial vaginosis (BV), although not all of them are symptomatic. Nonetheless, women with lower levels of *Lactobacillus* are at higher risk for sexually transmitted infections, including HIV, and at higher risk for urinary tract infections, miscarriage, preterm birth and endometriosis, among other things. Cone noted that commensal bacteria, primarily certain *Lactobacillus* species present in the vaginal tract, play an important role in protecting against BV-associated bacteria. Disruption of the *Lactobacillus*-dominated vaginal microbiota often leads to overgrowth of disease-causing microbes that are associated with BV and its related risks. Studies suggest that a healthy vaginal microbial ecosystem may play a critical role in reducing the risk of urogenital infections and dysbioses. One laboratory has developed a *Lactobacillus crispatus* probiotic product that adheres to vaginal epithelial cells and antagonizes bacteria associated with BV and uropathogenic *E. coli*, which is responsible for most UTIs. Though this bacterial product is considered a probiotic not a microbial transplant (see discussion infra), Dr. Cone’s talk highlighted the potential that understanding and manipulating the microbiome of the vagina has in improving women’s urogenital health.

Dr. Elizabeth Grice of the University of Pennsylvania described the microbiome of the skin. The topography of the skin is highly varied with hair follicles, sebaceous (oil) glands, sweat glands, folds, and varied thickness and hair/gland density. The multiple different skin sites of a single person have their own site-specific microbiomes and these are highly variable across the population. The skin also supports other organisms that have their own microbiomes. These arachnids – or small mites – live on the skin of humans and feed on sebum and dead skin cells.

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3 *Id.*
Little research has been done on the skin microbiome beyond identification of site-specific bacterial colonies, but early research is focusing on studying the microbial communities present on skin with such conditions as atopic dermatitis (AD), acne and psoriasis. One clinical research study noted by Dr. Grice has shown that AD skin is deficient in *S. epidermidis* strains that naturally inhibit *S. aureus*. The study, currently underway, will transplant *S. epidermidis* strains to AD skin to evaluate its ability to decrease *S. aureus* abundance on lesional skin and assess reduction in severity of AD. The treatment will be applied via an external cream and would likely be considered a probiotic.

Given the paucity of research in this area, Dr. Grice noted many gaps in current research on transplantation of the skin microbiome including the need to identify the beneficial microbes on the skin; understanding the mechanisms of colonization resistance on the skin; knowing the best way to transplant skin microbiota (i.e. topical application, cream, spray); learning how long a transplant persists; and developing techniques to differentiate dead versus live and transient versus resident microbiota. Dr. Grice also identified risks that need to be studied including the risk of infection, especially with broken skin; determining what level of bacterial burden is acceptable on the skin; and how to manage inadvertent microbial transfer, especially if transplant is on a hand, for example.

Dr. Grice discussed two types of products that may or may not be considered microbiome transplants. The first was a product made of bacteria called Nitrosomonas, which are gram-negative bacteria that oxidize ammonia and urea to produce nitrite and nitric oxide. These bacteria are becoming rare on the skin in Westernized countries, but are abundant on the skin of people with traditional lifestyles (such as aborigines in the rain forest). The product is called AO+ Mist or Mother Dirt and sold as a cosmetic at the moment. However, therapeutic studies with the product are underway for the treatment of acne, rosacea, eczema, diabetic foot ulcers, and even bacterial vaginosis. A second type of product is a “biocellulose” cosmetic skin mask that claims to use acetic acid bacteria to improve skin tone and quality. These products raise questions about how we should define “microbiota transplant”, how it might differ from traditional drugs or other regulated products, and if specific evidence of safety or effectiveness should be required for that designation.

Dr. Floyd Dewhirst of the Forsyth Institute in Cambridge, MA, discussed his current work developing the Human Microbiome Oral Database, a resource designed to provide the scientific community with comprehensive information about the [microbial community in the oral cavity](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5605338/). Like the skin, the oral cavity is divided into zones – each with its own community of microbiota. The oral microbiota are thought to be associated with the following diseases of the oral cavity: caries (tooth decay); periodontal disease (gum disease); alveolar osteitis (dry socket); otitis media (middle ear infection); tonsillitis; and strep throat, as well as “distant” non-oral diseases including bacterial endocarditis; brain, liver, lung, and bone abscesses; cardiovascular disease; stroke; preterm birth; and low birth weight.

Oral microbiome transplants are only at the early theoretical stage. Researchers are attempting to understand the resiliency in the various oral microbiomes and the dysbioses that occur in oral diseases. Understanding how these alterations occur and how they might be resolved is a first step to possible use of MT in the oral cavity in the future. Dr. Dewhirst noted that future
Therapies for oral diseases will attempt to modify existing microbiomes by targeting specific key pathogens for elimination or adding selected species to push microbiome composition in a desired direction. For example, in the case of periodontitis, researchers may consider targeted elimination of the keystone species *P. gingivalis* and, in the case of caries, they may look at targeted elimination of *S. mutans* with the goal of “normal” plaque restoration, in essence a process similar to what is performed for the elimination of *C. difficile* in the GI tract.

Dr. Katherine Lemon, also at the Forsyth Institute with Dr. Dewhirst, focuses her research on the microbiomes of the nares or nasal passages. Microbes live throughout the human nasal and sinus passages including in the nostrils (anterior nares), nasopharynx, oropharynx, and laryngopharynx. Two key pathobionts colonize the human nose: *Staphylococcus aureus* which colonizes the nostrils of ~25% of the U.S. population and *Streptococcus pneumoniae* which colonizes the nose of ≥40% of children ages 6 months to 7 years. These pathobionts invade and reside in a microbiota with commensal bacteria. For purposes of disease control the issue is whether other members of the microbiota community in the nares keep these pathobionts out or under control.

Dr. Lemon stated that twin studies demonstrate that nasal microbiota are environmentally, not genetically, determined. This makes the nares amenable to microbiota-targeted therapy. Potential areas for future microbiota-targeted therapeutics include chronic rhinosinusitis (CRS), recurrent otitis media, asthma, and recurrent *S. aureus* infection. In the case of patients with CRS, researchers have found reduced bacterial diversity and sinonasal microbiome dysbiosis and nasal microbiome community collapse (i.e., rapid decline in the diversity of bacterial species). Current treatments for CRS includes antibiotics, immunomodulation via corticosteroids, antihistamines, and/or endoscopic surgery. Dr. Lemon stated that CRS might be a particularly good disease candidate for microbial therapy as none of the existing therapies are highly effective. However, Dr. Lemon noted that much research needs to be done in the area of nares microbiota, including whether microbiome changes instigate and/or perpetuate disease; whether microbiota-targeted therapies impact sinus/nasal microbiome composition and alter disease course; the functional significance of different species and strains within common genera; and if differences in composition correspond to differences in community function. Dr. Lemon also set forth potential risks of nasal microbiota transplantation, most particularly the risk of introducing common pathobionts, e.g., *S. aureus* and eukaryotic viruses to the nasal area.

The presentations demonstrated that all areas of MT are in their infancy from a research and clinical perspective. FMT is the most developed area of MT and significant research has been conducted demonstrating that infusion of feces from a healthy donor to a recipient patient’s GI tract is highly effective in treating recurrent CDI, and more effective than vancomycin alone. FMT for treatment of CDI is becoming increasingly common and accepted. However, like the other forms of MT, there are significant gaps in research regarding FMT, including its mechanism of action and whether it is effective for conditions other than recurrent CDI. The talks highlighted the timeliness of the grant project as a way of ensuring that the science and practice do not get too far ahead of an appropriate regulatory structure to guide the safe and effective development and use of MT. Currently, there are a number of stool banks that are providing fecal material to physicians performing FMT. Examples include Openbiome and Advancing Bio that provide hospitals with screened frozen fecal material ready for clinical use. In addition, various applications of microbiome-based products to treat CDI and other conditions
are currently being studied by pharmaceutical companies and biotechnology start-ups. Some companies are commercializing bacteria and fecal microbiota products for the marketplace, including artificial and processed human fecal material. “These products are in various stages of development and testing, with some undergoing research in laboratories and others in patients.” Some of the companies working in this space include Seres Health, Rebiotix, and Repopopulate. They are developing specially-designed biotherapeutic products that treat CDI and other conditions by transferring microbial communities or cocktails to a recipient via enema, colonoscopy or orally in pill form.

Small Group Discussion Reports

Following these introductory talks, the working group members met in small groups to consider the following questions:

a. Since there is no regulatory definition of “microbiota transplant” - how should we define it for purposes of this project?
b. Is there anything intrinsically different about microbiota transplantation (MT) that makes it different from other transplants or regulated transplanted substances, e.g., blood and blood products, organs, and cells and tissues, in terms of safety, harvesting, collection, storage, distribution, and clinical use?
c. For regulatory purposes, is MT a procedure, a product or both? What analogs are there in medicine?
d. What are the significant legal, regulatory, or institutional barriers to researching or clinical use of MT?

The primary issue tackled during the first small group session related to the first issue – the definition of MT. As noted in the question, there is no regulatory, or even accepted, definition among researchers or clinicians of MT. The co-investigators set forth an initial definition as a starting point (“microorganisms transplanted from one human to another”) and, within the time given for discussion, the four small groups spent the majority of their time discussing and proposing a definition of MT.

Distinguishing MT from probiotics and phage therapies

Working group members raised the question of how MT differs from phage therapy and probiotics so initial discussion focused on the distinction between these different uses of microorganisms. Like MT, there is no statutory or regulatory definition of probiotics in the United States. The most widely used definition of probiotics is the definition proposed in the 2001 report of a Joint FAO/WHO Expert Consultation on “Evaluation of Health and Nutritional

4 http://thepowerofpoop.com/resources/innovation/
5 Id.
6 In preparing for talk for the working group meeting, Dr. Grice asked whether phage therapy would be considered a microbiota transplant. The co-investigators were not sure and said they would raise the question with working group members.
Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria.”7 In that document, probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” In a 2005 presentation, Commander Julienne Vaillancourt of the FDA Center for Biologics Evaluation and Research (CBER) stated that the working definition of live biotherapeutics used by CBER’s Office of Vaccines Research and Review, i.e., “live microorganisms with an intended therapeutic effect in humans” includes “probiotics for clinical use.”8

Phage, or bacteriophage, therapy also has no regulatory definition but generally is the use of a bacteriophage – a virus that infects, replicates within, and kills a bacterium - to specifically target pathogenic bacteria. Phages are used in veterinary medicine and just starting to be considered by FDA for human use. There is hope that phage therapy will lead to fewer side effects than antibiotics because a phage will only kill a bacterium if it is a match to the specific strain. Therefore phage therapy is less likely to negatively impact the normal microbiota in the gut or create the risk of opportunistic infection.

MT is similar to probiotic therapy in the sense that bacteria are introduced or re-introduced into or on a human being specifically to impact the recipient’s microbial balance. However, probiotics are generally cultivated bacteria whereas, at least in the case of FMT, the transferred material is less manipulated. MT is also similar to phage therapy in that one of the many goals of MT is to reduce pathogenic bacteria, e.g., in the case of introducing fecal material to eliminate C. diff. However, MTs may go beyond targeted destruction of a specific strain of bacteria and aim to transfer all the microbes in a specific body site microbial community to the same body site in a recipient to restore a healthy and protective microbiota. As such, working group members generally agreed that a clear definition was needed to clarify what MT is and how it is different from probiotics and phage therapy.

Upon considering the definition proposed at the meeting (“microorganisms transplanted from one human to another”) many agreed that this was a good starting point but several critical issues emerged that led the groups to expand upon or rewrite the proposed definition.

First, participants queried the use of the word “transplant.” As background, one participant noted that “bacteriotherapy” was an early word for MT but it was deemed inadequate because MT involves transferring more than just bacteria and further, involves the engraftment of the microbial components, something similar to a transplant. Therefore the word “transplant” was adopted widely. However, MT is clearly not a transplant procedure in the same way single organs are transplanted to conduct the same defined function in the recipient. The transplanted microbiota may serve different functions based on the composition of the transplanted materials. Further, unlike organ transplants, MT might lead to transient changes and adaptation in the body


8 Julienne Vaillancourt, U.S. Food & Drug Administration, Regulating Pre- and Pro-biotics: A US FDA Perspective (PowerPoint presentation, Mar. 17, 2005), available at http://www.iom.edu/~media/Files/Activity%20Files/PublicHealth/MicrobialThreats/Vaillancourt17Mar05ProbioticsRegulation.pdf.
of the recipient. Long-term persistence of the donor microbial composition after FMT are currently poorly understood. Alternative terms to “transplant” that were raised by participants include microbial inoculation, engraftment, and transfer.

A second critical point relating to the definition of MT is the appropriate way to set forth what is being transplanted. In addition to the word “microorganisms” used in the draft definition, other possibilities proposed to describe the matter transferred during an MT include:

- “Set of organisms existing in a human site”
- “Community of organisms” (noting that “community” has connotations of interaction)
- “System of organisms” (noting that “system” implies interaction with the host)
- “Community of interacting microbes in a defined environment”
- “Assemblage of interacting microbes”

Another critical issue that participants felt was missing from the proposed definition was reference to the degree of manipulation the transferred materials are subject to prior to implantation into the recipient. Many felt that anything more than “minimal manipulation” transforms the transfer of human material from one person to another into something other than MT, for instance into a probiotic or possibly something that would be considered – and regulated as – a drug by FDA. However, many noted that some degree of manipulation is necessary or inevitable but could not agree on whether there is – or should be – a well-defined degree of manipulation to stay within the definition of MT. For instance, prior to conducting an FMT, feces is typically liquefied and filtered, which might be considered manipulation. Further, if part of the transferred material is killed, this might be a manipulation as well. Participants suggested including the following words and concepts about the transplanted material to indicate that MT involves minimal manipulation:

- “Organisms in native form with minimal manipulation” (native meaning, in this case, organisms that occur naturally in the site or are present in the harvested material)
- “Uncultivated materials” (in other words, not having been cultivated in the laboratory in a growth environment or medium)
- “Material that is not or cannot be characterized” (characterization refers to the use of external techniques to probe into the internal structure and properties of a material and document those structures and materials.)
- “Material from a single donor” (because a single donor disallows “pooled” samples, implies minimal manipulation, and the availability of saved aliquots)
- “Maintaining the integrity of the microbial consortium of organisms”
Working group members also discussed whether the definition of MT should include the concept of “restoration” or “restoration to balance” or, like the definition of probiotics, include the concept that MT “confers a health benefit to the host.” In other words, should the definition of MT indicate that the transferred materials restored a “normal” or “healthy” microbiome and/or restored the recipient to health? Working group members noted this is complicated for several reasons. First, the microbiome of the recipient may never have been in balance. Further, at present, it is impossible to measure restoration of the microbiome - other human health endpoints are used instead. Implying a health benefit, some argued, would require clinical studies to demonstrate the health benefit, thus limiting the use of the definition to only MT with clinical effectiveness data. Some suggested that the definition should not include therapeutic intent, a hallmark characteristic of products regulated as drugs or biologics by FDA. However, there may be a way to include the impact that MT makes on the structure and function of the human body in the definition which would not necessarily move MT into the drug category.9

Many agreed that the definition should reflect that the transfer is from one human to another and not from an animal or environmental sample.

Proposed definitions included:

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9 “Structure/function” claims describe the role of a nutrient or dietary ingredient intended to affect the normal structure or function of the human body. Pursuant to the Dietary Supplement Health and Education Act of 1994 (DSHEA), FDA allows manufacturers to use these types of claims for conventional foods and dietary supplements and, because these claims are not considered drug claims, using them does not cause the product to be regulated as a drug.
Transfer of an assemblage of minimally manipulated live microorganisms from a human donor to a recipient.

- Minimally manipulated microbes obtained directly from humans and administered to humans.
- Biological material containing microbe(s) transferred from one human to another to confer health benefit (or medical treatment).

As to whether there is anything intrinsically different about MT that makes it different from other transplants or regulated transplanted substances, working group members noted that the most significant difference between MT and other transplanted substances is that MT involves transferring material from one human being to another that is not composed of human DNA (although some human DNA may be present in the transferred material). Further, unlike other regulated products, complete characterization of the transplanted material is not possible, nor can samples be manufactured consistently, mostly because the material transferred via MT is dynamic and not predictable with a mechanism of action that is not well understood. A single sample obtained for MT may do different things in different patients or have a different effect depending on the condition for which the patient was given an MT or the status (microbiological or immunological) of the recipient. This is one of the major challenges associated with predicting the effect and understanding the mechanisms of action of MT.

When considering whether MT is a procedure, a product or both, participants agreed that MT is both a product and a procedure. This complicates the definitional issue because FDA regulates products and procedures differently. Further, some procedures, such as surgeries and colonoscopies, are not regulated by FDA but are considered as part of the “practice of medicine” under which physicians are held to the appropriate standard of care. Products are regulated by FDA primarily according to the claims the manufacturer makes regarding the product’s intended use. WG members agreed that thought should be given to these differences when formulating the definition of microbiota transplantation.

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Figure 2.\textsuperscript{10}

\textsuperscript{10} Organ transplantation is regulated by the Health Resources & Services Administration (HRSA) through the Organ Procurement and Transplantation Network \url{https://optn.transplant.hrsa.gov/}. Blood, blood products and live biotherapeutics are regulated by FDA’s Center for Biologics Evaluation and Research \url{http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/}. 

12
Current Regulation of FMT

Moving from the general discussion of MT to discussion of an appropriate regulatory framework for FMT, Rachel Sachs, an Academic Fellow at Harvard Law School’s Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics discussed the current regulatory framework for FMT.¹¹ From a legal and regulatory perspective, FMT and related treatments raise unique concerns including whether FMT should be regulated as a procedure using a biological product (a category of drugs) requiring an IND application or, for example, as a transplant of human cells/tissues that is regulated by FDA but differently than drugs. Each regulatory option raises unique issues if applied to FMT.

In April 2013, in response to a physician inquiry, FDA’s Center for Biologics Evaluation and Research categorized fecal microbiota as a biological product, a subcategory of drugs. FDA defines a drug as an “article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and a biological product as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product … applicable to the prevention, treatment, or cure of a disease or condition of human beings.” Because biological products are a subset of drugs, both are regulated under provisions of the Food Drug and Cosmetic Act. However, biological products are also licensed under section 351 of the PHS Act. FDA has affirmatively stated that “microbiota isolated from fecal matter of a donor is not an HCT/P” (human cells, tissues, or cellular or tissue-based products).

Based on their determination that fecal microbiota is a biologic, FDA stated that physicians performing FMTs would need to submit an Investigational New Drug (IND) application in advance of using the procedure on patients. At a subsequent public meeting co-hosted by FDA and NIH, representatives from several professional medical societies and the CDC, as well as patients and clinicians, expressed concern to FDA that FMT is not appropriate for study under

¹¹Sachs is the author of an article that discusses how FMT is currently regulated and makes recommendations for future regulation. See Rachel E. Sachs & Carolyn A. Edelstein, Ensuring the Safe and Effective FDA Regulation of Fecal Microbiota Transplantation, 2 J. L. & Biosciences 396 (2015).
the FDA’s IND regulations and that applying IND requirements would make widespread use of FMT unavailable to patients. In guidance released in July 2013, FDA acknowledged these concerns and agreed “to exercise enforcement discretion regarding the IND requirements” solely for CDI not responding to standard therapies, provided that the treating physician obtain adequate informed consent from the patient. Thus, the guidance allows physicians to use FMT to treat CDI in patients who have not responded to standard therapies without filing an IND with the agency. FMT for this specific purpose is thus exempt from regulation and is being treated like the practice of medicine. The guidance notes that “FDA intends to exercise its discretion on an interim basis while the Agency further considers the matter.”

The current enforcement discretion policy does not address other MTs and does not extend to other uses of FMT. Therefore, providers who wish to use FMT for any purpose other than CDI must submit and obtain FDA approval of an IND application prior to studying the product in clinical trials. Following initial laboratory and animal testing that show that investigational use in humans is reasonably safe, biological products (like other drugs) can be studied in clinical trials in humans under an IND. In her talk, Sachs described what she calls an “uneasy fit” between the IND process and FMT because of the difficulty of characterizing active ingredients in FMT which is typically required of drugs; the cost and exclusivity of the drug approval process which may lead to an increase in unsafe “do-it-yourself” FMTs; the inadequacy of the IND process to provide for ongoing monitoring for the presence of possible pathogens; and the availability of off-label prescribing that may discourage research into the use of FMT for other indications.

If the data generated by the IND studies demonstrate that the product is safe and effective for its intended use, the data is submitted as part of a marketing application called a Biologics License Application (BLA). A BLA is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical effects of the biologic product. A BLA is required before a product is marketed.

In March 2014, FDA published draft guidance (not yet finalized) that added another qualification to the use of FMT for CDI – that the FMT product must be “obtained from a donor known to either the patient or to the licensed health care provider treating the patient” and that the stool donor and stool are qualified by screening and testing. The March 2014 guidance, if finalized, would have a strong negative effect on the several organizations (mentioned earlier) that are commercializing fecal microbiota products for the marketplace as well as physicians and patients who use stool banks and companies like Seres and Rebiotics that use donor stool. Health care providers transplanting fecal microorganisms into patients from these sources, i.e. sources unknown to either the patient or to the health care provider, would be acting outside of this guidance. It appears that FDA is in an interim period, and that the long-term regulatory status of

FMT to treat CDI is unresolved, potentially complicating research into the use of FMT for other conditions.¹³

Working group participants were divided into small mixed profession groups to discuss the pros and cons of regulation of FMT as a biological product based on the seven characteristics of an effective regulatory framework. The table below represents a synthesis of the preliminary conclusions of the four small groups:

| Regulation of Microbiota Transplantation as a Biological Product |
|---|---|---|
| Regulatory criteria | PRO | CON |
| Ensures the safety of the substance/procedure | The biological product approach would ensure the safety of the substance and procedure. BLA and IND applications focus on various aspects of safety including side effects and toxicity. The required Good Manufacturing Practices (GMPs) for biologics focus on disease communicability. Required adverse event reporting for drugs and biologics would help ensure long term safety of MT products.¹⁴ | The BLA process is too rigid to allow use of improved assays (tests to determine ingredients and quality) as technology advances and too inflexible to update screening protocols for new conditions/pathogens. Safety under BLA and IND do not address longer term adverse events. In the context of FMT, there is the potential for longer term adverse effects such as obesity and other microbiota associated chronic disease. Another safety concern is that |

¹³ Subsequent to the Working Group meeting, on March 1, 2016 FDA issued another draft guidance document on FMT. The draft is designed to seek comments and does not alter FDA’s current enforcement discretion policy, published in July 2013 that states that physicians may perform FMT outside of an IND application to treat C. difficile infection (CDI) that is not responsive to standard therapy, so long as they obtain informed consent. The new guidance is a revision of - and replaces - guidance the FDA published in March 2014. The most recent March 2016 draft guidance does not include the requirement that the donor be known to the recipient but rather states that FMT may be used for recurrent CDI if “the FMT product is not obtained from a stool bank.” The draft guidance explicitly states that stool banks must have an IND in place before distributing FMT product but – importantly - under the new guidance an IND sponsor may request a waiver of certain IND regulations when they are giving FMT product to doctors treating patients with recurrent CDI. In the draft guidance, FDA defines a stool bank as an establishment that collects and distributes stool to other establishments and specifically states that a hospital laboratory that creates FMT products for its own patients is NOT a stool bank. FDA is using the new March 2016 guidance to solicit feedback on this general proposal, and on which parts of the IND application would be appropriate to waive.

¹⁴ http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm
<table>
<thead>
<tr>
<th>Ensures the effectiveness of the substance/procedure</th>
<th>INDs encourage off-label use and safety is hard to determine and monitor with off-label use.</th>
<th>This framework would ensure effectiveness of MT because a BLA requires evidence of effectiveness with regard to specific uses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provides reliable information to recipients about the safety and effectiveness of the substance/procedure</td>
<td>The BLA is rigid and inflexible over time as to study criteria (e.g. inclusion criteria) and therefore limits effectiveness data. No effectiveness evidence is required or obtained for off label use of a biologic.</td>
<td>Once a product is approved, regulations for biological products require package labeling and inserts for providers and patients. The process has a strong framework for consumer information.</td>
</tr>
<tr>
<td>Ensures that patients who need them have access to these substances/procedures</td>
<td>The prohibitive cost of drug manufacturers will lead to higher costs for patients. Can and should FDA provide market exclusivity to a product (fecal matter) in the public domain? How many BLAs would the FDA approve in this area? These questions relate to whether the BLA process is appropriate for FMT where composition/chemistry/structure may differ from sample to sample.</td>
<td>FDA approval of a biologic often leads to rapid clinical adoption because FDA has given its stamp of approval and manufacturers have processes in place to inform providers about products. FDA approval as a drug will mean that the MT product will likely be covered by insurance.</td>
</tr>
<tr>
<td>Ensures that the IND/BLA process requires</td>
<td></td>
<td>Required package labeling and inserts provide information to patients but some noted that this information is technical and dense and may be hard for patients to understand.</td>
</tr>
</tbody>
</table>
regulations do not unnecessarily discourage research on MT

clinical trials.

research (as required for an IND) is difficult for academics in contrast to pharmaceutical manufacturers.

The rigidity of the BLA process is a concern. It is hard to modify BLAs and product design which may impede evolution in research.

Supports public health objectives relating to MT, including its potential to mitigate hospital acquired-infections and to discourage unsafe home use of MT

This paradigm would allow for long term surveillance for safety.

Alternative Regulatory Framework for FMT: transplantation and implantation of human cells, tissue and cellular and tissue-based products

Scott A. Brubaker, Senior Vice President of Policy at the American Association of Tissue Banks described how HCT/Ps are currently regulated. HCT/P products are defined as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”15 Examples include bone, ligament, skin, dura mater, heart valve, cornea, epithelial cells on a synthetic matrix, and semen or other reproductive tissues but does not include vascularized human organs for transplantation; whole blood or blood components; secreted or extracted human products except semen (e.g., milk collagen, and cell factors); minimally manipulated bone marrow for homologous use.

The current regulatory framework for HCT/Ps, rolled out in 1997, is a risk-based approach that is designed to be broad enough to cover a wide range of products.16 The level of regulation is designed to be commensurate with the risk posed by the product. Manufacturers do not have to demonstrate effectiveness of products regulated in this category. FDA’s main regulatory concerns with regard to HCT/Ps are prevention of communicable disease transmission and safe processing and handling. As such the HCT/P framework has detailed regulations regarding donor screening and methods, facilities, and controls for manufacturing to prevent contamination and cross-contamination.17 Clinical effectiveness and regulation of product claims are less

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15 21 CFR 1271.3(d)(2).
16 21 CFR Part 1271 – Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps)
17 Id.
important in the HCT/P regulatory framework. Unlike drugs and biologics, most HCT/Ps (unless they are considered biologics) do not require premarket approval by FDA.

In 21 CFR Part 1271, FDA sets forth the regulatory scheme for HCT/Ps including: 1) registration and listing; 2) donor screening and testing; 3) Current Good Tissue Practices; 4) labeling; 5) adverse-event reporting; and 6) inspection and enforcement. An HCT/P that meets the Part 1271 criteria for regulation solely under section 361 of the Public Health Service (PHS) Act and the regulations in Part 1271 is called a “361 HCT/P” and is not subject to premarket clearance or approval. Examples of 361 HCT/Ps are amniotic membrane when used alone or without added cells; bone; cartilage; cornea; fascia; and ligament. However, HCT/Ps that do not meet the criteria for regulation as a 361 HCT/P because they have characteristics of a biologic, device, or drug product are subject to an additional layer of regulation and are regulated under section 351 of the PHS and called “351 HCT/Ps.” Examples of 351 HCT/Ps are all allogeneic, unrelated hematopoietic stem cells from cord and peripheral blood; bone marrow that is more than minimally manipulated; and bone marrow that is intended for non-homologous use.

To be a 361 HCT/P, the product must meet all four of the following criteria:

- It is minimally manipulated.
- It is intended for homologous use as determined by labeling and advertising.
- Its manufacture does not involve combination with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent (not raising new clinical safety concerns for the HCT/P).
- It does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, or if it has such an effect, it is intended for autologous use or allogenic use in close relatives or for reproductive use.

The definition of “minimal manipulation” depends upon whether the HCT/P is a structural tissue, as opposed to cells or nonstructural tissue. For structural tissue, FDA defines “minimal manipulation” as “processing that does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement.”

Working group participants were divided into small mixed profession groups to discuss the pros and cons of regulation of FMT as an HCT/P based on the seven characteristics of an effective regulatory framework. The table below represents a synthesis of the preliminary conclusions of the four small groups:

<table>
<thead>
<tr>
<th>Regulatory criteria</th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensures the safety of the substance/procedure</td>
<td>Under the HCT/P framework, donor selection, communicable</td>
<td>No requirement to report adverse events.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>disease transmission, and product preparation guidelines are robust. The HCT/P framework provides useful 'tiered' regulatory categories that allow for different regulation based on high/low risk. Safety criteria can be flexible and change as safety issues become known in contrast to the more rigid BLA framework. Under this framework, which involves more limited FDA oversight than for drugs, it is easier for outside bodies to interact with manufacturers and update safety criteria and monitor safety.</th>
<th>No incentive for rigorous placebo RCTs to look at other safety issues, apart from communicable disease transmission.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensures the effectiveness of the substance/procedure</td>
<td>There is no requirement for efficacy data for HCT/Ps.</td>
<td></td>
</tr>
<tr>
<td>Provides reliable information to recipients about the safety and effectiveness of the substance/procedure</td>
<td>There are no product inserts or packaging labels for consumers required under this framework. Patients will not be informed of safety information and no effectiveness information is available for consumers.</td>
<td></td>
</tr>
<tr>
<td>Ensures that patients who need them have access to these substances/procedures</td>
<td>Patients are likely to have more access to FMT under the HCT/P framework relative to the biologics framework because the BLA and the exclusivity granted to drug developers increases the cost of drug products. Patients would have greater access to FMT under this framework because there would be no need for costly trials to demonstrate efficacy. The tiered regulation (high to low increase) possibility that MT will be used for unproven indications.</td>
<td>Increased possibility that MT will be used for unproven indications. The limited oversight of tissue banks raised the concern that some banks might engage in price gouging or other unethical practices that would reduce patient access to the procedure.</td>
</tr>
</tbody>
</table>
Risk) in this framework would be useful for FMT with different requirements for directed donors or autologous use.

Tissue banks can accommodate multiple types of products and are therefore flexible as new products come onto the market which may be useful for MT.

Insurance would likely pay for MT if sample comes from bank system that had some type of certification from FDA or a private regulatory organization.

Increased possibility that FMT will be used for unproven indications which might expand the use of FMT to conditions beyond CDI.

<table>
<thead>
<tr>
<th>Ensures that the regulations do not unnecessarily discourage research on MT</th>
<th>Allows for research to be done relatively easily because there is no need for a costly IND or BLA application to FDA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue bank framework opens door to other researchers wanting data. Tissue bank data could be more informative than data available through a BLA because patient population is more representative.</td>
<td>Since no market exclusivity is available under HCT/P framework, industry may be unwilling to invest in drug development which might keep the cost of FMT more accessible to patients.</td>
</tr>
<tr>
<td>FDA does not require research to be conducted for approval so MT might be understudied under this paradigm.</td>
<td>No required collecting or tracking of safety or efficacy data that may have otherwise been required for IND or BLA application.</td>
</tr>
<tr>
<td>There is no incentive for rigorous trials under this paradigm.</td>
<td>Industry unlikely to invest in R&amp;D under this paradigm because no market exclusivity is granted.</td>
</tr>
<tr>
<td>Supports public health objectives relating to MT, including its potential to mitigate</td>
<td>Public health goals are supported by tissue donor and manufacturing regulations.</td>
</tr>
</tbody>
</table>
### Hospital Acquired-Infections and to Discourage Unsafe Home Use of MT

- Increased access may have public health benefit by reducing burden of CDI in the community.
- Decreased barriers to use in the clinical setting discourages DIY use (which may lead to transfer of communicable diseases).

### Alternative Regulatory Framework for FMT: Transfusion of Blood and Blood Products

The final alternative framework considered for FMT at the meeting was the current framework for transfusion of blood and blood products. Dr. John Hess, Professor of Laboratory Medicine and Hematology at the University of Washington, described how blood is currently regulated in the United States. Blood for transfusion is considered a drug and regulated by the FDA.

Dr. Hess noted the differences between blood and HCT/Ps from a regulatory perspective. He noted that blood and its mechanism of action are well understood and the product is highly reproducible and “minimally manipulated.” On the other hand, he noted that HCT/Ps involve poorly understood processes, are highly variable, and often highly manipulated. Finally, unlike HCT/Ps, there is a huge need for blood and therefore a huge need for voluntary, non-remunerated donors. Blood is unique to each donor and, because of the short shelf life and scarcity of the blood supply in relation to the need, each unit is not tested for efficacy. Therefore, safety and efficacy cannot be measured prospectively as with other drug products and the FDA focuses primarily on purity and potency. The blood product industry is highly regulated with regulations falling into the following categories: recruiting donors; qualifying donors; blood collection; blood testing; making blood components; labeling; storage; and shipment. Because blood is collected, transported and used widely and quickly, labeling is of critical importance and much more highly regulated than in the case of HCT/Ps. Further because of prior scandals with tainted blood and fear of HIV contamination in the blood supply, product testing regulations are very strict and strongly enforced.

The blood banking paradigm is relevant to FMT because of the recent development of stool banks, or establishments that collect and distribute stool to other establishments. However, working group members acknowledged the very different factors that distinguish blood and stool donations that are relevant to the banking and distribution process. Blood banks must be highly regulated because blood is frequently used in emergency circumstances and therefore must be tested for communicable diseases prior to storage so that it can be used immediately. Further, if a blood transfusion is administered inappropriately by, for example, mismatching the blood type to the needs of the recipient, the result can be fatal. However, at this time, stool is not typed and does not need to be matched to a recipient which may indicate that stool does not require as rigorous a screening process as that required for blood products.
Working group participants were divided again into small mixed profession groups to discuss the pros and cons of regulation of FMT as blood for transfusion is regulated based on the seven characteristics of an effective regulatory framework. The chart below represents a synthesis of the preliminary conclusions of the four small groups:

<table>
<thead>
<tr>
<th>Regulatory criteria</th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensures the safety of the substance/procedure</td>
<td>Strong focus on product safety under this paradigm. Strict testing for pathogens, strong chain of custody and tracking of samples. Stringent safety processes would promote safe MT practices to the fullest extent possible.</td>
<td>Overly stringent and rigid processes under this paradigm may not be appropriate for fecal material and FMT. There is a lack of efficacy or long-term safety data for patients under the blood transfusion paradigm. (Although CDC collects adverse event reports there are no long term outcome data collected after blood transfusion.)</td>
</tr>
<tr>
<td>Ensures the effectiveness of the substance/procedure</td>
<td>This framework requires extensive record keeping about how samples are obtained and tracked. Substantial information given to patients in the informed consent process. High degree of regulation creates trustworthy/rigorous manufacturing process.</td>
<td>This framework does not require effectiveness data for specific indications.</td>
</tr>
<tr>
<td>Provides reliable information to recipients about the</td>
<td>High availability of product through an efficient existing structure of blood banks is a good model for potential MT banks.</td>
<td>Lack of 'tiered' regulatory levels (as present in HCT/Ps) that allow for different regulation based on high/low risk. Blood collection and banking processes are onerous and therefore, if used to regulate MT banks, might limit the number of MT banks with</td>
</tr>
<tr>
<td>safety and effectiveness of the substance/procedure</td>
<td></td>
<td></td>
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<tr>
<td>Ensures that patients who need them have appropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>access to these substances/procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expertise/Resources to Meet Requirements</td>
<td>Overly Stringent Processes Would Be Burdensome for Independent Researchers or Small Research Groups and Thus Could Impede Research. For Instance, Hospital, Laboratory and Free Standing Blood Banks Are Subject to Accreditation by Multiple Organizations Including the Joint Commission, College of American Pathologists, American Association of Blood Banks and State Health Departments.</td>
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</tr>
<tr>
<td>Supports Public Health Objectives Relating to MT, Including Its Potential to Mitigate Hospital Acquired-Infections and to Discourage Unsafe Home Use of MT</td>
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</tr>
</tbody>
</table>

**Conclusion**

The first working group meeting raised several issues that will require additional discussion at future working group meetings, including a definition of MT that encompasses both current and potential future uses of MT. The first working group meeting raised several possible regulatory frameworks for MT. A potential recommendation is that FMT requires a hybrid regulatory scheme that draws on features of existing regulatory models. Future meetings should be used to further define what such a hybrid framework might look like. The next working group meeting is scheduled for May 2-3, 2016.