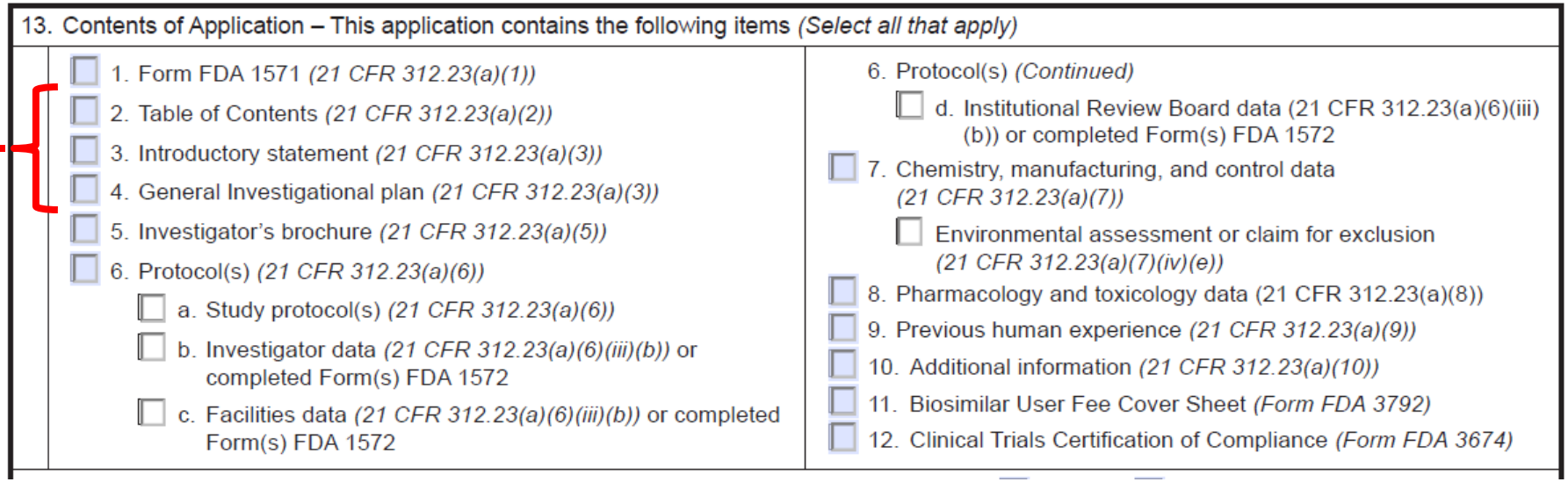
Guidance on completing FDA Form 1571

(Taken from "Fecal Microbiota Transplantation: A Practical Update for the Infectious Disease Specialist" – **[insert reference]**)



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Parts 2-4 can be addressed in the form of a cover letter; however, the sponsor is expected to provide some background information about FMT. It does not need to be an exhaustive review of the literature, but should provide the FDA with a rationale behind the proposed treatment with citations of relevant literature supporting its use. For example: "The concept of FMT is to restore the fecal microbiologic diversity of a patient with CDI by directly instilling fecal material collected from a healthy donor. This has been proven effective in numerous case reports and retrospective case series [1,2] in patients with recurrent CDI resulting in superior cure rates compared to previously reported cure rates with standard therapy. Most recently, an open-label, randomized, controlled trial directly comparing FMT with two different antibiotic regimens clearly demonstrated the superiority of FMT in patients with recurrent CDI[3]".

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[1] Bakken JS. Fecal bacteriotherapy for recurrent Clostridium difficile infection. Anaerobe **2009 Sep 22**; 15(6):285-9

[2] Petrof EO, Gloor GB, Vanner SJ, et al. Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: "RePOOPulating the gut. Microbiome 20**13**;1(1):3-10

[3] Van Nood E, Vrieze A, and Nieuwdorp M: Duodenal infusion of donor feces for recurrent Clostridium difficile. NEJM 2013;368:407-415.

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Part 5 (Investigator's Brochure): Creation of a brochure will be necessary if the applicant plans to conduct the study at multiple sites, and a copy will need to be submitted with the IND to the FDA. A brochure is not required for emergency INDs. The purpose of the brochure is to provide co-investigators involved in the trial with the information necessary to participate and should include—in lieu of the treatment protocol, if desired—a brief summary, introductory statement, background of the disease, summary of known safety and efficacy data, description of the product, proposed indications, dosing form/regimen, route of planned administration, description of the instillation technique, and other information about the clinical trial (i.e., data to be gathered, time-points, endpoints, etc.). The brochure should be reviewed annually and revised when necessary to include any new relevant information.

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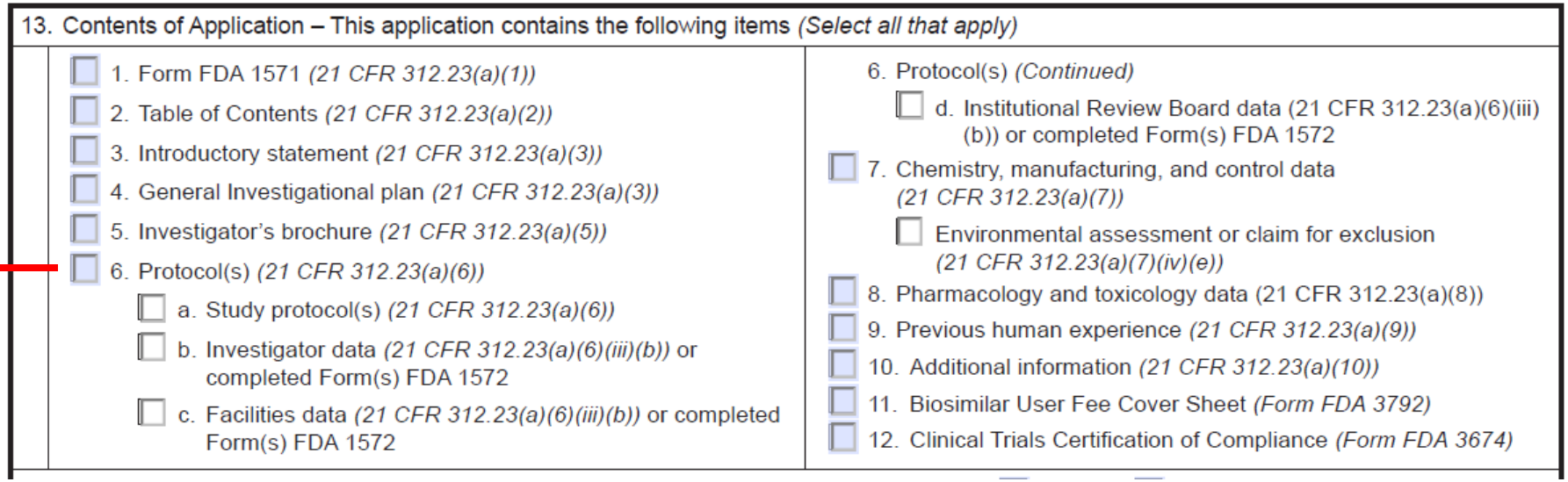

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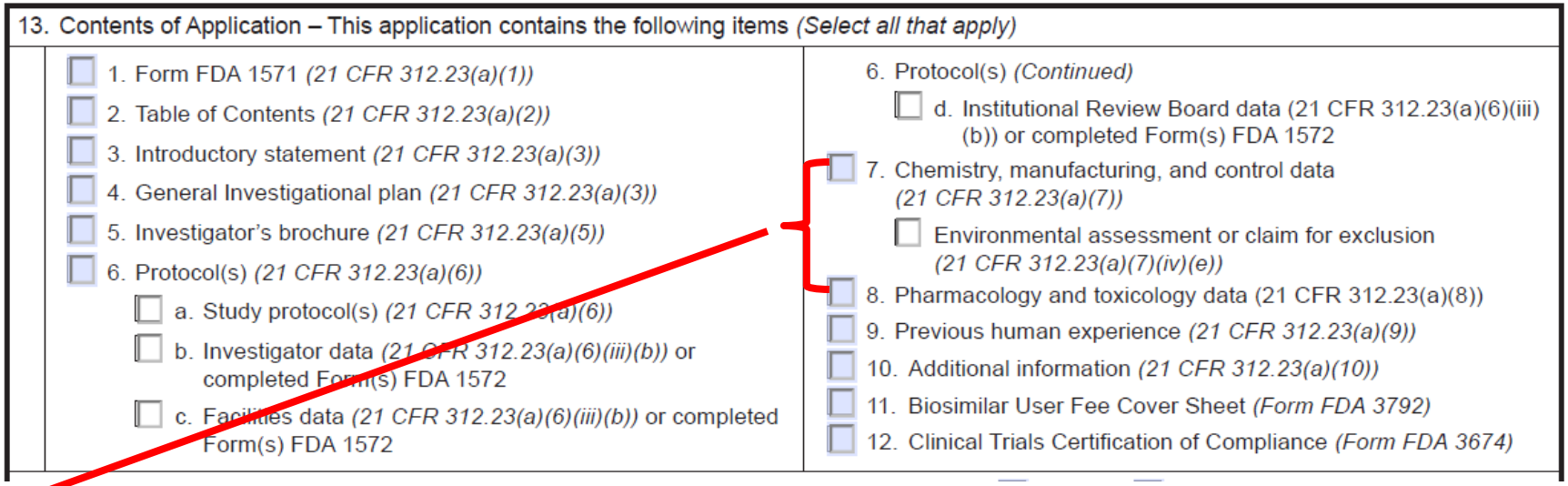
Part 6 (Protocols). Section a, Study protocol: This section will require the submission of the study protocol itself. The protocol must provide detailed information about patient (recipient) and donor evaluation and testing procedures. Guidance has been published previously and can be used as a template.[4] The protocol should include detailed information regarding the collection and handling of fecal material, methods of preparation of the fecal sample, as well as indicate the dose, route, and duration of administration. Details regarding endpoints (e.g., resolution of diarrhea, conversion to negative *C. difficile* testing by toxin assay and/or PCR) and long term follow up of treated patients must also be included. If the sponsor has created a case report form (CRF) to collect data, the form should be included with the IND application.

The protocol must include a description of risks associated with FMT, including those not yet reported (e.g., intestinal perforation, sepsis, transmission of an infectious agent from the donor stool). If the protocol will include endoscopy, the risks associated with these procedures should be discussed separately. An informed consent form that includes specific language explaining that FMT is an investigational procedure

[4] Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol **2011 Dec**; 9(12):1044-9

that may be associated with potential defined risks should also be included with the IND application. The protocol must have a section detailing the potential Adverse Events (AE) the clinician/investigator plans to capture. Most protocols should outline specific AEs at baseline and solicit potential AEs at follow up visits; however, unsolicited AEs (symptoms that patients volunteer) may need to be recorded as well. All documented AEs should be reported to the FDA in a timely fashion—within 7 calendar days for serious AEs (e.g., death, illness requiring hospitalization). Detailed guidance for safety reporting requirement can be found here: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM333226.pdf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Part 7 (Chemistry, manufacturing, and control data): This requires a brief description of donor material. An example of appropriate language would include statements about the heterogeneity of human stool from person to person; however, human stool consists mostly of bacteria and water.

Part 8 (Pharmacology and Toxicology data): This section should include a statement of the potential risks associated with FMT. However, it should be emphasized that the overall risk is low and there have been no significant reported complications to date.