

Part B. Statistical Methods

1. Respondent Universe and Sampling Methods

The population of potential interviewees consists of all combination product sponsors and applicants with submissions between September 1, 2018 and January 31, 2020 as follows: Group 1, RFD/pre-RFD submitted to FDA; Group 2, IND/pre-IND submitted to FDA; and Group 3, NDA/BLA with a first review cycle action from FDA. For each group, FDA's independent contractor (ERG) will sample submissions representing the following traits of interest:

- **Sponsor size:** small, medium, large, and private
- **Sponsor experience:** Yes (has had at least one combination product NDA/BLA filed), No (has not had a combination product NDA/BLA filed)
- **Combination product category and type:** 1, 2, 3, 4, 5, 6, 7, 8, 9 and device (if applicable)
- **Lead-Consult Centers:** CDER or CBER as lead Center, with CDRH or CDER or CBER or consulted Center (lead and consulted Centers must be different)
- **Therapeutic area:** as defined by MedDRA System Organ Class (SOC)

ERG will assign target distributions for these traits of interest based on their prevalence in submissions from CY 2017. Each target distribution will apply to the samples as a whole. Where feasible, ERG will oversample submissions with uncommon traits.

Group 1: RFDs/pre-RFDs. The number of combination product RFDs received by FDA has decreased each year, while pre-RFD receipts have increased. For the purpose of this estimate of population size, we estimate an average of 180 RFDs/pre-RFDs per year. ERG will interview one to three sponsor representatives for each of up to 35 RFDs/pre-RFDs per year; this yields a total of up to 105 respondents per year, and up to 150 respondents in total.

Group 2: INDs/pre-INDs. The number of combination product INDs/pre-INDs received by FDA has increased each year. For the purpose of this estimate of population size, we estimate an average of 240 INDs/pre-INDs per year. ERG will interview one to three sponsor representatives for each of up to 47 INDs/pre-INDs per year; this yields a total of up to 141 respondents per year, and up to 201 respondents in total.

Group 3: NDAs/BLAs. The number of NDAs/BLAs that receive a first review cycle action from FDA varies from year to year. For the purpose of this estimate of population size, we use a high-end estimate of 30 such applications per year. ERG will interview one to three sponsor representatives for each of up to 30 NDAs/BLAs; this yields a total of up to 90 respondents per year, and up to 129 respondents in total.

Based on experience with previous PDUFA-related assessments, FDA expects that the response rate for this information collection will be at least 90%.

Table 4. Expected response of Group 1.

Estimated Average Number of RFDs/Pre-RFDs Received	Number of RFDs/Pre-RFDs Selected for Interview	Number of Interviewees Per RFD/Pre-RFD	Size of Potential Respondent Universe	Expected Response Rate	Estimated Number of Respondents
180 per year	35	1-3	105 per year	90%	95
255 in total	50	1-3	150 in total	90%	135

Table 5. Expected response of Group 2.

Estimated Average Number of INDs/Pre-INDs Received	Number of INDs/Pre-INDs Selected for Interview	Number of Interviewees Per IND/Pre-IND	Size of Potential Respondent Universe	Expected Response Rate	Estimated Number of Respondents
240 per year	47	1-3	141 per year	90%	127
340 in total	67	1-3	201 in total	90%	181

Table 6. Expected response of Group 3.

Estimated Average Number of Applications Receiving a First-Review Cycle Action	Number of Interviewees Per Application	Size of Potential Respondent Universe	Expected Response Rate	Estimated Number of Respondents
30 per year	1-3	90 per year	90%	81
43 in total	1-3	129 in total	90%	116

2. Procedures for the Collection of Information

Selection Methods

Based on the total target number of submissions to examine for each group (n), FDA's independent contractor (ERG) will randomly select n/17 submissions to add to each of the three samples on a monthly basis for 17 months. ERG will assess each sample for

conformance with target distributions. If some traits are underrepresented, ERG will remove new submissions with overrepresented traits and replace with submissions with underrepresented traits. Sponsors of RFDs/ pre-RFDs, INDs/ pre-INDs, and NDAs/BLAs selected for the samples are subject to the proposed interviews for this collection of information.

Estimation Procedures

None are required.

Unusual Problems Requiring Specialized Sampling Procedures

None are required.

Use of Periodic (Less Than Annual) Data Collection

This request is for a one-time data collection as described above.

3. Methods to Maximize Response Rates and Deal with Non-response

FDA's contractor for this PDUFA VI combination product review practices assessment, ERG, has conducted other PDUFA-related information collections with response rates exceeding 95%. ERG will implement the same procedures successfully used with those previous information collections to maximize response rates. These procedures include:

- When FDA makes decisions on RFDs/pre-RFDs, INDs/pre-INDs, and NDAs/BLAs in the sample, ask FDA to notify sponsors/applicants that ERG will contact them to request participation in interviews.
- Where appropriate, ask FDA staff to incorporate reminders about possible interview requests from ERG in the form of notices in routine written communications to combination product sponsors/applicants.
- Send interview requests by email specifically to sponsor/applicant staff most engaged in interacting with FDA.
- For a first non-response, send a follow-up email.
- For additional non-responses, call sponsor/applicant representatives directly to request participation or to identify alternative representatives to participate.
- Continue to follow up until the sponsor/applicant confirms participation or explicitly declines to participate.
- Send interview reminders before scheduled interviews.

4. Test of Procedures or Methods to be Undertaken

FDA expects only fine tuning changes to the information collection activity. FDA therefore seeks a combined approval of a pretest (consisting of the first five interviews administered for the assessment) and the main interviews.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

FDA consulted with the following people on statistical aspects of the assessment design:

- Louis Nadeau, ERG (781) 674-7316
- Valerie Overton, ERG (781) 674-7398

The people who will collect and analyze the information for FDA are:

- Hannah Busey, ERG
- Marc Goldstein, ERG
- Kuang-Heng (Jason) Hsiao, ERG
- Louis Nadeau, ERG
- Valerie Overton, ERG
- Christopher Sese, ERG