Appendix A: Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting with the Sponsor

Note: The specific topics for discussion will depend on the product, therapeutic area, proposed indication, development phase, and specific development program issues.

The communication plan between the sponsor and the review committee must be discussed and documented in the meeting summary using *T820.06: Meeting Summary Template.*

General and/or Regulatory

1. The planned target date for BLA/NDA submission, including plans for rolling review
2. The specific indication that studies are intended to support
3. Other indications in development
4. Expanded access plans, including the intent to communicate these plans publicly
5. Plans to seek accelerated approval
6. Regulatory status with non-U.S. regulatory agencies
7. Plans to defer or waive specific studies (e.g., pediatric studies), including those that may be conducted as postmarketing requirements/postmarketing commitments
8. Critical aspects of proposed studies, including enrichment designs, non-inferiority designs, historical controls, and any planned novel approaches
9. Plans for submission of a proprietary name request
10. If a biologic/device combination product, the device development information and plan
11. If the use of the product will require a diagnostic test, the in vitro diagnostic development plan with the Center for Devices and Radiological Health (CDRH) or Center for Drug Evaluation and Research (CDER) as appropriate
12. The proposed communication plan for managing interactions between CBER and the sponsor, including the timing and format of these interactions

Clinical and Statistical

1. Existing and planned clinical sites and accrual data
2. Efficacy:
    a. The status of all clinical trials and topline summary results

b. The preliminary evidence of effectiveness

c. The planned or completed clinical trials intended to support effectiveness including:

i. The overall trial design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials or any other adaptation, type I error control, and expected initiation and completion dates.

ii. The validity of the outcomes and endpoints. If using patient-reported outcomes or surrogate endpoints, support for those endpoints or plans to support or validate them, as necessary.

3. Safety:

a. Potential safety issues identified in nonclinical studies and early clinical trials

b. Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, reproductive and developmental, and immunogenicity safety profiles

c. The clinical trial safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for postmarketing drug safety and surveillance (pharmacovigilance)

d. The proposed size of the safety population

e. The plan or the need for long-term safety studies or trials

i. Preapproval

ii. Post-approval

f. The plans to mitigate or minimize risk, proposed risk evaluation and mitigation strategies, if needed

4. The proposed pediatric development plan with outlines and synopses of additional studies

Clinical Pharmacology and Pharmacokinetics

1. The justification for all dose selections, including number of doses and dose intervals and a discussion of all clinical trials that will provide dose-response information

2. Specific populations:

a. The dose, trial design, efficacy endpoints, size and composition of the population, and additional safety trials for populations such as:

i. Elderly patients

ii. Pediatric patients

iii. Hepatically and renally impaired patients

3. The clinical pharmacology, pharmacodynamic, and pharmacokinetic trials: completed, ongoing, planned, and requests for deferral

   a. Immunogenicity assessments

   b. Dosing information from pharmacodynamics studies

      i Single ascending dose

      ii. Multiple ascending dose

      iii. Dose response study

   c. Food-effect

   d. Drug-drug interactions (DDI)

   e. Thorough QT/QTc

   f. Pharmacokinetic studies in patients with renal or hepatic dysfunction

   g. Pharmacogenomics

4. The plans for an *in vivo* bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation

5. The plans for conducting population pharmacokinetics, exposure-response modeling and simulation analyses

6. The plans to describe dose modifications in labeling based on DDI, age, organ impairment, among others

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

1 . The nonclinical studies completed, ongoing, and planned, including the number and sex of animals per dose, doses, route of administration, toxicities, duration of study, and study results.

2. For planned studies, the timelines for initiation and submission of study reports. Examples of such studies include:

   a. Subacute and chronic toxicology and associated toxicokinetics

b. Genetic toxicology

c. Reproductive and developmental toxicology

d. Carcinogenicity studies

e. Animal models of disease and pharmacokinetic parameters associated with efficacy

f. Evidence of mechanism of action

g. Absorption, distribution, metabolism, and excretion

h. Safety pharmacology, where appropriate

Chemistry, Manufacturing, and Controls

1. Drug product:
    a. The dosage form
    b. The formulation description
    c. Administration instructions, delivery systems (e.g., vials, prefilled syringes) proposed draft packaging, and disposal instructions
    d. Critical quality attributes
    e. The control and stability strategies
    f. The proposed shelf life and required stability studies
2. Drug substance:
    a. Characterization
    b. Critical quality attributes
    c. The control and stability strategies
    d. The proposed shelf life or retest period and required stability studies
3. Proposed commercial processes:
    a. The manufacturing process, in-process controls, scale-up plans
    b. A comparison of the proposed commercial manufacturing process to the clinical manufacturing process

c. Comparability of lots used in clinical trials and commercial lots or a plan to establish analytical comparability

d. The current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines

e. The current release and stability testing site(s) and proposed commercial testing site(s), if different

f. The anticipated market demand at launch

4. Proposed validation approaches:

    a. The drug substance and drug product manufacturing process

    b. Microbial control and sterility assurance

    c. Viral clearance

    d. The analytical methods