Boehringer Ingelheim

Draft FDA Guidance on the **Development of Cancer Drugs for Use in Novel Combination**

Determining the Contribution of the Individual Drugs' Effects

Stephan Wojciekowski | 17 Feb 2026 | EFSPI Webinar Series 2026

Life forward

Disclaimer

- The views and opinions expressed in the following presentation are those of the individual presenter and do not necessarily represent the views of Boehringer Ingelheim.
- Thanks for reading this statement ; -)

Agenda

1. Introduction & Background

2. Demonstrating Contribution of Effect
   - Factorial Designs
   - External Data

3. Development Program Considerations
   - Two or More Investigational Drugs
   - An Investigational Drug With a Drug Approved for a Different Indication
   - Two or More Drugs Approved Individually for Different Indication(s)

Introduction & Background

Purpose

- FDA Draft Guidance “Development of Cancer Drugs for Use in Novel Combination – Determining the Contribution of the Individual Drugs’ Effects”
- Provides **recommendations** for characterizing the **safety and effectiveness of individual drugs** when used in a novel oncology combination.
- Demonstrating each drug’s contribution of effect (CoE) is a legal requirement under 21 CFR 300.50.
- The guidance applies to:
  - Two or more investigational drugs
  - An investigational drug + an approved drug (different indication)
  - Two or more previously approved drugs being used together in a new indication

Development of Cancer Drugs for Use in Novel Combination - Determining the Contribution of the Individual Drugs’ Effects | FDA
Title 21 of the Code of Federal Regulations - Food and Drugs

Background

- Challenges & opportunities that motivated the draft guidance:
  - Monotherapy activity often minimal or absent in immunotherapy combinations (e.g., IO+IO, IO+TKI, IO+ADC)
  - Toxicity may preclude monotherapy dosing
  - Lack of appropriate animal models
  - Increasing availability of external clinical data and real -world data
- The guidance recognizes the following pathways:
  - Factorial and modified -factorial designs
  - Hybrid randomized & external data approaches

Short Regulatory Overview

- FDA
  - 2013: Codevelopment Guidance focused on investigational drug combinations
  - 2025: Draft Guidance broadens the scope and explicitly introduces external data and flexible designs.

- EMA Perspective
  - 2017: Fixed-combination guideline (Rev.2) demands **evidence that each component contributes** to efficacy and/or safety with strong emphasis on:
    - dose justification
    - PK/PD bridging
    - monotherapy evidence where feasible

Codevelopment of Two or More New Investigational Drugs for Use in Combination | FDA
Development of Cancer Drugs for Use in Novel Combination - Determining the Contribution of the Individual Drugs' Effects | FDA
Guideline on clinical development of fixed combination medicinal products | EMA

Demonstrating CoE

CoE: Contribution of Effect

Evidence Sources FDA Accepts

- Adequate and well -controlled trials
  - Factorial trial design (preferred)
  - Modified factorial (e.g., 3 -arm)
  - Adaptive factorial designs
  - Designs including external data (clinical trials, registries, RWD)
- Primary endpoint can be PD/response biomarker that
  - Provides direct evidence of a treatment effect (e.g., OR with DoR)
  - Can be measured earlier than other clinical endpoint (e.g., PFS or OS)

Figure 1: Factorial Trial Design

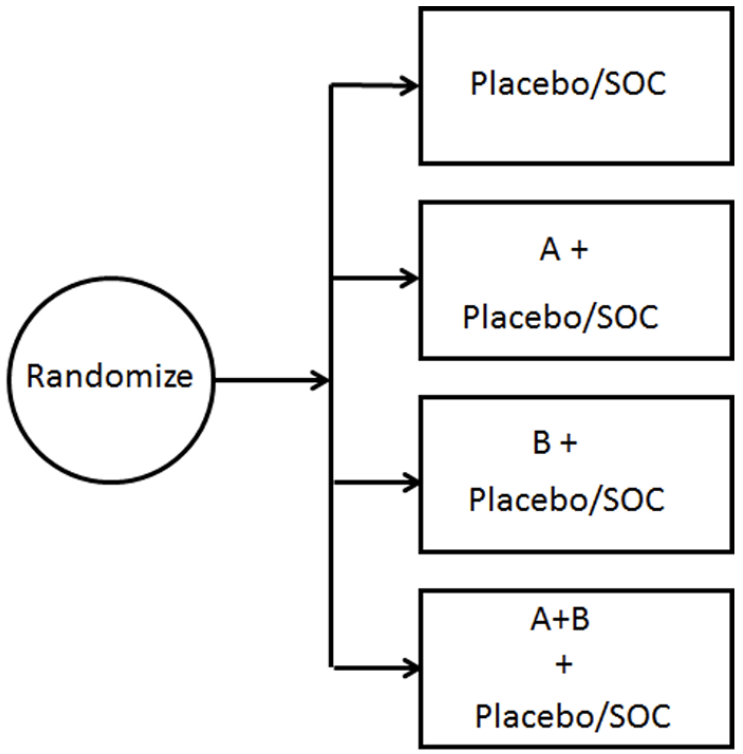

Figure from: Development of Cancer Drugs for Use in Novel Combination - Determining the Contribution of the Individual Drugs' Ef fects | FDA - page 5, lines 158 -160

A. Factorial Designs to Demonstrate the Contribution of Effect

- **Highly recommended** when feasible [1] because they provide the **clearest isolation of individual effects**
- Feasible, e.g.,
  - if the individual drugs each have activity and can be administered separately
- Not feasible, e.g.,
  - if the individual drugs cannot be administered separately
  - if one individual drug is active and the other one has minimal activity with regards to efficacy as monotherapy

- Strengths
  - Clear estimation of main effects
  - Allows interaction assessment
  - Provides direct evidence of CoE
- Limitations
  - Large sample sizes & long timelines

1: Check conditions in 2013 Codevelopment Guidance

Boehringer Ingelheim

Modified and Adaptive Factorial Design

- Modified factorial designs (e.g., 3-arm)
  - If one of the investigational drugs in a novel combination regimen is not active by itself
    → 3 arm factorial design
  - Assess contribution of components with the effect of the combination

- Adaptive factorial designs
  - Start with full factorial design and potentially drop futile trial arm in interim analysis
  - Decreases sample size & limits exposure to potentially less effective therapies
  - Adaptions and SAP must be pre-specified
  - Overall type I error rate & power to detect treatment effect must be considered

Korn, EL, CJ Allegra, and B Freidlin, 2025, Phase III Evaluation of Treatment Combinations in Three-Arm Trials, JCO, 43(2):226-233.
FDA Guidance Adaptive Designs for Clinical Trials of Drugs and Biologics (December 2019).

B. External Data to Demonstrate the Contribution of Effect

- When use of external data may be possible:
  - Strong biological plausibility for the combination regimen
  - Natural history of the disease is highly predictable
  - Drug as a single agent has been demonstrated to not be as effective as compared with its use in combination with other classes of drugs
  - Magnitude of the treatment effect of the combination is expected to be large
- Include external data in incomplete factorial design, e.g., A+B vs SOC, to supplement or replace single agent arm(s)
  - External data must be complete, high -quality, patient -level data (contemporaneous or previous clinical trial)
  - Summary-level evidence from published trials only for hypothesis generation
  - If data is not fit for purpose: only appropriate for hypothesis generation

B.1. Suitability of External Data Source for Contribution of Effect

- External data must
  - Be **patient -level** with sufficient sample size **including covariates to inform comparability** (prognostic and predictive factors)
  - Come from **comparable populations** studied across the combination and the components
  - Use **similar methods of response assessment** and variable collection across data sources
  - Be traceable and **auditable**
  - Allow to select participants for comparison while **remaining blinded** to outcome
- Inclusion of external data and comparison of experimental must be **pre -specified** in SAP
- **Deviations** from external data requirements (e.g., different baseline characteristics) **may be mitigated using** statistical methods for **causal inference / Bayesian methods**

FDA Guidance on Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (December 2023)
FDA Guidance on Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (July 2024)

B.2. Potential External Data Sources & B.3. Endpoint Considerations

- External Data Sources
  - External data from clinical trials
    - Same setting, same indication
    - High degree of relevance if contemporaneous, previous may introduce temporal bias
  - Prospectively collected patient -level data
    - including demographics, disease characteristics, treatment, and outcomes of interest
  - Vaguely specified other patient -level RWD
  - Summary-level evidence from publications
    - Only for hypothesis generation (see above)

- Endpoint Considerations
  - TTE: May be subject to immortal -time bias
    - OS: objective but certain real world data sources can be incomplete and confounded by subsequent therapies
  - Other endpoints: PROs, clinical outcomes & validated biomarkers
  - Timing of assessments & evaluation criteria must be comparable across arms

Boehringer Ingelheim

Development Program Considerations

For Demonstrating Contribution of Effect

Boehringer Ingelheim

C.1. Two or More Investigational Drugs (Refer to the 2013 Codevelopment Guidance)

- Evaluate CoE as early as possible to inform development of combination
  - Allows sponsors to evaluate approriateness of codevelopment approach as per 2013 Codevelopment guidance
- Factorial design highly recommended

Codevelopment of Two or More New Investigational Drugs for Use in Combination | FDA

C.2. An Investigational Drug With a Drug Approved for a Different Indication

- Randomized trial performed early in clinical development highly recommended to demonstrate CoE
- Greater uncertainty with use of external data, in particular for
  - An investigational drug without prior determination of safety of effectiveness in indication [of interest]
  - Disease settings where identification of treatment effect is less reliable based on the natural history of the disease
  - Settings in which the magnitude of treatment effect for the combination is [expected to be] modest
- For use of external data:
  - Strong biologic rationale & nonclinical and/or early clinical evidence for necessity of each drug present
  - Availability of external clinical trials investigating previously approved drug as monotherapy

C.3. Two or More Drugs Approved Individually for Different Indication(s)

- **Randomized trial** recommended as efficacy and safety unknown for new indication
- External data in other indications may mitigate uncertainties
- Appropriateness of use of external data depends on
  - Similarity of tumor types or clinical contexts of the diseases
  - Strength of the rationale based on mechanism of action for use of combination
  - Strength of evidence from external data, including adequacy of source and appropriateness of endpoint
  - Quantity of clinical data demonstrating contribution of individual drugs, e.g., across multiple cancer types
  - Expected magnitude of benefit of novel combination

Take-Home Messages

- Contribution of Effect is a **mandatory regulatory requirement** and must be demonstrated **for each component** in a combination.
- Factorial designs remain the gold standard, but **modified, adaptive, and externally supported designs** are now **explicitly recognized** due to oncology feasibility constraints.
- Use of external data requires rigorous statistical justification, including comparability, adjustment for confounding, and pre-specification in a statistical analysis plan.
- Early planning is highly recommended: contribution of component evaluation should not be deferred to Phase III.
- Sponsors should consult the relevant FDA Review Division [early].

Thank you!