# Regulatory Considerations for the Registration of Products for Prevention or Reduction in the Incidence of Healthcare-Associated Infections

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# Outline

- Healthcare-Associated Infections (HAI)
- Standards for approval
- Characteristics of adequate and well-controlled trials
- Illustrative examples:
  - Drugs to prevent surgical site infections (SSIs)
  - Drugs to reduce the incidence of catheter-related bloodstream infections (CRBSIs)
- Safety database considerations

# Healthcare-Associated Infections (HAI)

- Broadly defined as infections that develop while receiving healthcare or shortly after
  - Includes catheter-associated bloodstream infections, catheter-associated UTIs, surgical site infections, and ventilator-associated pneumonias
- Pathogens responsible frequently develop antimicrobial resistance
- Drugs developed to prevent or reduce the incidence of HAIs may have diverse clinical development pathways

Antibiotic Resistance & Patient Safety Portal

# Statutory Standards for Drug Approval

President John F. Kennedy hands Sen. Estes Kefauver the pen he used to sign the 1962 Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act. Those looking on include Frances Kelsey, second from left, the FDA medical officer who refused to approve the new drug application for Kevadon, the brand name for thalidomide in the United States.

The Kefauver-Harris Amendments established the framework that required drug manufacturers to prove scientifically that a drug was not only safe, but effective

# Statutory Standards for Drug Approval

- A drug's effectiveness must be established by substantial evidence defined as
  - "evidence consisting of adequate and well-controlled investigations, including clinical investigations, . . ." [The United States Federal Food, Drug, and Cosmetic 505(d) 21 USC 355(d)]
  - Interpretated generally as requiring two adequate and well-controlled (A&WC) trials, each convincing on its own
- The Food and Drug Administration Modernization Act amended the provision to add that FDA may consider "data from one A&WC clinical investigation and confirmatory evidence"

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft, December 2019): https://www.fda.gov/media/133660/download

# Adequate and Well-Controlled Trials

- The purpose of these trials is to distinguish the effect of the drug from other influences (spontaneous change, placebo effect, observational biases)

- 21 CFR 314.126 describes the trial design elements intended to minimize bias and permit a valid comparison with a control to assess the drug's effect

21 CFR 314.126

# Characteristics of Adequate and Well-Controlled Trials

| | |
|---|---|
| 1 | Clear statement of objectives and proposed methods of analysis |
| 2 | Permits valid comparison with a control to provide quantitative assessment of drug effect |
| 3 | Method of selecting subjects provides assurance they have disease being studied – or evidence of susceptibility and exposure to disease to be prevented |
| 4 | Method of assignment to study arm minimizes bias and is intended to ensure comparability between groups |
| 5 | Measures to minimize bias on the part of subject, observers, analysts of the data |
| 6 | Method of assessing treatment response is well-defined and reliable |
| 7 | Analysis of the results is adequate to assess the drug effects – analytic methods used, comparability of test and control groups, effects of any interim analyses |

21 CFR 314.126

# Trial Controls

| | |
|---|---|
| **Placebo concurrent** | Comparison to inactive preparation designed to resemble test drug |
| **Dose-comparison concurrent** | Comparison of at least two different doses of test drug |
| **No treatment concurrent** | Comparison with no treatment (usually includes randomization, used when outcome measure is objective and placebo effect is negligible) |
| **Active treatment concurrent** | Comparison with a known effective therapy (usually where placebo/no treatment is contrary to interest of the patient)<br>**Note:** similarity of test drug and active control can mean either that both drugs were effective or that neither drug was effective (analysis of study should reference evidence for effectiveness of the control) |
| **Historical control** | Comparison with experience historically derived from natural history of disease or results from active treatment in a comparable population<br>(usually reserved for special circumstances such as diseases with high, predictable mortality or studies where effect is self-evident) |

# Trial Endpoints

- The methods assessing the response to the drug should be well-defined and reliable
- Endpoints should be clinically meaningful
- Clinical endpoint
  - Characteristic/variable that directly measures a therapeutic effect (how a patient feels, functions, or survives)
  - Microbiological outcomes are not clinical endpoints
- Validated surrogate endpoint
  - An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft, December 2019): https://www.fda.gov/media/133660/download; BEST resource https://www.ncbi.nlm.nih.gov/books/NBK453484/

# Surrogate Endpoints

- Surrogate endpoints are used as a substitute for a direct measure of how a patient feels, functions, or survives
  - Must be supported by evidence that shows they can be relied upon to predict a clinical benefit
- Traditional approval can be supported by A&WC trials establishing an effect on a validated surrogate endpoint which has data, including from clinical trials and epidemiologic studies, that demonstrate its ability to predict a clinical benefit
- Accelerated approval* can be supported by A&WC trials establishing an effect on a surrogate endpoint reasonably likely to predict clinical benefit, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.
  - Such approval requires that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome
- FDA maintains a public list** of surrogate endpoints used as basis of approval
  - Acceptability of these surrogate endpoints for use in a particular drug development program is determined on a case-by-case basis and is context-dependent (disease, patient population, mechanism of action, availability of current treatments)

*Subpart H – Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses 21 CFR 314.510
https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development
** https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

# Trial Objectives

| Superiority Trial | Non-Inferiority (NI) Trial |
| --- | --- |
| • Demonstrates efficacy by showing test drug is superior to control<br>• Generally, the strongest evidence of effectiveness | • Demonstrates efficacy by showing test drug is not less effective than active control by more than a pre-defined amount (NI margin)<br>• Relies upon an assumption, not confirmed in the trial, that the control had its anticipated effect (which is the basis for the NI margin) |

# Illustrative Examples: Drugs to Prevent SSI*

## Topical Antibacterial for *S.aureus* Nasal Decolonization

- Trial endpoint: SSI incidence
- Inconsistent data on whether nasal decolonization results in reduction in SSI
- Requires assessment relative to placebo because there is no active comparator with demonstrated efficacy

## Systemic Antibacterial for Peri-Operative Prophylaxis

- Trial endpoint: SSI incidence
- Multiple trials demonstrating reduction in SSI with peri-operative antibiotics compared to placebo/no-treatment
- Allows justification of an NI margin for an active comparator-controlled NI trial

*SSI: surgical site infections

# Topical Antibacterial for Nasal *S. aureus* Decolonization to Prevent SSI

- Published literature regarding the clinical benefit of nasal *S. aureus* decolonization is inconclusive
  - Studies to date have not demonstrated consistent outcomes for prevention of SSI
  - Most studies reporting clinical benefit used bundled nasal and skin decolonization strategies; determination of the benefit of nasal decolonization alone is not possible
  - Limitations include heterogeneity in patient populations, differences in reported endpoints and treatment effects, variable methodologic quality

Ridenour et 2007; Bode et al 2010; Liu et al 2017; Wilcox et al 2003, Nicholson et al 2006, Walsh et al 2011; Konvalinka et al 2006; Kalmeijer et al 2002; Perl et al 2002

# Topical Antibacterial for Nasal *S. aureus* Decolonization to Prevent SSI

Trial design considerations

- Control
  - Placebo vehicle (controls for physical effects of topical application, blinding)
- Patient selection
  - Enrichment for nasal *S. aureus* carriers, surgical population
- Concomitant prophylaxis measures
  - Timing/type of skin decontamination, systemic peri-operative antibacterials
- Randomization
  - Cluster (by hospital, by surgical unit) vs individual patient
- Clinical endpoints
  - Incidence of SSI, incidence of all infections due to *S. aureus*, mortality
  - Consider secondary endpoints for hospital length of stay, readmission rates, re-operation rates
- Endpoint analysis
  - Superiority of treatment to placebo

# Systemic Antibacterial for Peri-operative Prophylaxis to Prevent SSI

- Multiple trials in published literature demonstrate a clinical benefit relative to placebo/no-treatment in surgical procedures with high rates of infection (clean-contaminated, contaminated)
- Example: Eykyn et al 1979 Lancet
  - Randomized, double-blind, placebo-controlled, single center trial
  - Patients undergoing elective colorectal surgery randomized to IV metronidazole or placebo dosed immediately prior to surgery, repeated at 8h and 16h
  - Pre-operative bowel preparation identical for both groups
  - Overall SSI incidence (deep, superficial, perineal):
    - 15/44 (34%) metronidazole arm
    - 30/39 (77%) placebo arm

# Systemic Antibacterials for Peri-operative Prophylaxis to Prevent SSI

**Parenteral Antibacterials With Approved Indications for SSI Prophylaxis in Clean Contaminated/Potentially Contaminated Procedures**

| Drug | Relevant Indication |
|---|---|
| Metronidazole | Reduce the incidence of post-operative infection in patients undergoing elective colorectal surgery classified as contaminated or potentially contaminated |
| Ertapenem | Prevention of SSI following elective colorectal surgery |
| Cefotetan | Reduce the incidence of certain post-operative infections in patients undergoing contaminated or potentially contaminated procedures |
| Ceftriaxone | Reduce the incidence of post-operative infections in patients undergoing contaminated or potentially contaminated procedures |
| Cefazolin | Reduce the incidence of certain post-operative infections in patients undergoing contaminated or potentially contaminated procedures |
| Cefuroxime | Reduce the incidence of certain post-operative infections in patients undergoing contaminated or potentially contaminated procedures |
| Cefotaxime | Reduce the incidence of certain infections in patients undergoing contaminated or potentially contaminated procedures |

# Systemic Antibacterial for Peri-operative Prophylaxis to Prevent SSI

## Trial design considerations

- Control
  - Active-control for surgical procedures with established efficacy in SSI prevention, placebo control possible for procedures without demonstrated efficacy
- Patient selection
  - Surgical procedure, similarity to population in which efficacy demonstrated for comparator, enrichment strategies
- Concomitant prophylaxis measures
  - Timing/type of skin decontamination, bowel prep
- Randomization
  - Cluster (by hospital, by surgical unit) vs individual patient
- Clinical endpoints
  - Incidence of SSI, mortality
  - Consider secondary endpoints for length of stay, readmission rates, re-operation rates
- Endpoint analysis
  - Superiority to control; non-inferiority to active control (with adequate justification of the NI margin)

# Illustrative Example: Antibacterial to Reduce the Incidence of CRBSI*

- Antibacterial locally administered in a catheter lock solution (CLS)
- FDA approved CLSs include saline solutions that physically occupy the catheter space to provide hydraulic lock +/- anticoagulant drug to reduce incidence of clotting
- Antibacterial could be evaluated as an add-on to CLS containing saline +/- anticoagulant and compared to a control CLS with otherwise identical composition

*Catheter-related blood stream infection

# Antibacterial to Reduce the Incidence of CRBSI

## Trial design considerations

- Control
  - No FDA-approved antibacterial CLS but could consider active control with FDA-approved anticoagulant CLS (add-on therapy) or placebo control with saline CLS
- Patient selection
  - Catheter type, long-term vs. short-term catheter use, catheter function (hemodialysis, nutrition, chemotherapy), enrichment for patients at highest risk (past infection, frequent access, etc.)
- Concomitant prophylaxis measures
  - Protocols for aseptic technique, use of chlorhexidine-gluconate-impregnated sponges or other dressings, standardization of tubing changes
- Clinical endpoints
  - CRBSI incidence (protocol definitions, blinded adjudication), catheter loss, mortality
  - Consider secondary endpoints to evaluate potential effects on clotting, catheter patency
- Endpoint analysis
  - Superiority to control

# Safety Database Considerations

- Approval decision requires both a finding of substantial evidence of effectiveness AND a determination that the drug is safe for its intended use
  - Benefits of the drug outweigh its risks under the conditions of use defined in the labeling
- For drugs used as prophylaxis/reduction in incidence of infection, the benefit may only be experienced by a fraction of the treated patients (the subset that would have developed the disease without the prophylactic intervention)
  - A larger safety database would generally be required for a drug intended for prophylaxis of a serious infection than a drug intended for treatment of a serious infection

Premarketing Risk Assessment (March 2005) https://www.fda.gov/media/71650/download;
Benefit-Risk Assessment for New Drug and Biological Products (Draft, September 2021)
https://www.fda.gov/media/152544/download

# Conclusions

- Products developed for prevention or reduction of healthcare associated infections may have diverse modes of delivery and mechanisms of action
  - Decolonization of skin or mucosal surfaces, topical application at sites of pathogen entry, systemic administration to decrease risk in a defined time period
- Approval for an indication of prevention or reduction in the incidence of healthcare associated infections requires:
  - Demonstration of efficacy using a clinically meaningful endpoint (such as reduced incidence of serious infections or decreased mortality) or validated surrogate endpoint
  - Adequate safety database to determine whether benefits of the drug outweigh its risks for the use defined in its labeling


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