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Evolving Antimicrobials: The Circuitous Path from Discovery to Clinical Use

Mentoring

- A mentor is someone whose hindsight can become your foresight!

Objectives

- At the conclusion of this presentation participants will be cognizant of:
  - The various phases for clinical trials in drug development
  - The required components of an FDA submission for approval of an antimicrobial agent
  - The challenges in making *in vitro* susceptibility testing materials available to clinical microbiology laboratories at the time of antimicrobial launch
- Today's presentation will hopefully provide a glimmer of the process; regulations & guidelines in the FDA Federal Register are voluminous

Background

- Developing a new antimicrobial agent for humans can take >10 years from discovery to market
- Can cost close to a billion dollars (3014)
- <10% of drug development projects will lead to an FDA approval
- Antibiotics particularly challenging from a financial perspective for PHARMA because they are only prescribed for short periods of time

Development and Approval Process – Quick Overall Summary

- FDA states that American consumers benefit from having access to the **safest** and most advanced pharmaceutical system in the world
- The primary watchdog in this system is FDA's Center for Drug Evaluation and Research (CDER)
- CDER is most widely known for evaluating drugs before they can be sold
- Prevents "quackery", but also provides clinicians and patients with the information required to use such medications widely (label and advertising)

CDER (continued)

- Center ensures that drugs (both brand name and generic) work correctly and that their health benefits outweigh their known risks (risk/benefit ratio)
- Companies hoping to bring a drug to market must first test it per FDA guidance (FDA itself does not conduct testing)
- Company then sends CDER all data from such studies to prove that the drug is safe and effective for its intended use
- Team of CDER physicians, statisticians, chemists, pharmacologist, and microbiologists (among others) reviews the shared data and proposes labeling

CDER (continued)

- Before a drug can be tested in people, the drug company or sponsor performs animal (mice, rabbits, etc.) and laboratory tests to assess how the drug works and whether it is likely to be safe and work well in humans
- Next, a series of tests in people is begun to determine whether the drug is safe when used to treat a disease and whether it provides a real health benefit
- If the CDER review establishes that a drug's health benefits outweigh its known risks, then the drug is **approved** for sale

FDA Approval: What Does It Mean?

- FDA approval of a drug means that data on the drug's effects have been reviewed by CDER, and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population.
- Drug approval process takes place in a very structured framework

Framework Components of Drug Approval Process

- Analysis of the target condition and available treatments: FDA reviewers analyze the condition or illness for which the drug is intended and evaluate the current treatment landscape providing the context for weighing the drugs risks and benefits.
- For example, a drug intended to treat patients with a life-threatening disease for which no other therapy exists may be considered to have benefits that outweigh the risks even if those risks would be considered unacceptable for a condition that is not life-threatening.
- Assessment of benefits and risks from clinical data: FDA reviewers evaluate clinical benefit and risk information submitted by the drug manufacturer, taking into account uncertainties that may result from imperfect or incomplete data.

Framework Components of Drug Approval Process

- Generally, CEDER expects that results will be submitted from 2 well-designed clinical trials to assure that the findings from 1st trial are not a function of chance or bias.
- In certain cases especially if the disease is rare and multiple trials may not be feasible, convincing evidence from one clinical trial may suffice. Evidence, however, that the drug will benefit the target population must outweigh any risks or uncertainties.
- Strategies for managing risks: All drugs have risks. Risk management strategies include an FDA-approved drug label which clearly describes the drugs benefits and risks, and how those risks can be detected and managed. Ads!

Drug Approval Process

- Sometimes the benefits and risks are uncertain and may be difficult to interpret or predict. In such cases CEDER and the drug manufacturer may reach different conclusions after analyzing the same data, or there may be differences of opinion among members of the FDA review team.

Accelerated Approval

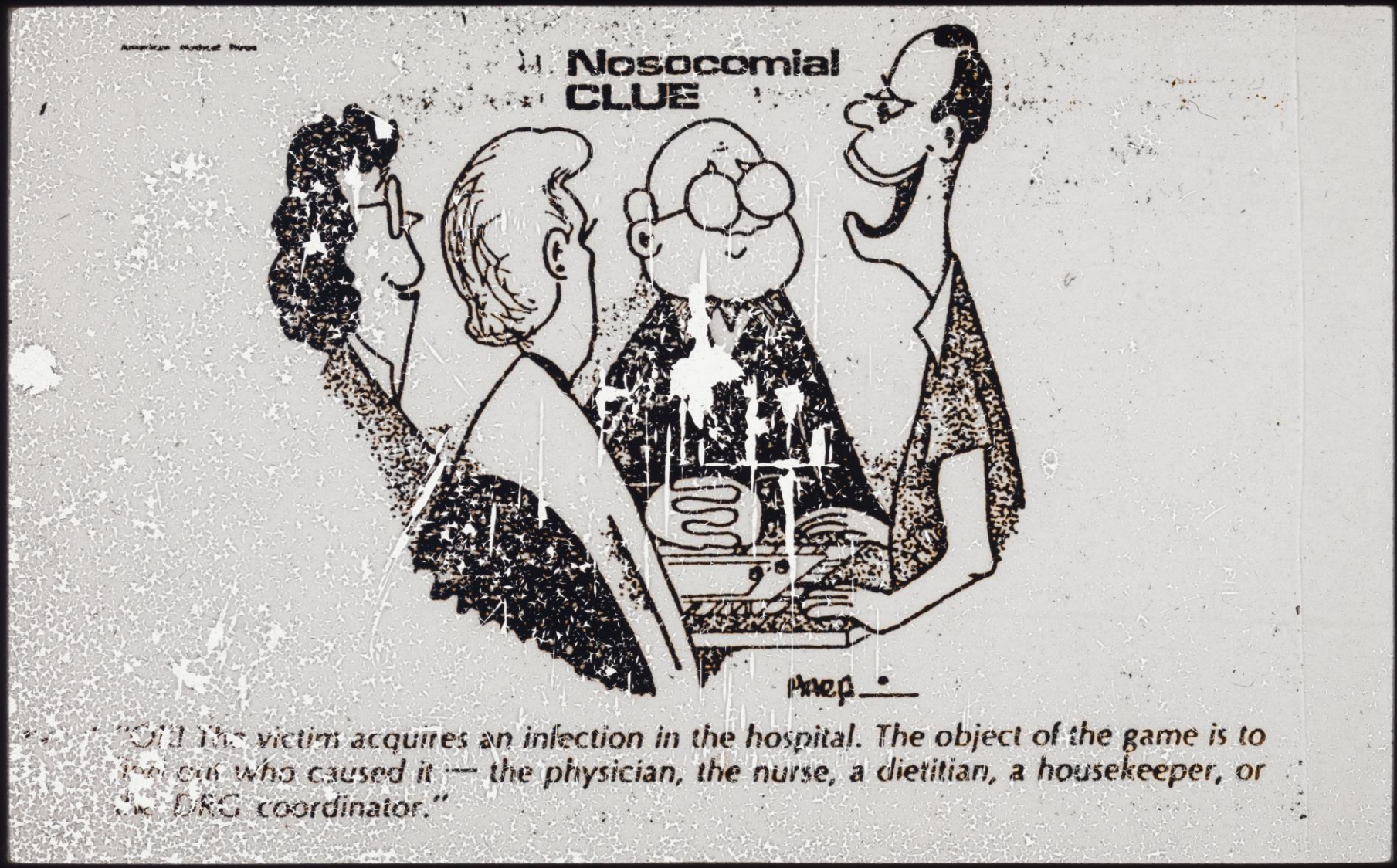
- In some cases the approval of a new drug is expedited. Accelerated approval can be applied to promising therapies that treat a serious or life-threatening condition and provide therapeutic benefit over available therapies.
- This approach allows for approval of a drug that demonstrates an effect on a “surrogate endpoint” that is reasonably likely to predict clinical benefit, or on a clinical endpoint that occurs earlier but may not be as robust as the standard endpoint used for approval.
- This approval pathway is especially useful when the drug is meant to treat a disease whose course is long and an extended period of time is needed to measure its effect.

Accelerated approval (continued)

- In such cases, after the drug enters the market, the drug manufacturer is required to conduct post-marketing clinical trials to verify and describe the drug's benefit.
- If further trials fail to verify the predicted clinical benefit, FDA may withdraw approval.
- Many antiretroviral drugs used to treat HIV/AIDS entered the market via accelerated approval and subsequently altered the treatment paradigm.

Drug Development Designations

- The agency also employs several approaches to encourage the development of certain drugs (e.g., antibiotics for MDR bacterial pathogens), especially drugs that may represent the first available treatment for an illness, or ones that have a significant benefit over existing drugs.
- These approaches are designed to address specific needs, and a new drug application may receive >1 designation. Each designation ensures that therapies for serious conditions are made available to patients as soon as reviewers can conclude that their benefits justify their risks.


Nosocomial
CLUE
"Oh! The victim acquires an infection in the hospital. The object of the game is to find out who caused it — the physician, the nurse, a dietitian, a housekeeper, or the DRG coordinator."

Drug Development Designations

- Fast Track: A process designed to facilitate the development and advance the review of drugs that treat serious conditions, and fill an unmet medical need, based on promising animal or human data.
  - Example: experimental, broad-range, two-antibody Ebola drug, known as MBP134 and developed by Mapp Biopharmaceutical, “protected monkeys and ferrets against the Bundibugyo and Sudan strains, as well as the deadliest Zaire strain responsible for the 2013-2016 epidemic in West Africa and the current outbreak in the Democratic Republic of Congo.”
  - Example: Food and Drug Administration “granted Fast Track designation to” Acurx Pharmaceuticals LLC’s “ACX-362E, an investigational new treatment for *Clostridioides difficile* infection.” The company recently started a phase 1 trial of the “targeted, narrow spectrum antibiotic.”
- Goal: to get important new drugs to the patient earlier

Breakthrough Therapy

- Designation expedites development and review of drugs that are intended to treat a serious condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy.
- A drug with a Breakthrough Therapy designation may also be eligible for the Fast Track process.

Priority Review

- Indicates that CEDER aims to take action on an application within 6 months, compared to 10 months under standard review.
- A priority review designation directs attention and resources to evaluate drugs that would significantly improve the treatment, diagnosis, or prevention of serious conditions.

Some of the Submissions Required During Drug Evaluation Process

- Investigational New Drug Application (IND)
- New Clinical Trial Submitted to an IND
- New Drug Application (NDA)
- Efficacy Supplement to an Approved NDA
- Premarket Approval Application (PMA)
- Humanitarian Device Exemption (HDE)

Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)

- Evolved as a byproduct of the 21st Century Cures Act
- Law mandated FDA to issue guidance "describing criteria, processes, and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial an antifungal drugs".
- FDA recognized the decline in antibacterial drug research even as serious antibacterial drug resistant infectious were on the increase and development and perceived it as a critical public health and patient care concern.

Unmet Medical Need Guidance

- FDA published guidance for industry entitled: "*Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Infections*"
- Recognized that there are a # of challenges associated with conducting clinical trials to evaluate antibacterial and antifungal drugs for the treatment of such patients
- A component (Title V) of the FDA Safety and Innovation Act titled *Generating Antibiotic Incentives Now* (GAIN act) offered financial incentives to industry for the development of antibacterial and antifungal drug products that treat serious or life-threatening infections

LPAD Pathway

- Drugs eligible for approval under LPAD pathway may follow streamlined approaches such as:
  - Clinical trials using noninferiority designs, including a single noninferiority trial at a body site of infection, or trial designs with wider noninferiority margins than used in traditional development programs
  - Nested noninferiority/superiority clinical trials
  - A streamlined clinical development program for a limited population may involve smaller, shorter, or fewer clinical trials.
  - In such circumstances, robust nonclinical evaluations (including animal modes of infection) and pharmacokinetic/ pharmacodynamic (exposure response) data may provide important supportive information to help assess the benefits and risks of the drug in the intended limited population.

LPAD Pathway

- Examples of drugs for which approval under the LPAD pathway could be appropriate include the following:
  - An antibacterial drug with a narrow spectrum of activity (e.g., only active against a single species [or a few species] within a genus) and the target pathogen or pathogens occur infrequently at any body site of infection
  - An antibacterial or antifungal drug that, based on available therapy, would only have a role in the therapeutic armamentarium for a select patient population with no other options (metallo-β-lactamase producing Enterobacteriaceae)

The Drug Development Process
Step 1: Discovery and Development

- Discovery - Typically, researchers discover new drugs through:
  - New insights into an infectious process that allow them to design a product to stop or reverse the effects of the disease
  - Blast testing of molecular compounds to find possible beneficial effects against any of a large number of organisms
  - Existing treatments that have unanticipated effects: Metronidazole
  - New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material

Discovery

- At discovery stage in the process, thousands of compounds may be potential candidates for development as antimicrobials. After early testing, however, only a small number of compounds look promising and call for further study.

Development

- Once researchers identify a promising compound for development, they conduct experiments to gather information on:
  - How it is absorbed, distributed, metabolized, and excreted
  - Its potential benefits and mechanisms of action
  - The best dosage
  - The best way to give the drug (such as by mouth or injection)
  - Side effects or adverse events that are often referred to as toxicity
  - How it affects different groups of people (such as by gender, race, or ethnicity) differently
  - How it interacts with other drugs and treatments
  - Its effectiveness as compared with similar drugs

Early Steps (“Baby Steps”)

- Stage 1 involves imagination. Considerations include:
  - Conditions and syndromes in need of additional medicines
  - Current and emerging resistance patterns
  - Market
- Important are the relationships and interdependencies between chemical, microbiological, and clinical disciplines; the 3 groups must collaborate effectively for successful development

Step 2: Preclinical Research

- Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm (toxicity). The two types of preclinical research are *in vitro* and *in vivo*

Preclinical Research

- FDA requires researchers to use good laboratory practices (GLP), defined in medical product development regulations, for preclinical laboratory studies. These regulations set the minimum basic requirements for study conduct, personnel, facilities, equipment, written protocols, operating procedures, study reports, and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated product
- Typically, preclinical studies are not overly large.
- However, these studies must provide detailed information on dosing and toxicity levels.

Preclinical Research

- After preclinical testing, researchers review their findings and decide whether the drug should be tested in humans

Step 3: Clinical Research

- “Drugs are tested on humans to make sure that they are safe and effective”
- While preclinical research answers basic questions about a drug’s safety, it is not a substitute for studies of ways the drug will interact with the human body.
- “Clinical research” refers to studies, or trials, that are done in people. As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins.

Clinical Research

- Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific study plan, called a protocol, that is developed by the researcher or manufacturer. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. Then, they decide:
  - Who qualifies to participate (selection criteria)
  - How many people will be part of the study
  - How long the study will last
  - Whether there will be a control group and other ways to limit research bias
  - How the drug will be given to patients and at what dosage
  - What assessments will be conducted, when, and what data will be collected
  - How the data will be reviewed and analyzed (bias)

Clinical Research: Phase 1 Clinical Trials

- **Study Participants:** 20 to 100 healthy volunteers or people with the disease/condition (infection).
- **Length of Study:** Several months
- **Approximately 70% of drugs move to the next phase**
- Phase 1 studies are closely monitored and gather information about how a drug interacts with the human body. Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate and what its acute side effects are.

Phase 1 Clinical Trials(continued)

- As a Phase 1 trial continues, researchers answer research questions related to how it works in the body, the side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2 studies.

Phase II Clinical Trials

- **Study Participants:** Up to several hundred people with the disease/condition.
- **Length of Study:** Several months to 2 years
- **Approximately 33% of drugs move to the next phase**
- **Purpose: Efficacy and side effects**
  - In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition (infection) for which the drug is being developed. Typically involving a few hundred patients, these studies aren't large enough to show whether the drug will be beneficial

Clinical trials (continued)

- Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols.

Phase II Trials (continued)

- Phase 2 studies begin if Phase 1 studies don't reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition (infection).
- For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment--usually an inactive substance (placebo), or a different drug (resistance issue). Safety continues to be evaluated, and short-term side effects are studied.

Phase III Clinical Trials

- Purpose: Efficacy and monitoring of adverse reactions
- Researchers design Phase 3 studies to demonstrate whether or not a product offers a treatment benefit to a specific population - sometimes known as “pivotal studies”
- Phase 3 studies provide most of the safety data. In previous studies, it is possible that less common side effects might have gone undetected.
- Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side effects.

Phase III Clinical Trials

- Phase III:
  - **Study Participants:** 300 to 3,000 volunteers who have the disease or condition (infection)
  - **Length of Study:** 1 to 4 years
  - **Approximately 25-30% of drugs move to the next phase**

Step 4: FDA Drug Review

- If a drug developer has sufficient evidence from its early testing, as well as from preclinical and clinical trials that a drug is safe and effective for its intended use, the company can file an application to market the drug (antibiotic)
- The FDA review team then thoroughly examines all submitted data and makes a decision to approve or not approve it

NDA Application

- Drug developer must also include in this application:
  - Proposed labeling
  - Safety updates
  - Patient information
  - Any data from studies that may have been conducted by another entity outside of the U.S.
  - Informational review board compliance information
  - Directions for use

FDA NDA Review

- 1st, FDA Review Team decides if it is complete. If incomplete, they can refuse to file the NDA.
- If it is complete, the team has 6 – 10 months to make a decision as to whether to approve the drug.
- The review team analyzes study results and looks for possible issues with the application, such as weaknesses of the study design or analyses.
- Reviewers determine whether they agree with the sponsor's results and conclusions, or whether they need any additional information to make a decision. (Approvable designation)

FDA NDA Review

- Each member of the team conducts a thorough review of his or her section
- For example, the microbiologist reviews all of the *in vitro* data on an antimicrobials' spectrum of activity.
- On occasion, when safety and effectiveness questions exist, the FDA organizes Advisory Committees to garner independent, expert advice and to permit the public to make comments.
- These Advisory Committees include a Patient Representative that provides input from the patient perspective.

FDA NDA Review Process: Microbiology

- Anti-infectives are “special”
  - Submission requires a number of unique components
  - Examples include (CLSI M23 relied upon heavily[1]):
    - *In vitro* spectrum of activity against a wide range of organisms focused on those agents causative of a specific infectious process
    - Recommended testing methods (glucose-6-phosphate requirement for fosfomycin disk testing)
    - Suggested breakpoints (organism specific)
    - Quality control recommendations (organisms and acceptable ranges)
    - Specifics on mechanisms of antimicrobial action against microorganisms
    - Mechanisms of resistance
    - Mutation rates in *in vitro* systems

[1]Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters. CLSI guideline M23 (ISBN 1-56238-842-8 [Print]; ISBN 1-56238-843-6 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2018.

FDA Approval

- In cases where FDA determines that a drug has been shown to be safe and effective for its intended use, CEDER then works with the sponsor to develop and refine prescribing information – “labelling”
- Often, though, issues remain that must be resolved prior to drug marketing
- Sometimes the FDA requires the sponsor to address questions based on existing data (e.g., collateral damage)
- In other cases the FDA requires additional studies
- Mechanisms exist for formal appeal

Phase IV Clinical Trials

- Post-market safety monitoring is required post-approval
  Purpose: Further assess both safety and efficacy
- Phase 4 trials are carried out once the drug or device has been approved by FDA during the Post-Market Safety Monitoring (e.g., for additional indications)
- For antimicrobials, ongoing surveillance studies to detect antimicrobial resistance are required and data must be submitted to FDA for their review

"Don't forget to take a handful of our complimentary antibiotics on your way out."

Testing “Devices”

- “Devices” include: disks, gradient agar strips, broth microdilution panels, etc. (Regulated Devices)
- Drug manufacturers make efforts to have testing materials available by antibiotic launch, but rarely, if ever, the case
- Device manufacturers must submit 510ks with very specific testing and result requirements from trials to the FDA for approval
- Expensive and time-consuming process that is not generally initiated by device manufacturers until they are certain that an antibiotic will receive FDA approval

Testing Devices

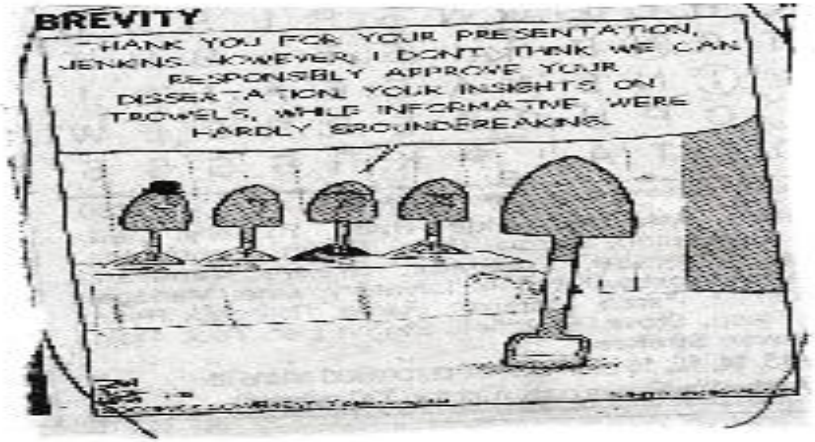
- Drug manufacturers typically are requited to cover costs of such development to device manufacturers
- Prior to receipt of FDA approval, some “devices” may become available for Research Use Only (RUO) applications
- For broth microdilution panels, real estate issue
- For those labs performing agar dilution testing, standard antibiotic powder is usually available from drug manufacturer at time of drug launch
- Many medical centers will not add a drug to its antibiotic formulary addition until testing can be performed on site

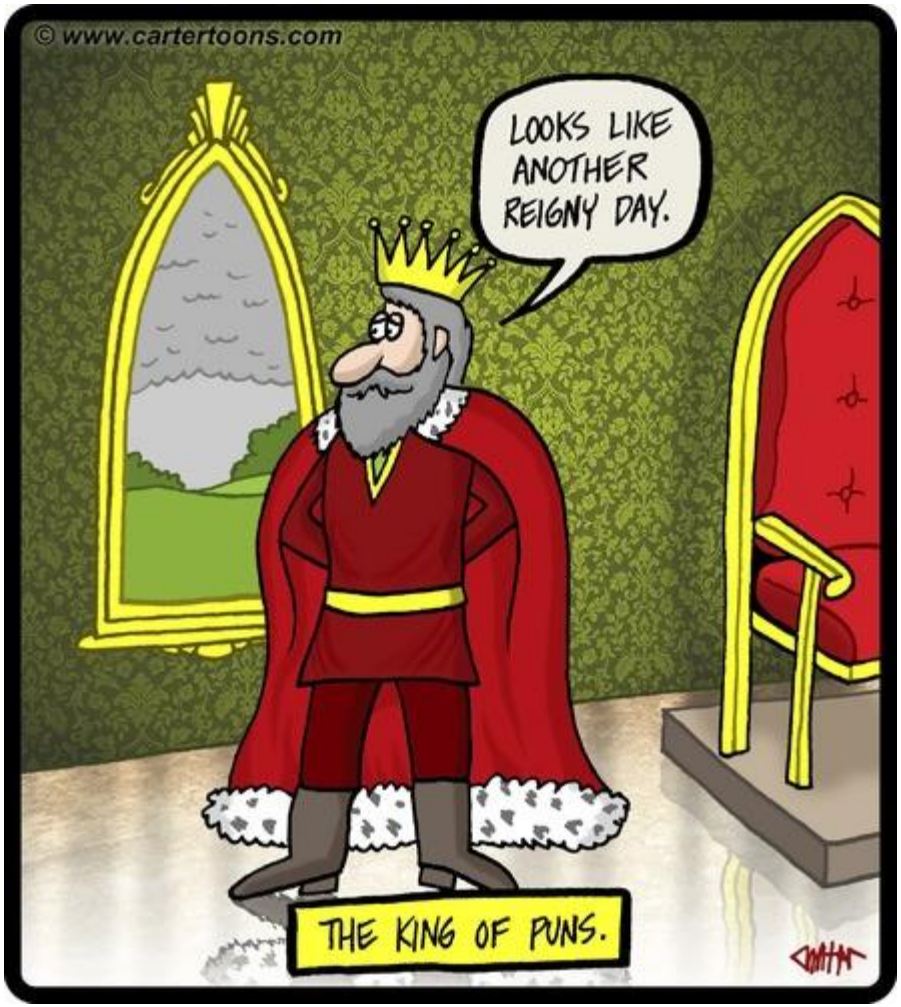
Testing of Newly Marketed Antibiotics

- Some drug manufacturers establish contracts with reference labs for performance of drug testing prior to availability of testing devices for microbiology labs, but results not available in clinically relevant time frame
- January 17, 2019 headline: "FDA Encourages Coordinated Development of Antimicrobial Susceptibility Tests and Drugs"
- The goal of this guidance is to:
  - **Minimize time** between the approval of new antimicrobial drugs and clearance of antimicrobial susceptibility tests used to determine the potential effectiveness of those drugs; and
  - **Provide recommendations** to the medical device and drug industries on how to work together to facilitate timely clearance of antimicrobial susceptibility test devices by the FDA

The FDA's Strategic Approach for Combatting Antimicrobial Resistance

- The FDA has developed a strategic approach for combatting antimicrobial resistance to better coordinate drug and device development, promote stewardship, support antimicrobial resistance surveillance, and advance regulatory science.
- Part of this approach involves providing this guidance that aims to facilitate the availability of antimicrobial susceptibility tests in a timely manner once a new antibacterial drug is approved


BREVITY
THANK YOU FOR YOUR PRESENTATION, JENKINS. HOWEVER, I DON'T THINK WE CAN RESPONSIBLY APPROVE YOUR DISSERTATION. YOUR INSIGHTS ON TROWELS, WHILE INFORMATIVE, WERE HARDLY GROUNDBREAKING.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