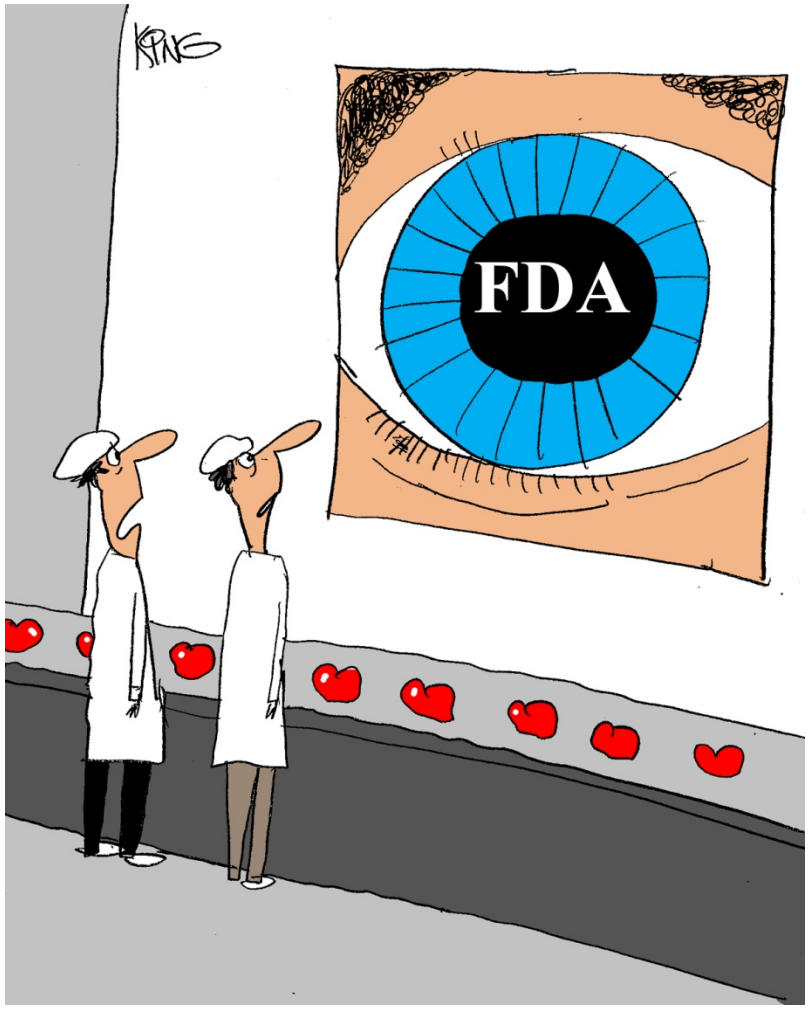
FDA Drug Approval Process

American Institute of Chemical Engineeers
Clif Hotvedt
March 21, 2016


KING
FDA


The AUTOMAT = as famous as the New York Skyline itself
AUTOMAT
HORN & HARDART
HORN & HARDART
AUTOMAT
AUTOMAT
TIMES SQUARE - NEW YORK
HOT COFFEE
PIES
SECTION OF AUTOMAT MACHINES


PIES
CAKES

HOW AN AUTOMAT WORKS

FIRST DROP YOUR NICKELS IN THE SLOT

THEN TURN THE KNOB THE GLASS DOOR CLICKS OPEN

LIFT THE DOOR AND HELP YOURSELF

HORN & HARDART

Interior of One of the Fifty Automat-Cafeterias in Philadelphia and New York

Today's Agenda

- FDA Overview
- Drug Approval Pathways
  - Shortcuts
- Advisory Committees
- Pharmaceutical Advertising/Oversight

…but first a brief quiz

A Brief True or False Quiz

- FDA ensures the safety of meat
- FDA ensures the safety of chickens
- FDA regulates *shell* eggs
- FDA regulates liquid eggs
- FDA regulates pet food
- FDA regulates influenza vaccine
- FDA regulates microwave ovens
- FDA regulates make-up
- FDA regulates airport security scanners
- FDA regulates lethal injection drugs

What FDA Does *Not* Regulate

- Advertising – Federal Trade Commission
- Alcohol – Alcohol, Tobacco and Firearms
- Consumer Products – Consumer Product Safety Commission
- Drugs of Abuse – Drug Enforcement Administration
- Meat and Poultry – Department of Agriculture
- Pesticides – Environmental Protection Agency
- Restaurants and Grocery Stores – Local health departments
- Water – Environmental Protection Agency
  - Collaboration between agencies
    - "Gray areas" and overlap exists
      - Dietary Supplements – FTC/FDA

Dietary Supplements

- Dietary supplement manufacturers and distributors **are *not* required to obtain approval from FDA** before marketing dietary supplements. Before a firm markets a dietary supplement, the firm is responsible for ensuring that
- the products it manufactures or distributes are safe
- any claims made about the products are not false or misleading
- the products comply with the Federal Food, Drug, and Cosmetic Act and FDA regulations in all other respects

FDA Mantra

No drug is entirely safe.

No drug is entirely effective.

Development of Food and Drug Law

- **Pure Food and Drugs Act of 1906:** Required only that drugs meet certain standards for **strength and purity** but not for safety.


QUICK, JUDGE WE MUST RECOVER THE BODY FROM THE LARD VAT
ALL STAR FEATURE CORP. IN MOTION PICTURES
– UPTON SINCLAIR'S –
WONDERFUL STORY OF THE BEEF PACKING INDUSTRY
THE JUNGLE
FEATURING
GEORGE NASH – GAIL KANE
AND THE AUTHOR
5 DARING ACTS — 210 ASTOUNDING SCENES

Development of Food and Drug Law

- **Orphan Drug Act 1983:** Passed to stimulate the development of drugs and biological products for the treatment of **rare diseases.**

- **Drug Price Competition and Patent Term Restoration Act 1984 (Waxman-Hatch):** The Act enables a generic pharmaceutical manufacturer to develop copy of a patented innovator drug **without duplicating the clinical and non-clinical studies or risking liability for patent infringement damages.** The generic manufacturer must only demonstrate **bioequivalence** to the innovator.

- **Prescription Drug User Fee Act 1992 (PDUFA):** PDUFA allows the FDA to collect substantial fees from drug manufacturers to fund the new drug approval process.

FY2016 Fees

- PDUFA – Prescription Drug User Fee Act (Human)
  - NDAs $2,374,200
  - Supplemental application – $1,187,000
  - Establishment fee – $585,200 (per site)
  - Per product fee – $114,450
- ADUFA - Animal Drug User Fee Act
  - $351,100 per original animal NDA
  - $175,550 per abbreviated application with clinical data for a generic animal drug
- GDUFA - Generic Drug User Fee Act (Human)
  - ANDA $76,030
  - Domestic establishment fee $40,867
  - Foreign establishment fee $55,867
- BsUFA – Biosimilar User Fee Act (Human)
  - Biosimilar biological product application - $2,374,200
  - Without clinical data - $1,187,100

PDUFA V (2013-2017)

- Goals-
  - NME NDAs and original BLAs: Review 90% within 10 months of 60 day filing period; Day 74 letter with indication of need for an AdCom
  - Non-NME NDAs: review 90% within 10 months of filing data
  - **Priority NMEs** and original BLAs: Review 90% within 6 months of 60 day filing period.
  - More meetings with sponsors, proprietary name review as early as Ph II, advancing use of biomarkers, advancing drugs for rare diseases, enhance, modify FDA drug safety system, enhance risk evaluation and mitigation strategies (REMS)

New Drug Development

Drugs under Development

- Over 7,000 drugs are under development worldwide:
  - 1,813 for cancer
  - 1,329 for neurological disorders
  - 1,120 for immunological diseases
  - 1,256 for infectious diseases
  - 599 for cardiovascular diseders
  - 511 for mental health disorders
  - 475 for diabetes
  - 150 for HIV/AIDS
  - 12 % of drugs entering clinical trials make it to patients
  - Thousands never get past discovery/preclinical testing

Drug Development: Costly and Risky

- The average cost of developing a new drug is $2.6 billion
- It takes an average of 10 to 15 years to bring a new medicine from the laboratory to your medicine cabinet
- On average, only 3 out of 10 prescription medications available to treat Americans generate revenues that meet or exceed average R&D costs. (PhRMA)

JAK inhibition for solid tumors flops, forcing Incyte to pull the plug on a slate of trials

- Jakafi has failed to help patients in a late-stage study for pancreatic cancer, and Incyte feels that it now has all the data it needs to prove that a JAK1 inhibitor is the wrong way to go in solid tumors.
- Just ahead of its annual numbers release, Incyte reported today that it is slamming the brakes on a range of studies for Jakafi as well as the experimental INCB39110, another JAK1. Already halted on one colon cancer trial failure, Incyte is ending the Phase III pancreatic cancer study, a separate midstage trial in colorectal cancer, a Phase II for breast and lung cancers and a dose-ranging trial for INCB39110 in pancreatic cancer.
- Shares of Incyte plunged 23% on the news of the setback.

Drug Development: Costly and Risky

- Hepatitis C can now be cured in a matter of weeks with oral drugs versus injectables or treatment failure leading to liver transplant – for $54,000 - $120,000 for 3 months of treatment.
- Specialty medicines accounted for 1 percent of prescriptions but 31 percent of all drug spending in 2014.

Specialty Medicines

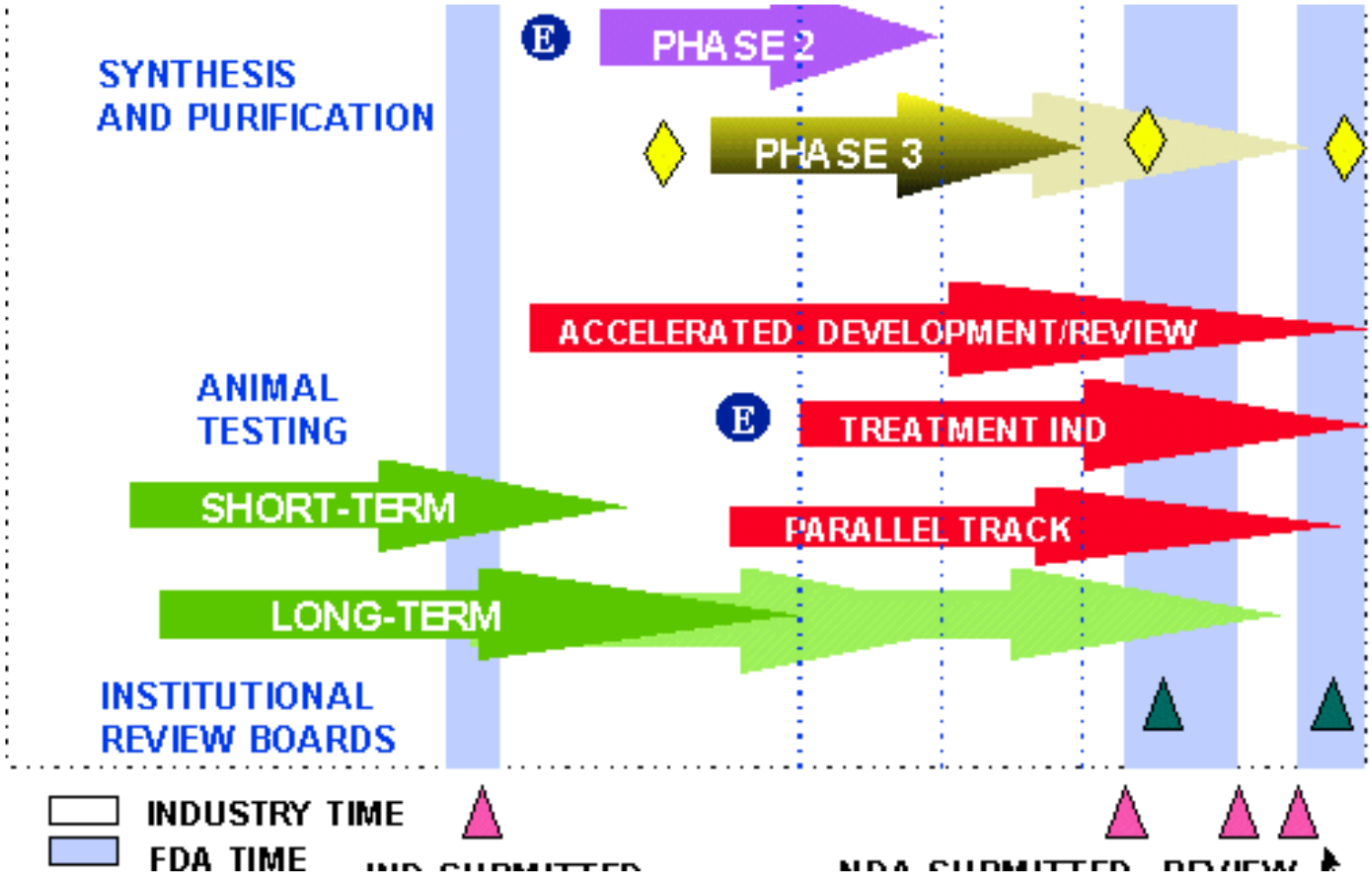
These drugs treat complex and chronic conditions, including:

- Anticoagulants
- Cancer
- Chronic kidney failure
- Growth hormnes
- Multiple sclerosis
- Organ transplants
- Rheumatoid arthritis

Eureka! New Drug Discovery

- Many drugs are typically developed to treat a certain disease based on modeling (rational drug design)
- However, drugs/uses may also be discovered by accident (e.g., Rogaine, Viagra)
- Research and development conducted by pharmaceutical companies, academic institutions and the government – i.e. National Institutes of Health

Drug Development Process



Investigational New Drug Application

- The FDA first enters the picture when a drug sponsor submits an IND
  - Sponsors are those who take responsibility for marketing a drug - companies, institutions, etc.
- The IND includes results of pre-clinical testing and the plan for human testing
- FDA determines if it is reasonably safe to move forward with human testing
- Trials properly designed, protocol determined

INDs and IRBs

- Human testing begins after the IND is reviewed and approved by the FDA
- Next individual study sites review the protocol
- Institutional review board (IRB) at academic medical centers and major research centers review the protocol and consider allowing the trial to occur at their site
  - IRB is a panel of scientists, doctors, nurses and lay people
  - Usually meet once a month to review a number of protocols

IRBs and Informed Consent

- The informed consent form, to be reviewed and signed by the patient and parent/guardian, is often the most challenging aspect of receiving IRB permission to begin a trial
  - Informed consent form must clearly discuss the purpose of the study – **lay language is mandatory**
  - Unknown risks and potential benefits outlined
  - Procedures, tests and requested time explained
  - Translation services, access to protocol physicians if needed

Stages of New Drug Development

- Investigational New Drug Application (IND) submitted to the FDA prior to trials beginning
- Phase 0
- Phase 1
- Phase 2
- Phase 3
- New Drug Application (NDA) submitted to the FDA after trials completed.

Clinical Trials – Phases and Why Participate

- It is important to conduct research in a variety of people because different people respond differently – i.e. men, women, ethnic groups, age groups, comorbidities
- People frequently enroll in clinical trials because they have exhausted standard (approved) treatment options
- Treatments do not work or side effects intolerable

Types of Clinical Trials

- New drugs, biologics and devices
- New indications for existing products
- Pediatric indications
- Treatment, prevention and diagnostic
- Combined treatments – i.e. oncology trials

Clinical Trials – Phase I

- **Phase I**
  - Determines the most frequent side effects
  - Determines toxicity levels
  - Examines how the drug is metabolized and excreted (including interactions)
  - Conducted in healthy adults, 20-80 subjects

Clinical Trials – Phase II

- **Phase II**
  - Initiated when Phase I does not reveal unacceptable toxicity
  - Focus on effectiveness - gain preliminary data on if the drug works for a certain disease or condition
  - Mostly controlled trials - patients receiving the drug are compared with similar patients receiving a different treatment or placebo
  - Safety continues to be examined
  - Usually contains a few dozen to about 300 subjects

Clinical Trial – Phases III

- **Phase III**
  - After efficacy is proven in Phase II trials, the sponsor and FDA meet to agree on large-scale studies
  - Information gathered on safety and efficacy
  - Studied in different populations, at different does and/or in combination with other products
  - Number of subjects ranges from several hundred to thousands (toxicity with torcetrapib was seen in the midst of a *15,000* patient study.)

New Drug Application (NDA)

- Formal step a drug sponsor takes to ask that FDA consider approving a new drug for marketing in the US
- NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured
  - ***Risks and benefits weighed – No drug is entirely safe or effective***

Standard NDA Review

- FDA has 60 days to decide whether to file an NDA so that it can be reviewed
- The FDA can refuse to file an application that is incomplete (e.g., some required studies are missing)
- FDA usually meets with the drug sponsor twice in preparation for NDA submissions
- Once the NDA is filed, the Center for Drug Evaluation and Research (CDER) will begin review.
- Standard review – 10 months.
- There are continual meetings throughout the NDA review process to address questions and discuss labeling

Three Possible FDA Actions

- Application approved
- Application receives a “complete response” letter (47% of CRLs due to chemistry/ manufacturing issues)
- Application declined or non-approvable

Complete Response Letter

- The drug can probably be approved, provided that some issues are resolved first
- This may involve:
  - The FDA and sponsor coming to a final agreement on what should go on the drug's label
  - Inadequate information on how people respond to various dosages of the drug
    - ✓ **Complete response letters are not public, they are considered part of the application,**
    - ✓ **Only the sponsor can reveal the letters and their content**

Declined/Non-Approvable

- Describes deficiencies significant enough that it is not clear that approval can be obtained in the future, at least not without substantial additional data
- Common problems include:
  - Unexpected safety issues
  - Failure to demonstrate effectiveness
  - Inappropriate patient populations
  - Manufacturing concerns
- Sponsors may need to conduct additional studies -- perhaps studies of more people, different types of people or for a longer period of time

Manufacturing Issues

- Manufacturing issues are also among the reasons for denied or delayed approval
  - Drugs must be manufactured in accordance with standards called good manufacturing practices
  - FDA inspects manufacturing facilities before a drug can be approved
  - If a facility is not ready for inspection, approval can be delayed
  - Any manufacturing deficiencies must be corrected before approval (including for *other* drugs)

The Quality of Clinical Data

- The FDA's Division of Scientific Investigations (DSI) conducts inspections to:
  - Protect the rights and welfare of people in clinical trials
  - Verify the quality and integrity of data
  - Review records of IRBs to be sure they are fulfilling their role in patient protection

Shortcuts to approval

Accelerated NDA Review

- In accordance with the Prescription Drug User Fee Act (PDUFA), CDER expects to review and act on at least 90% of NDAs for standard drugs within 10 months after submission
- Priority drugs received review within 6 months
- Priority review is for drugs that treat life-threatening or orphan/rare conditions or conditions that lack satisfactory treatment options
  - Surrogate endpoints may be used to evaluate effectiveness
  - Example time to disease progression for anticancer drugs

Accelerated Approval

- Most drugs to treat HIV have been approved under accelerated approval provisions
- Companies have been required to continue its studies after the drug is on the market to confirm that it ultimately benefits the patient
- If studies do not confirm the initial results, the FDA can withdraw the approval

Case Study: Gleevec

- Gleevec (for a life-threatening form of leukemia) received accelerated approval
  - **Gleevec blocks enzymes that play a role in cancer growth**
- It was also approved under the orphan drug program, which gives financial incentives to sponsors for manufacturing drugs that treat rare diseases
- Gleevec was approved based on results of three large Phase 2 studies, which showed the drug could substantially reduce the level of cancerous cells in the bone marrow and blood
- IND was submitted in April 1998, the NDA was received in February 2001 and the drug was approved in May 2001
- The sponsor made commitments to conduct Phase 4 studies that investigate Gleevec's clinical benefit

“Breakthrough!”

- What is breakthrough therapy designation?
- Breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. **A breakthrough therapy designation conveys all of the fast track program features (see below for more details on fast track designation), as well as more intensive FDA guidance on an efficient drug development program. The FDA also has an organizational commitment to involve senior management in such guidance. Section 902 of FDASIA requires the following actions, as appropriate:**

- holding meetings with the sponsor and the review team throughout the development of the drug
- providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable
- **taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment**
- assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the cross-discipline members of the review team (i.e., clinical, pharmacology-toxicology, chemistry, manufacturing and control (CMC), compliance) for coordinated internal interactions and communications with the sponsor through the review division’s Regulatory Health Project Manager
- **involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review**

- http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm#accelerated

Breakthroughs publicly disclosed?

"Breakthrough therapy designation requests are typically submitted to an IND, and the FDA *cannot* disclose the existence of an IND, or any submissions that have been submitted to the IND, unless it has previously been publicly disclosed or acknowledged per 21 CFR 312.130(a)."

But the sponsor can disclose

- Merck Announces Breakthrough Therapy Designation for Lambrolizumab an Investigational Antibody Therapy for Advanced Melanoma
- Wednesday, April 24, 2013 7:30 am EDT
- Dateline: WHITEHOUSE STATION, N.J.

- WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, announced today that **the U.S. Food and Drug Administration (FDA) has designated lambrolizumab (MK-3475) as a Breakthrough Therapy** for the treatment of patients with advanced melanoma. Lambrolizumab is Merck's investigational antibody therapy targeting Programmed Death receptor (PD-1) that is currently being evaluated for the treatment of patients with advanced melanoma, and other tumor types.

- "We are pleased that the FDA has designated lambrolizumab a Breakthrough Therapy for patients with advanced melanoma," said Gary Gilliland M.D., Ph.D., senior vice president and oncology franchise head, Merck Research Laboratories. "The FDA's decision to place lambrolizumab in a category that may enable expedited development and review is an important milestone for Merck as we advance ongoing programs in multiple cancer indications."

Accelerated Approval can be withdrawn

Ariad Shares Sink as Sales of Only Drug Iclusig Suspended (Nov 1, 2013 – stock dropped 44%)

- A recent investigation found about 24 percent of patients using Iclusig in a mid-stage clinical trial experienced heart attacks, strokes and other serious vascular events, the Food and Drug Administration said in a statement today. It also found 67 percent of patients in clinical trials experienced high blood pressure and 8 percent had heart failure, including fatalities.
- Iclusig was approved last year for two rare blood cancers based on an **accelerated process that relied on a single trial showing it helped patients. Companies that gain accelerated approval must conduct additional study to prove the medicine is effective; Those further results for Iclusig showed the increased safety risks.**

when there's bad news too

- **FDA Wants More Testing of Muscular Dystrophy Drug**

- **Company Expects Approval to Be Delayed Two Years or More**
- An experimental muscular-dystrophy drug made by Sarepta Therapeutics Inc. will be delayed at least two years after U.S. regulators suggested that the company's current study data are inadequate.
-
- **The company had hoped to have its drug, eteplirsen, considered for approval by the first half of next year under a special accelerated process designed to bring promising therapies faster to patients with fatal conditions. However, the U.S. Food and Drug Administration told Sarepta last week that such a filing would be "premature" without a larger, late-stage study, according to the company.**
-
- **Shares of Sarepta plunged 64% to $13.16 through the close of trading on Tuesday**.

- Some analysts had predicted an approval in late 2014 or early 2015. The FDA declined to comment on the matter, citing the confidentiality of its discussions with drug makers.

- The company, buttressed by a vocal group of patient advocates, had **expressed confidence in the past that the FDA would grant accelerated approval based on a midstage study** involving **12 boys** between the ages of 7 and 13 with Duchenne muscular dystrophy, a rare condition that destroys the muscles and frequently kills patients by their 30s.

- **Drugs are typically approved after showing long-term safety and clinical benefit in multiple late-stage studies. But at the prodding of Congress, the agency has become more open to approving drugs based on so-called biomarkers—indirect biological evidence thought to indicate outcomes, such as dystrophin in Duchenne patients.**

- Wall Street Journal November 12, 2013

Golden Ticket

Incentive for developing rare pediatric disease drugs

- News | February 5, 2016

Amarantus Requests Rare Pediatric Disease Designation From FDA

- San Francisco, CA /PRNewswire/ -
- Amarantus BioScience Holdings, Inc. announced that it has requested Rare Pediatric Disease Designation (RPDD) from the US Food and Drug Administration (FDA) for treating retinitis pigmentosa (RP) with MANF. MANF was previously granted orphan drug designation (ODD) by the US FDA in December 2014.
- The FDA defines a "rare pediatric disease" as a disease that affects fewer than 200,000 individuals in the U.S. primarily aged from birth to 18 years. Under the FDA's Rare Pediatric Disease Priority Review Voucher program, a sponsor who receives an approval of a new drug application (NDA) or biologics license application (BLA) for a rare pediatric disease may be eligible for a voucher, which can be redeemed to obtain expedited FDA review for any subsequent marketing application. Vouchers may be sold or transferred by the recipient; in the last 6 months, 2 priority review vouchers have been sold for a combined $595M in cash.

Advisory Committee Meetings

What are Advisory Committees?

Definition:

- Panels of outside experts that provide recommendations to the FDA on the safety and efficacy of products, generally pending applications
- Exist across all areas regulated by the FDA: pharmaceuticals (Rx & OTC), biologics, devices, veterinary medicine and foods (additives/labels/claims)

Role:

- Provide advice on "close calls" for pending applications
- Provide recommendations on first-in-class, serious adverse reactions, black box warnings, major public health concerns, new indications and special regulatory concerns
  - Antidepressants and suicide in children/adolescents
  - Acutane labeling

  - **Vast majority of products reviewed by the FDA are *not* reviewed by Advisory Committees**

Committee Structure

- 32 different committees, each with a specific focus:
  - **May 22, 2013: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting Announcement (suvorexant tablets, Merck)**
  - **August 5-7: Cardiovascular and Renal Drugs Advisory Committee (riociguat??)**
  - **September 10: Pulmonary-Allergy Drugs Advisory Committee (riociguat??)**
  - Endocrinology and Metabolic Advisory Committee
  - Gastrointestinal Drugs Advisory Committee
  - Oncology Drugs Advisory Committee
  - Blood Products Advisory Committee
- Joint Committee mashups can occur
  - **June 5-6, 2013: Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (AVANDIA (rosiglitazone maleate) tablets)**
  - May 3, 2013: Joint Meeting of the Medical Imaging Drugs Advisory Committee and Oncologic Drugs Advisory Committee Meeting Announcement (The committees will discuss the safety and efficacy of currently approved leukocyte growth factors (LGFs) as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident.
  - Rx to OTC switches
  - Circulatory System devices and Cardiovascular and Renal Drugs (drug coated stents)
- 10 – 15 members on each committee
- Committees generally meet 2 – 4 times a year

Committee Structure

- Broad range of expert opinions adds greater understanding and aids the FDA in making balanced evaluations
- Even with a wide range of experts it can still be challenging to convene the proper group –
  - Example – oncology reviews
- Small stipend for their time
- Intensely vetted for potential conflicts of interest

Typical Advisory Committee Meeting

- Each AdCom is a half day (common) to several days (very rare)
- Virtually always open to the public – partially closed if proprietary information will be discussed
- FDA may preempt sponsor and provide a positioning overview
- Sponsor presents and defends the product
- FDA will provide an overview of the product as they see it, offering original re-analyses of data as they see fit
- Committee members ask pointed questions following the presentations
- Public Comment session
- Committee discusses further and votes

Typical Advisory Committee Meeting

- After a full day of presentations and debate the committee is asked to vote (simultaneously) on questions regarding the drug
- For pending approvals, each committee member votes:
  - "Yes" or "No" if they consider it <u>safe</u>
  - "Yes" or "No" is they consider it <u>effective</u>
- Other questions regarding dosing, labeling, post-marketing studies, specific populations, etc. are frequently asked
  - ➢ FDA usually makes its final determination shortly after the meeting
  - ➢ Committee recommendations are advisory, not binding, but the FDA usually follows their guidance. However….

AdCom Meeting Announcement

- **Acute pain treatment from KemPharm to be considered by FDA committees**
- KemPharm's new-drug application for the use of KP201/APAP, an abuse-deterrent formulation of benzhydrocodone, in managing acute pain on a short-term basis is scheduled to be reviewed by the FDA's Drug Safety and Risk Management Committee and Anesthetic and Analgesic Drug Products Committee on May 5. A final decision from the agency is expected by June 9. BioCentury (3/14)

. **FDA steamrolls over panel vote, spurns Titan's addiction drug** Probuphine (May 1, 2013)

- In the end, a vote by an outside panel of FDA experts favoring approval of Titan Pharmaceuticals' Probuphine didn't influence the outcome at all. Agency staffers stuck with the opinions outlined in a harsh internal review and rejected the opioid addiction drug, outlining some extensive demands for new clinical data that would be needed for an approval.
- The news was a disaster on Wall Street. Investors bailed on the sudden reversal of fortune, driving the stock down 80% and leaving Titan as a penny stock as it faces a tough period.

But not all AdComs end in a vote

- Sometimes the agency has meetings to discuss an issue rather than a specific drug
- For example, there were two two-day meetings on noninferiority analyses in antimicrobial studies

Who Attends Advisory Committee Meetings?

- Advisory Committees are open, public forums attended by a number of entities:
  - Sponsor company
  - Competing companies
  - FDA
    - Review team and division, Policy, Public Affairs
  - Media
    - Wires, trades, possibly broadcast
    - Stories filed throughout the day
    - Strong financial media interest – Bloomberg, CNBC
  - Financial community/analysts
    - Reports issued shortly upon the conclusion
  - Patients and advocacy organizations

Who doesn't attend?

- Since the FDA move to their White Oak campus, meetings are less accessible.
- FDA now web streams most meetings live and for free
- Webcasts have better production values than old FDC Reports versions – you can actually see the slides
- A transcript is released several weeks after the meeting.

- But you *do* miss the in-room *gestalt*.

Media Relations

- Ironically, often AdComs offer the *best* opportunity to share the *full* data story
  - Safety and efficacy is the basis for the meeting
- AdComs can trigger more media coverage than the actual approval
  - Sense of the unknown, public debate, difficult issues, advocacy groups, financial implications
  - Craft media strategy for all scenarios, consider volumn of interest, issues, timing and stakeholders
- Brief key media in advance
  - Desk side briefings to provide context, scientific understanding, company positioning
  - Vital since stories are filed throughout the meeting

Drug Advertising

What is OPDP?

- OPDP is the **Office of Prescription Drug Promotion**, formerly known as The Division of Drug Marketing, Advertising and Communications (**DDMAC**). This is a "super office" under the Office of Medical Policy within the Center for Drug Evaluation and Review (CDER) at the Food and Drug Administration (FDA).

- <u>Mission:</u>

  "To protect the public health by assuring prescription drug information is truthful, balanced and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering better communication of labeling and promotional information to both healthcare professionals and consumers."

The Role of OPDP

- Responsible for reviewing prescription drug advertising and promotional materials including:
  - Broadcast and print advertisements
  - Brochures
  - Press Releases
  - Sales Aids
  - Etc.
- Ensures that information containing promotional materials is <u>not false or misleading</u>

Regulatory Requirements

- Manufacturers must submit promotional materials to OPDP at the time of publication or initial use (pre-clearance under discussion)
- Per FDA regulations promotional materials:
  - Must not be false or misleading
  - Must present "fair balance" between benefits and risk information
  - Must disclose "material" facts in light of claims made about product
  - Must be based on Package Insert
    - Only approved indications can be discussed

What Does this Mean?

- Accurately communicate only approved indication(s) including context for any claim
    - Relevant patient population
    - Concomitant therapies/treatments
    - Likelihood of benefit(s)
- Communicate most important risks in a manner reasonably comparable to benefits (presentation and language)
- Cannot omit important information
    - <u>In plain language</u> → Ads must communicate an accurate and balanced picture of the product

Addressing Violations

- OPDP can take the following actions to address promotional materials that are false or misleading:
  - Untitled letters – notices of violations issued to sponsors directing that they discontinue use of false or misleading advertising materials
  - Warning Letters – issued to sponsors for more serious violations, such as those possibly posing serious health risks to the public
  - Injunctions and consent decrees
  - Referrals for criminal investigation or prosecution
  - Seizures

You know it's a warning letter when it says WARNING LETTER and goes to the president

- **Department of Health and Human Services**
- Food and Drug Administration
- Chicago District

- **WARNING LETTER**
  CHI-10-10
- **DELIVERED BY HAND**

- Mr. Gregory D. Wasson
- President and CEO
- Walgreen Company

- Dear Mr. Wasson:

- This letter is in reference to the Walgreen Mouth Rinse Full Action distributed by your firm. The label for this product makes the following claims: "Freshens breath, Helps prevent cavities, Restores enamel, Helps strengthen teeth, Helps kill germs that cause bad breath, Helps fight visible plaque above the gum line."

… or other executives

- **Warning Letter**
- **WL: 320-13-015**
- **CERTIFIED MAIL**
- **RETURN RECEIPT REQUESTED**
- May 6, 2013
- Dr. Gerhard Gigl
- Senior Vice President
- Boehringer-Ingelheim Pharma GmbH & Co. KG
- 55216 Ingelheim am Rhein
- Germany

- http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm352325.htm
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM168174.pdf Merck!

Xarelto Untitled Letter

- The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer (DTC) print advertisement (K02XS121040 AF) (Print Ad) for XARELTO (rivaroxaban) tablets (Xarelto) submitted by Johnson & Johnson International, Inc. (Johnson & Johnson) on behalf of Janssen Pharmaceuticals, Inc. under cover of Form FDA 2253 **and observed during routine surveillance in the January/February 2013 issue of WebMD magazine. The Print Ad is false or misleading because it minimizes the risks associated with Xarelto and makes a misleading claim. Thus, the Print Ad misbrands Xarelto** in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(n) and FDA implementing regulations. 21 CFR 202.1(e)(5)(i); (e)(7)(viii), (ix).

Xarelto untitled letter

…. In contrast, the risk information is presented on the preceding adjacent page without any of the emphasis (i.e. color scheme, borders, layout, and graphics) used with the efficacy claims. The result is a presentation which appears unconnected to the efficacy claims and is therefore not likely to draw readers' attention. **This overall presentation misleadingly minimizes the risks associated with Xarelto because it fails to convey this important risk information with a prominence and readability reasonably comparable to the efficacy claims.** We note that the Print Ad contains the statement, **Please see accompanying Medication Guide on the following pages**" (emphasis original) at the bottom of the page, and that risk information is presented on an adjacent page, but this is not sufficient to mitigate the overall misleading presentation.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM357833.pdf

Questions?