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## OBJECTIVES

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- Describe how the FDA is currently funded and the implications for patient safety
- Describe how the nation's inability to control concierge or Internet prescription drug purchasing endangers patients
- Describe how the DSHEA act has placed patients in danger from adulterated or contaminated dietary supplements
- Describe how foreign inspections of manufacturing plants are separate and unequal and jeopardize patient health
- Describe how relying on the Interstate Commerce Act allows pharmaceutical companies to circumvent research subject protections overseas
- Describe how to remedy or ameliorate these issues

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## DISCLOSURE

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- Dr. White has nothing to disclose with respect to the content in this presentation.

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## HIV EPIDEMIC CHANGES FDA FUNDING STRUCTURE

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- FDA was fully funded by U.S. taxpayers until 1992
  - HIV activists incensed by the prolonged time to FDA approval of new drug treatments like AZT
  - Congress passed the Prescription Drug User Fee Act (PDUFA) and signed into law by Pres. George H.W. Bush
  - Authorizes FDA to collect user fees from drug manufacturers in exchange for achieving negotiated metrics
  - Needs to be renegotiated and approved by Congress every 5-years

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## USER FEES NOW UBIQUITOUS

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- The FDA's funding has increasingly come from the industries that it regulates.
  - Other user fees for generic, over-the-counter, biosimilar, animal and animal generic drugs, and medical devices were created
- FDA's total budget is \$5.9 billion
  - 45% comes from user fees, but 65% of the funding for human drug regulatory activities are derived from user fees

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## METRICS OF “SUCCESS”

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- Performance measures: how quickly the FDA responds to meeting requests and generates correspondence, and how long it takes from submission of a new drug application until the FDA approves or refuses to approve a drug or product.
  - In 1987, it took 29 months from the time a new drug application was filed by the manufacturer for the FDA to decide whether to approve a medication in the U.S. In 2014, it only took 13 months and by 2018, it was down to 10 months
  - Standard new drug applications approved the first time went from 38% in 2005 to 61% in 2018
  - Priority NDA review process, 89% of new drug applications were approved the first time around and the approvals were completed in eight months in 2018

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## INCREASED NUMBER OF BOXED WARNINGS AFTER APPROVAL

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- Before the user fee act was approved, 21% of medications were removed or had new boxed warnings as compared to 27% afterwards
- Some potential reasons that more adverse effects are coming to light after drug approval include senior FDA officials overturning scientist recommendations, a lower burden of proof for medication approval, and more clinical data in new drug applications coming from foreign clinical trial sites that require additional time to assess in an environment where regulators are rushing to meet tight deadlines

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## QUESTION 1:

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- Why did the FDA start applying user fees to manufacturers and what percentage of overall FDA funding comes from the companies they oversee?

- A. HIV/AIDS Crisis – 65%
- B. HIV/AIDS Crisis – 45%**
- C. Ebola Crises – 45%
- D. Ebola Crisis – 65%

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THE MAIN RISK IS NOT IN YOUR  
PHARMACY

# COUNTERFEIT MEDICATIONS

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## COUNTERFEIT DRUGS IN TRADITIONAL DRUG SUPPLY CHAIN

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- In U.S., 1 in 100 filled prescriptions in the legitimate drug supply chain (wholesalers, hospitals, and licensed community or mail-order pharmacies) are counterfeit according to WHO
- The Pharmaceutical Security Institute counts the annual discovery of “incidents” that encompass counterfeit, illegally diverted, or stolen pharmaceuticals in Developed Countries
  - There has been a continuous rise over the past 5 years in the number of discovered incidents from 2177 in 2014 to 4405 in 2018
  - 49% involved more than 1000 dosing units of product
  - 1750 of these incidents occurred in North America, and 665 occurred in Eurasia

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## MAJOR EXAMPLES IN TRADITIONAL DRUG SUPPLY

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- Approximately 2 million oral contraceptive tablets lacking active ingredients were intercepted as they were smuggled into U.S.
- >18 million atorvastatin tablets were recalled after the detection of a smuggling operation that compromised the brand name Lipitor drug supply
- Patients with breast cancer and anemia received bevacizumab and erythrocyte-stimulating drugs with no active ingredients in them
- Heparin products tainted with highly sulfated chondroitin were inserted into the supply chain causing anaphylactoid reactions with more than 80 deaths

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## LAW AGAINST COUNTERFEITING

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- The Drug Quality and Security Act of 2013 bridges vulnerabilities that existed between FDA's jurisdiction over sourcing and production manufacturers and the individual state's jurisdiction over wholesalers and licensed pharmacies
- This act requires a national electronic track-and-trace system that allows a specific drug to be followed from the manufacturer to the pharmacy
  - There is still theft of approved medications from warehouses and amplifying supply from counterfeit products, packaging it with lot numbers, expiration dates, and fraudulent packaging that duplicate those of major brand name drugs before reinsertion in the supply chain

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## WHAT CAN BE DONE?

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- Drug supply chain artificial intelligence and blockchain technologies can reduce the risk of counterfeit drugs
- In blockchain, the drug product's location is recorded at each step, but tracking is restricted to specific users using step specific coding that limits the ability to move a shipment into a warehouse undetected, substitute it with other products, or ship a drug out of a warehouse from places not already within the approved blockchain
- Medication should only be purchased from reputable distributors, and pharmacists should confirm with them that they were purchased directly from manufacturers or other reliable sources
- Pharmacists receiving drug shipments should examine all products for suspicious appearance, including outside packaging, water seals, or tamper-resistant features, and the color, shape, size, and feel of the pills
- Pharmacists should instruct patients that if pills seem different, do not seem to work the same, or generate new adverse effects, they should let the pharmacist know right away
- Pharmacist should alert FDA, the manufacturer, and the distributor

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## ROGUE INTERNET PHARMACIES ARE THE MAIN CAUSE OF COUNTERFEIT MEDICATION USE IN U.S.

- 80% of the 50,000 rogue Internet pharmacies target English speaking countries
- According to a 2016 Kaiser Family Foundation survey, 8% of households in America (19 million people) obtained medication through non-U.S. online pharmacies or while traveling abroad
- In August 2017, the National Association of Boards of Pharmacy (NABP) issued an update to their ongoing analysis of online pharmacies. NABP found that 95.8% of the 11,688 Internet pharmacies they analyzed did not comply with U.S. federal or state laws
- Of these, 88.9% dispensed prescription drugs without a valid prescription, 12.9% dispensed controlled substances, 62.4% did not reveal their physical location, and 17% did not have encryption technology to prevent financial or personal data breaches
- Overall, 74.1% of the 108 Internet sites stating they were from Canada were not sourcing drugs approved for use by Canadian citizens
  - Of these "Canadian Pharmacies," 46% did not reveal the actual source of their medications, 50% received their drugs from Indian manufacturers or a combination from India and other countries, and the rest were manufactured from other countries
  - None of the Canadian sites require a valid prescription

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## PEOPLE ARE DUMB

- In a study of 1914 undergraduate U.S. college students from 2005 to 2008, participants were told that a neighborhood pharmacy charged \$165 for a 1-month supply of the fictitious drug Beozine. They then reviewed 2 Internet pharmacy websites, created specifically for this study, on which the prices were \$37.99 and \$57.60 for a 1-month supply. The sites each had a number of features that were warning signs according to FDA guidance above. They were asked to indicate if each Internet pharmacy was a good place to buy the drug on a scale of 0-10 with 0 being very bad and 10 being very good. Fifty percent of students who reviewed the first pharmacy website and 37% of students who reviewed the second chose a rating above 5 (designating good or very good). More than 22% of the respondents said they would recommend the first pharmacy site to friends and family. When asked for the most likely reason for the lower cost versus the neighborhood pharmacy, the predominant explanations were lower operation costs, ad revenue offsetting drug costs, pressure to lower costs because of comparison shopping, or high sales volume.

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## WHAT CAN BE DONE?

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- All health professionals need to be educated about how pervasive rogue Internet pharmacies are and how harmful they can be
  - They need to proactively tell patients about the dangers of counterfeit drugs during their encounters and provide them or direct them to information that explains the risks during patient care visits
- Community and mail-order pharmacies need their pharmacists to proactively counsel about the dangers of rogue Internet pharmacies
- Pressure Social Media Sites to prevent online rogue internet purchases
  - In a 2015 study, content for rogue online pharmacies was found in 17% of all Facebook pages reviewed, not to mention myriad user-generated comments for those posts.
  - Another study from 2015 found that 76% of all tweets containing a generic name for a controlled substance were linked to online pharmacies selling them
- Search engines could remove rogue Internet pharmacy results, set their websites further down in their search result pages by altering their search algorithms, or have a website warning about the dangers of rogue Internet pharmacy purchases prominently featured in the search results

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## QUESTION 2

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- What is the primary way that people are accessing counterfeit drugs?
  - A. Through the local pharmacy
  - B. Through a licensed domestic mail order pharmacy
  - C. Through an unlicensed foreign mail order pharmacy**
  - D. From traveling abroad

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# DIETARY SUPPLEMENTS

NATURAL DOESN'T ALWAYS MEAN SAFE, OR NATURAL

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## DSHEA ACT OF 1994

- Manufacturers and distributors of dietary supplements are prohibited from marketing products that are adulterated or misbranded
  - Manufacturers are responsible for evaluating the safety and labeling of their products before marketing to ensure that they meet all FDA requirements
  - Manufacturers do not have to provide data supporting quality manufacturing practices to the FDA before sale
- FDA is responsible for taking action against adulterated or misbranded dietary supplement products after it reaches the market
  - Burden on FDA to prove a product/ingredient is unsafe before removing from market
  - No central regulatory home, funding for oversight of dietary supplements very small

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## ISSUES WITH DIETARY SUPPLEMENTS: MICROBIAL CONTAMINATION

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- Analysis of 183 dietary supplement products
  - Herbal products (alfalfa, coriander, echinacea, garlic, ginkgo, juniper, licorice, psyllium, and St John's wort) frequently contaminated one or more toxigenic fungi/mold/yeast and/or bacteria in levels above USP specifications
- 37 different products containing kratom were contaminated with one or more different types of Salmonella between January 2017 and May 2018, resulting in 199 adverse events, including 50 hospitalizations.
  - There have been dozens of other dietary supplement products and Cannabis/CBD products recalled for Salmonella outbreaks from 2015 to the present

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## ISSUES WITH DIETARY SUPPLEMENTS: HEAVY METAL CONTAMINATION

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- Concentrations of heavy metals in 121 dietary supplements purchased in Canada were compared with the concentrations designated for safe daily consumption by the National Science Foundation (NSF) International
- 5% of dietary supplements exceeded the upper limit for arsenic; 1.7% of samples exceeded the levels for lead, cadmium, and aluminum; and 0.8% of samples exceeded the levels for mercury
- The average concentrations of these heavy metals were compared against those seen in the subset of products that were manufactured in North America and with 49 prescription drugs.
  - Arsenic (21.7 vs 0.782 vs 0.0069 µg), lead (1.49 vs 0.362 vs 0.0237 µg), cadmium (0.199 vs 0.0918 vs 0.0035 µg), aluminum (21.7 vs 0.782 vs 0.0069 µg), and mercury (0.366 vs 0.0007 vs 0.0146 µg)

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## ISSUES WITH DIETARY SUPPLEMENTS: ADULTERATION

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- FDA dietary supplement warning letters 2007 through 2016
  - Unapproved pharmaceutical ingredients were identified in 776 products
    - 20% of these dietary supplement products for sexual enhancement, weight loss, or muscle building contained more than 1 unapproved prescription ingredient
    - Phosphodiesterase type 5 inhibitors, diuretics, banned or never FDA-reviewed drugs such as dapoxetine (international drug), fenfluramine, sibutramine, and phenolphthalein.
- FDA Warning Letters 2017-2019
  - 178 new products with synthetic drugs were identified, and all except for one were used for sexual enhancement or weight loss

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## ISSUES WITH DIETARY SUPPLEMENTS: BAIT AND SWITCH

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- Some products use active ingredients other than those listed on the label
- Kava had been used safely for years before 93 cases of presumed kava-induced hepatotoxicity (7 deaths and 14 liver transplants) occurred
  - The change in the safety profile was likely secondary to the depletion of the Piper methycticum variety of the kava plant
  - Manufacturers started using other varieties of kava that contained a hepatotoxic constituent called flavokavain
- In 2000, Stephania tetrandra was replaced by Aristolochia fangchi.
  - 105 patients exposed to the herb developed nephropathy, and 43 had reached end-stage renal failure, 18 developed urothelial carcinoma, 17 carcinoma of the ureter and/or renal pelvis, and 1 bladder tumor
  - Although the US bans aristolochic acids from the US market, aristolochic acids I and II were found in 20% and 7% of Chinese herbal products sold in the United States via the internet and selected for additional scrutiny in 2014

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## ISSUES WITH DIETARY SUPPLEMENTS: BAIT AND SWITCH

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- Sometimes the substitution of an herb is accidental because of the inconsistent nomenclature system for Chinese herbs and the similarity of their names
  - Han Fang Ji has been replaced by Guang Fang Ji, Mu Tong by Guan Mu Tong, and Mu Xiang by Qing Mu Xiang in some products
- Herbal products can also be enriched with natural or synthetic constituents of the herbs
  - Some manufacturers enriched kava products with synthetic kavain to bolster the effects
  - Some kratom products were found to contain a far greater concentration of 7-hydroxymitragynine than would occur naturally

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## ISSUES WITH DIETARY SUPPLEMENTS: NO ACTIVE INGREDIENTS AT ALL

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- In an assessment of cannabidiol (CBD) products, only 12.5%, 25%, and 45% of vaporization liquids, tinctures, and oils were labeled correctly ( $\pm 10\%$  of the labeled value) and in most cases contained far less CBD than promised
- In two studies using DNA barcoding, many dietary supplement products contained little to no herbal content
  - There was undisclosed herbal material in many products such as pine (*Pinus strobus*), spruce, wheatgrass, dracaena (a tropical houseplant), oryza (rice plants), *Asteraceae*, *Ranunculaceae*, primrose, French bean, wild carrot, and *Phaseolus fabaceae* (bean vines), designed to make the products look herbal in nature

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## REFORM BEGINS IN 2015

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- In 2015, the FDA's Office of Dietary Supplement Programs began
  - Gave FDA a single place to oversee dietary supplements and ability to probe weaknesses in manufacturing quality and product labeling systems
  - Warning letters for false claims accelerated as greater scrutiny occurred
- Starting in 2019, the FDA began new procedures to close loopholes
  - Required new dietary ingredients to be reviewed to ensure they meet the definition of dietary supplements before being sold in the country
  - Very limited product spot inspections began (products procured from store or internet and tested in FDA or contractor labs)
  - Inspections of domestic and foreign manufacturing facilities began on a very limited basis

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## FURTHER STEPS TO PROTECT CONSUMERS/PATIENTS

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- Pharmacists should advocate that dietary supplement manufacturers provide testing data to the FDA like OTC manufacturers do
- Stores should only sell products verified for manufacturing quality by independent labs such as USP, NSF, and ConsumerLabs
- FDA should have more resources to spot test products and inspect dietary supplement manufacturers

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### QUESTION 3

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- What is a validated way to assure a dietary supplement does not have excessive microbial or heavy metal contamination and has the ingredient in the tablets/capsules advertised on the label?

**A. USP certification**

B. Better Homes and Gardens Certification

C. It is expensive so it must be good

D. My brother's friend's uncle sells it, and he is a great guy

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## DRUG MANUFACTURING SHIFTING OVERSEAS

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- Over the past 30 years, U.S. pharmaceutical companies have laid off tens of thousands of U.S. manufacturing workers and moved their drug manufacturing overseas. The main reasons for this outsourcing include cheaper labor, looser environmental regulations and less oversight. Meanwhile, pharmaceutical companies in India and China captured a greater share of the U.S. generic drug market. As of May 2020, 74% of facilities manufacturing active ingredients and 54% manufacturing finished drugs for the U.S. were located overseas.

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## US LAW WRITTEN FOR US MANUFACTURING

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- US law specified that manufacturers needed to be inspected at least every other year
  - US inspections were frequent and unannounced
- US laws were not updated as the migration of drug manufacturing shifted overseas
  - No requirement for inspections of foreign manufacturers, FDA relied on their documentation that their products were of acceptable quality
  - FDA had no budget to pay for inspections overseas

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## RANBAXY, THE CANARY IN THE COAL MINE FOR TRUST DON'T VERIFY

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- In 2004, a whistleblower alerted the FDA that Ranbaxy Corp., one of the largest generic drug companies in the world, was fabricating its drug test reports. Ranbaxy ultimately paid a \$500 million fine in 2013 for knowingly producing substandard drugs for the U.S. market
  - Ranbaxy manufactured drugs that they knew tested out-of-specification, had unknown impurities, and would not maintain their expected shelf life. They sometimes recorded stability test results they never conducted
- FDA created a GDUFA surcharge in 2012 of \$15,000 annually for every overseas manufacturing plant to pay for inspections
- After the Ranbaxy fiasco, the FDA increased foreign manufacturing inspections from 333 in 2007 to 966 in 2019. The proportion of foreign manufacturing plants that had never had an FDA inspection shrank from 64% in 2010 to 16% in 2019

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## MANUFACTURING INSPECTIONS

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- When FDA increased inspections in India and China:
  - Over 70 manufacturing facilities were barred from shipping drugs to the US for one or more of the following: (1) alteration/manipulation of product and air quality data; (2) failure to review consumer complaints and hiding incident reports off site; (3) back dating quality testing; (4) alteration of training records for quality assurance personnel or functions; (5) presence of unauthorized quality assurance stamps;; (6) performed multiple retesting of deviant samples and only recording the one that passed (7) shredded documents late at night before an FDA inspection, (8) allowed unsanitary manufacturing conditions.

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## OVERSEAS INSPECTIONS STILL UNEQUAL

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- Domestically, inspections are frequently unannounced, whereas in foreign countries, this almost never occurs
  - “Preannounced inspections are necessary when conducting international inspections. This is due primarily to the potential waste of resources if the establishment is not operating or not producing the product in question, political sensitivities, availability of English-speaking personnel, local holidays, etc.”
- Prescheduling gives manufacturers time to clean their facilities, get their paperwork in order, and ensure that workers are on their best behavior
- Inspectors rely of translation services from the sites under review, a conflict of interest

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## NEW FDA RULES AND HIRING ISSUES ALLOWS DOMESTIC MALFEASANCE

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- Vacancies prevalent in India and China, where 33% and 30% of available overseas-based inspector jobs unfilled as of 2019
- The 2012 FDA Safety and Innovation Act removed the legal requirement to inspect U.S. manufacturing facilities every two years. All facilities worldwide including U.S. should be inspected every 5 years
  - Domestic inspections subsequently decreased from 1,122 in 2007 to just 698 in 2019
  - Domestic + foreign inspections have not increased since 2010
- Overstretched inspection personnel not at their best:
  - U.S. Office of Special Counsel discovered in March 2021 that FDA administrators had downplayed whistleblower concerns about serious quality issues in U.S. vaccine manufacturing facilities from 2017 to 2018.
  - A 2020 FDA inspection had already identified numerous facility and manufacturing issues in Emergent BioSolution's Baltimore facility. Had these findings been immediately addressed, cross-contamination with the Johnson & Johnson COVID-19 vaccine would have been less likely

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## COVID-19 GUT PUNCH

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- The gap between foreign and domestic inspections has widened over the course of the COVID-19 pandemic.
- Because international travel shut down after March 2020, the FDA conducted only three overseas inspections, and 52 in the U.S. in 2020
  - As of 2020, 17% of manufacturers have not been inspected for over five years and will grow in 2021
  - With current staffing levels, it will likely take a long time to remedy the backlog

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## WHAT REMEDIES ARE NEEDED?

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- FDA needs to ramp up number of inspectors, work with partners like European Medicines Agency to eliminate duplication
- FDA needs to support inspectors, so they want to do the tough job of inspecting
- FDA needs more spot checking of products upon arrival in the U.S. for quality manufacturing
- U.S. Govt needs to ensure that inspections at all sites are unannounced and of the same rigor

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## QUESTION 4

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- What occurred simultaneously with the increase in foreign manufacturing site FDA inspections that attenuates the safety benefits to the US patient?

- A. **A reduction in domestic inspections**
- B. A lower caliber of foreign inspections
- C. A reduction in the FDA inspector workforce

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# OVERSEAS CLINICAL SITE OVERSIGHT

SEE NO EVIL, HEAR NO EVIL, SPEAK NO EVIL

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## CLINICAL TRIALS FOR FDA APPROVAL DRAMATICALLY MOVING OVERSEAS

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- <1% of Investigational New Drug (IND) clinical investigators worked outside the U.S. in the 1980s, 22% in 2000 and 43% in 2013
  - Rate of growth in foreign research sites is most pronounced in central and eastern Europe (41.4% growth), Latin America (27.3% growth), Asia (mostly Russia, China, India, Turkey: 25.6%), and the other emerging areas (Africa, Pacific Islands: 11.0%)
- In 2008, 80% of applications for drugs and biologics contained data from non-US studies, 78% of all participants were enrolled outside the United States, and 8.3% of new drug applications (NDAs) were conducted entirely outside of the United States

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## DIFFERENT RULES FOR DIFFERENT RESEARCHERS

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- For U.S. researchers, work cannot begin without the filing of an IND application
  - The FDA reviews the IND to determine if preclinical trials support that the drug is safe enough for human testing, whether the drug can be consistently and safely manufactured, and if the proposed clinical trials have reasonable safeguards to protect human subjects
  - FDA rules predicated on the Interstate Commerce Act – if drug crosses state lines, the FDA has jurisdiction
  - But what if the drug is made overseas and the study is conducted overseas?

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## DIFFERENT RULES FOR DIFFERENT RESEARCHERS

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- It is possible for a sponsor to conduct a trial without the knowledge of the FDA and if troubling adverse events occur, redo the study elsewhere without divulging the initial study's results
- It is also possible for a clinical trial to be conducted in humans based on animal data that the FDA would have felt was insufficient to ensure research subject well-being
  - The FDA is unaware whether a non-IND trial has been conducted until it is concluded and included in a NDA

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## LITTLE REAL-TIME OVERSIGHT OF OVERSEAS CLINICAL TRIALS

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- FDA tried to add a user fee for overseas clinical trial inspections (like in GDUFA) in 2017, but manufacturers said no
  - Was not part of ensuring faster drug approval times
- According to the OIG, a domestic site is 16 times more likely (odds ratio = 15.87 [95% CI = 9.69 to 25.99]) to be inspected by the FDA than a foreign one, and there are dozens of countries where clinical trials conducted under an IND have never been inspected
- Inspections can cost up to \$40 000 to complete when the sites are in remote areas of the world, and the total inspection length is limited to 7 days

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## TRUST BUT NOT VERIFY, AGAIN

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- In 2016, China's State Food and Drug Administration (cFDA) led a 1-year intense investigation by assigning 366 staff to verify the details of clinical trial dossiers supplied to support drug approvals
  - 1308 of the 1622 NDAs contained fabricated, flawed, or inadequate data from clinical trials and should be withdrawn
  - They found many instances of discrepancies between trial data from the original record books and the submitted files, selective reporting of data, fabrication of data, and nonreporting of adverse events

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## TRUST BUT NOT VERIFY, AGAIN

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- The WHO issued a "notice of concern," the second highest level of serious violation, to Quest Life Sciences Ltd, an Indian-based CRO
  - Study "LAZ/032/13" assessed combination lamivudine, zidovudine, and nevirapine treatment for HIV in 2014
  - The team described problems with record integrity, subject safety, and poor-quality assurance
  - Two-thirds of prestudy electrocardiograms (ECGs) in the documents were duplicates, suggesting actual ECGs may not have been performed, as required in the protocol, or were substituted when the participants' own ECGs made them ineligible
  - Some forms in the files were also blank, suggesting that they would be filled in later. The WHO rejected the study
- This is similar to issues with Indian-based CRO GVK Biosciences that included data manipulation of ECGs between 2008 and 2014
  - The EMA recommended suspending the sale of approximately 700 drugs that were involved in this notice of concern
- Similarly in 2017, European inspectors determined widespread data issues with studies conducted by Indian CRO Micro Therapeutic Research, and the EMA recommended that studies for manufacturers such as Aurobindo, Sandoz, Sanofi, and Mylan be suspended pending new and ethically conducted study results

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## MALFEASANCE INVADES MAJOR CLINICAL TRIALS

- The TOPCAT Trial assessed the impact of spironolactone versus placebo in patients with heart failure with preserved ejection fraction
  - Overall, no significant benefits were seen, but there were regional differences between participants in the Americas and those in Russia
  - In 2017, it was revealed that concentrations of spironolactone's active metabolite, canrenone, were undetectable in 30% of Russian participants randomized to active treatment versus only 3% of participants in the United States and Canada.
- The TRUE-AHF trial was published assessing the efficacy of the experimental drug ularitide in acute heart failure
  - Only 2% of US sites had 3 or more ineligible patients enrolled as compared with 63% of sites in the Czech Republic, Estonia, Poland, and Serbia
- The FDA looked carefully at Chinese sites in the ARISTOTLE trial after one site's data were found to be an outlier in terms of survival benefit and subsequently determined to be fraudulent
  - They recommended that data from not just that site but 23 additional Chinese sites with questionable data be excluded
  - This clinical trial was comparing apixaban to warfarin in patients with atrial fibrillation. Publications resulting from the ARISTOTLE trial do not mention the controversy, even ones that came out over a year afterward
  - The data used in these journal publications and the apixaban label is based on the full data set, not the data set excluding the questionable sites

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## FDA DOES NOT PREVENT FRAUDULENT DATA FROM MAKING IT INTO THE LITERATURE

- One assessment of FDA data found 57 clinical trials that had research sites classified for "Official Action Indicated" (the most serious finding) after an FDA inspection for the following: protocol violations (74%), inadequate or inaccurate recordkeeping (61%), failure to protect the safety of patients and/or issues with oversight or informed consent (53%), falsification or submission of false information (39%), problems with adverse events reporting (25%), and violations not otherwise categorized (35%). Only 3 of the 78 resulting publications (4%) resulting from these trials mentioned the objectionable conditions or practices. This makes malfeasance a lower-risk endeavor because, even if caught, the FDA only disregards the data from its deliberations, and investigators are free to publish the questionable data openly.

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## CAN YOU REALLY TRUST THE DATA WHEN YOU DON'T CONTROL THE SOURCE?

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- In an assessment of 139 meta-analyses, large differences judged to be beyond those resulting from chance occurred in 8% of trials and always showed more favorable treatment effects in less-developed countries (relative risk: 1.12 [95% CI = 1.06 to 1.18])

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## WHAT CAN BE DONE?

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- There should not be two sets of rules that disadvantage U.S. researchers and call into question research results needed for FDA and formulary review as well as clinician decisionmaking
- The FDA needs to ensure that funding for inspections of overseas sites are not a barrier to oversight in the next approval of PDUFA being negotiated now for 2022

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## QUESTION 5

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- What are the risks from drug trials shifting overseas?
- A. Ethical violations or subject harm will become more prevalent
- B. The FDA will not have the sufficient dataset to discern drugs with an unfavorable risk/benefit balance
- C. American jobs will be lost in part due to an unequal playing field
- D. **All of the above**

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# ANY QUESTIONS?

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