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INTRODUCTION TO FDA REVIEW AND APPROVAL OF BIOLOGICAL PRODUCTS

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The Statutory Framework for Biological Products

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BIOLOGICS IN THE 19TH CENTURY AND BEFORE: THE DEVELOPMENT OF VACCINES

“Variolation” preceded “vaccination” with cowpox and, later, the vaccinia virus.

From the CDC website :

> The basis for vaccination began in 1796 when the English doctor Edward Jenner noticed that milkmaids who had gotten cowpox were protected from smallpox. Jenner also knew about variolation and guessed that exposure to cowpox could be used to protect against smallpox. To test his theory, Dr. Jenner took material from a cowpox sore on milkmaid Sarah Nelmes’ hand and inoculated it into the arm of James Phipps, the 9-year-old son of Jenner’s gardener. Months later, Jenner exposed Phipps several times to variola virus, but Phipps never developed smallpox. More experiments followed, and, in 1801, Jenner published his treatise “On the Origin of the Vaccine Inoculation.” In this work, he summarized his discoveries and expressed hope that “the annihilation of the smallpox, the most dreadful scourge of the human species, must be the final result of this practice.”
>
> Vaccination became widely accepted and gradually replaced the practice of variolation. At some point in the 1800s, the virus used to make the smallpox vaccine changed from cowpox to vaccinia virus.

https://www.cdc.gov/smallpox/history/history.html

EARLY VACCINES

From J. Esparza, “Early smallpox vaccine manufacturing in the United States: Introduction of the “animal vaccine” in 1870, establishment of “vaccine farms”, and the beginnings of the vaccine industry” https://doi.org/10.1016/j.vaccine.2020.05.037:

> “Animal vaccine“ referred to the vaccine that was obtained directly from a cowpox or horsepox lesion on cows and serially propagated in calves, without undergoing human passages before it was ultimately used to vaccinate humans.

From M. Dixon, “Why Nine Camden Children Died from Smallpox Vaccines in 1901” (9/2/2016) https://mainlinetoday.com/life-style/why-nine-camden-children-died-from-smallpox-vaccines-in-1901/:

> The production of a smallpox vaccine began by gathering the fluid seeping from lesions on the udders of infected cows. Smallpox vaccination spread widely, but was equally opposed, with some critics believing it caused syphilis. Mulford’s reputation for excellent sanitation overcame distaste for what was essentially pus scraped from the undersides of cows.

EARLY ANIMAL-DERIVED ANTITOXINS

From the FDA website https://www.fda.gov/files/Biologics-Centennial--100-Years-of-Biologics-Regulation.pdf:

> Researchers Emil von Behring and Shibasaburo Kitasato in Robert Koch's lab, for example, discovered that animals injected with diphtheria and tetanus toxins produced anti-toxins which could be inoculated into other animals to both cure and provide future immunity from these dread diseases. Their serum therapy was tested at Berlin's Charite` hospital at the end of 1891 and the chemical company Hoechst began commercial antitoxin serum production soon after. Mortality rates from diphtheria in Europe dropped dramatically and laboratories in the United States quickly rushed to begin production of these new life-saving biological products.

From M. Dixon, “Why Nine Camden Children Died from Smallpox Vaccines in 1901” (9/2/2016) https://mainlinetoday.com/life-style/why-nine-camden-children-died-from-smallpox-vaccines-in-1901/:

> Horses were inoculated with gradually increasing doses of diphtheria toxin, isolated from cultures of the bacillus grown in vitro. Eventually, the animals became “hyperimmune,” meaning their blood contained massive quantities of diphtheria antibodies. They were then bled from the jugular vein, and the serum was separated by straining.

A HORSE NAMED JIM

In 1901 a horse named Jim was used to prepare an antitoxin for diphtheria.

> He was a bay horse, 16 hands high, weighed over 1600 lbs, and named Jim. Originally, he was an ambulance horse, had been injured in the shoulder, and was turned over [for production of antitoxin] in 1898. He has been under treatment for the production of diphtheria antitoxin for nearly three years, has been bled a number of times and has furnished over 30,000 c.c. (30 quarts) of diphtheria antitoxin. In fact, the greater art of the antitoxin distributed by the Health Department during the years 1900 and 1901 came from this horse.

JAMA. 1901;XXXVII(19):1260-1261. doi:10.1001/jama.1901.62470450032014 (Report of the Bacteriologist)

After the death of 13 children who received the antitoxin in St. Louis, Missouri, health authorities discovered that Jim was dead, too - destroyed after becoming sick with tetanus. The manufacturers had distributed the antitoxin despite Jim's illness.

That same year, nine children in Camden, New Jersey died from tetanus linked to contaminated smallpox vaccine. Less is known about the source of the contamination, but one manufacturer, Mulford, was identified as the source of the vaccine used to vaccinate eight of the nine children.

BIOLOGICS CONTROL ACT 1902
PUBLIC LAW 57-244

Among other things, the law:

Prohibited the sale, barter, or exchange in interstate commerce of “any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man” unless

- the establishment manufacturing the product has an unsuspended and unrevoked license;

- the product package is plainly marked with the proper name of the article, the name, address, and license number of the manufacturer; and the product expiration date.

Authorized government inspection of manufacturing establishments.

Authorized the issuance of regulations.

Established penalties for non-compliance.

THE 1902 ACT ESTABLISHED A FRAMEWORK FOR THE REGULATION OF "BIOLOGICAL PRODUCTS"

Now defined as an article that:
falls into one of the categories identified in PHS Act 351(i)(1)*; and
is "applicable to the prevention, treatment, or cure of a disease or condition of human beings."

*Throughout this presentation, I cite to section 351 of the Public Health Services Act (PHS Act), codified at 42 U.S.C. 262. References to the FDCA are to the Federal Food, Drug, and Cosmetic Act, codified at 21 USC 301-399f.

CATEGORIES OF "BIOLOGICAL PRODUCTS"

- Virus
- Therapeutic serum
- Toxin
- Antitoxin
- Vaccine
- Blood, blood component, blood derivative
- Allergenic Product
- Protein
- Or analogous product
- Or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound)

EVOLUTION OF DEFINITION

1902 Virus, therapeutic serum, toxin, antitoxin, analogous product

1944 Added “arsphenamine or its derivatives (or any other trivalent organic arsenic compound)”

1970 Added ”vaccine, blood, blood component or derivative, allergenic product”
- following Blank v. US 400 F.2d 302 (5th Cir. 1968)

2010 Added ”protein (except any chemically synthesized polypeptide)”

2019 Deleted “(except any chemically synthesized polypeptide)” removed from definition

ARSPHENAMINE?*

“Salvarsan” – German-manufactured small molecule syphilis treatment

1917 - Trading with the Enemy Act authorized US manufacture of Salvarsan under Public Health Service oversight, as well as Novocain and other German-manufactured drugs.

1919 - Following the war, PHS continued to regulate arsphenamine as “analogous product”

1944 - Definition modified to reflect then-current practice of regulating arsphenamine as a biological product.

**See Coleman, “Early Developments in the Regulation of Biologics,” 71 F.D.L.J. 544 (2016)

PROTEIN

21 CFR 600.3(h)(6) defines a protein as any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of this paragraph (h)(6) will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence.

ANALOGOUS PRODUCT?

21 CFR 600.3(h)(5) definition describes analogous to a virus, therapeutic serum, toxin or antitoxin – but not to the other articles named in the statutory definition

United States v. Loran Medical Systems, 25 F.Supp.2d 1082 (C.D.Ca. 1997) ruled that rabbit and human fetal cells used for the treatment of diabetes fell within the regulatory definition of products "analogous" to a toxin or antitoxin because the cells were intended, irrespective of the source of origin, to be applicable to the prevention, treatment, or cure of human disease or injuries through a specific immune process. Accordingly, the product was subject to licensure as a biological product. The court also held the products were unapproved new drugs.

POLL QUESTION

Is elderberry extract a biological product?

-Yes

-No

-Maybe

THE PUBLIC HEALTH SERVICE ACT OF 1944

Consolidated and revised almost all legislation relating to federal public health services.

The Public Health Service Act compiled federal public health provisions, including the requirements for licensure of biologics established in 1902 and provisions for the control of communicable diseases.

Under the Public Health Service Act, FDA can issue regulations to prevent the spread of communicable diseases. That includes not just some of the products regulated by CBER, but also the interstate movement of turtles, because of the potential spread of salmonella. FDA has issued regulations in that area.

REGULATION OF “DRUGS”
1906: PURE FOOD AND DRUGS ACT

Prohibited interstate commerce of misbranded and adulterated food, and drugs

- focused on penalties, with provisions for criminal penalties, including imprisonment and fines.
- authorized seizures of products.

No requirements for premarket authorization of drug products.

REGULATION OF ”DRUGS”
1938: FEDERAL FOOD, DRUG, AND COSMETIC ACT

Enacted as a result of a tragedy involving a drug, elixir sulfanilamide, which contained an unlabeled solvent that caused the death of a number of people. The existing law did not address the failure to disclose that information.

The 1938 FDCA:

- required that a manufacturer demonstrate drug product safety before it could be marketed.

- provided inspection authority.

- added the injunction authority.

- did not require manufacturers to demonstrate their products were effective

- added additional authority over products such as cosmetics and therapeutic devices, although the term device was not used.

REGULATION OF "DRUGS"
1962: KEFAUVER-HARRIS AMENDMENTS

Enacted after it was shown that the drug thalidomide, marketed for numerous indications including morning sickness, had caused birth defects in babies born in Europe and other regions.

FDA had not allowed marketing of the drug but Congress realized that stricter standards should be required to be met before a drug product could be put on the market.

The Kefauver-Harris drug amendments required manufacturers to provide substantial evidence of the safety *and* effectiveness of the product before it can be marketed.

> the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 USC 355(d).

1976: MEDICAL DEVICE AMENDMENTS TO THE FDCA

Intended to provide reasonable assurance of the safety and effectiveness of medical devices.

Created a three-class, risk-based classification system for all medical devices.

Established the regulatory pathways for new medical devices (devices that were not on the market prior to May 28, 1976, or had been significantly modified) to get to market: Premarket Approval (PMA) and premarket notification (510(k)).

Created the regulatory pathway for new investigational medical devices to be studied in patients (Investigational Device Exemption (IDE)).

Established several key postmarket requirements: registration of establishments and listing of devices with FDA, Good Manufacturing Practices (GMPs), and reporting of adverse events involving medical devices.

Authorized FDA to ban devices.

1990: SAFE MEDICAL DEVICES ACT

Improved postmarket surveillance of devices by:

- Requiring user facilities such as hospitals and nursing homes to report adverse events involving medical devices
- Authorizing the FDA to require manufacturers to perform postmarket surveillance on permanently implanted devices if permanent harm or death could result from device failure

Authorized the FDA to order device recalls and to impose civil penalties for violations of the FDCA

Defined substantial equivalence (the standard for marketing a device through the 510(k) program)

Modified procedures for the establishment, amendment, or revocation of performance standards

Created the Humanitarian Use Device (HUD)/Humanitarian Device Exemption (HDE) programs to encourage development of devices targeting rare diseases

SIGNIFICANT AMENDMENTS OF THE FDCA AND PHS ACT NOW OCCUR AT LEAST EVERY 5 YEARS

The Prescription Drug User Fee Act (PDUFA), first passed in 1992, established a 5 year user fee program that requires legislative renewal every 5 years.

Additional user fee acts have joined PDUFA, including:

- MDUFA (first passed as MDUFMA in 2002)
- ADUFA (first passed in 2003)
- AGDUFA (first passed in 2008)
- BsUFA (first passed in 2012)
- GDUFA (first passed in 2012)
- OMUFA (first passed in 2020)

PERIODIC LEGISLATION TO RENEW USER FEES PROVIDES A VEHICLE FOR PERIODIC REVISIONS

- The Food and Drug Modernization Act of 1997 (FDAMA)
- The Food and Drug Administration Amendments Act of 2007 (FDAAA)
- The Food and Drug Administration Safety and Innovation Act (FDASIA)
- The 21st Century Cures Act

2022 is a year that human medical product user fees must be renewed. Additional topics under consideration include:

- Changes to FDA's accelerated approval program
- Additional use of real world evidence
- Many more

BIOLOGICS PRICE COMPETITION AND INNOVATIONS ACT (BPCIA)

Established the “biosimilars” pathway in PHS Act 351(k).

By referencing an already licensed biological product, a follow on biological product may be licensed as a “biosimilar” based on a showing that the product is “highly similar” to the reference product and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

In addition, a biosimilar may be determined to be “interchangeable” with the reference product, which would permit pharmacy level substitution.

Biological products approved under PHS Act 351(a) have 12 years reference product exclusivity.

NDA APPROVALS "DEEMED TO BE A LICENSE"

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) required that a marketing application for a "biological product" that previously could have been submitted under section 505 of the FDCA must be submitted as a biologics license application (BLA) under section 351 of the PHS Act subject to a 10-year transition period ending on March 23, 2020.

On March 23, 2020, the BPCI Act required that an approved marketing application for a "biological product" under section 505 of the FDCA shall be deemed to be a license for the biological product (i.e., an approved BLA) under section 351 of the PHS Act.

FDA website posts a list of 96 NDAs that, on March 23, 2020, were deemed to be biological products licensed under 351(a).

Important Principle:

Product definitions determine regulatory pathways

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“DRUG” DEFINITION

21 USC 321(G)(1) (EXCERPTED)

Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals

"BIOLOGICAL PRODUCTS" MAY ALSO MEET THE DEFINITION OF "DRUG"

Under the PHS Act, biological products are licensed after demonstrating that they are "safe, pure, and potent."

In 1972, responsibility for regulating biological products transferred from NIH to FDA.

In recognition that the drug efficacy standard should also be applied to biological products that met the definition of "drug," FDA undertook a review of the efficacy of biological products. Some products were removed from licenses.

STATUTORY APPROVAL STANDARDS (summarized)

Drugs:

Approval based on substantial evidence consisting of adequate and well controlled investigations, including clinical investigations, by investigators qualified by scientific training and experience to evaluate the effectiveness of the drug. Assessment of safety and effectiveness must be based on a balanced consideration of benefits and risks under the conditions of use prescribed, recommended or suggested in the labeling.

Biological Products:

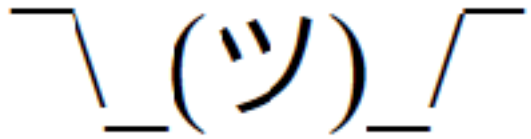
License issued on the basis of a demonstration that the product is safe, pure, and potent, and that the manufacturing facility meets standards designed to assure that products manufactured there are safe, pure, and potent.

POLL QUESTION

Is the “safe pure and potent” standard for biological products the same as the “substantial evidence” standard for drugs?

Yes

No



HOW ARE BIOLOGICAL PRODUCTS DIFFERENT?
(SUMMARIZING FDA'S SLIDE)

Most drugs: chemical compounds with known structures.

Most biological products

- Complex mixtures, not easily identified or characterized.
- Greater risk of microbial contamination due to growth-supportive environment.
- More heat-sensitive, making terminal sterilization unsuitable.
- Aseptic processing applied from initial manufacturing steps.

But consider - arsphenamine?

BLA/NDA - WHAT IS THE SAME?

Statutory GMP, as well as CGMP regulations in Parts 210 and 211 [however, additional standards in biological product regulations apply only to biological products]

IND regulations

Expanded access

Fast track, accelerated approval, priority review, breakthrough therapy

Priority Review Voucher Programs

Pediatric Requirements under PREA

Other statutory provisions applicable to a “drug” where “drug” is not qualified by “approved under section 505” or other language that excludes application to products regulated under the PHS Act, section 351.

BLA/NDA - WHAT IS THE SAME? (more)

Development programs follow the same sequence – preclinical work, clinical studies, marketing application.

But – for a complex biological product, there are additional concerns linked to the manufacturing process. If the manufacturing process or location changes during development, the changes may significantly affect the biological product. And even if the product does not change significantly, the sponsor must be prepared to demonstrate that the product is consistent.

To do this, the sponsor must have identified the product's critical quality attributes, which define the adventitious agents, safety, purity, potency, identity, and stability of the product. These can be difficult to establish early in development of a complex product.

There have been several Complete Response Letters to cell and gene therapy sponsors issued because of manufacturing issues.

EXCLUSIVITIES APPLICABLE TO BOTH 351(a) BLAs and NDAs

Orphan Drug Exclusivity – FDA will not approve the same drug for an orphan designated indication for seven years from the first approval of the orphan designated drug for the orphan indication, unless the second drug is clinically superior to the first-approved drug.

- Clinically superior means that the drug has been shown to provide a significant therapeutic advantage over and above that provided by the approved drug in terms of
  - Greater effectiveness (in most cases, direct comparative clinical trials would be necessary)
  - Greater safety in a substantial portion of the target populations (in some cases, direct comparative clinical trials would be necessary)
  - In unusual cases, a demonstration that the drug otherwise makes a major contribution to patient care

Pediatric Exclusivity – FDA may issue Written Requests for pediatric studies of an active moiety if FDA has determined that information related to the use of the active moiety in the pediatric population may produce health benefits. A sponsor in receipt of a Written Request may receive an additional 6 month period of exclusivity if the sponsors conducts studies that fairly respond to the Written Request and submits study report(s) and appropriate labeling and other information at least 15 months before expiration of the listed patent or period of exclusivity sought to be extended.

NDA EXCLUSIVITIES NOT APPLICABLE TO BIOLOGICAL PRODUCTS

New Chemical Entity Exclusivity - 5 years, granted to “a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Act”

New Clinical Investigation Exclusivity – 3 years, granted for a drug product that contains an active moiety that has been previously approved when the application contains “new” clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were “essential "to the approval

GAIN (Generating Antibiotic Incentives Now) Exclusivity – FDA-designated Qualified Infectious Disease Products may receive a 5-year extension to any exclusivity that the application qualifies for upon approval.

EXCLUSIVITY FOR INTERCHANGEABLE BIOSIMILAR PRODUCTS AND GENERIC DRUGS

First Interchangeable Biosimilar Product – PHS Act 351(k)(6) provides a period of exclusivity for the first interchangeable biological product. The length of the exclusivity period varies from 12 to 42 months based on whether or not the sponsor is sued for patent infringement by the sponsor of the referenced biological product.

Patent Challenge Exclusivity – 180-day exclusivity for first applicant to submit substantially complete ANDA containing Paragraph IV certification by the ANDA applicant that a patent is invalid, unenforceable, or will not be infringed.

Competitive Generic Therapy Exclusivity – 180-day exclusivity for the first approved ANDA applicant for a drug for which there were no unexpired patents or exclusivities listed in the Orange Book at the time of original submission of the ANDA and which has been designated by FDA as a CGT.

BLA/NDA – WHAT ELSE IS DIFFERENT?

- Regenerative Medicine Advanced Therapy Designation – created by 21st Century Cures
- For some products, the possibility of being regulated solely as a human tissue or cellular based product
- Additional provisions established in the biological product regulations for lot release, license suspension and revocation
- More limited reliance on Master Files for biological products

HARMONIZATION

PHS Act 351(j): FDCA applies to a biological product except that a licensed product shall not be required to have an approved drug application.

FDCA (21 USC 392(b)): Nothing contained in this chapter shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of section 351.

Uncodified note to 21 USC 355: Requires FDA to take measures to minimize differences in the review and approval of BLAs and NDAs.

“DEVICE” DEFINITION (1)

21 USC 321(H) (EXCERPTED)

means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory . . .

“DEVICE” DEFINITION (2)

intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals . . .

“DEVICE” DEFINITION (3)

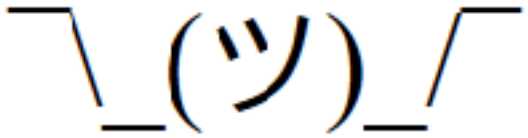
which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

POLL QUESTION

Is a virus that is used as a control in an in vitro diagnostic test kit a biological product?

Yes

No



BOTH CBER AND CDER REGULATE BIOLOGICAL PRODUCTS

CDER – responsible for therapeutic biological products

CBER – responsible for a variety of products, including blood, vaccines, allergenics, probiotics, cellular products, and gene therapy

CBER is also responsible for certain NDAs, ANDAs, 510(k)s, and PMAs. The products covered by those applications are not subject to regulation as biological products.
CBER has responsibility for those drugs and devices because of CBER program areas (example: articles used in blood collection or to screen donors).
CBER also regulates diagnostic tests for retroviruses (example: HIV).

Pathways to Market

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KEY POINT

The regulatory category is applied to a product has significant implications, such as:

- User fees vary widely
  - Examples of FY2022 application fees (other types of fees may also apply):
    - $ 3,117,218 for a BLA or NDA with clinical data
    - $ 1,746,745 for a biosimilar BLA with clinical data
    - $ 225,712 for an ANDA (generic drug application)
    - $ 374,858 for an application for pre-market approval (PMA) for a Class III device
    - $ 12,745 for a 510(k) notification for a device

- Abbreviated pathway for generic or follow on products
  - BLA under 351(a), followed by 351(k) biosimilar
  - NDA filed under FDCA 505(b) may be referenced in a 505(b)(2) application or a 505(j) ANDA
  - 510(k) pathway permits devices to come to market based on a showing of “substantial equivalence” to a legally marketed device.
- Scope and size of clinical trials to support approval

BIOLOGICAL PRODUCT LICENSING

Biological products are approved as licensed products under

- PHS Act 351(a); or
- PHS Act 351(k) (biosimilar pathway)

BIOSIMILAR PATHWAY

- Approval only after expiration of 12 years of reference product exclusivity

- Based on a demonstration that the product is highly similar to and has no clinically meaningful differences from a single FDA-approved reference product.

- The biosimilar sponsor demonstrates that its product is highly similar to the reference product by extensively analyzing (i.e., characterizing) the structure and function of both the reference product and the proposed biosimilar. Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable.

–The biosimilar sponsor must demonstrate that its product has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness). This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.

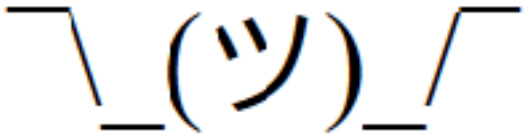
- The sponsor may also demonstrate interchangeability with the reference product by showing that the product is expected to produce the same clinical result as the reference product in any given patient. Switching studies required for products administered to a patient more than once. Interchangeable products may be substituted for the reference product at the pharmacy level.

POLL QUESTION

If you were the sponsor of a new product and you had complete discretion to take the product down either the NDA or the BLA pathway, what would you choose?

NDA

BLA



NUMBERS OF BIOSIMILAR APPROVALS

By the end of 2022, FDA had approved 33 biosimilars.

The first interchangeable biosimilar was an insulin glargine product licensed on 7/28/2021.

The second interchangeable biosimilar was an adalimumab product licensed on 10/18/2021.

GENERIC DRUG PATHWAY – ANDA, FDCA 505(j)

Timing of applications and approvals are tied to the date of approval of the reference listed drug, as well as to patent provisions listed with FDA by the innovator drug sponsor.

- A reference listed drug approved as a new molecular entity has five years of exclusivity
- A reference listed drug that is not an NME, but that was approved for an indication on the basis of clinical trials that were essential to the approval has three years of exclusivity

ANDA applicants must also certify that the application will not violate valid patents held by the innovator drug sponsor, and provide notice of the ANDA to the patent holder.

- FDA lists these patents in the Orange Book.
- Patent litigation may delay full approval of the ANDA.

FDA IS NOT REQUIRED TO MAINTAIN AN ORANGE BOOK FOR BIOLOGICAL PRODUCTS; 351(k) APPROVAL IS NOT TIED TO PATENT CERTIFICATIONS BY THE BIOSIMILAR APPLICANT

This does not mean that the sponsor of a reference product approved under 351(a) cannot enforce their patents; it means that the timing of the FDA approval is not tied to that litigation. We have seen that many licensed biosimilar products have not yet been marketed, presumably because of patent issues.

FDA does publish a “Purple Book” which lists licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations.

Currently, the Purple Book database contains information about all FDA-licensed biological products regulated by the CDER, including any biosimilar and interchangeable biological products, licensed (approved) by the FDA and FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by CBER.

ANDA APPROVAL STANDARD

Approval is based on a demonstration that the generic drug is bioequivalent to the reference listed drug, with:

- The same active ingredient
- The same strength
- The same presentation type of product and route of administration
- The same labeling (with limited exceptions)
- The inactive ingredients of the medicine are acceptable.

Some differences, such as in inactive ingredients, are acceptable if they are shown to have no effect on how the drug functions.

CONTRAST TO 505(b)(2) NDA

An NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference or use.

One type of information that may be relied on by the applicant is FDA's prior finding of safety and effectiveness in a prior approval of the active ingredient.

As in an ANDA, the sponsor of a 505(b)(2) application that relies on FDA's prior finding of safety and effectiveness must certify to patents listed for the reference listed drug. Timing of applications and approvals are tied to the date of approval of the reference listed drug, as well as to patent provisions listed with FDA by the innovator drug sponsor.

- A reference listed drug approved as a new molecular entity has five years of exclusivity
- A reference listed drug that is not an NME, but that was approved for an indication on the basis of clinical trials that were essential to the approval has three years of exclusivity

CONTRAST TO MEDICAL DEVICE PATHWAYS

Premarket Approval Application

Humanitarian Device Exemption

510(k)

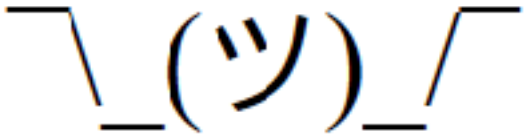
510(k) Exempt

POLL QUESTION

If you were the sponsor of a new product and you had complete discretion to develop the product as a medical device or as a biological product approved under BLA, what would you choose?

Medical Device

BLA



GENUS MEDICAL TECHNOLOGIES V. FDA, NO. 20-5026 (D.C. CIR. 2021)

From the FDA Federal Register notice implementing the decision:

Both the District Court and the Court of Appeals, as a matter of statutory interpretation, disagreed with FDA's view that the Agency had discretion to regulate products meeting the device definition as drugs. The Court of Appeals determined that FDA cannot classify as a drug any product that meets the definition of device, stating "[e]xcepting combination products, . . . Devices must be regulated as devices and drugs—if they do not also satisfy the device definition—must be regulated as drugs."

BIOLOGICAL PRODUCT

Intersection with dietary supplements

- October, 2014 death of pre-term Infant who was treated with mold-contaminated probiotic dietary supplement
- CBER guidance on Early Clinical Trials with Live Biotherapeutic Products

Some interest in using biological material (for example, placental tissue) in cosmetics

Combination Products

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COMBINATION PRODUCTS

First addressed by statute in the 1990 Safe Medical Device Amendments which amended section 503 of the FDCA (21 USC 353).

Statutory Description – Products that constitute a combination of a drug, device, or biological product

REGULATORY DEFINITION – 21 CFR 3.2(e)

Two or More Medical Product Components
- physically, chemically, or otherwise combined or mixed and produced as a single entity
- packaged together in a single package or as a unit; or
- packaged separately, but requiring cross labeling

POLL QUESTION

Consider this fictional product:

- a gene therapy composed of a viral vector that delivers the gene to the patient's cells;

- copackaged with an injectable therapeutic protein intended to be co-administered with the gene therapy.

The therapeutic protein is administered to prevent a serious adverse event.

Is this a combination product?

INTERCENTER AGREEMENTS

CBER, CDER, and CDRH entered into three Intercenter Agreements (ICAs) in 1991.

- although these are 30 years old, they are important for any practitioner in this space to be aware of.

From FDA website: in 2006 (71 FR 56,988), the Agency reviewed these agreements and preliminarily determined that they continue to provide helpful, nonbinding guidance, and proposed to continue them in effect, with the understanding that they should not be independently relied upon as the Agency's most current, complete jurisdictional statements. The Agency suggests that persons wishing to get the most current information also consult the various other sources of information about jurisdictional determinations.

PRIMARY MODE OF ACTION

The FDCA requires FDA to determine the primary mode of action (PMOA) of the combination product.

PMOA directs Center assignment.

PMOA DEFINITION

PMOA defined in 21 CFR 3.2(m): the single MOA expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.
Incorporated into statute by 21st Century Cures, section 3038.

PMOA REGULATION

Mode of action defined in 21 CFR 3.2(k): the means by which a product achieves an intended therapeutic effect or action.

1. Biological product MOA
2. Device MOA (does not have biologic MOA)
3. Drug MOA (does not have biologic or device MOA)

WHEN PMOA CANNOT BE DETERMINED WITH REASONABLE CERTAINTY – "GO TO THE ALGORITHM"

1. Assignment should be to agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole.
2. If none, assign to agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product.

OFFICE OF COMBINATION PRODUCTS, IN OFFICE OF THE COMMISSIONER

Decides Requests for Designation – FDCA section 563, 21 CFR 3.7-3.9

- Request classification as drug, biological product, device, or combination product, or identify agency component to regulate.
- 60 days to decide . . . or the hammer falls –
- decision by operation of law

Modified only with consent or for public health reasons based on scientific evidence.

OFFICE OF COMBINATION PRODUCTS ENCOURAGES INTERACTIONS

Pre-RFD – New guidance on informal, non-binding process (1/2017)

21st Century Cures – provides opportunities for interactions between sponsor and OCP.

REMEDY FOR RFD FILER AFTER ADVERSE DECISION?

Appeal

21st Century Cures adds a new remedy – sponsor may conduct study and use that data to support reassessment of PMOA.

THANK YOU

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