Generic Drug Development and Globally Divergent Regulations

SBIA Generic Drug Annual Forum; April 26-27 2022

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Center for Drug Evaluation and Research

U.S. Food and Drug Administration

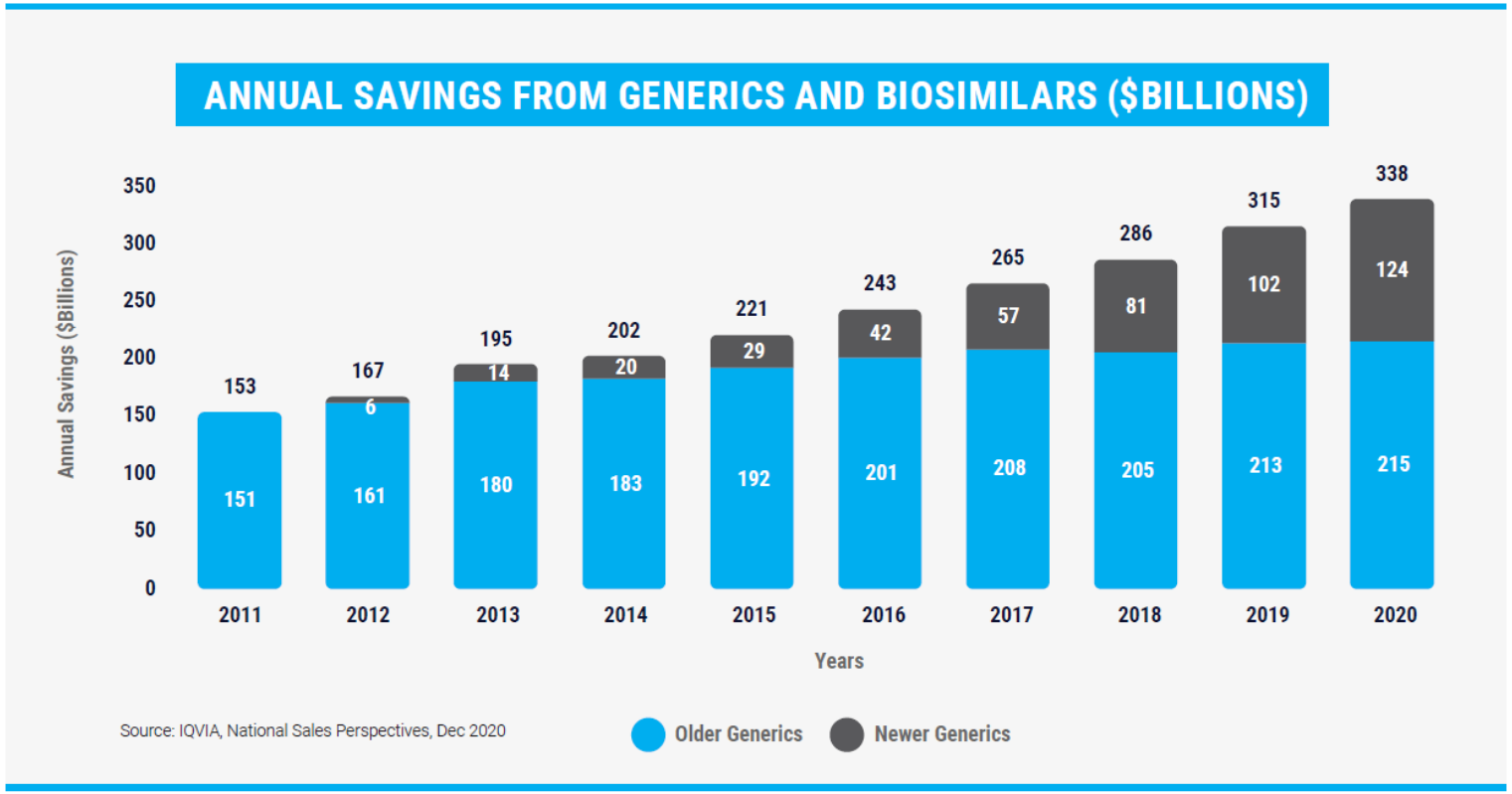
Agenda

OGD's global affairs program

Generic Drug Cluster and Parallel Scientific Advice

Paving the Path to Harmonization

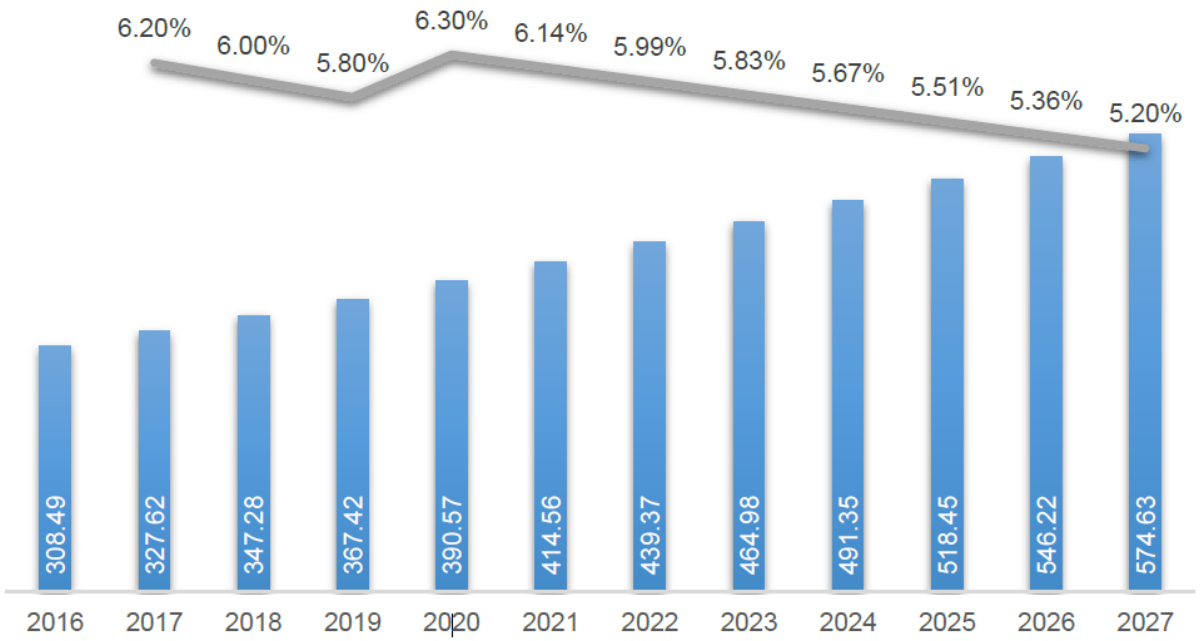
GENERIC DRUGS AND PATIENT COSTS



- The average generic copay: $6.61
- The average brand-name copay: $55.82
- 93% of generics have a copay less than $20, while only 51% of brands have a copay less than $20

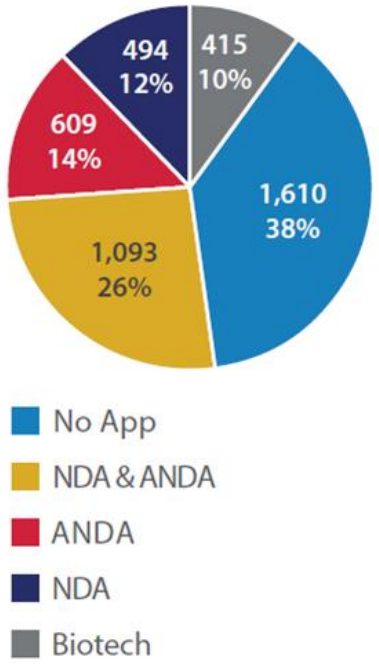
Generic Drug Global Landscape

Global generic drugs market snapshot



Generic Drugs Market-Market Size, Trends Analysis, Segment Forecasts, Regional Position 2021-2027

GLOBAL PHARMACEUTICAL INDUSTRY



Distribution of the FY2020 Site Catalog by Application Type

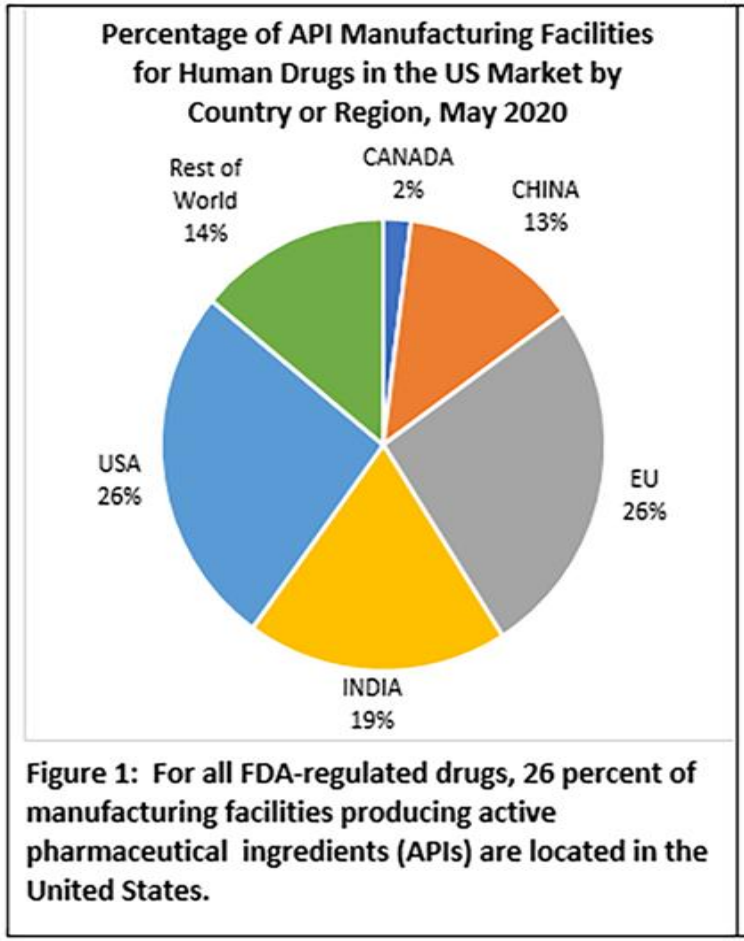


Figure 1: For all FDA-regulated drugs, 26 percent of manufacturing facilities producing active pharmaceutical ingredients (APIs) are located in the United States.

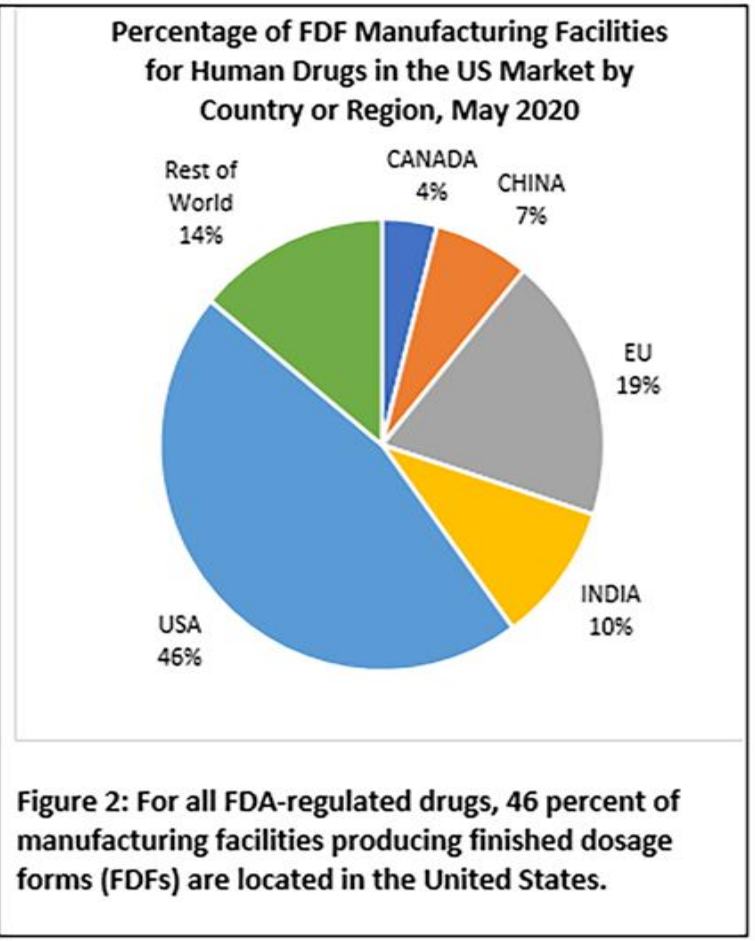
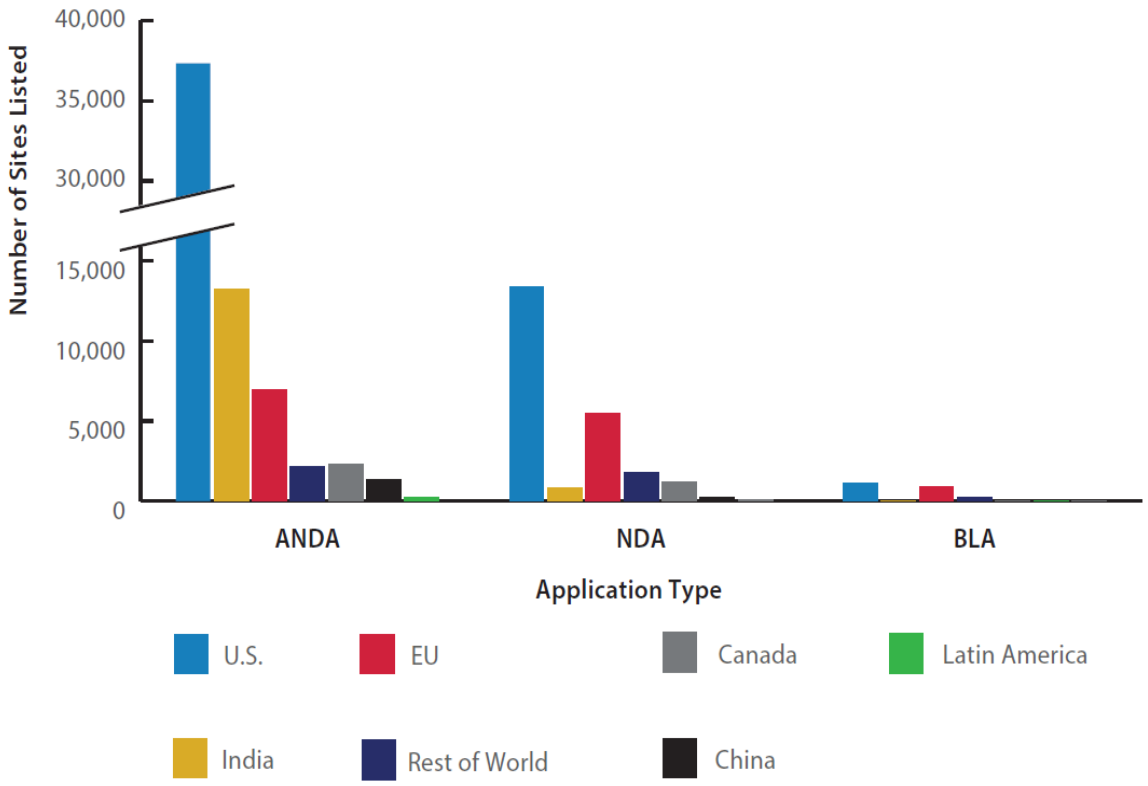


Figure 2: For all FDA-regulated drugs, 46 percent of manufacturing facilities producing finished dosage forms (FDFs) are located in the United States.

https://www.fda.gov/news-events/congressional-testimony/covid-19-and-beyond-oversight-fdas-foreign-drug-manufacturing-inspection-process-06022020
https://www.fda.gov/media/151561/download

MANUFACTURING SITE DEMOGRAPHICS

Country	Sites in FY2020	Sites maintained	Sites Removed	Sites Added	Percentage Shift		
					% Removed	% Added	% Net
UNITED STATES	1780	1644	286	136	-16.1%	7.6%	-8.4%
All Others	1266	1152	170	114	-13.4%	9.0%	-4.4%
INDIA	502	457	53	45	-10.6%	9.0%	-1.6%
CHINA	367	334	70	33	-19.1%	9.0%	-10.1%
GERMANY	160	150	26	10	-16.3%	6.3%	-10.0%
CANADA	146	137	19	9	-13.0%	6.2%	-6.8%
TOTAL	4221	3874	624	347	-14.8%	8.2%	-6.6%



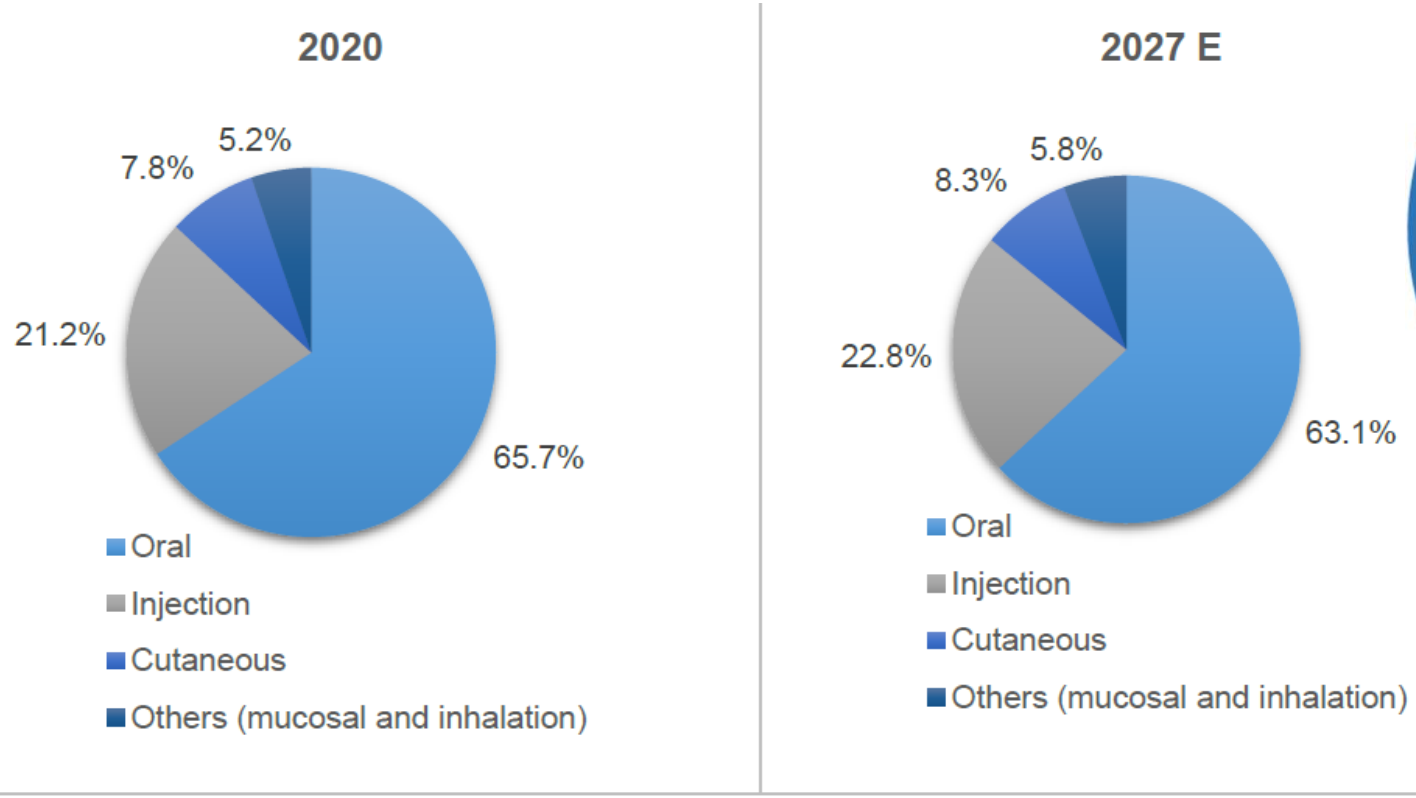
https://www.fda.gov/media/151561/download

BLA: Biologics License Application

GENERIC DRUG GLOBAL AFFAIRS PROGRAM

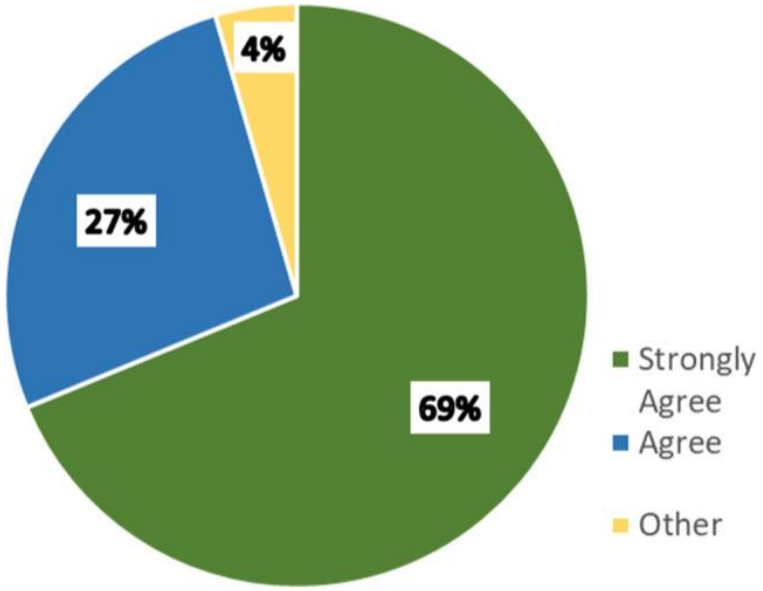
- Ensuring a strong FDA impact by promoting a high level of quality culture and standards
- Information Collection and Dissemination to assist in making better regulatory decisions about the pharmaceutical products that are being developed and exported for the U.S. market
- Identify emerging regulatory changes and manage proactive engagement with stakeholders concerning issues related to the pharmaceutical regulations
- Engage proactively and consistently with regulatory counterparts and industry representatives to facilitate FDA's domestic mission of assuring the safety, efficacy, and quality of FDA-regulated products

ADVANCES AND CHALLENGES FOR CURRENT REGULATORY FRAMEWORKS



Source: Industrial Journals, Experts Interview, Technical Publications, and Precedence Research Analysis, 2021

Global generic drugs market, by route of administration, 2020 & 2027 (%)



Level of agreement on the importance of a harmonized international approach for regulatory standards related to the development and approval of complex generic products.

Stern S, Coghlan J, Krishnan V, et al. Research and Education Needs for Complex Generics. Pharmaceutical Research. 2021 Dec;38(12):1991-2001. DOI: 10.1007/s11095-021-03149-y. PMID: 34950975; PMCID: PMC8732887.

GAPS FOR COMPLEX GENERIC DRUG APPROVAL

There are a significant number of important complex products that are off patent but lack generic competition.

It is estimated that the United States experiences an annual lost savings of $1.3 billion from seven complex generics that are currently approved in Europe and/or Canada but not the United States.

DRUG NAME (GENERIC NAME)	MANUFACTURER	CONDITIONS TREATED	FIRST APPROVED C = CANADA, EU = EUROPE	US SALES (2019, $ MILLION)
Abraxane® (paclitaxel)	Bristol Myers Squibb	Breast, lung, and pancreatic cancers	Mar. 2019 (EU)	$122
Forteo® (teriparatide)	Eli Lilly	Osteoporosis	Aug. 2019 (C) Oct. 2016 (EU)	$646
Invega Sustenna® (paliperidone)	Janssen/Johnson & Johnson	Schizophrenia, schizoaffective disorder	May 2019 (C) Jul. 2019 (EU)	$1,685*
Restasis® (cyclosporine)	Allergan/AbbVie	Suppressed tear production	Mar. 2017 (C)	$1,138
Risperdal Consta® (risperidone)	Janssen/Johnson & Johnson	Schizophrenia, bipolar I disorder	Oct. 2020 (EU)	$314
Sandostatin LAR® (octreotide)	Novartis	Symptoms of certain metastatic carcinoid tumors	Aug. 2020 (C) Apr. 2019 (EU)	$881
Venofer® (iron sucrose)	American Regent/ Daiichi Sankyo	Iron deficiency caused by chronic kidney disease	Jun. 2018 (EU)	$299

Recent U.S. FDA Generic Approved

Brill A. Potential savings from accelerating US approval of complex generics. February 2021.

COMPLEX GENERICS AND GLOBAL MARKET ACCESS

Partnership between industry, academia, and regulatory bodies

Development of a robust regulatory framework

Extensive scientific exchange of information enabling accelerated product development

Streamlining the regulatory requirements, and clarifying divergent regulations

Encouraging developers and manufacturers

Research and investment

ICH AND OGD

- Global harmonization for generic drugs dates back to 2001 WHO report
- FDA strategically leveraged ICH reform initiated at the end of 2015 to propose generic drug initiatives
- Established a unique global affair program at OGD at the end of 2015
- Advocating for the expansion of the ICH portfolio to include generic drug standards
- Proposed a generic drug topic to ICH for guidance development to industry on specific generic drug topics

KEY PROPOSALS IN THE ICH REFLECTION PAPER

Develop a series of ICH guidelines on standards for demonstrating equivalence [e.g., bioequivalence (BE)] for

(1) non-complex dosage forms

(2) more complex dosage forms and products

- Additional Strength Waiver for Immediate Release
- Statistical Analysis for BE
- BE Analysis for Highly Variable Drugs
- BE Analysis for Narrow Therapeutic Index

→ M13 Guideline (Series), Annex, or Addendum

→ Potential New Guideline

- BE for Modified Release oral dosage forms
- BE for Complex Products
  - Inhalation
  - Topical Dermatological
  - Long-acting Injectable
  - Other (e.g., Ophthalmic, Otic, Vaginal)

→ New Guideline

- Model-based BE

→ New Guideline

PROSPECTIVE HARMONIZATION EFFORTS

CONSENSUS BUILDING - TECHNICAL DOCUMENT

CONSENSUS ON TECHNICAL DOCUMENT / B. DRAFT GUIDELINE ADOPTION BY REGULATORS

REGULATORY CONSULTATION AND DISCUSSION

ADOPTION OF AN ICH HARMONISED GUIDELINE

IMPLEMENTATION

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FIRST GENERIC DRUG CLUSTER

Discussion of regulatory approaches to Generic Drug development

- Achieve a common understanding of each Agency's regulatory requirements for approval and current thinking on topics related to generic drug development through information sharing on approval requirements and recommendations conveyed in guidance documents.
- Offer a confidential forum for exchange and discussion on policies in development, including draft guidances for industry, and the scientific basis for decisions on those policies.
- Provide a forum for a discussion of general and product/class-related scientific review issues and foster alignment in approaches to scientific evaluation whenever possible.
- Address long term safety issues and ensure a global safety net for generic drugs through confidential sharing of reports.

https://www.fda.gov/drugs/generic-drugs/global-generic-drug-affairs

GLOBAL DIALOGUE BRIDGES THE GAPS FOR COMPLEX GENERIC DRUG APPROVAL

- Identify key differences among regulatory agencies regarding the approval of complex generics
- Identify aspects hindering fast approval of complex generics
- Case studies and experiences with complex generics
- Reach consensus regarding approval standards when possible

PARALLEL SCIENTIFIC ADVICE (PSA) PILOT

FDA/EMA Bilateral

- The pilot established a new PSA process for complex generic drugs (FDA)/hybrid products (EMA-European Medicines Agency)

- A new addition to the existing PSA programs for new drugs (OND) and vaccines or gene therapies (CBER)

Launched September 15, 2021

- PSA principles document can be accessed via the Office of Generic Drugs Global Affairs website

https://www.fda.gov/drugs/generic-drugs/global-generic-drug-affairs

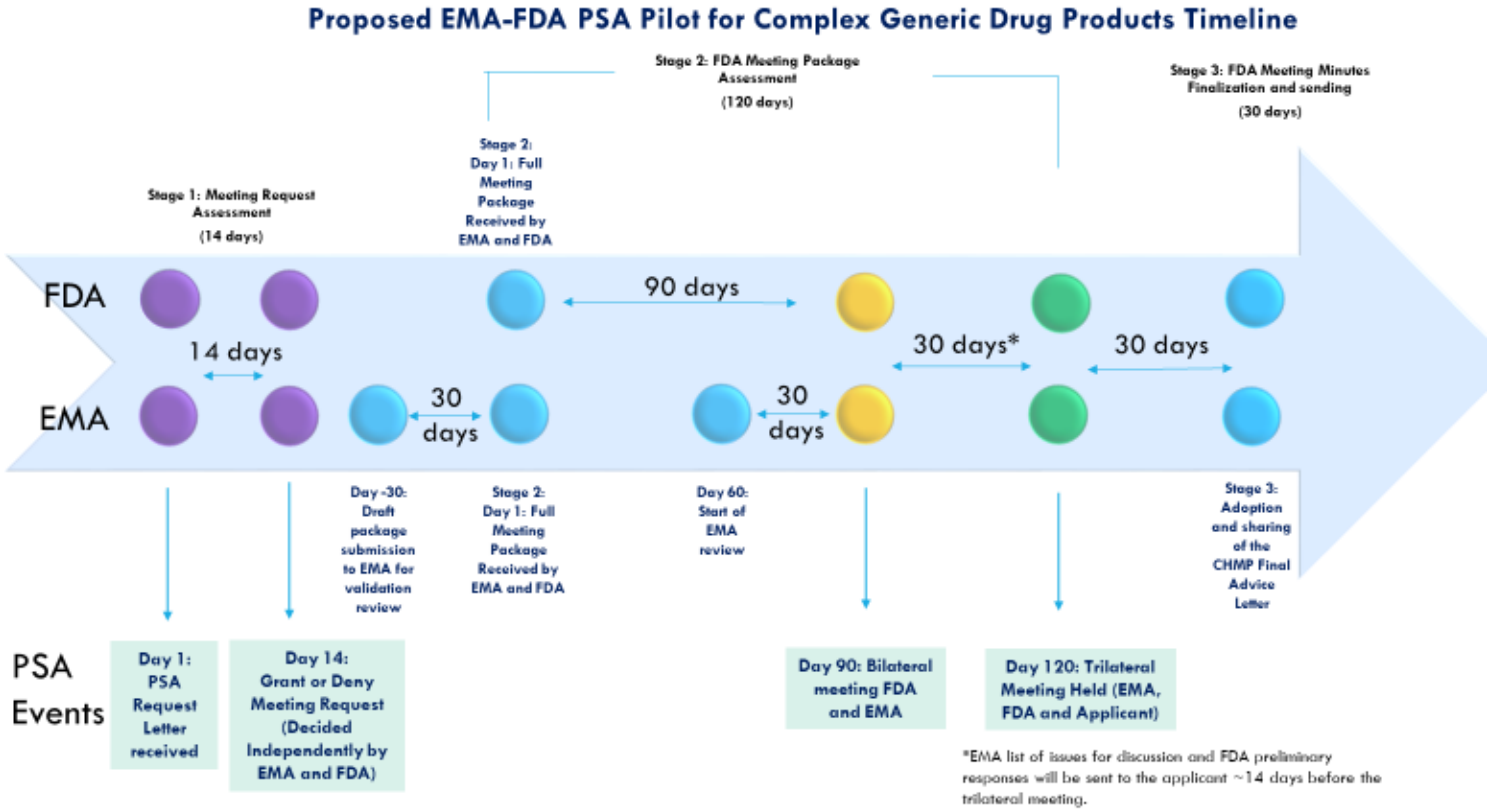
OVERALL GOALS OF PSA PILOT

To provide a mechanism for EMA and FDA assessors to concurrently exchange with applicants their views on scientific issues during the development of **complex generic drug/hybrid products**

- increase dialogue between the two agencies and applicants from the beginning of the lifecycle of a complex generic drug product
- provide a deeper understanding of the basis of regulatory decisions
- optimize product development
- avoid unnecessary replication of studies or unnecessary diverse testing methodologies

PSA HIGHLIGHTS

- The agencies conduct PSA meetings under the auspices of the confidentiality arrangement between the European Commission, the EMA, and FDA
- Voluntary
- Meeting requests will be received until enough PSA meetings are held to support the pilot program
- Candidates for the PSA program include product development programs that may benefit from the PSA process by potential harmonized approaches
  - "For example, the applicant may use the PSA program to determine whether a study design(s) might be acceptable to both regulatory agencies. Studies that may benefit from the PSA process include comparative non-clinical and comparative clinical studies involving innovative bioequivalence study designs and the use of methodologies such as modelling and simulation."



PSA PROCESSES

The PSA process is designed to align the process and timeline of the pre-ANDA meeting at the FDA as much as possible with the process and timeline mandated by EMA Scientific Advice Working Party (SAWP) for their Scientific Advice (SA) process

Stage 1: PSA Meeting Requests (14 days)

- Submit one single "Request for PSA" letter (justification letter) to both

emainternational@ema.europa.eu
preANDAHelp@fda.hhs.gov

- No full package needed

Stage 2: Meeting Preparation and Conduct (~120 days)

- Day 1: Once the meeting is granted, full package will be submitted
- ~Day 120: trilateral meeting between applicant, EMA and FDA

Stage 3: Post-Meeting Agency Communication (30 days)

REGULATORY HARMONIZATION AND CHALLENGES

- Social, economic, cultural, legal, and political differences
- Risk tolerance, regulatory policies, and decision-making processes differences
- Nomenclature, terminology, and labeling
- Attributes for assessment of therapeutic equivalence

QUESTIONS?