Financial Consequences of Good Intentions

The unanticipated costs of the Unapproved Drugs Initiative (UDI)

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What is the Unapproved Drugs Initiative?

- The Unapproved Drug Initiative (UDI), enacted in 2006, is an FDA mandate that unapproved drugs (e.g. ones that have been in use prior to FDA review of safety and efficacy) must be approved or removed from the market.
- The aim of the UDI is to:
  - Remove potentially unsafe medications to protect the public from direct and indirect health threats
  - Remove ineffective drugs to protect the public from using these products in lieu of effective treatments
- The majority of these products are well-defined chemically, require no R&D and are widely used in healthcare settings.

J Manag Care Spec Pharm. 2017;23:1066-1076.

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Unintended Consequences of Unapproved Drugs Initiative

- Four of these drugs have been formally approved in recent years:
  - Neostigmine Methylsulfate
  - Selenium 40 mcg/mL to Selenious Acid 60 mcg/mL
  - Vasopressin to Vasostrict
  - Dehydrated Alcohol 98% to Dehydrated Alcohol 99%
- Manufacturers that have obtained FDA approval for these products have instituted drastic price increases, which have serious implications for the U.S. healthcare system.

"Depending on the approval, manufacturers receive periods of exclusivity ranging from three to seven years. If a patent is awarded, the manufacturer could have market exclusivity for 20 years"

- Dan Kistner, PharmD, group senior vice president, pharmacy solution for Vizient

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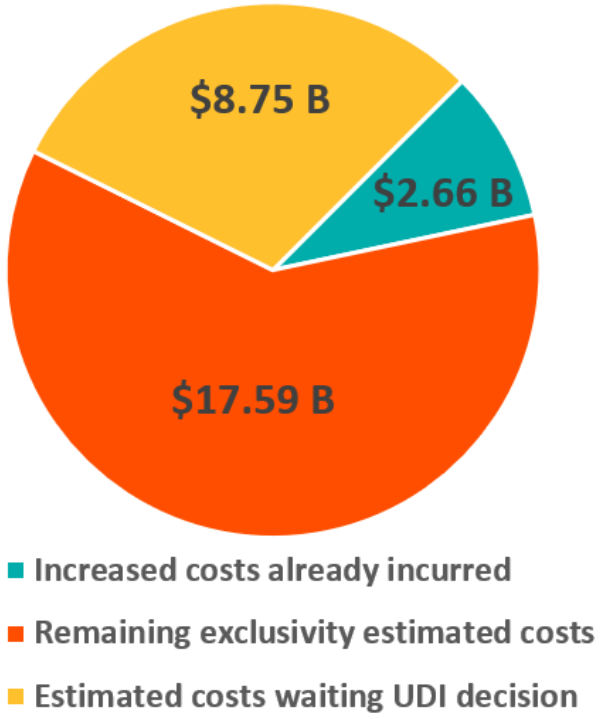
Key Findings from Vizient Analysis

Potential $29 billion in extra healthcare costs

- Vizient estimates that the four FDA approved products will increase healthcare spending by $20.25 billion
  - The products have experienced price increases ranging from 525% to 1644%
  - The two most recent approvals —Selenious Acid and Dehydrated Alcohol— have the potential to add $1.6 billion in increased cost over 5 years
  - One product, Neostigmine Methylsulfate, received de facto exclusivity. Competition returned to the market after 2 years and the price has eroded 82% from its highest point.
- Vizient identified 19 other unapproved products on the market that could experience similar increases potentially leading to $8.75 billion in added costs to the healthcare system over 5 years if manufacturers take similar increases during their periods of market exclusivity.

Outcomes of the UDI process



*Unapproved drugs identified by absence from Drugs@FDA and FDA Orange Book database

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Exclusivity and Patent Protection Outcomes of the Unapproved Drug Initiative

"De facto" exclusivity	"New Clinical Investigation" exclusivity	"New Chemical Entity" Exclusivity	"Orphan Drug" Exclusivity	Patent Protection
• The manufacturer is not entitled to additional market exclusivity from FDA • The duration of a sole source market is determined by how long it takes other suppliers to file and receive approval. • Example - neostigmine	• Although 505(b)2 applications usually do not involve clinical studies, FDA can require them • If a manufacturer has to conduct a clinical trial, they can receive an exclusivity period of 3 years	• Some medications can be considered products never evaluated by FDA and are recognized as new chemical entities. • New chemical entity exclusivity lasts for 5 years • Example – selenious acid	• Some suppliers have sought and successfully obtained recognition as an "orphan" drug given the indications they choose to pursue • Orphan drug exclusivity lasts 7 years • Example – dehydrated alcohol	• Separate from market exclusivity granted by the FDA, manufacturers can attempt to patent certain aspects of their newly approved product • Approved patents last for 20 years from the date of their initial submission • Example - vasopressin

J Manag Care Spec Pharm. 2017;23:1066-1076, https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity, accessed February 5, 2020, IPD analytics personal communications, January 31, 2020.

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Neostigmine Methylsulfate: 525% increase

Developed in 1931; gained formal FDA approval in 2013

UDI Status: de facto exclusivity

Used to reverse anesthesia, also used intravenously to control symptoms of autoimmune neuromuscular disorders

$157.90 → $987.50 → $173.40

Prior | Peak during exclusivity | Current

WAC increase of 525% on package of 10, then gradually decreased to 9.8% above prior WAC price

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$60.6M

Annual U.S. health care spend prior to UDI

$205.8M

Average annual U.S. health care spend from 2014-2019

$871M

Est total U.S. health care increased spend from 2014-2019

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Vasopressin to Vasostrict: 1644% increase

Developed in 1928; gained formal FDA approval in 2014

UDI Status: Patent approved as innovation through 2035

Used to treat critically low blood pressure

$283.25→ $4,939

WAC increase of 1644% on package of 25

$30.8M

Annual U.S. health care spend prior to UDI

$510M

Annual 2019 U.S. health care spend

$17.8B

Est total increased U.S. health care spend

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Selenium 40 mcg/mL to Selenious Acid 60 mcg/mL: 1190% increase (equivalence)

First introduced prior to 1938; received formal FDA approval as injection on April 30, 2019

UDI Status: 5-year New Chemical Entity (NCE) exclusivity thru April 2024

Trace mineral used to treat nutritional deficiency

$443.25→ $8,575

WAC increase of 1190%* on package of 25

$8.52M

Annual U.S. health care spend prior to UDI

$110M

Est. 2020 Annual U.S. health care spend since UDI

$503M

Est total increased U.S. health care spend

*Calculated to account for concentration change

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Dehydrated Alcohol 98% to Dehydrated Alcohol 99%: 668% increase

Introduced prior to 1938 for relief of intractable chronic nerve pain

UDI Status: Received 7-year* orphan indication

Used to treat severe heart disease

$1,295→ $9,950

WAC increase of 668% on package of 10

$28M

Annual U.S. health care spend prior to UDI

$215M

Est. 2020 Annual U.S. health care spend since UDI

$1.1B

Est total increased U.S. health care spend

*Increase based on 5 years following the market exit of competition at start of 2020

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Methodology

- **Wholesaler Acquisition Cost (WAC) was price used for all calculations and estimates.**
- **IQVIA was source for all US health care product units purchased.**
- **Medispan was source for baseline WAC prices (prior to UDI) and WAC price changes.**
- **Annual spend numbers are calculated using annual units purchased x WAC price.**
- **To calculate Baseline WAC Spend, the baseline annual units purchased were multiplied by corresponding baseline WAC price (prior to UDI).**
- **To calculate Actual WAC Spend, the annual units purchased during the UDI period were multiplied by the corresponding average WAC prices for the same period.**
- **To calculate increased spend as a result of UDI decision the calculated Baseline WAC Spend for period of UDI was subtracted from the calculated Actual WAC Spend for the same period of exclusivity.**
  - Example: [2015 to 2019 utilization x actual WAC at time of purchase (during UDI)] - [2015 to 2019 utilization x Baseline WAC (prior to UDI)] = Increased spend for UDI period.
- **Estimated increase cost to US healthcare was evaluated for each year of remaining UDI period and was summed into a total estimated increased cost.**
  - This was determined for each subsequent year by taking the product units purchased (from the most recent full year on record) multiplied by the difference between the inflated WAC (during remaining UDI period) and the baseline WAC price (prior to UDI).
  - A 7.5% year-over-year inflation impact was added for these years.

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Appendix

Key Dates in Pharmaceutical Regulatory History

- **1906 – Pure Food and Drug Act**
  - Medications must list ingredients accurately
- **1938 – Food, Drug, and Cosmetic Act**
  - Drug must be shown to be nontoxic
- **1962 Kefauver Harris Amendments**
  - Evidence of efficacy is required for approval
- **Drugs approved between 1938 and 1962** = Drug Efficacy Study Implementation (DESI)
- **Drugs marketed prior to 1938 = Unapproved drugs**
  - 2006 – FDA published draft guidance Unapproved Drug Initiative
  - Unapproved drugs must be approved or removed from the market

J Manag Care Spec Pharm. 2017;23:1066-1076., *JAMA* 2020;323:164-176.

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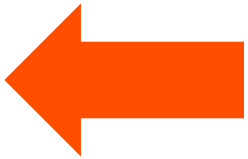
How Drugs Are Approved by the Food and Drug Administration

Product type	Application type	Application pathway	Clinical studies	Application requirements
Drug (Food Drug and Cosmetic Act)	New Drug Application (NDA)	505(b)1	Yes	Full evaluation of safety and efficacy
		505(b)2	Yes	Studies do not have to be done by the application sponsor; can be literature derived
	Abbreviated New Drug Application (ANDA)	505(j)	No	Approval based upon bioequivalence determination

"Unapproved" drugs are licensed using the 505(b)2 approval pathway



Most approvals of previously "unapproved" drugs do not require clinical studies

Drug Inf J. 2010;44:137-145; *J Manag Care Spec Pharm*. 2017;23:1066-1076.

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What Does Approval Mean for Competition?

- **After a previously "unapproved" drug receives formal FDA approval by the 505(b)2 application process, the manufacturers of remaining "unapproved" versions are asked to remove their products from the market**
  - A previously "multisource" market reverts to a sole source supply for that newly approved drug
  - The duration of time without competition can vary greatly

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