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Does It Get Any Worse Than Acne? It Does, Actually. An In-Depth Review of Accutane's Regulatory History.

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Does It Get Any Worse Than Acne? It Does, Actually.
An In-Depth Review of Accutane®'s Regulatory History

By

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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College

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ABSTRACT

Isotretinoin, most often recognized by the brand name Accutane®, is regarded by many patients and prescribers as the miracle cure for acne. Its unsurpassed efficacy is paired with serious risk of adverse events and birth defects, which poses ethical questions regarding its safety and necessity. Its regulatory history established precedent in Food and Drug Administration Risk Evaluation and Mitigation Strategies and brought awareness to the sharp dangers of teratogenic drug use.

This medication came as a breakthrough solution to patients that suffered years of unsuccessful regimens for the treatment of acne vulgaris. Some question the risk-benefit evaluation of such a toxic drug for acne. It was noted in Archives of Family Medicine that "although acne is not a life-threatening disease, it has significant physical and psychological ramifications such as permanent scarring, poor self-image, social inhibition, depression and anxiety" (Thiboutot). Significant health implications press the need for such an effective drug. Accutane® and isotretinoin generic drugs have changed the lives of over two million patients (AOCD).

Despite the remarkable success, the significant dangers must not be overlooked. Measures have been put in place such as a Black Box warning, categorization as Category X pregnancy risk, and the REMS program "iPLEDGE", but significant adverse events and pregnancy issues continue to be reported. Regulatory history and extreme legal backlash quickly caused the brand-name Accutane® by Hoffmann-La Roche to be taken off the market, but numerous isotretinoin generic formulations continue to be

profitable and prescribed to patients daily. Although many still confuse isotretinoin drugs and refer to all of these medications as "Accutane®", this drug is no longer distributed or prescribed. When a patient says they are taking "Accutane®", they are most likely receiving an isotretinoin drug almost identical to Accutane®, but produced by a different company. The household name recognition that Accutane® achieved after litigation remains in dermatological vocabulary although it has been discontinued.

The REMS of isotretinoin aims to (1) to prevent fetal exposure and (2) to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions (FDA). The stringent regulations of this drug and its implications on the pharmacological safety environment warrants scrutinous evaluation and review. How has the FDA, the pharmaceutical industry, and the healthcare industry, in general, responded to high risk drugs (like Accutane®) with significant adverse events in recent years?

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
AERS	Adverse Event Reporting System
ANDA	Abbreviated New Drug Application
DHCP	Dear Health Care Provider
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
NDA	New Drug Application
NIH	National Institutes of Health
RAR	Retinoic Acid Receptors
REMS	Risk Evaluation and Mitigation Strategy
SMART	System to Manage Accutane Related Teratogenicity

INTRODUCTION TO ISOTRETINOIN (ACCUTANE®)

Introduction

Isotretinoin, the oral acne medication more commonly known by the former brand name Accutane®, has been a miracle acne medication for numerous patients, but not without significant side effects. Its unmatched efficacy comes with serious questions regarding its safety. This medication approved for marketing in 1982 fights "severe recalcitrant nodular acne" (Roche Laboratories Inc.). This critical statement is repeated numerous times throughout the Accutane® package insert and holds a very particular meaning upon examination. This particular form of acne culminates in the presence of numerous, inflamed nodes that are usually larger than 5 millimeters. In the package insert it notes that this medication "should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics" (Roche Laboratories Inc.). In other words, this medication is withheld only for patients -who have already completed altogether unsuccessful or perhaps minimally successful months to years of topical acne treatments, antibiotic courses, or other dermatological treatments. This drug should by no means serve as a first-line acne medication. Once the patient has proven to be unresponsive to these other treatments, their doctor may talk to them about starting isotretinoin oral capsules.

The side effects of this medicine are far-reaching and can include dermatological implications, psychiatric diagnoses, gastrointestinal complications, skeletal issues, and other adverse events troubling other systems of the body. Incontestably, the drug's

intense efficacy affects body systems other than the integumentary system alone. The extremely high risk for severe birth defects is a huge aspect within precautions of the drug and warrants a Black Box warning from the United States Food and Drug Administration (FDA).

Due to the significant side effects and Black Box warning, Accutane® and its equivalents were eventually required to be dispensed only under a special restricted distribution program called iPLEDGE. The prescriber, patient, and pharmacist must meet the monthly required interactions of the program to be able to access the drug. This is a form of a Risk Evaluation and Mitigations Strategy (REMS) plan as specified by the FDA. The goals as stated on the Food and Drug Administration's website states that the goals of the isotretinoin risk evaluation and mitigation strategy are to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions (FDA).

Data Acquisition

As an in-depth review, this thesis required numerous sources from primary and secondary literature. The package inserts of the isotretinoin drugs are thorough and provided ample information about the pharmacologic properties of the drug along with lengthy descriptions of potential adverse events. The FDA REMS website provided up-to-date information regarding specific isotretinoin REMS goals. The iPledge website and materials served to explain the program and its goals. There are numerous published explanations of sections of Hoffmann-La Roche history, and I used many of these sources to create a timeline of the regulatory history. I read through numerous efficacy studies and published clinical trials regarding safe-use conditions. I also explored the

pharmacology of birth defects more as my topic developed, as this proved to be an interesting area of pharmacy that I am excited to learn more about.

As a personal anecdote, I was able to travel to Boston with the Honors College Junior Quest program to interview professionals with potential insight on my topic. I met with Dr. Kesselheim, who sparked my interests in the specific area of study into the iPledge program more particularly with regards to birth defects. This was when I began to switch my study focus from more of the lawsuit and litigation history to the specific goals and pharmacological implications of isotretinoin REMS. With all of my collected sources and personal experience, I produced my thorough case-study and in-depth review of Accutane®.

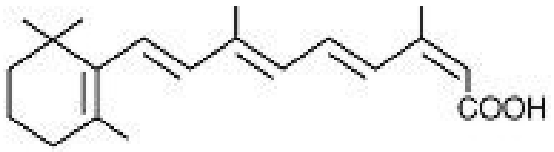
What is Isotretinoin (Accutane®)?

Isotretinoin is a retinoid drug that works to fight acne by inhibiting sebaceous gland function and keratinization (Leyden, et al.). Acne vulgaris is a "chronic inflammatory disease of pilosebaceous follicles commonly affecting adolescents and young adults" (On, et.al.). The disease pathogenesis of acne is "multifactorial, caused by a combination of follicular hyperkeratinization, sebum production, *Propionibacterium acnes (P. acnes)* colonization, and inflammation" (On, et al.). Acne affects patients of all ages and ethnicities. While isotretinoin is supposedly withheld for patients displaying severe recalcitrant nodular acne, this definition provides blurry standards. It is ultimately up to the discretion of the dermatologist and patient to determine the next step of their journey to clear skin. It has been brought to attention that in current practice, off-label uses include only moderate acne, as well as high-risk neuroblastoma, rosacea, and psoriasis (Leyden, et al). Isotretinoin treats acne caused by "androgen stimulation of

sebaceous glands leads [which] leads to an increase in sebum, which provides a favorable environment for *P. acnes'* growth" (On, et al.). What makes isotretinoin unique is that it treats not only one, but all of the top four most common causes of acne in the same oral dosage form.

Figure 1 shows the chemical structure of isotretinoin. Chemically, it is a 13-cis-retinoic acid. This active ingredient is related to retinoic acid and retinol (Vitamin A).

Figure 1. Chemical Structure of Isotretinoin



The ingredient description is described below.

Active Ingredient: Isotretinoin

Inactive Ingredients: beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil.

Chemical formula: $C_{20}H_{28}O_2$

IUPAC name: (2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (Lexicomp)

Pharmacology

The isotretinoin package insert states that "the exact mechanism of action of isotretinoin is unknown" (FDA). Isotretinoin is relatively water-soluble and metabolized

by the cytochrome P450 liver enzyme into active metabolite 4-oxo-isotretinoin. Isotretinoin acts as a "pro-drug… converted into five major active metabolites (13-cis-4-oxo-retinoic acid/4-oxo-isotretinoin, all-trans-retinoic acid/tretinoin, all-trans-4-oxo-retinoic acid/4-oxo-tretinoin, 9-cis-retinoic acid, and 9-cis-4-oxo-retinoic acid)" (Layton). These isomerize and bind to the alpha and gamma retinoic acid receptors (RARs) to "exert its anti-proliferative effect on sebocytes, consequently inhibiting cell differentiation, sebum secretion, and sebaceous gland size" (On, et al.). The maximum plasma concentration of isotretinoin is reached within 4-6 hours, and the peak of 4-oxo-isotretinoin is reached in 6-20 hours (Khoo). The duration and intensity of the dosage for this medication varies based on the individual patient case.

The decrease in sebum secretion is temporary and related to the decrease in sebaceous gland size. The differentiation of various sebaceous gland cells is inhibited during the isotretinoin therapy as well (Layton).

The package insert for Accutane® recommends 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks or until cumulative drug levels have been reached (Roche Laboratories, Inc). "The accepted target treatment goal is a cumulative dose of 120-150mg/kg, with a typical dosing of 0.5mg/kg for the first month, followed by 1mg/kg thereafter" (Zeichner). An important part of the dosing recommendations is the weight-based dosing regimen. Proper body weight should be recorded at initiation of therapy. Table 1 illustrates isotretinoin dosing by body weight, based on administration with food.

Table 1: Isotretinoin Dosing by Body Weight (Based in Administration with Food)

Body Weight		Total mg/day		
Kilograms	Pounds	0.5 mg/kg	1 mg/kg	2 mg/kg
40	88	20	40	80
59	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

In an example calculation of dosage, a female patient weighs 154 pounds. Her dermatologist suggests the less aggressive dosage of treatment and prescribes 1 mg/kg/day. Her lab tests come in as required, and all relevant parties complete their iPLEDGE requirements. She initiates therapy at her calculated total mg/day as follows:

$$154\ lbs \times \frac{1\ kg}{2.2\ lbs} = 70\ kg$$

$$70\ kg \times \frac{0.5\ mg}{1\ kg} = 35\ mg/day\ total$$

Pharmacokinetics

Absorption, Distribution, Metabolism, and Elimination are the constructs of pharmacokinetics. Absorption is influenced by the administration with a high-fat content meal (Colburn, et al). The high lipophilicity of isotretinoin means that this drug is well-absorbed through the membrane, but absorption is enhanced if high-fat meal is

concurrently being absorbed (Lexicomp). Safe-use conditions evaluate more studies behind the proper use of the drug to ensure most efficient absorption and highest success rate for therapy. A second round of isotretinoin therapy is not unheard of, but should aim to be avoided by reaching the proper cumulative dose in the first round of the medication.

Plasma protein, albumin, is responsible for the distribution of more that ninety-nine percent of isotretinoin. Isotretinoin acts like a prodrug. It is metabolized into different metabolites, 4-oxo-tretinoin being the most pharmacologically active (Lexicomp). P450 enzymes responsible for the metabolism of this drug include 2C8, 2C9, 3A4, and 2B6. Isotretinoin is excreted in the urine and feces equally.

Therapeutics

Indications determined by isotretinoin manufacturers typically describe severe nodular recalcitrant acne. It is deemed and reported that isotretinoin is most commonly prescribed off-label for treatment of moderate acne vulgaris.

Drug Interactions

Vitamin A, tetracycline antibiotics, and micro-dosed progesterone are among proven drug interactions with isotretinoin (Lexicomp). St. John's Wort also may work against the efficacy of co-administered birth control methods. Corticosteroid medications and Dilantin® (phenytoin) efficacy may also be affected while taking isotretinoin medication (FDA medication guide).

Overview of Side Effects and Adverse Events

Table 2 outlines the side effects and adverse events associated with isotretinoin.

Table 2: Isotretinoin Side Effects and Adverse Events

Dermatological	Dry, cracked, peeling skin
	Dry lips / dry mouth
	Rash, skin infection
	Extremely sun-sensitive skin
Skeletal	Muscle aches, joint pain, back pain
	Tenderness of the bones (decrease in bone mineral density)
	Hyperostosis and calcification of ligaments and tendons
	Potential for premature epiphyseal closure
Gastrointestinal	Possible upset stomach
	Inflammatory bowel disease (regional ileitis)
Pseudotumor Cerebri (Neurological)	Benign intracranial hypertension (associated with concomitant use of tetracyclines)
Psychiatric	Depression
	Psychosis
	Suicidal ideation
	Aggressive and/or violent behaviors
Other	Dry eyes and visual impairment
	Corneal opacities
	Decreased night vision
	Dry nose that may lead to nosebleeds
	Acute pancreatitis in patients with elevated serum triglycerides
	Possible elevated triglycerides (800 mg/dL)

	Impaired hearing (persistent even discontinuation of therapy)
Black Box Warning	Debilitating birth defects

(Lexicomp, Yoder, Khoo, Layton)

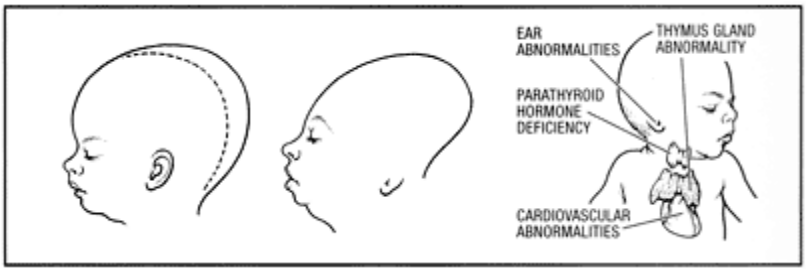
Dermatological side effects listed in the table above are the most commonly recognized side effects regarding isotretinoin. These symptoms are manageable in most cases, but can become severe in certain patients. Dry skin is an expected symptom due to the mechanism of action of isotretinoin. The reduction of sebaceous glands and therefore sebum production causes a shock that the skin takes time to adjust to (Yoder). Symptoms of this degree are typically managed by intensive-strength lotions and moisturizers. The sun-sensitivity brought on by the drug can be combated by avoiding direct sun exposure and applying sunscreen frequently. Patients who do not take these precautions may put themselves at risk for damaging acne scarring or burns. The skin dryness and dermatological side effects are typically the worst during the first two to three weeks of treatment (Khoo).

The skeletal symptoms caused by the drug are typically not debilitating, but should not be ignored. Joint pain, muscle aches, muscle stiffness, or muscle weakness can be expected, but medication should be discontinued if these become extreme (Layton).

Psychiatric side effects may include depressive thoughts or even suicidal thoughts or actions (Lexicomp). Mental health and isotretinoin treatment have brought up rising concern of association with suicidal events. Acne treatment is an area of medicine that is commonly associated with psychiatric struggles. Especially for Accutane® patients, the road to clear and healed skin may take the course of numerous years.

Birth defects resulting from fetal exposure of isotretinoin include “abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands” (iPLEDGE). A misshaped skull is depicted in Figure 2 below. Babies exposed to isotretinoin also are reported to have IQ scores of less than 85. Alongside the risk of birth defects, there is also a risk of spontaneous abortion or premature births (iPLEDGE).

Figure 2: Misshapen Skull Associated with Fetal Exposure to Isotretinoin



THE BLEMISHED HISTORY OF ACCUTANE®

Development and Discovery

Accutane®'s basic compound is first noted in scientific literature under the research of Dr. Werner Bollag of Roche laboratories in Switzerland during the 1960's (Green). The drug, originally tested for its potential efficacy against skin cancers, provided potency against cystic acne that was worthy of further pursuit. As many medications commonly are discovered, isotretinoin was not originally researched for the treatment of acne. This compound was clinically studied for treatments of dermatologically orphan diseases or other far-reaching skin conditions. Researchers conducting these trials all noted significantly clearer skin of their patients after treatment with isotretinoin. This remarkably potent compound, noted as a vitamin A derivative, was suspected to be a possible danger to pregnant women. The famous thalidomide crisis of the late 1960's had brought teratogenic drugs and their significant hazards to the forefront of society's conscience. "At that time [the 1970s], in the psychological climate engendered by the thalidomide tragedy, it would be inconceivable to develop an agent with teratogenic properties for the treatment of such a common complaint as acne" (Green).

This 13-cis-retanoic acid was also under development by two scientists at the National Institutes of Health (NIH), Dr. Frank Yoder and Dr. Gary Peck. Peck and Yoder hurriedly published news of their groundbreaking acne cure in the *Lancet*, a British medical journal, on November 27, 1976 (Franz). Miscommunication between the NIH

researchers and the Swiss Dr. Bollag led to unresolved ambiguity on the identification of the true discoverer.

Premarketing Studies

Isotretinoin underwent rigorous clinical research studies as "Accutane®" under Hoffmann-La Roche. Animal studies concluded significant deformities and defects in offspring, which secured Accutane®'s placement as a potent and potentially teratogenic drug. No documented studies were conducted on pregnant women, so the true extent of the fetal abnormalities was unknown. Trials in pregnant women spark controversy and prove to be difficult to approach properly. The premarket approval process outlined in the table above can take numerous years. Roche submitted Accutane® for FDA approval in July 1981 (Green). The clinical research data was presented to the Dermatologic Drugs Advisory Committee panel of specialists. This approval process approach is common among new medications, because this smaller committee is more knowledgeable in regards to dermatological medications. This committee suggested that Accutane® be approved for market finally in January of 1982 under contingencies that the label include stricter pregnancy warnings. Rather than a pregnancy risk of category C, FDA ordered Accutane® to be approved under pregnancy warning category X (Green). This changed the labelling as "studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans" to "studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience" (FDA).

The controversy shadowing this stipulation was that Hoffman-La Roche only tested female participants who were given contraceptives, and the one woman who did

become pregnant aborted (Green). The company sharply noted that they did not have influence in this abortion against accusations of coercion. As explained, the original label noted that no evidence proved the sure cause of birth defects in humans, while no data had actually proven this. Nine months after application submission, Accutane® was officially FDA-approved.

Early Years of Marketing

After the drug was first approved in 1982, obstacles quickly stacked against the manufacturing company Hoffmann-La Roche. The 1A, top priority, fast track approval medication surprised the company and required four additional months before the official launch in the United States in September 1982. Over 200,000 prescriptions for Accutane® were written in only the first six months (Green).

As the popularity of the drug grew exponentially, the rising concerns of potential toxicity rose as well. Researchers and prescribers across the country began to voice concerns for potential birth defects, and some of these concerns were published in esteemed journals. Even Dr. Yoder of NIH, the drug's discoverer, "wrote a letter to *JAMA* in January 1983 to "express [his] concern and anxiety over the potential tragedy that might arise from abuse and misuse of Accutane®…the potential toxicity of this drug has been seriously under-emphasized" (Yoder). Hoffmann-La Roche received many notes of caution and backlash, but continued manufacturing the drug with no alterations. The company released its first "Dear Doctor" letter of warning exactly nine months after the medication's release (Green). A "Dear Doctor" letter is formally known now as a "Dear Healthcare Provider" letter, or DHCP (FDA). These letters are "correspondence — often in the form of a mass mailing from the manufacturer or distributor of a human drug

or biologic or from FDA — intended to alert physicians and other health care providers about important new or updated information regarding a human drug or biologic" (FDA). This letter of caution was quickly followed by the distribution of red warning stickers and a second Dear Doctor letter. The Accutane® label was adjusted to include more details warning against the use of the medication in pregnant women (Petrocelli). The Dermatologic Drug Advisory Committee revisited Accutane®'s regulation to conclude Roche's need to establish strong warnings on the risk of birth defects. Other implications followed. The *JAMA* published a "Medical Directors Page" to advise doctors prescribing the drug to use proper precaution. Blood banks were also instructed to refuse donations from Accutane® patients, as the medication in their circulation could possibly interact with a pregnant woman if she receives the transfusion.

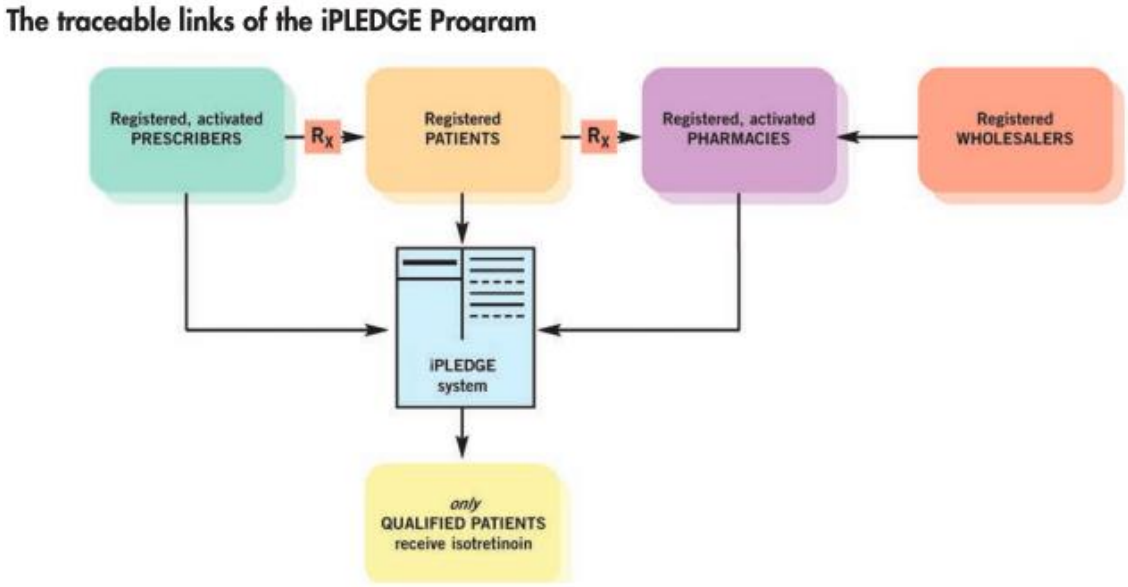
Furthermore in 1984, a "black box" warning was assigned to the Accutane® drug with regards to the potentially debilitating birth defects. In 1998, more issues regarding Accutane®'s psychiatric side effects were brought to the attention of physicians and the FDA. Depression, psychosis, and possible suicidal thoughts were linked to Accutane® through many different studies. The package label for Accutane® was updated to include warnings for these possible adverse events, and prescribers were notified to monitor their patients using the medication. Starting in 2000, the prescription could not be filled until the monthly negative pregnancy test was completed, which was helpful in part to reduce the numbers of birth defect adverse event occurrences. 2001 marked a year of furthering patient education and compliance. A clearer medication guide was distributed to patients via pharmacists. Hoffmann-La Roche starts the SMART (System to Manage Accutane Related Teratogenicity) program (Fain, et al). More and more adverse events came to the

FDA's attention via the Adverse Event Reporting system. After over 6,000 reports of psychiatric events, the officials at FDA decided to work with leaders at the National Institute of Mental Health and called for more research on retinoid's effects on the Central Nervous System. Hoffmann-La Roche started to include a Medication Guide in the Accutane® pack. This same year, 2002, the original patent for Accutane® expired, and FDA approved Amnesteem as the first generic version of isotretinoin. After 20 years on the market, over 23,000 reports in the FDA Adverse Reporting System showed that the top five events reported were alopecia (hair loss), depression, headache, dry skin, and induced abortion purposely to end a pregnancy. The generic drug brands of isotretinoin develop individual programs for pregnancy prevention. The FDA Joint Advisory Committee and all of the isotretinoin producers eventually agree to link a pregnancy test with each monthly prescription.

Increased Regulation

A huge mark in the history of Accutane® and isotretinoin generics was the development of the iPLEDGE program. Wholesalers, pharmacies, and prescribers started to register for this program in September 2005. Patients did not register for the program until December 30th of 2005. In March of 2006, iPLEDGE further progressed to require the iPLEDGE pharmacies to obtain iPLEDGE system authorization before dispensing the prescription. A designated Responsible Site Pharmacist is responsible the "point of contact for the pharmacy and the iPLEDGE program" (iPLEDGE). Figure 3 illustrates requirements of the iPLEDGE program.

Figure 3: The Traceable Links of the iPLEDGE Program



The End of Accutane®

Despite increased protections for patients taking Accutane®, the severe adverse events became too much to bear for Roche and it's Accutane® brand. In 2009, Roche withdrew Accutane® from its United States market, contrary to popular assumptions that the FDA pulled Accutane® from the market. It is presumed that Roche pulled its drug as a result of safety issues, declining sales, loss of market share, lawsuit losses, or most likely a combination of all four (Lamb). The following announcement was made on June 26, 2009:

> *"Roche Holding AG, the world's biggest maker of cancer drugs, is pulling its Accutane acne medicine from the U.S. market after juries awarded at least $33 million in damages to users who blamed the drug for bowel disease.*
>
> *Roche notified the U.S. Food and Drug Administration today that it was withdrawing Accutane after a "reevaluation" of its product lines showed it faced serious challenges from generic competitors, company officials said in a statement.*

"In addition, Roche has been faced with high costs from personal-injury lawsuits that the company continues to defend vigorously," according to the statement.

About 13 million people have taken Accutane since it went on the market in 1982. The medication was Roche's second-biggest selling drug before the patent expired in 2002 and rivals started selling generic versions. Roche's prescription market share of the drug is now below 5 percent, the company said." (Lamb)

Roche still markets isotretinoin as Roaccutane® in Europe. Many other generics are still available under names such as Absorica, Amnesteem, Sotret, Myorisan, and Zenatane, some of which were approved even after the withdrawal of branded Accutane®. Table 3, below, summarizes these isotretinoin drugs remaining on the market.

Table 3: Drug Name and Date of Market Entry

Drug Name	Labeler	Entry Into Market
1982 – FDA Approval of Accutane		
Amnesteem	Mylan Pharmaceuticals, Inc.	11/11/2002
Claravis	Teva Pharmaceuticals USA, Inc.	05/09/2003
2009 – Roche Withdrawal of Accutane		
Myorisan	Akorn, Inc.	05/01/2012
Absorica	Sun Pharmaceutical Industries, Inc.	06/08/2012
Zenatane	Dr. Reddy's Laboratories Ltd.	03/26/2013

CURRENT REGULATION OF ISOTRETINOIN

Given the compromised safety profile of isotretinoin, the FDA has established number safeguards for patients on the medication. Those include setting dispensing program requirements through the FDA REMS program for isotretinoin called "iPLEDGE", as well as black box warnings on their package insert, which specifically seeks to prevent fetal exposure through special dispensing requirements.

Risk Evaluation and Mitigation Strategies (REMS) and Applications to Isotretinoin

Prescription drugs on the market often come with numerous side effects ranging from minor to life-threatening. The benefit of the medication in some cases may outweigh the risks, so it is necessary for these drugs to pass the proper approval process. On September 27, 2007, the Food and Drug Administration (FDA) passed an Amendments Act that formally created a program of Risk Evaluation and Mitigation Strategies (REMS) for the approval of these high-risk drugs (FDA). This gives FDA the critical authority to require the manufacturer to outline and ensure that the potential benefit of their medication outweighs the risks. This program gave officials a mechanism to get drugs approved despite very focused safety concerns. They may have been more inclined to reject these kinds of drug applications in the past. The US FDA website published that there are currently 60 approved REMS (FDA). Each REMS report includes detailed information including product name, new drug application (NDA) or abbreviated new drug application (ANDA) application number, application holder, and the date that the REMS was added to the database.

REMS can be categorized as “elements to assure safe use (ETASU)”, “communication plan”, or “medication guide”. Below is a table that includes descriptions for the categories.

Table 4: REMS Categories

Elements to assure safe use (ETASU)	Typically require clinicians or healthcare settings to become certified prior to prescribing and to participate in additional REMS activities, such as training, patient counseling, and monitoring
Communication plan	Typically composed of letters, website, and facts sheets describing the specific safety risks identified in the REMS
Medication guide	REMS element typically included as part of their labeling

(FDA)

REMS data files are routinely monitored and modified. Currently 49 (82%) of the REMS include ETASU. 7 (12%) include only a communication plan. 4 (6%) include only the medication guide. Very commonly, REMS will include more than one of these elements (FDA).

It is up to the FDA and manufacturer to monitor if the REMS report is being properly followed to prevent these adverse effects. This has been an ambiguous task and proves to be difficult to assess. Adverse events can be reported in databases such as “AERS” (Adverse Event Reporting System), but monitoring continually proves difficult. Multiple studies, including Kevin Fain and G. Caleb Alexander’s study of “Are Food and Drug Administration prescription drug safety plans working? A case study of isotretinoin”, study the effectiveness of REMS (Fain, et al.). The study brings to light the fact that “numerous studies have evaluated the impact of FDA regulatory communications, [but] far less is known about the more recently implemented REMS program” (Fain, et al). A case study on isotretinoin in particular showed “the median

proportion of concomitant use of contraception with isotretinoin was 29%, which increased an absolute 1.3% during the 24 months after iPLEDGE implementation" (Fain, et al). This minor increase was concerning to researchers who had predicted a larger increase. The FDA's top priority is to ensure the safety of public health by monitoring drugs among other food and cosmetic products.

Black Box Labeling and Applications to Isotretinoin

A Black Box warning is the FDA's most urgent labeling system on a prescription package (Wagner, et al.). This boxed warning serves as a way to remind patients of the dangers of common adverse or potentially life-threatening adverse events. In a literal sense, a black box warning is a printed warning on promotional materials or medication guides that outline the adverse reactions you may experience during or after use (Weyant). A Black Box prescription typically comes paired with a risk mitigation strategy or other resources exceeding the base-level adverse event monitoring system. For example, Accutane®, and currently, isotretinoin, comes with a black box warning of severe birth defects and warned females to not get pregnant while taking this medication.

Mitigating Fetal Exposure

The first major component of the REMS of this medication is to prevent fetal exposure. Accutane® has great potential to cause debilitating birth defects, so the manufacturing company must take effective preventative measures. The teratogenic drug characteristics, pharmacokinetics of pregnant women, and proper categorization of pregnancy medications are crucial parts to this detailed risk evaluation and mitigation strategy.

As previously stated, Accutane® and isotretinoin generics are highly teratogenic compounds. A teratogen is broadly defined as a drug that has the potential to cause birth defects. Teratogenic drugs may cross into the developing fetus's blood supply via the mother's blood. The the transfer of blood from the mother to the placenta is illustrated. This transfer of blood carries all of the mother's important nutrients, gases, antibodies, and other molecules. Unfortunately, the mother's metabolism and ability to excrete harmful substances is much further developed than the unborn babies. This explains why pregnant women must closely monitor their intake of toxic substances, medications, and potentially harmful metabolites.

Drugs cross into the fetal blood supply via passive diffusion, facilitated diffusion, and active transport (Gunatilake). This indicates that mainly freely unbound drugs cross the placenta. As isotretinoin is a fat-soluble drug, the active metabolites easily cross over into the placenta. This harmfully affects development in numerous organ systems, especially the central nervous system, cardiovascular system, and endocrine system. In some cases, isotretinoin's teratogenicity and high potency may cause spontaneous abortions.

Broadly, birth defects may range in severity due to the variety of dose, gestational age at the time of exposure, and type of drug (Gunatilake). Higher doses of certain teratogenic medications may be discontinued if possible or lowered dose prescribed to minimize fetal toxicity. As a pregnant woman's blood plasma volume increases by thirty to fifty percent (Sachdeva, et al) and many other pharmacokinetic factors are altered, distribution of drug in maternal blood stream may vary widely. There is an increase in

body fat during pregnancy as well. This indicates that fat soluble drugs will be distributed to a greater volume which may have a more widespread potency (Gunatilake).

Furthermore, the gestational age at the time of drug exposure is also critical to the risk of birth defects. The fetal development is culminated in forty weeks. This time period can also be categorized into three trimesters. Women who are planning to become pregnant are typically advised to withdraw their unnecessary medication usage three to six months before conception. Drugs or harmful substances can remain within the mother's blood system for various ranges of time, but it is safer to ensure that drugs will not be transferred to the baby after conception. The early days and weeks following conception are crucial periods of development. Within the first two weeks after conception, the drugs cause an "all-or-nothing effect" (Gunatilake). Some women may not know that they are pregnant during this time and may not have discontinued harmful medications. The fertilized egg may not implant properly, spontaneous abortion may occur in early pregnancy, or the drug may have no effect. In three to eight weeks after fertilization the fetal organs are developing in a stage called organogenesis. During this stage, the baby is most susceptible to birth defects. In the second and third trimesters, fetal development is majorly growth and maturation. Since primary organ development is complete, drugs are unlikely to cause obvious birth defects.

The type of drug plays a vital part in the potential for birth defects. Examples of commonly used drugs that are teratogenic include Angiotensin Converting Enzyme (ACE) inhibitors, thalidomide, warfarin, male hormones, some anticonvulsant medications, high doses of Vitamin A, and numerous others (Sachdeva, et al.). Pregnancy poses a unique physiological state and pharmacology of all medications. The Food and

Drug Administration recognizes that total avoidance of all drugs or medications may be unfeasible for many patients. Certain women may require medication for chronic disease management such as asthma, epilepsy, hypertension, or psychiatric conditions (Sachdeva, et al). In addition to certain chronic conditions, some women develop acute conditions that require pharmacological intervention during gestation. Gestational diabetes, exacerbated migraine symptoms, high blood pressure related to pregnancy, anemia, or various infections can occur during pregnancy and must be treated (Sachdeva, et al).

The FDA has created a categorization for various drugs used in pregnancy in 1979. As a result of the thalidomide crisis in the late 1960's, many pregnant women were delivering babies with congenital abnormalities including phocomelia, a condition that involves the malformation of the arms and legs. This refined system developed rankings for teratogenic risk. The categories A, B, C, D, and X outline the level of risk associated with taking the drug while pregnant and are further defined in the table below.

Table 5: Pregnancy Categories and Description

Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite the potential risks
Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

(US Department of Health and Human Services)

The table below lists examples of commonly prescribed medications within each category.

Table 6: Pregnancy Category Examples

Category A	Vitamins B, C, D, E, folic acid
Category B	acetaminophen, amoxicillin
Category C	Antimalarials, antifungals, gentamicin, aspirin
Category D	Tetracyclines, streptomycin, ACE inhibitors
Category X	Androgens, estrogens, bronchodilators, thalidomide, oral contraceptives, statins

(FDA)

Specifically pertaining to isotretinoin, pregnancy precautions have been very closely considered and monitored. Isotretinoin is given both a Black Box pregnancy warning and Category X pregnancy medication rating. Manufacturers are required per their REMS agreement to ensure that patients are properly informed and measures are taken to prevent fetal exposure.

Dispensing Requirements

Accutane®, as a high-risk drug, has numerous stringent dispensing requirements in place in order to increase proper safety of the medication. A patient cannot simply get prescribed Isotretinoin and go to receive their prescription. The "iPLEDGE" program was developed as a strategy to further prevent pregnancy while completing isotretinoin therapy. Table 7 outlines monthly required iPLEDGE interactions, and Table 8 outlines laboratory requirements

Table 7: Monthly Required iPLEDGE Interactions

	Female patients of childbearing potential	Male patients, and female patients not of childbearing potential
Prescriber		
Confirms patient counseling	x	x
Enters the 2 contraception methods chosen by the patient	x	
Enters pregnancy test results	x	
Patient		
Answers educational questions before every prescription	x	
Enters 2 forms of contraception	x	
Pharmacist		
Contacts system to get an authorization	x	x

(iPLEDGE)

Table 8: Laboratory Requirements for Isotretinoin Prescription Monitoring

Pregnancy tests	TWO negative urine or serum pregnancy tests First "screening" test: obtained by prescriber Second "confirmation" test: CLIA certified laboratory at least 19 days after first test • During first 5 days of menstrual period preceding start of therapy
Lipids	Monitor for hypertriglyceridemia
Liver function tests	Monitor for elevation of liver enzymes
Glucose	Monitor for problems controlling blood glucose
Creatinine Phosphokinase (CPK)	Monitor for elevated levels of enzyme suggesting musculoskeletal problems

(iPLEDGE)

iPLEDGE

All patients must comply with iPLEDGE stipulations in order to receive their prescription. The following conditions must be met:

- Must be registered with iPLEDGE program by the prescriber
- Must understand that severe birth defects can occur with use of isotretinoin by female patients
- Must be reliable in understanding and carrying out instructions
- Must sign a patient information/ informed consent
- Must fill and pick up prescription within 7 days of specimen collection (female/childbearing potential)
- Must fill and pick up prescription within 30 days of office visit (male patients/non-childbearing potential)

- Must not donate blood while on isotretinoin and for one month after treatment cessation
- Must not share isotretinoin with anyone (FDA medication guide)

As discussed, strict prescribing rules require two forms of birth control and monthly blood monitoring including pregnancy tests. Commitment to abstinence can allow patients to avoid two forms of birth control Table 9 below outlines the primary and secondary forms of contraception outlined on the iPLEDGE website.

Table 9: Acceptable Primary and Secondary Forms of Birth Control

Primary forms of Birth Control	
Implantable Hormones	Hormonal IUD
Partners Vasectomy	Tubal Sterilization
Non-Hormonal IUD	Hormonal Injection
Hormonal transdermal patch	Hormonal Vaginal Ring
Hormonal Combination Oral Contraceptives	

Secondary Forms of Birth Control	
Male Latex Condom	Cervical Cap
Diaphragm	Cervical Sponge

Safe Use Conditions

Isotretinoin is advised to be administered with meals. Numerous case studies have proven that the oral absorption of isotretinoin is beneficially maximized when given with a high-fat meal. A crossover study of 74 healthy adult subjects receiving an 80 mg oral

dose compared the AUC of fasted and fed conditions. Both peak plasma concentration and area under the curve of the active ingredient more than doubled following a high-fat meal. A "high fat" is defined by the FDA "as [fat making up] 50 percent of total caloric intake of the meal" (Zeichner). High-fat ingredient suggestions include fatty fish like salmon, avocados, extra virgin olive oils, and cheeses. Many prescribers are not properly educating their patients on the proper safe-use techniques. This may lead to unsuccessful treatment and a need for a second round of isotretinoin therapy. The generic Absorica is the first to provide the same efficacy with or without a meal.

An open randomized crossover design study of twenty males also concluded that "coadministration of isotretinoin with food may be the best method of administration" (Wayne, et al). Isotretinoin blood concentrations determined by an HPLC method supported prior publications suggesting the increased bioavailability with food within a one-hour window of oral administration (Wayne, et al.). The relative bioavailability (AUC) of these subjects was found to be about two times higher when medication was "taken one hour before, concomitantly with, or one hour after a meal" (Colburn, et al.).

The responsibility of safe-use suggestions falls in the hands of the prescribing practitioners and dispensing pharmacists. In order to dispense isotretinoin, pharmacies must be registered and certified through the iPLEDGE program as active. Similarly, dermatologists or other prescribing physicians must complete a training program through iPLEDGE in order to be registered to prescribe the drug.

Patient Adherence

As outlined in the iPLEDGE regulations, the prescriber, pharmacist, and patient must all complete the required steps within the specified time frame. Strenuous

circumstances or undue hardship may lead to patient noncompliance. Failure to fill prescription on time may lead to an inefficient dosing schedule and decreased efficacy of the isotretinoin course. Under-dosing and patient noncompliance are common causes of relapse or re-treatment. Patient factors for unsuccessful therapy cannot be controlled, but prescriber-caused insufficiency should be minimized or eliminated.

CONCLUSION

Accutane® has a rich history of litigation and controversy. The conflict between brand-name discoveries and generic liabilities is an ongoing discussion that continues to prove difficult to reach a consensus. The FDA, the pharmaceutical industry, and the healthcare industry, in general, have responded to high risk drugs (like Accutane®) through many different pursuits including the establishment of lengthy Risk Evaluation and Mitigation Strategies. The REMS of isotretinoin aims to (1) to prevent fetal exposure and (2) to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions (FDA). These strategy's success and true significance is difficult to measure, and I intend to pursue further research on the data behind the success of the iPLEDGE program.

As a current discussion and implication of the COVID-19 public health emergency, FDA released a statement stating that it does not plan to punish sponsors that fail to adhere to the REMS requirements for certain laboratory testing. This is an unprecedented alteration to the REMS requirements as this is a difficult time for our general population. For patients currently taking isotretinoin, this means that laboratory monitoring requirements will be waived. In addition, pregnancy tests will be completed at-home and communicated to the prescribers via telehealth.

Throughout the process of this thesis, I learned about isotretinoin in great detail. I am interested in pursuing research behind other REMS programs and their success rates. In my opinion, the iPledge program may not be proving sufficient in protection and

prevention of the critical adverse events that isotretinoin can cause. Women are still becoming pregnant despite the strict warnings and requirements, and that is problematic! Moreover, I started this project with intentions to pursue more of the lawsuits and litigation side of Accutane®, but learned through my early research that I was much more interested in the regulatory side and specific goals of the REMS. The regulatory development of this high-risk drug is fascinating as well as its attempt to combat adverse events. The two goals of isotretinoin REMS were interesting to explore in further detail. In particular, I am very interested in the pharmacology of birth defects and the pregnancy categories. Isotretinoin is ranked as category X along with other medications, and I am interested in learning more about the other category X medications and what exactly their mechanisms of actions are. This broad category of isotretinoin as a whole has led me to many new interests in various area of study.

Accutane®'s unsurpassed efficacy is paired with serious risk of adverse events and birth defects, which poses ethical questions regarding its safety and necessity. Its regulatory history established precedent in Food and Drug Administration Risk Evaluation and Mitigation Strategies and brought awareness to the sharp dangers of teratogenic drug use. Some question the risk-benefit evaluation of such a toxic drug for acne. Accutane® and isotretinoin generic drugs have changed the lives of over two million patients (AOCD). These drugs will continue to be prescribed and dispensed to patients daily, so it is of utmost importance to ensure that these dangerous medications are being monitored properly while preventing adverse events.

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