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# REGULATORY PROFILE OF PHENFORMIN WITH ITS ADVERSE EVENT IN USA AND REST OF THE WORLD

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## ABSTRACT

Pharmaceutical market is vast growing market as per people need invention, modification and innovation is done in field of pharmaceuticals. As the market grow the safety and efficacy of drug is very important as drugs are consumed by a large number of populations. There has been mega outbreak before in the past time, so avoid that type of outbreak the post marketing studies is very important and should maintain pharmacovigilance data. The regulatory authorities of country should hold the responsibilities for the proper surveillance over the period of time up to particular drug is in market. Regulatory authorities should notify people of country about the ADR or the recalled drug. Just like drug phenformin was in the United States Market for long 20 years in spite of having fatal adverse drug reaction of Ketonuria and lactic acidosis. People should know the importance of aftermarket surveillance, ADR reporting, pharmacovigilance and should be aware about the drug use in day-to-day life.



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# INTRODUCTION

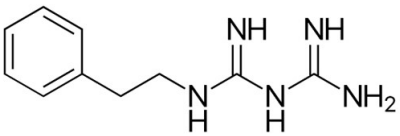
***N-ß-phenethylformamidinyliminourea*** **hydrochloride** substance was reported by Ungar, Freedman and Shapiro in 1957. Drug shows hypoglycaemic properties. It had been discovered in a synthetic diguanide compound designated DBI or phenformin. This substance is a white, crystalline, water-soluble compound with the following formula. Phenformin is fully ionized in body fluids and exerts its action as ion rather than free base. The molecule is stable and cannot be easily hydrolysed. [1]

***Phenformin:*** An antidiabetics agent.

**Molecular formula:** C10H15N5

**Chemical structure**: Biguanide (Two guanidine groups linked together with the phenyl-ethyl ring on a guanidine sidechain).

**Physical Property:** Phenformin hydrochloride with a melting point of 175-178°C is a white crystalline powder. Phenformin is less polar. Phenformin is well absorbed after oral administration.[1]




**Mechanism of Action:** The drugs work by reducing glucose uptake in the gut, reducing glucose production in the liver, and increasing the body's ability to use insulin more efficiently. Phenformin binds to AMP-activated protein kinase. (AMPK is a highly sensitive cellular energy sensor that monitors energy expenditure and, when activated, reduces ATP-consuming processes.) Phenformin biguanide has been shown to independently reduce ATP ion transport processes, affect cellular metabolism, and activate AMPK. Phenformin's glucose-lowering effects are related to its effect on activating AMPK, causing insulin-sensitive cells to think insulin levels are low and prompting the body to use glucose as if it were low-calorie disease condition
Phenformin is used to treat type 2 diabetes mellitus, Phenformin is a biguanide hypoglycaemic agent with actions by increasing the body's ability to use insulin more effectively.[3]

**Dose:** After meal single maximum dose of 400mg twice a day

**Dosage form:** Tablet, Route of Drug administration: Oral route[3]

**Manufacturer**

- Sold by Ciba-Geigy Corp. as DBI
- Sold by USV Pharmaceutical Corp. as Meltrol.[4]

**ADR (Adverse Drug Reaction):** "Any reaction to a medicine that is harmful, unanticipated, and occurs at dosages usually used in humans to prevent, diagnose, or treat disease, or to alter physiological function" is what the World Health Organization refers to as an adverse drug reaction (ADR). ADR, then, is the harm brought on directly by a drug when used normally and at regular doses. An unanticipated adverse reaction is one that is not expected given the characteristics of the drug or the national labelling or marketing authorization, regardless of its degree or kind. Adverse drug reaction and adverse drug reaction are synonymous terms.

- Type A (Augmented): Expected using the drug's well-known pharmacology.
- Category B (Bizarre): Because of the drug's well-known pharmacology, the response cannot be predicted.
- Type C (chemical/chronic): relates to the metabolism of chemicals and their structure.
- Type D (delayed): Applies years after therapy.
- Type E (End of Treatment): Takes place when medication is stopped. [5]

**Adverse effect of phenformin: Lactic acidosis**

An excess of acid in the body causes lactic acidosis, a condition. When the body cannot adjust to these changes and does not make or utilize enough lactate, lactic acidosis sets in. Liver (and occasionally renal) issues make it difficult for the organs to remove too much acid from the body in lactic acidosis patients. The body's fluids, including blood, become more acidic as lactate accumulates quicker than it can be excreted. The pH of the body, which should always be slightly alkaline or alkaline and not acidic, becomes unbalanced as a result of this acid build-up. Acidosis comes in many forms. When there isn't enough oxygen in the muscles to metabolise or break down the glucose and glycogen in the blood. Without oxygen, there is anaerobic metabolism. There are two types of lactates: L-lactate and D-lactate. Lactic acidosis is caused by too much L-lactate. [6]

**How drug phenformin cause lactic acidosis?**

Lactic acidosis is Adverse drug reaction of drug phenformin, it generally occurs in renal failure patient.In patient excretion of phenformin is decreased and its level increased in blood. Primary action of phenformin is to block primary gluconeogenesis, main substrate for gluconeogenesis is lactate, glycerol and alanine which convert glucose in liver. Increased phenformin level in blood in renal failure impaired. Hepatic utilization of lactic acid, that increase level of lactic acid in blood which eventually lead to lactic acidosis. Phenformin-associated lactic acidosis can occur acutely in an overdose but typically has a more gradual onset in patients with hepatic or renal dysfunction due to decreased excretion. Some of the symptoms are Nausea, abdominal pain, tachycardia, hypertension, tachypnoea. Lactic acidosis caused by Phenformin is primarily by Type B but in an overdose lactic acidosis can be compounded by Type A When lactic acid accumulation leads to cardiovascular collapse, tissue hypoperfusion and hepatic dysfunction thus it causes lactic acidosis

**Role of USFDA in recalling of drug?**

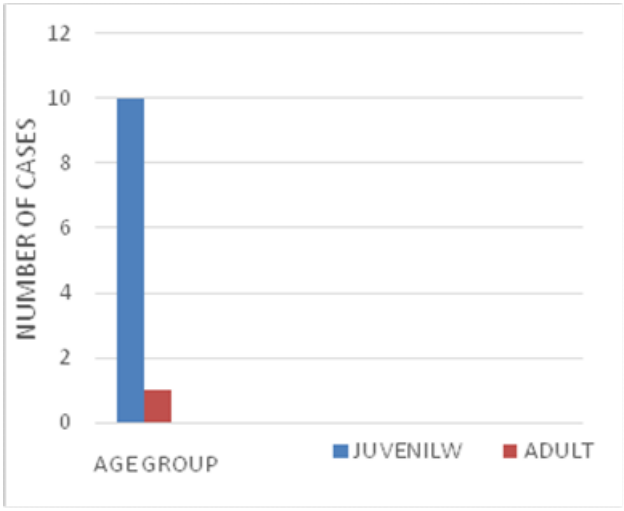
The best way to safeguard the public from a subpar or potentially dangerous product is through a drug recall. A voluntary step made by a corporation to remove a faulty drug product from the market is known as a recall. A business may recall drugs on its own initiative or at the FDA's request. The FDA's responsibility in a recall is to monitor a company's plan, evaluate how effective the recall is, and categorise the recall.

- **Class I:** A hazardous or flawed product that may result in major health issues or even death.
- **Class II:** A product that may present a minor risk of serious harm or a transient health issue.
- **Class III:** A product that deviates from FDA labelling requirements but is unlikely to have any negative health effects. [8]

**Alerting the Public:** Not every recall is reported on FDA.gov or by the media. When a product that has been widely used or constitutes a major health risk is recalled, a public announcement is typically made. Nonetheless, if the FDA decides it is necessary to protect patients, it may do so even if a firm doesn't publicly announce a recall. The manufacturer, the patient's healthcare provider, or the pharmacy may inform patients that their medication has been recalled. Consult your doctor about the best course of action for your health if you have a recalled medication, including the possibility of returning the medication to the retailer where you bought it. When a business declares a product recall, stores typically have a return and refund policy. Class I recall notices typically include instructions with action items for patients. The FDA advises patients to adhere to the directions given by the business issuing the recall. [8]

**Enforcement Report:** When a recall is classified, it is placed in the Enforcement Report along with all others that FDA is keeping track of. Recalls may also be listed before they are classified if FDA believes that a company's removal or correction of marketed product(s) fits the criteria for a recall. The Enforcement Report entry will be updated with the recall classification once FDA has finished the hazard evaluation. Via the weekly report release, the rapid and advanced search options, and an Application Programming Interface, recall data in the Enforcement Report can be accessed (API). [8]

**Clinical Data of phenformin for showing ADR**




109 diabetics of all sorts who were under the supervision of D.B.I. alone or with additional insulin were studied. According to the accepted standards, effective control was frequently attained. Results from a portion of the series have been published elsewhere. The prevalence of ketonuria in the presence of normal or only slightly raised blood sugar levels caught attention. Ketonuria was discovered to be associated with a frank decrease in alkali reserve in 11 instances. The emergence of acidosis was then noted to be associated with the volume of exercise performed. Careful examination revealed that among young diabetics on D.B.I., any moderately strenuous physical activity tended to cause ketonuria and acidosis. Further observation revealed that only individuals receiving D.B.I. had fresh pee with a pH of less than 5.6, whereas other diabetics' urine almost always had a pH higher than this. The incidence of two cases of very severe acidosis among the patients on D.B.I. highlighted the urgency

of the issue. Both were brought into the hospital while exhibiting signs of a diabetic coma. The blood sugar level in Case 1 was 208 mg/100 ml, and the alkali reserve was 4.9 mEq/l. The corresponding results in Case 2 were 280 mg/100 ml and 3.1 m Eq/1. Despite aggressive practical methods to treat acidosis, including intravenous glucose, insulin, and alkali, the latter patient passed away. In neither instance was there a clear predisposing cause, and both instances had a rapid onset and severe degree of the biochemical disruption. Case I was previously only managed by 100 mg of D.B.I. per day, but is now managed by 56 units of insulin. Case 2 was taking 12 units of 1.Z.S. along with 150 mg. of D.B.I. daily ("Lente" insulin). A few months later, a new case was admitted that shed some insight on the issue. Blood sugar levels were elevated and there was significant acidosis; D.B.I. had been discontinued for two days (alkali reserve: 15.2 mEq/l; blood sugar: 512 mg/100 ml), and empirical methods were once more employed. A total of 280 units of insulin were administered intravenously and intramuscularly in the first 12 hours. When blood sugar levels dropped as expected in the first four hours, the alkali reserve decreased and plummeted to 5.8 mEq/1; sodium lactate had been given as the alkali. With the substitution of sodium bicarbonate, the intended result was a rapid increase in the alkali reserve.Typically, giving sodium lactate intravenously increases the body's alkali reserve because the lactate ion is swiftly broken down in the Krebs cycle or transformed into glycogen, freeing up the sodium ion to generate sodium bicarbonate. In this instance, it is likely that the further metabolism of lactate has been halted, which has contributed to the elevated lactate pool already present in D.B.I. patients. [9]

**Regulatory laws for recalling of drug According to**,

Section 505(e) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 355(e)

Withdrawal of Approval; Grounds; Immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds

(1) That clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved
(2) That new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved
(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence 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 thereof
(4) the patent information prescribed by subsection (c) was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information
(5) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. [10]

**According to,**

Scope of review 5 U.S.C. § 706(2) (A)

hold unlawful and set aside agency action, findings, and conclusions found to be—
(A)arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law[11]

According to,

2 Lcer & 25-imminent hazard to the public health

(a) Within the meaning of the Federal Food, Drug, and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists

(b) In exercising his judgment on whether an imminent hazard exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.[12]

The Secretary (Joseph A. CALIFANO) stated in the Order that the following sources were taken into account when making his decision:

- The report and supplementary materials provided in October 1976 by the FDA Endocrinology and Metabolism Advisory Committee, which unanimously recommended that phenformin be taken off the market.
- Documents provided by the FDA Bureau of Drugs with their proposal to remove phenformin from the market on May 6, 1977, including published scientific research and other information.
- Oral and written comments made at the public hearing held by the FDA on May 13, 1977 to gather opinions regarding the HRG petition to stop phenformin.
- The FDA Commissioner's reports from June 27 and July 18, which examined the use of phenformin, its dangers, and other treatments.[13]

**Actions taken to Recalling phenformin form US market**

- On May 13, 1977, the Food and Drug Administration got ready to use a dramatic power Congress had granted it 15 years earlier: declaring a pharmaceutical to be a "imminent threat" to the public's health and immediately stopping sales.
- The medication is phenformin, which is offered by USV Pharmaceutical Corp. as Meltrol and Ciba-Geigy Corp. as DBI. At least 250,000 persons with moderate or so-called onset diabetes receive a prescription from their doctor to decrease blood sugar.
- If the FDA follows established procedures in attempting to stop the sale of phenformin, the legal process could take longer than two years. In the interim, sales, which are now operating at a retail rate of about $25 million annually, may continue unabated. Even in extreme situations, such as the example of an antibiotic drug called Panalba, which according to the FDA's own estimate annually was causing hundreds of thousands of unnecessary injuries, some of which were fatal, the agency had not exercised the imminent hazard power. The Upjohn Co. stopped distributing Panalba in 1970 after losing a legal dispute with the FDA.
- In the past, the FDA's definition of an urgent hazard was so strict as to make it use less. The courts have recently started to define "imminent hazard" in ways that appear to apply to phenformin, nevertheless.

- FDA attorneys point out, for instance, that the U.S. Court of Appeals in this location ruled in November that a pesticide can be declared an imminent hazard if there is only a "substantial likelihood" that it could cause serious harm if sold during the year or two that an administrative proceeding was ongoing.
- In the phenformin case, a panel of outside specialists from the FDA unanimously advised that sales be stopped in October due to a "clear and undeniable relationship" between the pills and lactic acidosis, an adverse response that is fatal in 50% of cases. Since then, the FDA has been informed of 22 fatal and 24 nonfatal incidents involving phenformin users.
- Nevertheless, scientists argued yesterday at an unusual - and strongly split - meeting held by the FDA as a lead-up to the anticipated sales cutoff that the agency's reports substantially underestimate the true toll.
- Thaddeus E. Prout, a former panel chairman from the Johns Hopkins University School of Medicine, said it "undoubtedly accurate" that the FDA never learns of a significant portion of lactic acidosis cases when advocating for a ban on behalf of the American Diabetes Association.
- Prout, speaking for himself, stressed that only one study has shown phenformin to be a life-saving medication and that the sooner it is banned, the better.
- Dr. Sidney M. Wolfe estimated that at least 1,000 users of phenformin die needlessly each year, citing data from numerous hospitals and sources around the world, including a medical officer in the FDA. He said, "There is no proof of any mortality occurring as a result of the absence of phenformin availability." at the same time."
- On April 21, Joseph A. Califano Jr., Secretary of Health, Education, and Welfare, was petitioned by Wolfe, the director of the Health Research Group, which is supported by Ralph Nader's Public Citizen, Ind., to declare phenformin an immediate danger.
- The FDA subsequently scheduled yesterday's hearing, which was presided over by Dr. J. Richard Krout, the organization's director of medicines, at Califano's request. Reporters were informed that he is "very seriously contemplating" proposing a suspension to Commissioner Donald Kennedy.
- If "this fatal medicine" is not deemed an imminent risk by the end of the week, according to Wolfe, the HRG will file a lawsuit to request a prohibition.
- Disagreeing scientists including a vice president of Ciba-Geigy argued that abrupt phenformin withdrawal would cause "chaos" and "panic" among users. They said that when taken in accordance with the FDA's strict new prescribing guidelines, phenformin poses a modest risk that is outweighed for some patients, particularly obese people for whom chemically distinct sugar-lowering medications are ineffective.[14]

**Withdrawal in USA:** Working for the US Vitamin Corporation, Ungar, Freedman, and Seymour Shapiro created phenformin in 1957. Sales of phenformin, which Ciba-Geigy marketed as DBI, started to fall down in the US in 1973 as a result of unfavourable trial results and reports of lactic acidosis. The FDA Endocrinology and Metabolism Advisory Committee suggested that phenformin be taken off the market by October 1976. Due to a significant risk of lactic acidosis, which proved deadly in 50% of instances, the FDA started official actions in May 1977 that eventually led to its withdrawal from US markets on November 15, 1978. [15]

**Reason for Withdrawal in Usa:** The Swedish Adverse Drug Reaction Committee received reports of adverse drug reactions to phenformin and metformin from 1965 to 1977. Sales and prescription data were examined in relation to these reports. Biguanides were responsible for 0-6% of all recorded medication adverse effects, but only 6% of fatal cases (all phenformin). Sixty-four ADRS to phenformin and eight to metformin were labelled as "likely" or "not excluded" causative relationships. 51 of these reactions (or 71%) were lactic acidosis, and all but one of them were phenformin-related. Lactic acidosis was the main ADR associated with this medication. [16].

**Withdrawal process of phenformin in Europe (EMA)**

A drug's removal from the market due to safety concerns is a significant and occasionally difficult decision. Due to its side effects, such as a significant risk of lactic acidosis, phenformin was outlawed in the US in 1977. However, it was still legal in certain other European nations, such as France and Germany, where it was sold without any limitations. Here in Sweden, observations were done on a group of 109 diabetics of all types who were being treated with phenformin. They discovered that phenformin causes the patient to experience acidosis and ketonuria, which results in a slightly elevated blood sugar level. Ketoneuria cases were lower than acidosis instances.The decision to pull a medicine off the market over safety concerns is major and occasionally challenging. Phenformin was banned in the US in 1977 as a result of its adverse effects, which included a high risk of lactic acidosis. However, in certain other European countries, including France and Germany, where it was freely sold, it was still lawful. 109 diabetics of all sorts who were receiving phenformin treatment were observed here in Sweden. They learned that phenformin leads in the patient having acidosis and ketonuria, which raises blood sugar a little bit. Cases of ketonuria were less common than those of acidosis.[17]

**India Banned drug theory of phenformin:** Up until 2002, phenformin was still marketed in India despite being prohibited in the US and EU. Since then, the Medicines Controller General of India has prohibited the production, sale, and distribution of phenformin formulations for use in humans. The government's announcement of the drug's ban came precisely one year after it was rumoured that officials had decided to forbid its usage in the nation. USV Ltd. The centre stated that it considered it was important to outlaw the drug starting on October 1, 2003 because better alternatives to drug formulations including phenformin are now readily available. Strangely, the majority of the nations where phenformin used to be marketed felt the need to outlaw the medication for the exact same cause decades prior. Due to a major adverse response, the medicine was removed off the US market 32 years ago. Phenformin is no longer authorised for the treatment of diabetes or any other ailment, according to the US review of the medication at the time they decided to outlaw its use in 1971. There is no circumstance in which the risk of treatment is greater than the clinical benefit received from phenformin.

Just three years ago, an editorial in a medical journal argued that the medicine should have been outlawed decades earlier, sparking a backlash against its continued availability in India. The issue was discussed at the 2001 meeting of the Drugs Technical Advisory Board (DTAB) thanks to the subsequent media campaigns. Because "cases of lactic acidosis owing to the drug were not that widespread in India," the subcommittee formed by DTAB came to the conclusion that there was no need to outlaw the substance. If reports using ORG data are to be believed, USV brands enjoyed annual sales of roughly Rs 7 crore in 2000, and 10,000 patients were using the medication on a yearly basis when the problem was discovered. Worldwide, the medicine had been removed by that point from 188 of the 191 WHO member nations. India was the only country still producing and selling the medication, along with Italy and Brazil. The medicine continued to be in the market with full approval for another year until the authorities declared in October 2002 that they have chosen to ban the drug due to "reports of side-effects and presence of better alternatives". Before the final notification, which sealed the drug's fate in the nation, was implemented, another year had gone. Industry watchers believe the government has been "pro-active" enough to allow USV ample time to develop a replacement (and safe) brand that contains metformin to replace its phenformin brands. Under the trade name "Glycomet," USV produces an anti-diabetic formulation incorporating metformin. It is well known that Glycomet sells for little over Rs 12 crore annually, and that this figure is rising by 11%

yearly. The combined sales of DBI and DBI-TD reach Rs 4.2 crore, with a 17% yearly decline in sales.[18]

**Hong Kong**

Phenformin was still being used to treat type 2 diabetes in Hong Kong as late as 2005, despite being outlawed in the majority of highly and moderately regulated nations such as the US, EU, India, Australia, Japan, etc. This is due to a possible under recognition of phenformin use and associated side effects in Hong Kong. to recognise its complications and negative effects Six instances of phenformin use, with or without problems, were confirmed by the Hospital Authority Toxicology Reference Laboratory between July 2005 and November 2006. They disclose these six incidents in order to draw attention to the risks that phenformin may pose. From these six cases the authority observed that the two of six patients were induced with lactic Two of the six patients in these six cases were diagnosed with lactic acidosis, according to the authority, and phenformin was imported from China as Chinese proprietary medicine, which is extremely harmful because it contains adulteration. As a result, the US FDA and Canada have both banned CPM from the market because of the adulteration in CPM's products, which is extremely harmful to the general public's health. According to those six cases, phenformin has a higher risk of lactic acidosis than other biguanides like metformin.Due to these factors, metformin has a lower risk of lactic acidosis than phenformin while simultaneously having the same impact on diabetes. Phenformin was likewise outlawed in Hong Kong in 2006, however it is still sold in many other nations, including Italy and Brazil.[19]

**Rest of the World:** Phenformin is a type 2 diabetes medication of the biguanide class. Broadly speaking, lactic acidosis can be caused by all biguanides, and phenformin is associated with a significant risk. Lactic acidosis was observed to occur less frequently with metformin medication (0-0.084 cases/1000 patient-year), but more frequently with phenformin (0.64 cases/1000 patient-year), an order of magnitude more frequently. Phenformin, buformin, and metformin were all used in 330 cases of biguanide-induced lactic acidosis that were the subject of a literature study. Despite the widespread use of metformin in those nations, research in France and Switzerland have revealed that phenformin was responsible for a greater number of cases of lactic acidosis. The mortality rate from biguanide-induced lactic acidosis was 50.3%. Although phenformin was taken off the market in the US in 1977 due to its high incidence of related lactic acidosis, most of the countries have done so using scientific evidence, even though the US also supplied information on the drug's toxicity and fatality rate. The rest of the world, including Canada, Australia, and Japan. The majority of nations have outlawed phenformin due to its high risk of lactic acidosis and the availability of a good substitute, metformin, which has the same effect and a lower chance of developing the condition. Several nations, such as China, Brazil, and Italy, continue to advertise this medicine into their markets with no limitations despite the fact that it is illegal in 188 of the 191 WHO member nations. [19]

# DISCUSSION

The oral hypoglycemic medication phenformin is effective for treating type 2 diabetes. Phenformin was created in 1957 by Ungar, Freedman, and Seymour Shapins while working for the US Vitamin Corporation. It was dragged along with the dangerous adverse drug reaction of lactic acidosis and elevated lewd of youngster over drug secretion. Phenformin sales in the US started to fall in 1973 as a result of unfavourable trial studies and reports of lactic acidosis. It was sold as DHL by Ciba-Geigy. The FDA Endocrinology and Metabolism Advisory Committee suggested that phenformin be taken off the market by October 1976. The FDA officially started its legal process in May 1977, and on November 15, 1978, it withdrew.The medicine has been on the market in the United States for 20 years, but due to low awareness and inadequate ADR reporting, the fatality rate has skyrocketed. People should be aware of the drugs they are taking, as well as any adverse drug reactions or side effects that may result. The establishment of ADR reporting centres and encouragement of ADR reporting would aid in the research and study of the medicine Phenformin, a biguanide that has a higher risk of lactic acidosis than the other drug in its class, metformin, buformin.With this study, one will learn about key details pertaining to the drug's suspension process and how international regulatory authorities handle pharmacovigilance. Also, it provides details on how international regulatory organisations cooperate and communicate to prevent unfavourable outcomes. The regulatory agencies of Europe and other nations' activities in response to adverse events or the reporting of any adverse reactions will be covered in depth.

# CONCLUSION

From this review article we can conclude that Phenformin drug which is chemically biguanides shows hypoglycaemic activity by decreasing the absorption of glucose by the intestines, decreasing the production of glucose in the liver, and by increasing the body's ability to use insulin more effectively but this drug cause adverse effect of lactic acidosis, action of phenformin is to block primary gluconeogenesis, main substrate for gluconeogenesis is lactate, glycerol and alanine which convert glucose in liver. Increased phenformin level in blood in renal failure impaired. Hepatic utilization of lactic acid, that increase level of lactic acid in blood which eventually lead to lactic acidosis. Action was taken by US government to recall this drug mainly under regulatory laws and by October 1976 phenformin was removed from US market. Phenformin contains high risk of lactic acidosis in other countries too, like EU, JAPAN, India etc. cases of lactic acidosis due to phenformin were reported in this countries. Case studies by sweedenphenformin cause and on the basis of case studies by sweeden and USA drug was banned by EMA. In 2003 phenformin was also banned as they have decided to ban the drug due to “reports of side-effects and presence of better alternatives. Metformin to replace its Phenformin brands. USV manufactures anti-diabetic formulation containing metformin under the brand name “Glycomet”. As per studies of US has given provided data about the toxicity and mortality rate of phenformin and alternative was found that is Metformin, Even though the drug phenformin where banned in 188 out of 191 countries of WHO some countries still market this drug into there market without any restrictions i.e. China, Brazil, Italy.

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