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HOW EXPIRED ARE THE EXPIRED DRUGS: THERAPEUTIC, REGULATORY & FINANCIAL IMPLICATIONS

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ABSTRACT

Expiry date is the date until which the drug manufacturer can guarantee that the medicine is fully potent and safe to take based on scientifically-sound product testing. If the drugs are stored under optimal conditions, they may retain 90% of their potency for at least five years after the labeled expiration date. However, expiry date is important for both manufacturers as well as consumers. From the companies' perspective, any liability or safety risk is diminished by limiting the period during which a consumer might misuse or improperly store a drug. Moreover, any new warnings or indications, newer devices for drug delivery; newer strength of the drug may not be brought to the market for the benefit of consumers if the older ones will not be expired/discarded. The expiration dates are very conservative to ensure that the patients get everything they paid for. A manufacturer could extend expiration periods again and again, but to support those extensions, it would have to keep doing stability studies and keep more in storage than it would like. Stability has for long been a major problem with Indian drugs due to improper storage conditions. Whether or not an expired drug can be safely taken depends on several factors like the way the drug is stored and the stability of its active ingredients or the condition for which it is being used. Therefore, it is not advisable to take expired medicines, without fully understanding the consequences.

KEYWORDS: Expiry date, Stability, Storage.

INTRODUCTION

Medicines are considered a health need and are important in maintaining health and ensuring that the person remains disease free. They are important from two perspectives: health and market. From the health perspective, medicines are considered social goods whose purpose is the prevention and solution of health problems. Medicines form an important share of healthcare budget. The global average of GDP spent on healthcare is 5.4 percent but India spends about 1.2 percent of the GDP on the healthcare sector.[1] Advances in medications have enabled doctors to cure many diseases and save lives. All pharmaceutical drugs are designed to create some type of beneficial effect in the body. From the market perspective, drugs and pharmaceutical industry play a vital role in the economic development. From this perspective, medicines are products that aim to generate profit. The Indian pharmaceuticals market is the third largest in terms of volume and thirteenth largest in terms of value accounting for 20 per cent in the volume terms and 1.4 per cent in value terms of the Global Pharmaceutical Industry as per a report by Equity Master.[2] India is the largest provider of generic drugs globally which exports affordable medicines to more than 100 countries and which has earned India the sobriquet of "pharmacy of the world"; also booming healthcare industry and thriving medical tourism.

The existence of well-defined and strong pharmaceutical industry is important for promoting and sustaining research and developmental (R&D) efforts and initiatives in an economy but drug discovery and drug development process itself are complex and expensive endeavors undertaken by pharmaceutical companies, academic scientists and governments. Drug discovery is still a lengthy, expensive, difficult and inefficient process with low rate of new therapeutic discoveries. In 2010, the research and development cost of each new molecular entity (NME) was approximately US$1.8 billion.[3] The drug requires very expensive Phase I, II and III clinical trials, and most of them fail.

The molecules which successfully clear all the stages are marketed with specific instructions that dictate when and how users should take them. These contain information regarding ingredients, uses, warnings, precautions, directions etc. Also the part of these labels is expiration dates, which suggest that there is a certain window of time within which users should take their drug. The expiration date indicates the date the manufacturer guarantees the full potency and safety of the drug. It is usually expressed by month and year. The product can legally be used or dispensed until the last day of the stated month and year. In general,

drugs expiration date is 2-5 years from production date.[4] However, this is not always true. If the drugs are not stored under optimum conditions, they may reach their expiry well before the defined expiry date. For example: Oral nitroglycerin (NTG), which is used for chest pain in angina, may lose its potency quickly once the medication bottle is opened. Also, the drugs which exist in solution or as a reconstituted suspension and require refrigeration (such as amoxicillin suspension) may not have the required potency if used after sometime.

So what does it actually means if a drug has reached expiry date? What happens to the efficacy of the drug after expiry? Are its effects potentially reversed? Will the drug simply do nothing? Will it cause harm or just not work after its expiration date?

Expiry date is the date until which the drug manufacturer can guarantee that the medicine is fully potent and safe to take based on scientifically-sound product testing. The expiration date does not indicate a point when a medication loses potency and is no longer effective or becomes harmful. This doesn't mean that the medicine "goes bad" after the expiration date, or even that a medicine has full potency the day before it expires and has zero potency the day after. Expiry date isn't a fool proof indicator of when medicines are no longer safe for use. At the time of the medication expiry date, the drug must be at least 90% of the original potency under proper storage conditions. The expiration date gives assurance that the labeled potency of the drug will last at least until that date. If the drugs are stored under optimal conditions, they may retain 90% of their potency for at least five years after the labeled expiration date and sometimes longer.[5] Even 10 years after the expiration date many pharmaceuticals retain a significant amount of their original potency.[6] But on the other hand, for certain prescription medicines such as nitroglycerin, insulin and liquid antibiotics, expiry date holds importance. Expired medicines may not work as well, they may be at risk of bacterial growth or a change in chemical composition could make them unsafe to use. They may degrade quickly, become discolored, may develop a strong smell or may turn powdery. People with diabetes need to get full potency of insulin but after the expiration date, we can't guarantee the full potency and safety and hence using expired insulin may become life threatening for the patient. Moreover, the expired medicines should be replaced by the new ones as they may have new dosing instructions or warnings; the strength may have changed to reduce the risk of errors; a new dosing device may be available to help measure doses more accurately; the product may be packaged in a new container more child-resistant than an older version of the drug; and so on.

Why need for expiry date?

Drugs are important from two perspectives: One from the health/ patient point of view and other from the market point of view and expiry date holds importance for both perspectives. Once a drug is launched, the manufacturers timely test the drug to ensure it continues to be effective up to its labeled expiration date. As per the regulations, the manufacturers are not required to check efficacy of the drugs beyond expiry date because it is expensive and time-consuming for manufacturers to extend expiration dates. A manufacturer could extend expiration periods again and again, but to support those extensions, it would have to keep doing stability studies and keep more in storage than it would like. Most of them would rather sell new drugs and develop additional products as there is no economic gain for drug companies to investigate further. Moreover, in India as per the new GST rules, there is no exemption for expired or damaged drug products from GST preview, because of which the industry is expected to lose Rs.500 crore annum.[7] Usually the retailers send back all their expired or damaged stocks to the pharma companies. However while doing so they will generate an invoice which will again attract a GST on the date expired and damaged drugs because of which an additional cost burden is being imposed on the pharma companies in the form of GST. Hence, expiration dates have a commercial dimension too.

Because of expiry dates, an enormous quantity of drugs are manufactured and sold or dispensed, but never consumed. New & more-beneficial drugs can be brought on the market more easily if the old ones are discarded within a couple of years. From the companies' perspective, any liability or safety risk is diminished by limiting the period during which a consumer might misuse or improperly store a drug. It gives enough time to put the inventory in warehouses, ship it and ensure it will stay on shelves long enough to get used. Also, if a drug manufacturer had to do expiration-date testing for longer periods it would slow their ability to bring new and improved formulations for the consumers. Moreover, any new warnings or indications, newer devices for drug delivery; newer strength of the drug may not be brought to the market for the benefit of consumers if the older ones will not be expired/discarded. While it may be true that expiry dates help to sell more drugs for manufacturers and pharmacies, they also serve an important purpose. The expiration dates are very conservative to ensure that the patients get everything they paid for. People think that, upon expiration, drugs suddenly turn toxic or lose all their potency. Expiration dates are designed to give users a basic time frame during which the drug is the most potent.

How expiry date is calculated?

At some point after major clinical trials are concluded, but before FDA approval, a series of quality standards are established for each new drug. These are the manufacturing and testing specifications, which include upper and lower limits for the amount of the Active Pharmaceutical Ingredient (API) in each dose unit (e.g., 500mg per tablet). The final dosage form may be a mix of the API as well as fillers, binders and other ingredients to ensure the API is delivered to the body in a reliable and predictable manner. In majority of cases the drug products are put through accelerated degradation testing, or "stress" testing, to estimate how quickly a drug will deteriorate. Depending on the dosage form, stress testing may include short-term exposure to extremes of heat, light, oxidation, and humidity. After exposure over different time periods, the quantity of the API and the other product characteristics are assayed again. For liquid and injectable drugs, there are additional tests for bacterial purity and chemical stability. All of these tests predict the overall stability of the dosage form – not just the amount of drug, but how that drug will be absorbed into the body. All of this is used to estimate what the expiry date should be.[8]

Stability testing analyzes the capacity of a drug to maintain its identity, strength, quality and purity for whatever period the manufacturer picks. If the company picks a two-year expiration date, the drug is tested by subjecting it to extreme heat and humidity for several months, then chemically analyzing each ingredient's identity and strength. After the date is set and the drug is marketed, testing continues for the full two years. The FDA also uses chemical analysis in testing for possible shelf-life extension. These tests simulate the long term effects of these factors on the stability of the active drug and the formulation in acute experiments lasting up to 45 days at temperatures of 45 degrees or more and humidity of 70 percent or more.[9] From the correlative data available, it is possible to predict the stability of the drug over long periods of even up to five year.

Factors affecting expiry date

Expiration date depends on several factors. The expiry date is dependent on recommended storage conditions, shelf life, dosage form, etc. The drugs lose their efficacy over a certain period of time. The drugs of plant origin have an even lesser shelf life.[10] The drugs of animal origin remain effective depending on the type of tissue. Soft tissues like blood etc remain effective for one year, while the harder tissues like horns may be used for many years.[11]

Certain external factors can affect expiry – contact with water, temperature, air, humidity, light etc. These factors mainly affect the drug stability.[4] For example; antibiotics to be taken as a liquid formulation are stored as a dry powder which is then reconstituted with water and then given a shorter expiry date.[12] Generally, solid dose formulations have a longer expiry date than liquid preparations. The manufacturer's expiry on a container is the unopened expiry date. After opening, the expiry date may be dramatically shortened. This should be highlighted on the medicine label or container or in the service user's medicine profile.

Storage in high heat and/or humidity can accelerate the degradation of some drug formulations, but it is not always the case. In one study, captopril tablets, theophylline tablets and cefoxitin sodium powder for injection, stored at 40°C and 75% relative humidity, remained stable for 1.5-9 years beyond their expiration dates.[13] In another study, theophylline retained 90% of its potency 30 years past its expiration date.[14] A study of eight products that had been stored in their unopened original containers for 28-40 years past expiration found that 12 of 14 active ingredients had retained ≥90% of their original potency; aspirin retained <5% of its potency and amphetamine <60%.[5] Humidity's effects are frequently noticable with old bottles of Aspirin (acetylsalicylic acid) which breaks down via hydrolysis to salicylic acid and acetic acid giving old bottles a characteristic vinegar odour.

The current Indian Pharmacopoeia defines the following storage conditions: Store in a dry, well ventilated place at a temperature not exceeding 30 °C; Store in a refrigerator (2° C to 8° C). Do not freeze; store in freezer (-2 °C to -18 °C); and store in deep freezer (below -18 °C).[15] Heat being the main factor responsible for drug degradation, storage in controlled temperature regulated environment (also with humidity controlled) retains the potency as expected. Every 10 °C rise in temperature is likely to double the rate of decomposition.[16]

Consuming expired drugs- Are they really safe?

The first concern related to expired drugs is whether they are potentially harmful if consumed. There is no published data to suggest harms from use of drug formulations after their expiry date. There are virtually no reports of toxicity from degradation products of outdated drugs.[4] There are very few reports of human toxicity due to ingestion, injection or topical application of presently available medicinal products after their expiration date.[17] According to The Medical Letter (2015) the only report of human toxicity that may have been caused by chemical or physical degradation of a pharmaceutical product is renal tubular damage that was associated with use of degraded tetracycline.[18] Since then tetracycline

products have been changed to eliminate the problem. There are very few examples where the products of degradation are significantly more toxic than the original active pharmaceutical ingredient. Tetracycline gets decomposed to epianhydrotetracycline and the decomposed product is shown to cause renal tubular damage. Chloroquine can produce toxic reactions as an attribute to photochemical degradation. Phototoxicity has also been reported following administration of chlordiazepoxide and nitrazepam.[15] Infusion of degraded Penicillin G is known to cause sensitization of lymphocytes and formation of antipenicilloyl antibodies.[16]

While recognizing that case reports are an inaccurate and imprecise way of identifying harms, the lack of documented harms suggests that degradation of useful chemicals into toxic compounds is rare, if it occurs at all. Additionally, current requirements for stability testing of drugs should identify if expired products pose a safety risk – and there do not seem to be any other documented cases.

Drugs really dangerous after their expiry date.[4]

Certain medications have a narrow therapeutic index and little decrease in the pharmacological activity can result in serious consequences for patients. Observing the expiration date is obligatory for the following medications.

- Anticonvulsants - narrow therapeutic index
- Phenytoin, phenobarbital - very quickly lose potency
- Nitroglycerin - very quickly lose potency
- Warfarin - narrow therapeutic index
- Theophylline - very quickly lose potency
- Digoxin - narrow therapeutic index
- Epinephrine - very quickly lose potency
- Insulin - very quickly lose potency
- Eye drops - eyes are particularly sensitive to any bacteria that might grow in a solution once a preservative degrades.
- Long-expired antibiotics- Increased antibiotic resistance and treatment failure

Expired drugs - to be used or not?

The answer might depend on a variety of factors, including how the drug was stored, how it was handled, how far past the expiration or beyond-use date it is and any additional

information that's available on the stability of the drug past the expiration or beyond-use date from the manufacturer or other references. But if there is a choice, where potency is further brought to question because of weather and storage and cost not a problem, there are certain conditions where 100% absolute certainty of potency is preferable - for heart conditions, strokes, transient ischemic attacks (TIAs) and life-threatening infections etc. Aspirin potency may not be as important for the simple ache or headache as it would be in a TIA, stroke prevention or heart conditions. Antibiotic potency might not be as critical in the empiric treatment for suspected sinus infections as they might be for respiratory infections in the elderly and lung-compromised patients. So, when the urgency of clinical situation dictates, or when the conditions of storage are of concern, together with length of time beyond expiry date-for both over-the-counter and prescription pharmaceuticals, opt for the new bottle or the new prescription.

Different rules?

The expiration date of the drugs is determined by stability testing described in CFR section 211.166 of US FDA. If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products. New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations.[R] As mentioned earlier, expiry date of drugs largely depends upon the stability studies. But many of the pharmaceutical companies give fabricated data on their stability studies and question the long term efficacy and safety of drugs. This was the basis that Ranbaxy was penalised by the US FDA for supplying fabricated stability test data to secure market authorisations for its product in the US.

Currently, in India, stability testing is compulsory only for those new drugs that are regulated by the Drug Controller General of India (DCGI). Once a drug loses its new drug status after 4 years, any new manufacturing applications are handled by the state regulators and the law currently does not require them to compulsorily require stability data. Since 2007, there have been numerous citations, for lack of stability data, to Indian pharmaceutical companies issued by the US FDA. Even domestically, stability has for long been a major problem with Indian drugs during random testing by Indian drug regulators. Every time a drug fails stability testing during random sampling by state regulators, our drug manufacturers palm off the

blame on poor storage conditions at the pharmacy. Hence, if the law is amended to make stability testing compulsory and if our drug manufacturers can resist the urge to fabricate or manipulate data, we may actually improve the quality of drugs made available to Indian patients.[19]

If some drugs remain effective well beyond the date on their labels, why hasn't there been a push to extend their expiration dates?

It's an open secret that many drugs maintain their ability to combat ailments well after their labels say they don't. FDA has long known that the shelf life of some drugs can be extended, sometimes by years. Though the government requires pharmacies to throw away expired drugs, it doesn't always follow these instructions itself. One reason is that the consumer market lacks the military's logistical reasons to keep drugs around longer. A manufacturer could extend expiration periods again and again, but to support those extensions, it would have to keep doing stability studies, and keep more in storage than it would like.[20] Instead, for more than 30 years, it has pulled some medicines and tested their quality. The federal agencies that stockpile drugs including the military, the Centres for Disease Control and Prevention and the Department of Veterans Affairs have long realised the savings in revisiting expiration dates.

In order to check the efficacy of drugs beyond their expiry date, the FDA and Defense Department created the Shelf Life Extension Program (SLEP) in 1986. SLEP facilitates an annual testing of drug stockpiles to identify medicines that could be extended beyond their original expiry dates. The drugs are selected based on their value and pending expiration and analysed in batches to determine whether their end dates could be safely extended. For several decades, the program has found that the actual shelf life of many drugs is well beyond the original expiration dates. In a study by Lyon et al, 122 drug products were evaluated and two-thirds of the expired medications were stable every time a lot was tested. Each of them had their expiration dates extended, on average, by more than four years.[21] Hence, it was found that each year the federal government saved $600 million to $800 million because it did not have to replace expired medication. According to a report, in 2016, a cost of $3.1 million was spent to run the extension program, but it saved the government from replacing $2.1 billion in expired drugs. To put the magnitude of that return on investment into everyday terms: it was like spending a dollar to save $677. During recent times, some

medical providers have pushed for a changed approach to drug expiration dates but the success has not been achieved so far.[22]

Pharmaceutical companies- Compliance over curiosity

Since 1979, the FDA has required pharma manufacturers to include expiry dates on the packaging of prescription and over-the-counter drugs. It requires drugmakers to guarantee the effectiveness of drugs up to an expiry date a certain period after their production. For the industry this is more a matter of compliance than curiosity, so companies are incentivised to aim for a date range that they can guarantee, rather than actually finding out the upper limits of their products' shelf-lives. As mentioned earlier, the manufacturers are not legally bound to check the efficacy of their drugs beyond their expiry dates. Manufacturers does not have any commercial interest in doing stability studies beyond expiry neither they are provided with any incentives for such studies. There is no economic win for drug companies to investigate further. They ring up more sales when medications are tossed as expired despite retaining their safety and effectiveness. Hence, developing and selling newer drugs will bring revenues for them and they are more interested in developing newer candidates rather than wasting time and money on stability studies. Unfortunately, this is a problem that is extremely difficult to address. This is firstly because no one has even begun to understand the extent to which the problem exists; certainly not in any kind of comprehensive way. Secondly, there is extremely little incentive for anyone, least of all pharmaceutical companies, to spend the money required to gain a better understanding of true drug shelf-lives. After all, being able to sell replacements of expired but effective drugs is an excellent stream of revenue, and if the current situation is costly for society now in terms of waste, a reversal of the situation could be even more ruinous for industry bottom lines. FDA requires companies to conduct longer-term studies into product shelf-life, it would also be impractical to simply take an initiative like SLEP and apply it to the market more widely. SLEP was created in recognition that "certain products remained stable beyond their labeled expiration dates when properly stored". Proper storage is imperative when trying to draw consistent conclusions about drug expiration, and consumer storage can't match the protocols employed by a programme like SLEP.[23] Short shelf lives make sense from a public-safety standpoint as well. New, more-beneficial drugs can be brought on the market more easily if the old ones are discarded within a couple of years. Moreover, packaging keeps on changing from time to time. If a patient keeps a drug for 10 years or more they'd have an old package insert that might omit new information or contra-indications and there is no control of manufacturer

over how they'd store the drug during this time. Hence, a relook need to be done both by the manufacturers and the regulatory authorities in order to maximize the benefit and reducing the wastage of money to tackle this problem.

CONCLUSION

The safety of intake of medicines and their potency is generally guided by the date of expiry. It is required by the regulatory authorities that the drug manufacturers must stamp the expiry date on all medicines to make sure that patients are getting safe medicines. Though, when stored under optimal conditions, drugs may retain 90% of their potency yet the considered opinion has been so far not to take expired medicines as a safer approach. Prolonging the expiry date may have its pros and cons. The current practices of drug expiration dating needs should be reviewed by both the manufacturers and the regulatory authorities keeping in view a huge potential of cost saving benefits to the consumers.

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