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Our patient at risk from unauthorized, unapproved, illegally imported fake "generic medicines"

Parikh P M, Bhattacharyya G S, Hingmire S S, Mehta P, Rangrajan B, Ganesh Natrajan, Ghadyalpatil N, Narayanan P, Singh Randeep, Parekh Bhavesh, Singhal M

Abstract

Introduction: We came across patients inquiring with oncologists about cheap copy medicines. These were of recently licensed innovator drugs that should have been available from original company holding their patents. In fact these copy medicines were manufactured in our neighboring countries and made available in India. We investigated further and this manuscript puts together the startling information that we were able to find regarding the thriving grey market for fake generic medicines.

Keywords: Cancer, hepatitis, dcgi, FDA, drug quality, lung cancer, patient safety, imported.

Introduction

The incidence of chronic non communicable diseases like cancer is growing at alarming rates (1). However certain infectious diseases remain a major healthcare problem especially when they can result in long term irreversible consequences, like hepatitis leading to chronic liver disease (Syn cirrhosis) and subsequently cancer(2). Government schemes like Ayushman Bharat Yojanaand their state level equivalents are a boon to the underprivileged, who can really benefit from free treatment for cancers and other serious illnesses (3). For those not eligible for such schemes, cost is an important factor in limiting access. And cost of some treatments available due to advances in technology can even make the rich think twice (egCar-T-Cell Medical Therapy, Robotic Surgery orCyberknife Radiation Therapy). This is because regulatory approval and compliance, requires new technology and new drugs to go through a rigorous and prolonged process to prove their safety and efficacy before being approved for use in human beings (4). And this process is very expensive. Such companies are therefore given a logical and reasonable time to recoup their costs under the intellectual property and patent protection laws(5). Taking the example of oncology, over the last two years (2017 and 2018), several new drugs have received approval from our DCGI for marketing in India (Table 1)(6). All of these are original molecules marketed by the innovator. Their Indian price is significantly lower than sold for in the western world. However, it is still out of reach of the pocket of a significant number of Indian patients (not covered by government schemes or not having adequate insurance cover). There are similar examples of medicines for Hepatitis B and/or Hepatitis C approved by FDA, USA (Table 2) and CDSCO, DCGI, India (Table 3)(6,7). Some of these drugs are outside of/ have completed patent protection and their generic medicine versions have been given approval by Indian drug authorities after careful quality evaluation of the entire supply chain (from procurement of human grade raw material to final distribution of the finished product) as well as proper testing in human subjects and/or patients (8). Generic medicines are legal copies of pharmaceutical drugs made up of the same chemical material as the original drugdiscovered, developed and patented (9,10). These are allowed to be manufactured and marketed only after the patent held by the original drug has expired. While the generic drugshave the identical active pharmaceutical ingredient (API), itusually differs in manufacturing process, preservatives, formulation, excipients, consistency, color, appearance, taste andstability (shelf life). Hence, generic drugs are also required to comply with and provide data to government regulations to satisfy them about fitness for human consumption, impurities, pharmacokinetic and pharmacodynamic properties. Once given regulatory approval, their label must include name of the manufacturer, generic drug name (egInternational Non-proprietary Name), batch no, manufacturing date and expiry date (10,11). It is not surprising that such generic medicines are significantly cheaper than their original counterpart. No wonder, that in 2014, such generic medicines accounted for as much as 88% of the total 4.3 billion dollar prescriptions market of USA (12) This is the current status of the ethical pharmaceutical landscape. But what happens when someone takes advantage of the system. What happens when unauthorized, unapproved, illegally imported fake "generic medicines" enter the grey market and put the lives of patients at risk? These questions originated in a chance discussion with a colleague from Chennai. One of his lung cancer patient inquired with him about a drug branded as Olanib

[1]Department of Oncology, ICON Trust, Sewri, Mumbai 400015

Address of Correspondence:
Dr. Purvish M Parikh,
Department of Oncology, ICON Trust, Sewri, Mumbai 400015
Email: purvish1@gmail.com

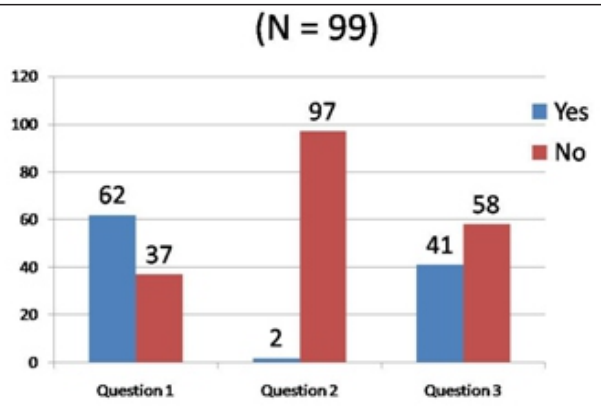

Figure 1: Survey of Senior Medical Oncologists from various parts of India.

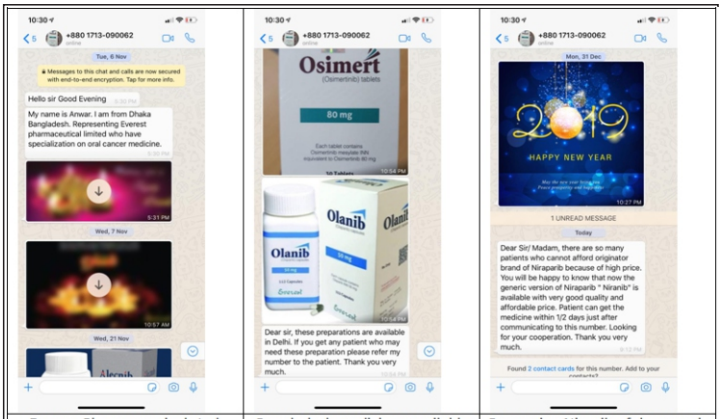

Figure 2: Sample marketing via WhatsApp from across our borders

(generic version of olaparib), which was manufactured in Bangladesh and was being offered to him for a fraction of the cost of the real medicine officially available in India.

Material and Mathod

We got together to discuss on the availability in India of drugs like Olanib. there was no evidence of it being approved by DCGI for marketing in India. Did our patients had access to unproven "medicines" from across our borders? How did they come to know about their availability? Were unscrupulous businessmen capitalizing on a perceived opportunity in their Devils mind? Or was this part of a bigger problem of economic and healthcare attack on our country. To unravel this mystery, we decided to begin by systematically conducting a survey of our fellow oncologists to identify whether this problem existed and if so what was its magnitude. This was a simple online survey (via encrypted communication to maintain confidentiality) among top medical oncologists of India asking them three simple yes / no questions. (Table 4) (13)The questions were regarding their personal experience of exposure to information and current status about "generic copies" of oral high end oncology drugs (like osimertinib andafatinib) in India. The answers were analysed after ensuring that duplicates (if any) were removed.Those who said yes to question three were contacted personally to find out further details. We did an internet search to identify whether high end anti cancer drugs were being offered by anyone online as generic versions. When we identified specific names of companies providing such medicines, we visited their websites to document details of the company, the products they were offering and other details they had placed in public domain. We also contacted colleagues in Bangladesh and Sri Lanka to help us understand the ground realities within these countries and to verify information available online. One of us even had a whatsapp conversation with +880 1713-090062 , a number being used by person who introduced himself as Mr Anwar doing digital marketing for Everest Pharma of Bangladesh. We sought specific details to ascertain the authenticity of the company he represented as well as the medicines being offered.

Table 1: Oncology & Hematology drugs that received regulatory approval from DCGI in 2017 and 2018

Sr No	DCGI Approval (India) *
1	Alectinib
2	Carfilzomib
3	Dabrefenib
4	Midostaurin
5	Netupitant + Palenosetron
6	Nilotinib
7	Nintedanib
8	Nivolumab
9	Trametinib
10	Olaparib
11	Osimertinib
12	Pomalidomide
13	Ribociclib/Palbociclib
14	Treosulfan

These medicines were approved by US FDA earlier; Indian approval is later lags behind in approval due to the stringency of our regulatory requirements

Result

We received a total of 99 unique answers. The answers are shown in Figure 1. The 41 resoondentswho said yes to question three and were contacted personally to find out further details. Of these, 22 replied with details, 12 oncologists did not reply and the remaining 7 said they did not remember who had contacted them. The 22 replies included names and/or phone nos of people providing such medicines or instances of unknown persons contacting the doctors via landline, WhatsApp and Facebook (Figure 2). We were also able to obtain inages of medicine packs provided to oncologists by patients (Figure 3). Most (19/22) of the oncologists contacted were practicing in Metro cities and the remaining three were from tier two cities. Other novel marketing strategies that the surveyed oncologists came to know from their patients and other colleagues included contacting potential patients directly via posts on social media, one to one conversations through medical shops outside cancer hospitals and even providing a "second income" opportunity to medical representatives of pharma companies. Our internet search identified several companies offering high end generic anti cancer drugs which were still under patent protection. Figure 4 is a screen grab of google search for crizotinib generics from bangladesh. It clearly shows at least four sources providing generic crizotinibinlcuding Beacon Pharmaceuticals Ltd of Bangladesh. Similar search results were obtained for other high end oncology and hepatitis oral medications. We visited the websites of shortlisted companies from

Figure 3: Images of packs provided by patients (in India)

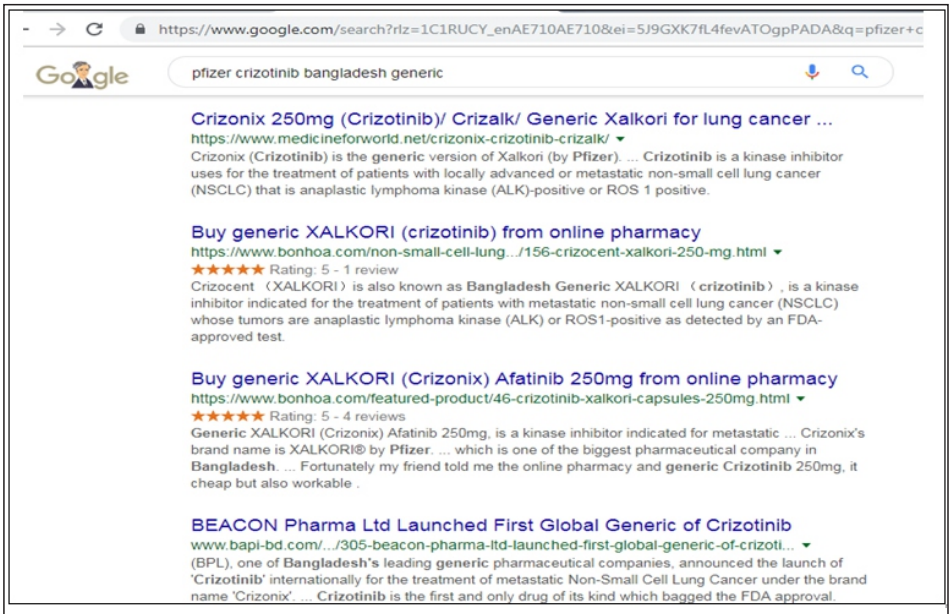

Figure 4: Google search of "PFizercrizotinibbangladesh generic"

Table 2: Oral medications approved by US FDA for treatment of Viral Hepatitis

Oral drugs for Hepatitis B			
Brand Name	Generic Names	Manufacturer Name	Indication
Baraclude	Entecavir	Bristol-Myers Squibb	chronic hepatitis B virus infection with evidence of active viral replication
Epivir HBV	Lamivudine	GlaxoSmithKline	chronic hepatitis B associated with hepatitis B viral replication and active liver inflammation
Hepsera	adefovirdipivoxil	Gilead Sciences	chronic hepatitis B in patients â‰¥12 years of age
Tyzeka	Telbivudine	Novartis	chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease
Vemlidy	tenofoviralafenamide	Gilead Sciences	indicated for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease
Viread	Tenofovir	Gilead Sciences	chronic hepatitis B in adults.
Oral drugs for Hepatitis C			
Brand Name	Generic Names	Manufacturer Name	Indication
CoPegus	Ribavirin	Roche	use in combination with Pegasys or with Roferon for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha
Daklinza	Daclatasvir	Bristol-Myers Squibb Company	an NS5A replication complex inhibitor is indicated for use with sofosbuvir for the treatment of patients with chronic HCV genotype 3 infection. Sustained virologic response (SVR) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving this regimen. The recommended dosage of DAKLINZA is 60 mg, taken orally, once daily in combination with sofosbuvir for 12 weeks. DAKLINZA may be taken with or without food.The optimal duration of DAKLINZA and sofosbuvir for patients with cirrhosis has not been established.
Epclusa	sofosbuvir, velpatasvir	Gilead	a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection -without cirrhosis or with compensated cirrhosis or with decompensated cirrhosis for use in combination with ribavirin
Harvoni	ledipasvir/sofosbuvir	Gilead	a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.
Incivek	telaprevir	Vertex Pharmaceuticals	in combination with peginterferonalfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C (CHC) in adult patients with compensated liver disease, including cirrhosis, who are treatment-naÃ¯ve or who have been previously treated with interferon-based treatment, including prior null responders, partial responders, and relapsers
Mavyret	glecaprevir and pibrentasvir	AbbieVie	• is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 6 infection without cirrhosis
			• with compensated cirrhosis (Child-Pugh A).
			• indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both
Olysio	simeprevir	Janssen Pharmaceuticals	for the treatment of chronic hepatitis C (CHC) genotype 1 infection as a component of a combination antiviral treatment regimen
Rebetol	ribavirin	Schering	use in combination with Pegintron for treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age
Sovaldi	sofosbuvir	Gilead Sciences	for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen

Bangladesh (Everest, Beacon, Incepta, SP labs and Indeed), Sri Lanka (Lucius Pharmaceuticals) and India (TherdosePharmaPvt Ltd Co). Everest Pharmaceuticals Ltd (https://www.everestpharmabd.com) had corporate (Dhaka) and factory (Narayanganj) address were both of Bangladesh (14). Their website offered and had images of finished medicines in sale packs for 6 hepatitis medicines and 8 oncology medicines that were still under patent protection. On whatsapp Mr Anwar, Everest Pharmaceuticals Ltd, Bangladeshhad contacted several oncologists in India as well as patients using phone no +880 1713-090062 and offering good unique molecules. Messages and images of medicines offered by him are shown in Figure 2 and 3. Theseimages showed that quality of sale package boxes and the printing on them seems to be of high quality. It also had batch number, manufacture date and expiry date. When we tried to verify their medicine product number on their website, the message was "Wrong Code". We had a whatsapp conversation with Mr Anwar on +880 1713-090062. He claimed to have worked with Beacon earlier for 10 years and having a total of 18 years of experience in the field. He did not give answers to specific questions regarding whether their "good unique molecules" were sold in Bangladesh, did they have licence from Bangladesh drug authorities for the same. There was also no evidence or publication that we could find of any testing of the products' quality, PK/PD studies in healthy subjects or clinical trials in human patients. We called our oncology colleague in Bangladesh. His answer was that these medicines are not available in Bangladesh at all. They have also not been approved by their drug authorities. Lucius Pharmaceuticals website (http://www.luciuspharmaceuticals.com) gives address as No. 68/186, Talakotuwa Garden, Polhengoda Junction Colombo – 05 (15). We looked it up in google maps and found instead, Ilma International Girls School at that location. When we investigated further by asking a Sri Lankan colleague to physically visit the address, no such company could be found. When we contacted the phone number (+94112358489) listed on their website, it was answered by a bank. Emails to their official email address

Table 3: Hepatitis Drugs approved by CDSCO, DCGI in India (2015 to 2018)			
S.No	Name of drug	Indication	Date of issue
1	Sofosbuvir 400 mg +Velpatasvir 100 mg Tablet	Chronic Hepatitis C virus, Genotype 1,2,3,4,5 or 6 infection without cirrhosis or with compensated cirrhosis AND with decompensated with chronic for use in combination with Ribavirin.	04.05.2017
2	TenofovirAlafenamideFumarate bulk & 25 mg Tablets	Chronic Hepatitis B virus infection in adults with compensated liver disease	10.11.2017
3	Sofosbuvir Tablet 400 mg	In combination with other medices for chronic Hepatitis C (CHC) in adults	13.01.2015
4	Ledipasvir (90mg)+ Sofosbuvir (400mg) Tablet	Chronic hepatitis C (CHC) Genotype 1 infection in adults	08.12.2015
5	DaclatasvirDihydrochloride bulk & Tablet 30mg/60mg	With Sofosbuvir for chronic hepatitis C virus (HCV) genotype 3 infection	14.12.2015

Table 4: Survey questions asked to Senior Medical Oncologists across India			
Sr No	Question	Answer Options	
1	Have you experienced your patient discussing, asking questions regarding or purchasing generic/ copyoral medicines like osimertinib or afatinib?	Yes	No
2	Was such a generic/ copy drug supplied to them through their government supported or funded scheme (eg ECHS, CGHS, ESIS, etc).	Yes	No
3	Have you been contacted by "marketing" person willing to provide such generic copy imports to patients inside India?	Yes	No

(luciuspharmaceuticals@asia.com) remain unanswered (15). TherdosePharmaPvt Ltd Co website(http://www.therdose.com) whose address is Mumbai (16). Its website shows specialty products including dasatanib andsorafenib. However it stated it is only a R&D 100% export oriented company and does not sell any medicines under their name within India.

Disucssion

We will restrict the discussion to only the aspects directly related to generic medicines and especially fake medicines. It is estimated that, in India, about 100 to 125 patients are consuming"generic"copies of osimertinib/ afatinib alone. Even at a conservative estimate, this means that in the year 2018, 1200 patients were exposed to fake generic medicines that put their lives at risk. It is said that between India and China this grey market is as big as Rs 500 Crores per month. The Bangladesh story is quite shocking and a big eye-opener. Bangladesh has many pharmaceutical companies like Square and Beximco Pharmaceuticals who seem to be genuine and not involved in fake medicines. Of interest regarding fake medicines supplied inside India are Everest, Beacon, Incepta, SP labs and Indeed. These claim to be providing high end oncology medicines at a fraction of the cost that the innovator company is selling for. Is the Everest Pharmaceutical Ltd and Mr Anwar's story anexample of exploiting the grey market with false promise. They are blatantly targeting doctors and patients from across the border using WhatsApp, email, social media, etc. The package boxes and their printing are of good quality and can entice even the educated into believing that its contents are also produced with care. However the batch numbers and barcodes do not followinternationally accepted norms of country code, produce code, batch no or other details.When it is coupled with the fact that there is no evidence of any testing in humans, no drug authority/ regulatory approval, not marketed within Bangladesh itself, no official presence in India, there is a serious question on whether the package contains simply an inert powder or, still worse, chemicals of questionable quality and activity that could potentially be lethal. The Lucius Pharmaceuticals, Sri Lanka is equally intriguing. The address on the website is wrong. The phone number is incorrect (15). There is no answer to emails sent to them. So where are their medicines manufactured? Where is their office? Who is behind this fraud? Why is this hoax allowed to continue to be propagated? Why are Sri Lankan authorities not taking any action? Oneoncologists said that his lung cancer patient, surreptitiously taking such generic osimertinibactually seemed to benefit. This is intriguing. How can this happen? Besides the placebo effect and subjective feeling of being better, could there be another reason? We can only speculate on the answer. One possibility is that the “manufacturers” might be using active ingredient supplied by companies like Sigma Aldrich (17). Such intermediaries are only meant for laboratory use and are not cleared for human consumption. Unethical companies might be using this raw material to manufacture fake generic medicines that are not fit for human consumption– let alone having been tested as required by drug authorities across the world. Questions also remain about active ingredient, preservative, stabilizer, filler or impurities these fake generic “medicines” contain. All that we know is that thousands of Indians are having to risk their lives by being exposed to such unlicensed, untested and unverified fake generic “drugs”. It may even be that deaths have occurred either due to toxicity or due to the underlying disease growing in the absence of real medicines(18,19). Who will protect and save our patients?

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