The growing menace of fake counterfeit and substandard medicines from across our borders

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Normally editorials are written by one or two authors. However the article written by Parikh et el in this issue of IJMS, is so serious for our country, that the editorial team decided to invite experts from across India to put their heads together and this is its outcome(1). Manufacturing of fake, spurious or substandard medicinal products is a major fraudulent activity that puts patient lives at risk and is therefore a major public health issue. There are two specific terminologist that we need to understand. NSQ stands for not of standard quality and SFFC means spurious/falsely-labeled/falsified/counterfeit drugs (2,3). Either of them can lead to treatment failure or even death. In India, the updated Drug and Cosmetic act of 1940 specifies poor quality drugs as misbranded, spurious and adulterated drugs under sections 17, 17A and 17B, respectively (4). Further the Central Drugs Standard Control Organization (CDSCO) 2008 amendment has categorised not of standard quality (NSQ) products as follows. Category A incorporates spurious and adulterated drug products; these conceal the real identity of the product or formulation and may deliberately be similar to well-known brand. These products may or may not contain active ingredients and are usually produced by unlicensed manufacturers. Category B include grossly substandard drugs in which product fails thedisintegration or dissolution test and where active ingredient is found to be below 70% of stated value. They may also fail other criteria for purity and sterility. Category C is for drugs with minor defects like emulsion cracking, change in formulation colour, small variation in net content, sedimentation in clear liquid preparation, failing of weight variation test, spot or discolouration on product, uneven coating, presence of foreign matter and labeling errors. A recent incident of cough syrup mislabeled as providone iodine falls into this category (5) It is therefore clear that fake, substandard or spurious drugs are a major issue that can result in life threatening situation, financial loss for consumer and loss in trust on the health system. No wonder there was discussion to have the death penalty for such crimes (6) Fake, counterfeit and substandard medicines are a global problem. Usually it is India that bears the brunt of most allegations. In fact there was an incidence where Africa alleged that India had supplied fake medicines, when in fact Chinese company had manufactured them and labeled then as made in India! Fortunately the truth finally prevailed when the National Agency for Food and Drug Administration and Control (NAFDAC) of Nigeria issued a press release stating that a large consignment of fake anti-malarial generic pharmaceuticals labeled as "Made in India" were, in fact, found to have been produced in China(7), It is estimated that fake medicines form 3% of Indian domestic market and 5% of Bangladesh domestic market. (8,9). In fact, the fake and counterfeit drug market In India alone could be as high as US$ 10 billion(10). This problem is not limited to these two countries alone. For instance, in 2012, 213 people died in 10 days in Punjab Institute of Cardiology, Lahore, Pakistan – in the same ward. Samples of an anti-hypertensive drug taken by all these patients were tested in an independent lab in the U.K. and revealed that 14 percent of the antimalarial was "mistakenly" added to the anti-hypertensive drug, and responsible for their deaths (11). And in China, 2-3 lakh people die every year due to counterfeit or substandard drugs (12) Now let us look at the situation related to Bangladesh. A google search for "fake medicines from Bangladesh" 2018 resulted on 99,80,000 hits. According to 2017-18 report of the DGDA, Bangladesh Government, they have filed 221 cases, imposed fines of Tk 163,57,000 and seized illegal medicines worth Tk 42,60,170 in one year (13). At Bangabandhu Sheikh Mujib Medical University, as many as 2,700 children died between 1982 and 1992, as a result of renal failure after taking a particular syrup for minor ailments. Dr Hanif had that syrup tested in a govt lab and found it positive for diethylene glycol. Public Prosecutor Shaheen Ahmad Khan and Dr Hanif worked tirelessly to bring the perpetrators of the crime to courts and finally on July 22 2014 ten years' rigorous imprisonment was pronounced for the director of Adflame, Helena Pasha, its manager Mizanur Rahman and its production officer Nrigendra Nath Bala. They were also fined Tk 2,00,000 each under the Drug (Control) Ordinance of 1982 (14). The Rapid Action Battalion of Bangladesh found a factory producing 30 types of fake drugs (including for cancer) using names of drugs of foreign companies since five years. They were regularly supplying to Apollo

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Hospitals in Dhaka Tk 300,000 for selling in their pharmacy 30 types of counterfeit drugs (15). Fake versions of medicines of a famed local drug company, usually used for chemotherapy of cancer treatment, were also being manufactured elsewhere and smuggled via commercial flights (16). In another instance, 40,000 strips of three kinds of counterfeit anti cancer drugs manufactured in China were mislabeled as electronic equipment and caught by Bangladesh customs (17). Yet another evidence was obtained when a local Bangladeshi was converting about 2 million Taka into 200,000 Yuan (RMB) from China for medicines (18) Government officials inspected 193 pharmaceutical companies in Bangladesh and categorized them into those who produced drugs in compliance with the Good Manufacturing Practice (GMP) and those that did not. A total of 62 companies fell into the non-compliance category.(19). Such unscrupulous activities are crafted by piggybacking and misusing the well intended exemption granted to Bangladesh from patent protection for pharmaceutical medicines (Doha Declaration of WTO on the exemption of TRIPS to 49 LDC countries including Bangladesh and subsequent extension of this opportunity till 2033) (20) While washing their hands off counterfeit drugs in the lucrative Indian Market, Bangladesh companies have found creative ways to deny wrongdoing. For instance Beacon Pharmaceuticals said that of the more than 95% of counterfeit oral lung cancer medicine sold in India, only about 5% of the product was made by them (18). They also issued a notice in clarifying that they had no authorized distributor in India and that they were initiating a third party survey to obtain data to clear their name of wrongdoing. At the same time, Bangladesh pharmaceutical companies openly make statements like, Ëverest launches the first global generic Olaparib for ovarian cancer (for export only) (Figure 1) (21). If it is for export only, who is importing them remains a mystery. Now let us address the issue of the patient being hoodwinked. Fake medicine produces are getting smarter. The "medicines" they sell are packaged craftily. The printing quality and pack "authenticity" is enhanced by using barcodes, batch numbers, manufacture date, expiry date and even holograms. Today, the best way to check for genuineness is to verify the batch code with the manufacturer or ensure that the barcode is inspected for meeting global standards. Barcoding for healthcare is supposed to follow universal GS1 standards (22).This is crucial since medicines are applicable across political borders. This international system allows verification right from the manufacturing through all the steps in the supply chain and going right to the patient purchasing the medicine from retailers. Coupled with the global trade item number (GTIN), fake generic medicines should be easy to identify. We need to make the general public aware about how to understand the GS1 and GTIN for spotting counterfeit medicines (22). Verifying via the DCGI and CDSCO website is another option (4). Let us now look at the offences committed under Indian laws and possible punitive action. Besides the Drugs and Cosmetics Act (eg any product that claims medical benefits should be backed by adequate safety and clinical data and be ratified by drug regulators), are there other regulations that have been violated? The Indian Information Technology (IT) Act is in operations since October, 2000.(23). Its prime purpose is to provide the legal infrastructure for e-commerce in India – and Parikh et als paper shows the use of whatsapp and internet to solicit patients and customers. This act covers electronic records and contracts expressed through electronic means of communication. It was amended in December 2008 so that police officers of the rank of Inspector and above can take action. Interestingly sending offensive messages is also a crime under this act. It defines this as sending … false information. To note is the fact that its jurisdiction is not only the whole of India, but also to offences committed outside Indian territory, provided the offence involved a computer (includes smartphone), computer system, or computer network located in India. The Indian Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954 prohibits advertisements of drugs and remedies that claim to have magical properties - to cure, diagnose, prevent or mitigate a disease in humans or animal (24,25). It gives drug regulatory departments and police the right to take action against misleading advertisements. The rules further clarify this as "directly or indirectly giving a false impression regarding the true character of the drug" OR "false or misleading claim in any material particular" (the whatsapp and facebook posts by Anwar of Everest Pharma will come under this definition) (26). In fact, the FDA office of Nagpur are alone has registered 25 cases of drugs and magic, and 11 cases of drugs and cosmetics in one year alone (27)

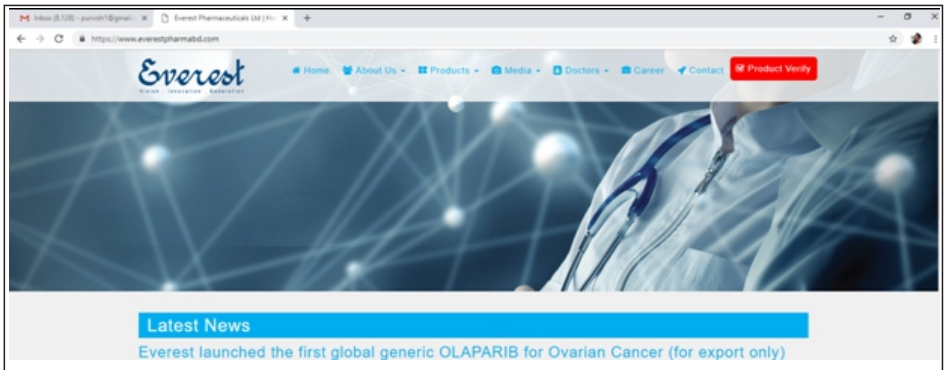

Figure 1: Everest Pharma website declaring the availability of first global generic olaparib for export only

In conclusion, we would like to quote the data from a study testing 31 branded generic docetaxel injections manufactured from 14 countries in Asia, Africa, the Middle East and Latin America (28). Of these 21 generic docetaxel formulations had less than 90% of stated active ingredient and 23 contained impurities amount to more than 3.0% of the vial content. These included an alarming 33 different types of impurities not present in the original innovator molecule. And these are branded generics marketed after careful testing and approval by their respective countries' drug authorities. Imagine what would be the status of unauthorized, unapproved, illegally imported fake "generic medicines" Using raw material meant for laboratories and passing it off as real medicine is a serious crime. Who will protect our patients? If a patient ever asks regarding cheap medicines from the grey market, it is our duty to categorically tell them not to risk their lives by purchasing so

called medicines that have not been tested in human beings or licensed by competent drug authority. We need to tell them what we would do for our family. Our country also needs to do everything in its power to ensure that such fake "generic medicines" do not enter India. The final question begging to be asked is whether this is a deliberate economic cum healthcare war being waged from across our borders?

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