"ME-TOO" DRUG REVOLUTION: A PRODUCT OF REGULATORY IMPROPRIETY

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REVIEW ARTICLE

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ABSTRACT

Amidst all the brouhaha, often the regulatory agencies, for instance the United States Food and Drug Administration's (US-FDA) role in bringing about what is being so cleverly termed as the 'me-too drug revolution', has escaped scrutiny. Bearing in mind the pre-eminent status of USFDA in regulatory world, it would be useful to examine some of their strategies that have helped facilitate this revolution. The surge seen in the approval of me-too drugs can be attributed to a regressive policy of evaluating a new drug against a placebo or using non-inferiority trials, which in turn has often allowed an easy rite of passage for the me-too drugs. So has the Prescription Drug User Fees Act (PDUFA) by allowing rapid approval of drugs. However, this has not necessarily translated into safer drugs! Further, advisory committees that are rife with conflicts of interest, a legally weakened status bestowed upon the USFDA and a no-holds barred approach adopted by the industry towards direct to consumer advertisements (DTCA), has allowed me-too drugs with dubious safety profiles to flourish in the markets. It has been suggested on many fronts that by undertaking measures, for instance an increment in the US congress appropriations to the US-FDA, vesting punitive powers in the agency to rein in the errant pharmaceutical companies as well as dealing with the conflicts of interest within the advisory committees could go a long way in preventing the undue and potentially dangerous proliferation of me-too drugs.

Keywords: PDUFA, me-too drugs, USFDA, DTCA, Advisory committees.

INTRODUCTION

Over the years, questions have been raised over the scientific and moral validity of expending a huge amount of resources and time for producing 'me-too drugs', which represent minuscule or sometimes, nil improvements on existing innovator molecules. In all the hue and cry, the contribution of the regulators, especially the US-FDA, in the proliferation of me-too drugs, has often slipped under the radar. It is after going through the whole rigmarole of clinical trials that the drugs make it upon the steps of the regulators for their blessing. The drug approval process is akin to a 'high stakes poker game'. With a single 'aye' or 'nay' of the regulators, years of toil and billions of resources could either bear fruition or go down the drainage. Hence, bearing in mind the high stakes involved here, pharmaceutical companies, over the years, have attempted to arm-twist the regulators into toeing their line using various 'innovative' tactics. Though these strategies are applicable to approval of all products and the discourse over each can run into sheaves of papers, we have tried in this manuscript, to put forth very succinctly, as to how a few of these 'creative' approaches (Fig. 1) have helped in producing what is now being termed as a 'me-too drug revolution' in United States of America (USA).

Clinical Trials: A Public Relation Exercise

Clinical trials are a powerful, yet an extremely pliable method of building up a drug's prospects. Ranging from manipulation of their designs to selective publishing of the positive results, the trials offer a plethora of opportunities to the drug companies, to inject in the new drugs, a fictive sense of transcendence over the existing molecules. At the study design level, the US-FDA policy of evaluating a new drug against a placebo and not the existent standard drug allows an opening to the companies to hype up their me-too drugs. (1) It also lays more emphasis on drug being

efficacious rather than evaluating the drug on the basis of its overall effect on the human system. Cerivastatin is a case in point. With its increased potency and its efficacy being compared to placebo in clinical trials, (2) it obtaining US-FDA's blessing was a formality. However, Cerivastatin's safety issues got buried under all the hype and hoopla about its increased efficacy. Its adverse safety profile came to limelight only when the manufacturers could not hold a lid on the number of cases with harmful adverse effects. (3) In addition, the use of surrogate markers as primary endpoints may have aided in rapid approvals as compared to the primary endpoint as seen in the case of me-too drugs like Encainide. (4) But it has also opened up the layman to various health hazards as evidenced in case of Encainide. Also, the trials for me-too drugs are designed with an aim of minimizing the detection of adverse reactions of the investigational product. (5) Hence, often, questionable practices seep in, for instance - choosing sites where the research workers are on the company's payroll as well as hobbling the comparator product by administering at the wrong doses in order to generate more adverse reactions and decrease the efficacy of the comparator standard drug with respect to the investigation product.

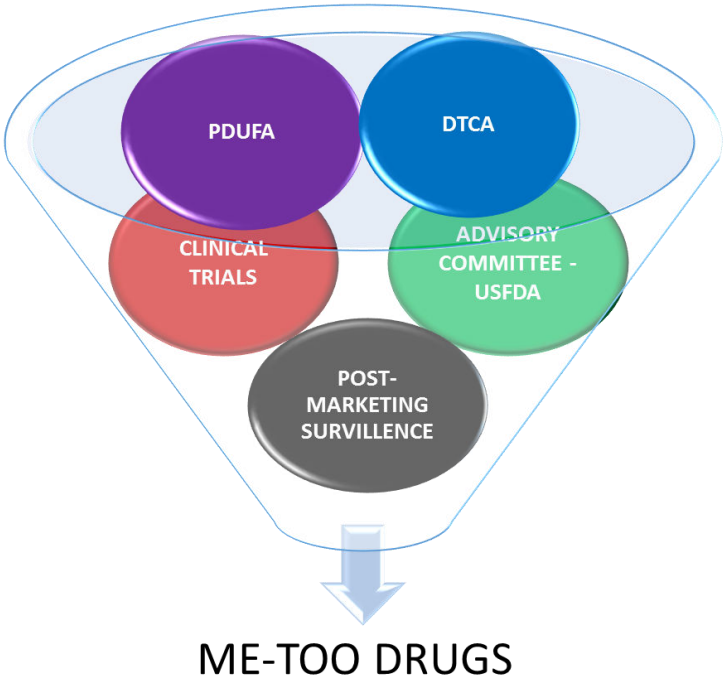

Figure 1: Contributory factors for me-too drugs proliferation

At a data collection and analysis level, many instances of data fabrication by the investigators, have come into limelight. Telithromycin is a case in point, where the investigator of a critical trial 3014, Dr. Maria 'Anne' Kirkman Campbell pleaded guilty of data misrepresentation. (6) Further, the sponsors have often been found to be guilty of weeding out the results that may not reflect favorably upon the drug in question as was seen in this case. Sanofi-Aventis®, as revealed later was aware of Dr. Campbell's misdeeds, but preferred to turn a blind eye to it. (7) Oft, the big pharma companies, ends up paying off academicians from prestigious institutes, in order to get their rubber stamp approval and provide scientific legitimacy to their trial results. This was clearly in evidence in the case of the selective COX-2 inhibitor, Rofecoxib, where multiple publications in some of the most prestigious journals like Annals of Internal Medicine, (8) New England Journal of Medicine (NEJM) (9) and others have waxed lyrical about the benefits of these drugs. Nonetheless, when reports of its cardiovascular adverse outcomes emerged and the lawsuits kept on piling up, the

authors failed to take full responsibility of the trials and the unseen hand of Merck® behind these publications came into the limelight. In light of the flagrant violation of the trial ethics and integrity on display, it has been astonishing to see the US-FDA take a backseat and allow things to carry on as they were. Despite possessing the power to pull up a company if it suspects any foul play or at the very least, making any data about possible health hazard posed by a product, known to the public, US-FDA chooses not to act thus. This is likely referable to the fact that the US-FDA at present holds 2 clients – the industry and the American public, with the industry being much higher in the pecking order.

Prescription Drug User Fees Act (PDUFA): A form of Legitimised Pay-Off

A controversial legislation, introduced in 1992, amidst a lot of clamor over the demand for faster drug approvals; it furnishes the most glaring example of complicity between regulators and the industry. It has been noted in a recent study that over the period of 1987-2014, the proportion of drugs arriving through expedited drug development and review, have consistently increased at a pace of 2.6% per year. (10) This exhaustive study concludes that the expedited drug development and review program has progressively expanded its scope of application. Interestingly, the authors state that it is not the innovator molecule, rather the me-too drugs that have been responsible for this surge seen in the drug approval rate. It would appear that in the guise of user fees that keeps increasing in its scope of application every 5 years, the big pharma corporations have been extorting the regulators into rapidly approving drugs with no or little incremental innovation and dubious safety records. Experts have often berated the expedited drug development and review processes, for its lax treatment of drug safety evaluation. The increased burden, of adverse drug reactions (ADRs) associated hospitalizations and mortality, the high number of drug label warnings, black box warnings and withdrawals can be tentatively attributed to faster drug approvals. (11) Withal, the US-FDA has generally taken on the character of a passive observer in the schema of things. The regulators' reluctance in pulling up various manufacturers with respect to drug safety issues probably stems from the fear of an impending interruption in the cash flow via the PDUFA into the agency, if punitive actions are taken against offending companies. (5) So much for the US-FDA being the watchdog of the American health care sector! Besides, expedited approvals have been beset with controversies limited not just to safety issues, but also involving efficacy as well. For illustration, the disappointment with Gemtuzumab, failing as a therapeutic agent against AML, despite having been sanctioned under the expedited approval process in 2000, forced its withdrawal ultimately in 2010. (12) Further, major fallout of an increased proportion of me-too drugs being approved via expedited review, would be the mis-allocation of resources that were primarily intended for truly novel drugs for the treatment of serious conditions. A glaring example of this can be understood in the manner Bimatoprost a prostaglandin analog (a me-too drug) had priority status as a drug for the purpose of cosmetically enhancing eyelashes / to treat hypotrichosis in 2008. (13) Though, PDUFA has never been categorically linked to the me-too drug revolution, it is the truth that nobody desires to say out loud, as both the regulators and the big Pharma stand to lose if any remedial measures are undertaken to rectify the situation.

US-FDA Advisory Committees: An example of administrative ineptitude

Advisory committees, come into the picture, if the product in question is supposedly a controversial one. These committees, though nobly intended, have been implicated of being in serious breach of financial conflicts of interest. This renders the virtuous thought of a diverse and objective scientific discourse, completely moot. The manner in which many initial vociferous voices of dissension, often capitulate at the time of voting, resulting in lopsided voting patterns and regulators' passivity during the whole shenanigan, only adds weight to the notion of US-FDA being partners in crime with the industry. (14, 15) The leading nature of the queries that are voted upon in these meetings opens up the regulator's association with the corporation for scrutiny. (14) Often the regulators and committee members have candidly acknowledged being

under tremendous pressure to either shape up or ship out! (14)

The lack of statistics limits us in our endeavor to supply evidence of the impact of advisory committees on me-too drugs. Still, a glance through recent history reveals me too drugs of being the greatest beneficiary of a convoluted advisory committee, as brought to light by the events concerning Rofecoxib in 2005. Rofecoxib, a follow-on drug to Celecoxib (selective COX-2 inhibitor), was under the microscope following large scale reports of cardiovascular adverse outcomes with its administration. Post its withdrawal from the market, a US-FDA panel comprising of two of the standing advisory committees, voted it back into contention with a 17-15 vote count. (16) But all hell broke loose, when in the subsequent weeks, 10 of the members of the USFDA panel were found to be in serious breach of financial conflicts of interest. (17) In the more recent times, over 12,000 litigations have been filed against 4 combined oral contraceptive pills introduced by Bayer AG®, by 2012. (18) These contraceptive pills containing a new steroidal progestin, Drospirenone, had been given the nod of approval by an US-FDA advisory panel. However, sensational revelations by the Washington Street Journal and the British Medical Journal (BMJ) revealed 4 members to be in either financial or intellectual conflict of interest. (19) Thus, the role of an advisory committee with an iffy moral compass stands to gain more attention in case of a me-too drug, given that there is a high likelihood of serious lacunae with respect to the conduct of their trials and safety evaluation in both pre- and post-approval stages.

Post-Marketing Surveillance: A Potent tool rendered impotent by regulators

As per the study mentioned earlier, a huge chunk (508/774) of the drugs approved by US-FDA through expedited development and review program from 1987-2014, pertain to the me-too class. (10) The swiftness of the drug approval, combined with the mandate to conform to the deadlines, often does not allow for a thorough but lengthy safety assessment of a drug; hence the demand for a substantial post-marketing surveillance system. The ADR reporting system in its present shape in the USA resembles a self-monitoring model. In light of a majority of the adverse drug reports (~90%) arriving from the companies, it seems that the industry is reporting against itself. (20) This is a recipe for disaster as it is unrealistic to expect the companies to jeopardize their investments by calling for mitigations in its scope of sale. The objectivity of the whole system is further compounded by the vagueness surrounding the definition of adverse drug reactions and the tipping point for undertaking remedial measures. (21, 22) Me-too drugs have been the beneficiary of this conflict of interest again as evidenced in the case of Cerivastatin. Trial results revealed that Bayer AG® had been aware of serious adverse drug reactions with Cerivastatin, since its approval. (3) Nevertheless, by withholding data about these adverse drug reactions, it had reaped benefits from the sale of the drug and continued to jeopardize human lives.

Additionally, post-marketing studies, too, have proven largely ineffective in bringing drug's adverse reactions to light. A whopping 71% of the open commitments (899/1259) for post-marketing studies had not been complied with up to 2006. (23)

The lack of statutory status and willingness of US-FDA to monitor and enforce these studies had allowed the big pharma to continue in its merry ways. Recent amendments to the Federal Food and Drugs Act (FFDA) too, have left the door open for the big pharma to get their toes in. The subjectivity associated with statements - "When the decision to require a post-marketing study or clinical trial is based on scientific data deemed appropriate by US-FDA, including information regarding chemically-related or pharmacologically-related drugs" gives the companies the little wriggle space that they bare always looking for. (24) In addition, whenever issues with respect to drug safety crops up, the practice of referring back the drugs to the same people who had been involved in the approval of the drug in the first instance, allows the issue of conflict of interest to rear its ugly head up again. Further, the organizational reputation of US-FDA disparages its workers from revisiting previously approved drugs; hence the step-brotherly treatment to drug safety review in comparison to new drug approvals.

Direct-To-Consumer advertisements (DTCA) : Applying the finishing touches

An incident that comes to mind with regards to the pharmaceutical companies' under handedness in DTCA is the case of Lipitor®. Me-too drugs like Lipitor® are a classic case of 'old wine packaged in a new bottle'. Despite it being the 5th drug in the long list of statins, with each statin being a blockbuster drug, it turned out to be the largest selling product from 1996-2012. (25) Bereft of any serious therapeutic innovation, it does not come as a surprise that Pfizer Inc. ® ended up spending US$ 1.43 billion in its DTCA. (26) In light of the vivid impact a television advertisement can have on the human psyche, Pfizer tried to exploit this using a commercial aired 2006 onwards that was founded on lies. It is apposite to note that of the US$ 258 million spent in advertising for Lipitor® since 2006, the majority had gone towards building this advertising campaign. (27) In the commercial, Robert Jarvik, the supposed inventor of the 'artificial heart' and a 'distinguished doctor', harps on the lipid lowering property of the drug. Further, to provide his stamp on the drug's efficacy, he goes on to row across a lake. Nevertheless, it was sensationally revealed afterwards that Robert Jarvik was not a licensed physician. There were some serious doubts over the claims of him being the inventor of the artificial heart too. Further, the 'distinguished doctor' had never rowed before in his lifetime. (27) A look at the last decade and a half's list of drugs with the highest DTCA expenditures reveals that the majority had belonged to the me-too class. In 2001, the top honors went to Vioxx®, Celebrex®, Nexium® and Allegra®; all of which were follow-on drugs to the innovator molecules in their division. (28) Fast-forwarding to 2015, me-too drugs like Lyrica®, Eliquis® and Cialis® still hog the lion's share of the most promoted drugs via DTCA. (29) Over the years the various pharmaceutical companies have been found to be in breach of the established guidelines for DTCA, be it promotion of Vioxx® and Celebrex® as super-aspirins (30) or marketing Nexium® vigorously as being superior to Prilosec® despite the absence of any evidence to suggest otherwise. (31) In light of these frequent transgressions, one is often forced to wonder as to what the role of US-FDA could be in all of this!

Alas, it appears that over the years, by progressively loosening its hold over the DTCA, US-FDA has now been left to play catch-up. The relaxation of policies pertaining to DTCA was primarily brought about in an atmosphere, where the need for increased consumer education through advertisements had been drummed up by various agencies, for instance the pharmaceutical and advertisement industry, consumer organizations and medical societies. The fact that now the pharmaceutical companies are only required to submit and not obtain US-FDA's approval of the promotional materials, hands them the license to go overboard with their drug marketing campaigns. It is only after the 'horse has bolted', that the agency can reprimand the pharmaceutical companies. Nevertheless, the lack of statutory authority and absence of any punitive powers being vested within the regulatory agency renders these reprimands often toothless. Though, pharmaceutical companies are known to comply promptly with the agency's mandate; the misleading information shown in the advertisements would have already exerted their impact within the excessive time that elapses between the dissemination of the advertisement and the issuing of the reprimand by the US-FDA. It was clearly in evidence in the case of Diclegis® (long acting formulation of doxylamine and pyridoxine), when a popular American reality television star, who was incidentally being paid by the manufacturers, endorsed this product on social media. (32) All the same, this advertisement was observed to be in serious breach of US-FDA's guidelines for DTCA and a reprimand was issued by the agency. However, in today's digital age when dissemination of information occurs within seconds, it was surprising to note that it took the agency about one month to take any action. (32) In the meantime, Diclegis® continued to reap benefits from the positive publicity that it had picked up on various social forums. Very often, the hyperbole associated with such endorsements, even within a span of 1 month, can successfully sway the consumer's opinions, even before a visit to the physician. This in turn interferes with the decision-making process of the physicians and hikes up the health care

expenditures. The above episode with Diclegis® can attest to this. Following this incident, there is an increased buzz surrounding it. Its sale is only expected to head northwards in the near future, despite it being 20 times more expensive than the generic formulations of doxylamine and pyridoxine available over the counter. (33)The short-staffing, underfunding and the bureaucratic red-tape involving the Office of Chief Counsel (OCC) in the Division of Drug Marketing, Advertisement and Communication (DDMAC) (34) has been implicated as the major contributory elements to the time lag. Thus, with the US-FDA's passivity in display, it would appear that the marketing zealots in the companies have been given a free hand to 'indoctrinate' the layman.

CONCLUSION

In light of the 'significant' role that these 'tricks of the trade' have played in ushering in a me-too drug revolution, it would make sense to abdicate these approaches. Nevertheless, we think that each of these strategies occupies a singular place in the complex relationship that survives between the US-FDA and the manufacture. The demand of the hour is that of minor tinkering of these strategies (Figure 2), and not a complete overhaul. Measures like -

• Increasing the congressional appropriations to the agency.

• Bestowing legal powers upon the US-FDA to take action against the offenders, be it in the case of drug promotion or post-marketing surveillance

• Conducting statistics seminars for members of advisory committees.

• Mandating the experts on the panel to declare their past and previous pecuniary relations.

• Keeping close tabs on clinical trials by regular visits to random sites by agency staff.

• Insisting on the superiority of new drugs over existent ones could go a long way in restoring credibility and objectivity into US-FDA's proceedings.

Unless corrective measures are taken and soon, the premier drug regulatory agency in the world could end up becoming the stooge of the pharmaceutical industry. That would be a day, when a me-too drug revolution would be the least of our concerns.

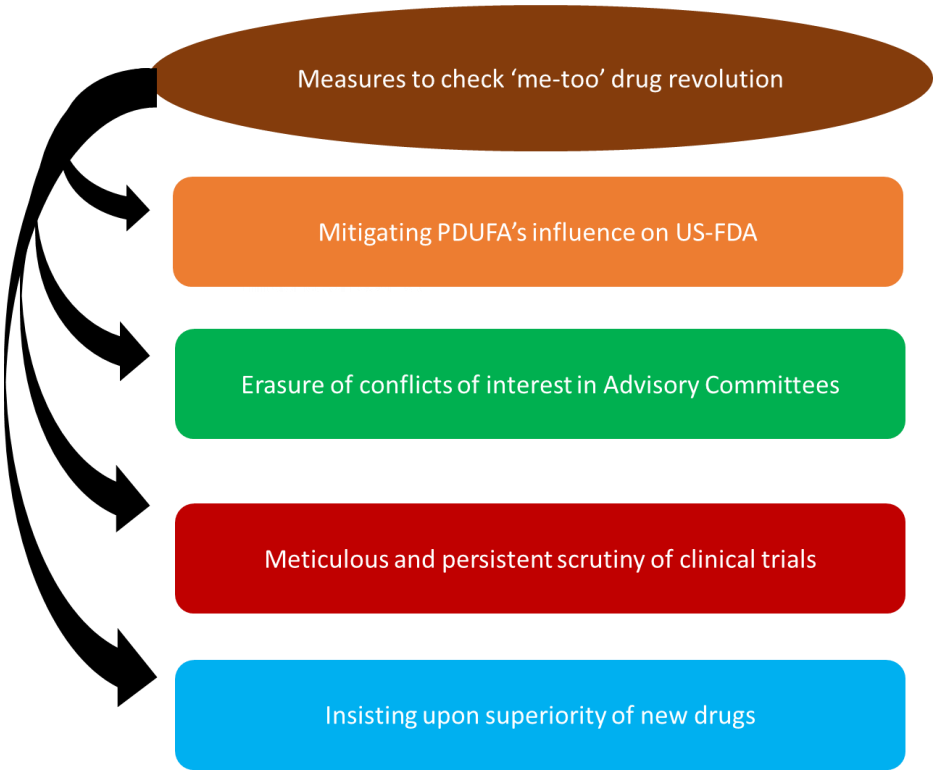

Figure 2: Potential measures to counter 'me-too' drug revolution

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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