

A Public Policy Plan to utilize the Pharmaceutical Industry and Pharmacogenomics to reduce serious Adverse Drug Reactions, develop Personalized and Individualized Therapy, and provide a Functional Map of the Human Genome

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In any type of scientific endeavor, “mistakes”, “wrong turns”, and numerous “failures” on the road to the original hypotheses, intentions, and goals occur. Learning from one’s “mistakes”, whether in life or in science, can often provide as much or more knowledge and insight to the problem at hand as the successes. Indeed, many times “failure” can set the course for a new path, with surprising unexpected outcomes, products, and new successes in ways not originally envisioned.

Adverse drug reactions (ADRs) are a serious public health problem. Serious adverse drug reactions represent the sixth major cause of death in the USA, are the main reason for post marketing drug withdrawal, and represent billions of US dollars in costs every year in all developed countries. These ADR’s essentially represent the “failures” of the pharmaceutical drug development process to provide a drug that will work safely in all cases. Small clinical trials that occur during drug development can never mimic the huge post marketing “clinical trial” that naturally occurs when a drug is unleashed on the general population. Even with the best of studies, scrutiny, and intentions, there is simply no way to predict how a single drug will react in all people in all cases. So this may be necessarily how the system has to work.

However, currently, the responsibility of the pharmaceutical companies for the ADR’s that might occur for the most part end when the drug is brought to market. Too often it’s only when enough people are maimed or killed that lengthy legal action or the FDA will result in increased warnings or actual withdrawal of a drug from the market. There is little to no recourse available to individuals harmed by ADR’s, and the regulatory process is essentially frozen in place the day the drug is approved and put on the market. The pharmaceutical companies benefit and profit from this system while the problem continues on unabated at great cost to individuals and society. Additionally, there is little incentive for the pharmaceutical companies to get the best product out on the market. From a financial perspective, there is no real incentive for the pharmaceutical companies to look at the “failures”, to learn from them, and to improve their products. In fact, with the current system, the opposite occurs. The incentives instead are to downplay, minimize, or outright deny if possible the ADR’s as much as possible, so as to avoid culpability and possible litigation and lost profits. This results in tremendous losses to individuals who suffer from these ADR’s, in tremendous financial losses to society as a whole as a result of these ADR’s, and prevents any real scientific progress in “learning from the mistakes” from occurring.

Pharmacogenomics is a rising field providing a link between ADR’s and genetic variations within a population contributing to or causing those ADR’s. The ultimate goal of Pharmacogenomic information is to make drug and dose selection more personalized and precise, leading to improved efficacy and reduced side effects. This field is in its infancy, because although the coding map of the estimated 6.4 billion nucleotides that make up the Human Genome was considered completed in 2003, very very little is known about the actual functions of the genes that are comprised of that code. In fact, it’s currently completely unknown what over 98% of the genome actually

codes for. Mapping out the human genome is essentially useless unless we know how the genes and various mutations and epigenetic mutations affect function. Drugs that target a variety of mechanisms in the body can provide us with those answers, not only the drug “successes”, but the “failures” in the form of ADR’s as well. In fact, it’s these ADR’s, these “mistakes” and “failures” that can open the door to the new, unknown, and unexplored areas of the Human Genome. And the pharmaceutical industry can and should do their share to help provide the funding to find those answers. They have as much or more of a responsibility to become part of the solution to the problems they help create, rather than leaving government agencies and the public to pick up the pieces when ADR “failures” occur post marketing.

To this end, the following is a simplistic outline of a public policy proposal to utilize the Pharmaceutical Industry and Pharmacogenomics to reduce serious Adverse Drug Reactions, develop Personalized and Individualized Therapy, and provide a Functional Map of the Human Genome. With such a policy, everyone benefits – including the pharmaceutical companies in the long run. Additionally, such a program would not increase liability on pharma any more than already exists when it comes to ADR’s.

1. Legislation would **require** that a percentage of the profits or revenues of **every** prescription **and** non-prescription drug on the market be dedicated annually to the study of ADR’s specific to that drug. For example, 1% of the profit or revenue generated from the sales of the antibiotic “Levaquin” would be REQUIRED to be provided BY THE PHARMACEUTICAL COMPANIES manufacturing, marketing and profiting from that drug to fund research into the major adverse effects of Levaquin already stated on the drug labels. The same would be true of each of the antibiotics within that same class, ie: 1% of the profit from the sales of Ciprofloxacin would be dedicated to funding research into the ADR’s of Ciprofloxacin, and 1% of the sales from Avelox would be dedicated to funding research into the ADR’s of Avelox. The same would occur for over the counter drugs such as Advil, generic Ibuprofen, and all other drugs within the same class of non-steroidal anti-inflammatories for example. Using a percentage, rather than any fixed amount, of dollars coming from any one drug, basically insures that the most popular and widespread drugs will generate a lot of research into their ADR’s, regardless of which class they belong to. The percentage of sales of each drug would “fund itself” in terms of researching ADR’s. Although convincing the pharma industry to “give up” some dollars in this way might initially seem impossible, there are longer term benefits to pharma, including financial, with this idea.
2. An organization or agency completely independent from the pharmaceutical company’s interests, most likely governmental in nature, would exist to funnel and grant said funds to scientists and researchers on studies, also independent from the pharmaceutical industries interests. This actually may ultimately be the hardest goal to achieve, trying to create and consistently provide an independent agency whose members hopefully could not be politically bought off or influenced by the drug companies or any other interests, thereby assuring unbiased research and publishing of results.
3. Using the Levaquin example above, there is a Black Box Warning on Levaquin stating that this antibiotic can cause tendinopathies, including rupture. With this known ADR as a starting point, the independent agency would seek out, or solicit requests from, scientists and researchers who would be able to incorporate Levaquin into their existing studies on a variety of fronts related to tendon issues. Levaquin would be tested and used as a “stressor” in a variety of studies. In fact, the goals of these studies would be to actually seek out the ADR’s, somewhat similar to the software industry searching for bugs in software. The number of research studies that could be done with this one single ADR, and what could

be learned from it, can appear unlimited as each study would no doubt generate new questions as well as answers for all populations suffering from tendon issues, not just Levaquin-induced ones. Additionally, systemic factors, such as acetylcholine, glutamate, magnesium, thyroid hormone, and mitochondria, are suspected of playing a role in these Levaquin-induced tendinopathies, opening the door to discovering the connections between multiple organ systems such as brain, heart, muscle, and eyes with tendons.

4. Research from multiple specialties and a wide variety of scientists, from biochemists to molecular and evolutionary genetics to statisticians would publish their data and findings, as they do now. Most importantly, this data would be open to all, eliminating “publishing bias” when it comes to these ADR’s. The results will also no doubt open the door to new metabolic, enzymatic, biochemical, molecular, genomic, etc. pathways into disease and toxicity, spurring further and new interests in research in a wide web. New understandings on mechanisms of ADR’s and potentially how to avoid them in certain populations, prevent them in populations at risk, and treat them if they do develop will result. The pharmaceutical companies will gain in the long run, as they also utilize this openly published research as a springboard to develop new pharmaceuticals or other medical treatments.

Who would want an approach to improve drug safety for all and back a proposal such as this one or a similar one? Well for starters, just about everyone but the pharmaceutical industry. Given that virtually everyone in the US will be exposed to pharmaceutical drugs and their adverse effects in their lifetime, I think most would agree that improving safety for all is a worthwhile priority. But when it comes to Pharma, we all know their first priority is their own short term interests in retaining profits and power, with everything else a distant second. They’ll do everything they can to fight such an idea tooth and nail. They’ll say it can’t be done. They’ll say it will only add to the costs of drugs and drug development overall. They’ll say they work so hard for so little in return they can barely keep afloat as it is, due to all the existing regulations and costs of “new drug development”. They’ll say it’s “anti-American” and “anti-capitalism” to increase such regulation as well as force them to utilize their profits in this way. They’ll say they’ll have to pass that one percent increase on to the general public (and then they’ll probably raise their prices well above one percent as evidence, or simply because they can). They’ll attempt to hide their profits and revenues overseas and with “funny accounting”, and who knows what else (probably all things they’re doing now anyway). If something like this passed, most of all, the biggest danger would lie in the pharmaceutical industry gaining control of the independent researchers and once again creating publishing bias and outcomes and it would basically be back to business as usual.

There’s no doubt there would be plenty of obstacles, most of them in the form of the pharmaceutical industry, with such a proposal. However, there are a number of benefits I see to this approach: ultimately, safer drugs for all, more responsible development, and decreased costs of adverse effects:

1. The drug companies would actually start to become a part of the solution, instead of only the problem, of addressing the adverse effects profile of the drugs they create. Currently, their responsibility in this issue appears to end with the “appropriate warnings” provided in size 5 font on the drug inserts or via fast-talking monologues over the “happy commercials” on TV as they market directly to the consumer. And it’s usually only until enough people are maimed or killed that legal action or the FDA will actually make a difference in their behavior. There is a “buyer beware” mentality under the guise of “informed consent” – which is essentially “blaming the victim” for their own adverse reaction – but as far as the drug companies

are concerned, they've "done their part". The reality is, if the pharmaceutical companies and the FDA were truly concerned about the "health and safety" of the population they market to, they would put their money where their mouth is and take some of their billions in profits to study and research 1)who and why some people have these adverse reactions, 2)how to prevent these adverse reactions from happening, and 3) how to effectively treat them so as to return health and functionality to those who have been severely hit. Ultimately, this will help patient consumers by better identifying risk factors for individuals, and preventing these adverse reactions from occurring as well as provide appropriate treatments when they do occur.

2. Within the US, there would be a huge step-function "jump" in our knowledge of the biochemical, molecular, and genomic actions and reactions occurring in vivo of humans and other mammals. Drug companies currently try to develop drugs to "correct" whatever is perceived to "be wrong" in patients. Our data on "what is wrong" with patients is still rather crude and limited, because there is limited knowledge on the biochemical and molecular mechanisms of living organisms and how those tie in at the genomic level. We've mapped the human genome – but have very little idea of what the vast amounts of DNA actually code for. "Side effects" can give as much or more clues as to how these systems interact and eventually provide a "functional map" of the genome and epigenome of the healthy state as well as the diseased state on all levels. Research from multiple specialties and a wide variety of scientists, from biochemists to molecular genetics to statisticians putting all the data together would be involved in this mapping function. The US could become a leader in this effort. This would in many cases be driven cooperatively and collectively vs competitively, because the monies are already available for this, and these drugs are being used to help elucidate knowledge about whatever specialty the researchers are interested in studying (incorporated into their current interests and studies) and not driven by the next "quarterly report" or profits. It's not a for-profit initiative. However, as research expands, and the "functional mapping" increases, the drug companies will compete to develop new drugs or other medical treatments for the new targets discovered (receptors, enzymatic, genomic, etc.) so they will benefit from this research as well, completing the cycle.
3. Jobs will be created, and the sciences will look attractive as a field to enter, because a steady source of income will be readily available, courtesy of the pharmaceutical companies. Currently University and government agencies struggle to compete for grants from a variety of sectors to fund their research. With this idea, one problem, such as "tendonitis" or "peripheral neuropathy" can be tackled by a wide range of researchers who might not normally get the funding to do so. A huge source of money is the pharmaceutical companies who often benefit off public research, but use it only to further their own profits. With an idea such as this one, the drug companies would be "giving back", as well as becoming part of the solution when it comes to the adverse effects their drugs create. Society at large will benefit, not just the drug companies.

Such a program would not increase liability on pharma any more than already exists, as the adverse effects that would be targeted for further research are already known and stated (such as Black Box Warnings for tendon issues with the fluoroquinolone antibiotics). Importantly, all current requirements for bringing a drug to market and FDA approval would not change or become more lax either. This policy only pertains to drugs already on the market. Additionally, whatever current protections and checks and balances exist for safety and efficacy of drugs on the market, also would not change. Pharma will argue endlessly that they will have to increase the costs of

drugs to the public, but ultimately I don't think that will be the deciding factor here. They currently spend billions on advertising and marketing alone; they can spare 1% of profit per drug to be more proactive in helping to resolve some of the problems they create. There are thousands of drugs currently being marketed to the public, and that 1% of all of them will add up to spur a huge research initiative not seen before in this country from a wide range of sectors.

Adverse drug reactions are becoming a major reason for ER visits in this country, and it's estimated that 100,000 – 200,000 deaths per year occur due to adverse drug reactions. Long term chronic illness caused by ADR's only add to the burden of health care costs in this country. Right now, the drug companies are doing NOTHING to help resolve these issues. The only people profiting from this are the drug companies and the entire industry of attorneys which have sprung up supposedly on behalf of the injured. We all know the problem exists, but no one is tackling the real problem underlying this. Adding more warnings to drug inserts and labels are essentially useless, as no one would ever take any drug if they really believed they might be the one to suffer these adverse reactions. All it does is shift the responsibility – *all of it* – onto the consumer, who essentially plays "Russian roulette" with their life, and if they lose, they lose it all. All the warnings do is help lawyers quibble about the legalities of language while deflecting off the real problem – that adverse drug reactions are a reality of pharmaceutical use, and that the pharmaceutical companies should take more responsibility for the risks, as well as the benefits, of the drugs they create, market, and profit from. Mapping out the human genome is essentially useless unless we know how the genes and various mutations and epigenetic mutations function. Drugs that target a variety of mechanisms in the body can provide us with those answers, and the drug companies can do their share to provide us with the funding to find those answers. In the long run, they will only profit more as well. "Safety and efficacy" of pharmaceuticals can take on a whole new meaning when adverse drug reactions are acknowledged and dealt with truthfully and responsibly from all parties involved, including the pharmaceutical industry. Rather than try and hide, minimize, and deny the adverse effects that we all know are occurring anyway, let's not only acknowledge them as part of the risks of pharmaceutical usage, but actively utilize them as a source of knowledge and change for the better.

Even as I wrote this, I was thinking "No way would this ever happen". When I first wrote up this proposal a couple of years ago, I contacted a few people involved in the fight for pharmaceutical safety and accountability to ask their opinion on the chances of such an idea occurring. As expected, the initial reactions were that "something like this could never happen", for many of the reasons I stated. Since then Senator Elizabeth Warren has come up with her own plan to tackle Big Pharma. So maybe I wasn't as far off in left field as I thought. Her plan is moving in the right direction, and we can only hope that some inroads for more accountability will be made into the untouchable behemoth that is Big Pharma.

<http://www.nationaljournal.com/health-care/elizabeth-warren-vs-big-pharma-20150122> "Elizabeth Warren took on the pharmaceutical industry Thursday, as she proposed requiring drug makers to foot more of the bill for federally funded research".