From: Deepak Chopra <[redacted]>
Sent: Monday, August 1, 2016 12:29 PM
To: Jeff Epstein
Subject: Fw: Draft OpEd piece on FDA sharing confidentially

Writing this up for WSJ now

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The Chopra Foundation <http://www.choprafoundation.org/> <http://www.choprafoundation.org/>

<http://ecx.images-amazon.com/images/I/51ryZ4SaSrL._SL500_SS115_.jpg>

<http://www.amazon.com/Super-Genes-Astonishing-Optimum-Well-Being/dp/0804140138/deepakchcom07-20>

<http://www.amazon.com/Super-Genes-Astonishing-Optimum-Well-Being/dp/0804140138/deepakchcom07-20> Super Genes: Unlock the Astonishing Power of Your DNA for Optimum Health and Wellbeing <http://www.amazon.com/Super-Genes-Astonishing-Optimum-Well-Being/dp/0804140138/deepakchcom07-20>

From: Speaking of Health <[redacted]>
Sent: Monday, August 1, 2016 12:08 AM
To: Deepak Chopra
Subject: Re: Draft OpEd piece on FDA

Of course, brevity will enhance the Op-Ed piece. The first draft was written while I was 'under-meditated', and I should have taken an anti-inflammatory as well! 😇

1) The FDA has studied and approved 1,453 drugs in its entire history.

2) Seventy percent of the US population takes at least one prescription drug each month. The number of deaths from prescription drugs in the US each year exceeds deaths from illegal drugs, as well as from automobile accidents. Over 4 billion prescriptions were written in the US last year by health care professionals.

3) The total number of prescription drugs on the marketplace in the US is unknown, unpublished, and not tracked by the FDA. The clearest database is from the National Library of Medicine which lists 88,212 prescription drug compounds on file in the US. There are over 300,000 over-the-counter (OTC) drug products marketed in the US. The number of nutraceutical products is unknown, but sales in the US are estimated to be approaching $200 billion dollars per year, while dietary supplements and vitamins sales exceed $27 billion per year. Probiotics are rapidly growing in popularity, and worldwide sales are expected to exceed $50 billion dollars per year by 2020.

4) Most physicians and the public are unaware that the vast majority of prescription drugs in the US marketplace have not been studied or approved by the FDA. They are legally marketed only because of a 1938 legislative loophole grandfathering the continuation of their marketing and sale to physicians and the public.

5) A significant number of the 440,000 deaths in US hospitals each year arise from medical errors due to pharmaceutical adverse reactions or interactions. The cost to society of adverse drug reactions in the US exceeds $136 billion per year.

6) In 2004 an FDA approved drug was withdrawn after five years on the marketplace, and only in retrospect was found to be responsible for an estimated 38,000 fatalities in the US alone. Ironically, thousands of unproven drugs continue to be legally marketed while an FDA committee denied approval for a novel potentially lifesaving drug for Duchenne Muscular dystrophy. The denial was because the small number of study subjects, as expected with a rare disease, did not reach statistical proof of safety even though no participants had an adverse reaction.

7) Comprehensive and conscientious post-marketing surveillance should be required for all products promoted and sold as therapeutic, including prescription, OTC, nutraceuticals, probiotics, etc. There should be an emphasis on precision genomic information to enhance safety by identifying sub-populations with optional benefits and higher risk of adverse events.

8) The cross referencing of poly-pharmacy risk of drug-drug interaction including over the counter (OTC), nutraceuticals, probiotics, etc., and other data end points subject to meta-analysis, while preserving individual privacy rights, will greatly enhance public health and safety.

On Sun, Jul 31, 2016 at 3:56 PM, Deepak Chopra <[redacted]<mailto:[redacted]> > wrote:

How do you feel about an 800 word Op ed , slightly less inflammatory

Also when you cite over 10,OOO drugs without science documentation are you referring to over the counter drugs

Can you summarize everything in a few bullet points ?

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From: Speaking of Health <[redacted]<mailto:[redacted]> >
Sent: Sunday, July 31, 2016 11:02:52 AM
To: Deepak Chopra
Subject: Re: Draft OpEd piece on FDA

Absolutely!

On Jul 31, 2016, at 1:56 AM, Deepak Chopra <[redacted]<mailto[redacted]> > wrote:

May I do a rewrite ?

Deepak Chopra
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Super Genes: Unlock the Astonishing Power of Your DNA for Optimum Health and Wellbeing <http://www.amazon.com/Super-Genes-Astonishing-Optimum-Well-Being/dp/0804140138/deepakchcom07-20>

On Jul 30, 2016, at 5:13 PM, Speaking of Health <[redacted] <mailto:[redacted]> > wrote:

Hello Deepak,

Rough draf is attached as a Word document, feel free to modify, edit, add, delete, rewrite, etc. (We should probably aim to tighten it to below 2,000 words from its present word count of 2,408)

If you approve, we can send the final version to our friend Dan Henninger, Deputy Editor at WSJ. The WSJ editorial on the FDA Duchenne drug denial was published on July 6, 2016, so we would still be timely, and the FDA final decision coming soon will make the news again.

Perhaps you would like to expand on Personalized Precision Medicine, with reference to Super Genes?

Would Rudi Tanzi be interested in joining as a co-author? Perhaps he has additional insights on Duchenne's as a neuromuscular disorder?

We have not heard back from Paul & Bess, so do not know their level of interest, or if they wish to be listed as co-authors.

We have not approached Dave Brenner or other signatories to our previous OpEd pieces, perhaps they would be interested, and if you believe that more voices add credibility, they can be invited?

Eric Topol may have an interest since he was instrumental in exposing Vioxx as a major cardiovascular risk agent, and having it withdrawn by the FDA.

Looking forward to your thoughts, comments, and suggestions.

Love,

Joe & Nancy

Can the Food and Drug Administration (FDA) be made Safe and Effective?

For one-hundred and ten years the FDA has allowed the marketing of tens of thousands of unapproved drugs without any safety and efficacy evidence. Ironically, it bases its denial of a novel therapy that offers hope for those with a lethal disease on theoretical statistical safety concerns.

An FDA committee has recommended that the agency deny approval for Sarepta Therapeutics new drug Eteplirsen, a potentially lifesaving drug for Duchenne Muscular dystrophy, a rare and invariably fatal disease that affects young boys. The preliminary data is very encouraging with several years of experience on the drug showing young boys continuing to walk and maintain function where statistics would have expected them to already be wheelchair bound. No significant adverse effects on safety were reported. The denial is based on the small number of subjects evaluated, which is to be expected when dealing with a rare disease. The panel also wants to require the pharmaceutical company to repeat years of study with placebo controls, an ethical conundrum when the disease is invariably progressive and fatal. If it were their child facing a lethal disease, we doubt that they would be willing to give their own child repeated, uncomfortable, and not without risk sugar water injections instead of a potentially beneficial treatment for an invariably fatal disease.

The greatest irony of all however, is the proverbial unspoken giant elephant in the room. In spite of its insistence that the public safety is its greatest concern, the FDA has repeatedly failed to address the regulatory loophole in which tens of thousands of unapproved drugs remain on the marketplace. The FDA was created in 1906 but surprisingly was not required to assess drug safety and efficacy until 1938. It began to do so in that year, but in deference to the financial benefit of industry over public health and safety, grandfathered all existing drugs from requiring FDA overview. It allowed them to remain on the marketplace purely to avoid imposing a financial burden on industry to prove that the products they were marketing were safe and effective.

In 1962, Congress passed amendments to the 1938 law, to require manufacturers to show that their drug products were effective, as well as safe. As a result, all drugs approved between 1938 and 1962 were to be reviewed for effectiveness and safety, yet the FDA has repeatedly issued administrative rulings that have actually helped the pharmaceutical industry avoid regulatory oversight and keep these unproven products on the open market. In 2013 the FDA announced it will continue to grant national drug code (NDC) numbers to pharmaceutical and other drug products not approved by FDA for a given indication. NDC's are applied to three classes of products: FDA-approved products, products without FDA approval for a particular claim, and products that were grandfathered in under the 1962 Kefauver-Harris Amendments or the Federal Food, Drug and Cosmetic Ac of 1938. The FDA itself estimates that there are thousands of non-approved drugs with NDC's marketed and prescribed in the US, but is unable to quantify or identify these products. These include drugs such as the Vitamin E product E-Ferol which was held responsible for the death of 40 infants in 1984, and a carbinoxamine containing drug product responsible for the deaths of 21 infants in 2006.

The FDA has achieved limited success in that It has removed approximately five hundred unapproved drugs from the marketplace since 1962. In spite of its congressional mandate, the FDA has not been able to complete its task of ensuring marketplace drug safety and efficacy, and in 2006 once again reaffirmed its intent to eventually do so. Ten years later the progress on tens of thousands of grandfathered drugs has yet to produce basic safety and efficacy data. The most comprehensive list of unapproved drugs is not maintained by the FDA, but rather by the National Library of Medicine, which identities 88,212 drugs that have been reported to the FDA. Many of these drugs are routinely prescribed by health care professionals and purchased by the public who are unaware of their unapproved status.

The extent of the issue has not been quantified or publicized by the FDA but includes many commonly prescribed pharmaceuticals with tens of millions of unaware consumers and many billions of dollars in sales. After forty years of being marketed without FDA approval the manufacturer of the popular thyroid replacement drug Synthroid finally reluctantly agreed to safety and efficacy guidelines and was approved by the FDA in 2002. The resistance to FDA regulatory oversight is both financial and practical for the manufacturer. It is expensive to provide research proving that a drug is safe and effective is just one half of the equation. The other half is that if the drug fails to be proven safe and effective it will lose its market share and profitability, and open a Pandora's box of product liability lawsuits. The protection of public health and safety is unfortunately only a public relations interest of the manufacturer.

In the one-hundred and ten-year history of the FDA it has studied and approved a grand total of 1,453 drugs. A number of drugs had their approval withdrawn when safety risks were subsequently identified, leaving only 1,246 drugs of the potentially marketed total of 88,212 remaining on the FDA approval list. In other words, over 98% of

the prescription drugs that can be legally marketed in the United States have not only not been approved by the FDA, they have never been objectively evaluated for for their basic safety and efficacy by their manufacturers or distributors. In 2014 US prescription drug sales exceeded $374 billion dollars. The amount spent on unsafe, unproven, and ineffective drugs is undoubtedly a significant portion of this total. Adding to this dangerous and wasteful expenditure are the financial consequences of ineffective treatment allowing disease progression, and the prohibitive expense of resulting morbidity and mortality. Congress and the FDA should assure that these tens of billions of dollars per year are redirected from unethical and wasteful practices, and instead utilized to protect the public health and safety.

A significant number of the staggering 440,000 deaths in US hospitals each year that arise from medical errors are due to pharmaceutical adverse reactions or interactions. The cursory voluntary post-marketing surveillance of drugs is widely recognized as haphazard and inadequate, and has resulted in prohibitive and avoidable excess mortality and morbidity rates. One of the more recent drug approvals that was later withdrawn was in 2004 for Merck's anti-inflammatory drug Rofecoxib (Vioxx ®) which has been conservatively attributed with over 38,000 deaths in the US, and 60,000 worldwide. The number of deaths related to Vioxx ® is probably a multiple of the conservative figure. In 1999, the year Vioxx ® was introduced, the US experienced a jump in cardiovascular deaths by an unprecedented 50,000+ excess deaths per year. The surge of 50,000+ deaths per year persisted until Vioxx ® was withdrawn from the market in 2004, contributing to a potential 250,000 deaths in the US alone.

The FDA has extremely high, and arguably excessive, safety and efficacy standards for new drugs and generic versions of pre-1938 drugs. What is incomprehensible is that it has protected from regulatory oversight inappropriately grandfathered drugs for over eighty years that have no safety or efficacy data. Ironically, a generic version of the eighty plus year old protected pharmaceutical would require FDA regulation. FDA guidelines are in essence giving the grandfathered drugs not only a regulatory protection pass, but also monopoly status by creating a financial and regulatory barrier to the entry of generic manufacturers.

The FDA and Congress have consistently failed to addressed this major public health and safety issue. By emphasis on excessive and unreasonable safety and efficacy statistical data, the expense and uncertainty of approval have skyrocketed drug development costs. This has hindered pharmaceutical and industry innovation, and delayed and prevented bringing new products and therapy to the market. The outdated grandfather status of drugs from 1938 and before has allowed tens of thousands of unapproved drugs to remain in the marketplace. The hundreds of billions of dollars spent on unproven drugs is exceeded only by the exorbitant cost in human mortality and morbidity. The numbers are not known, but if 250,000 Americans can be killed in only five years by one drug over that was approved by the FDA, imagine the numbers killed over eighty years with 88,000 unapproved drugs that were never evaluated for safety or efficacy.

The FDA will require pharma to spend hundreds of millions to billions of dollars to bring a new drug to market, yet old ones that have been never seen even the most basic of safety studies are marketed with impunity. Grandfathered drugs are still marketed over eighty years after first appearing without safety or efficacy data, or any form of post marketing surveillance. Contrast this lack of oversight with the bureaucratic logic by which an FDA panel which has declined to approve a new drug for Duchene muscular dystrophy, a fatal disease of children without effective therapy, because the number of subjects is too small for statistical proof of safety. This is in spite of the fact that none of the subjects were harmed, and many had dramatic benefit. The denial of a potentially life-saving drug because of a small statistical and theoretical possibility of harm flies in the face of the FDA's cavalier attitude about the flood of grandfathered drugs with unknown safety and efficacy.

The interaction between a subject patient and a pharmaceutical product can be summarized as falling into one of four categories. Only one of the four categories has an optimal outcome, where the drug is efficacious providing benefit, without creating an adverse reaction. A mixed result is where the drug does provide therapeutic benefit, but also causes an adverse reaction which may override its benefits. A relatively neutral outcome, except for the negative financial impact and delay in effective therapy, is where the drug is not efficacious and does not provide therapeutic benefit, but does not cause an adverse reaction. The worst case scenario is where there is no therapeutic benefit, but an adverse event occurs, potentially with significant morbidity and mortality. There is growing recognition in

the life sciences that drug efficacy and safety can be masked when the traditional human population studies are used to assess drug safety and efficacy. These studies neglect to account for the unique genetic background of the individual subjects, with growing evidence that such differentiation is critical to the accurate assessment of pharmaceutical therapy efficacy and safety.

The use of the advances in genomics and gene sequencing technology underlies precision personalized medicine. These advances are revolutionizing cancer care as well the management of other disorders with the identification of genetic markers that can predict with great accuracy the proper selection of pharmaceuticals to maximize efficacy and minimize adverse events. The old adage that one man' medicine may be another's poison remains all too true. Removing penicillin from the pharmaceutical armamentarium because some people have severe allergies is a false logic which would lead to more deaths because those who would benefit are deprived the drug. Likewise, rejecting a potentially beneficial drugs because a subset of the population does not benefit or has adverse effects is illogical. The identification of those who would benefit and those who would be harmed should be the priority. Pharmaceutical submissions to the FDA should include genomic analysis of subject populations and outcomes. A national database of robust post-marketing surveillance, including genomics, would greatly enhance public health and safety and should be an integral part of the precision medicine initiative.

The FDA and congress needs to take the lead, and public health and safety should be its priorities. Grandfathered status of unapproved drugs should be withdrawn and safety and efficacy confirmed to allow continued access to the the marketplace. All drugs marketed to the public and professions, including over the counter, supplements, nutraceuticals, and probiotics, should have established minimal standards of safety and efficacy if any beneficial or therapeutic claims are made in their marketing. The public must recognize that a perfect safety record cannot be reasonably expected, as even aspirin could not pass the excessive FDA requirements for drug safety today, yet it is one of our most effective drugs.

Comprehensive and conscientious post marketing surveillance should be required for all drugs in the marketplace, with an emphasis on identifying precision genomic information to enhance further safety by identifying sub-populations with optional benefits and higher risk of adverse events. The cross referencing of poly-pharmacy risk of drug-drug interaction including over the counter (OTC), nutraceuticals, probiotics, etc., and other data end points such as gender, age, ethnicity, health and disease status, while preserving individual privacy rights to provide further clinically relevant safety and efficacy insights from metadata analysis, should be encouraged. The requirement to meet established minimal standards of safety and efficacy should be mandatory for any product sold and marketed as therapeutic.

Using sophisticated post-marketing surveillance can create a more responsive and resilient FDA, reduce pharmaceutical development costs, enhance the efficiency and timeline of the product advancement pipeline, offer greater therapeutic options to the health care professions and consumers, and greatly enhance the ability to identify and respond to drug safety issues. This is especially true by bringing grandfathered drugs into compliance, these costs savings alone could make this initiative budget neutral. The drug for Duchenne muscular dystrophy should be accessible to the children and families who are already suffering from a terrible disease, and should not be subjected to misguided and unreasonable overregulation.

By bringing grandfathered drugs out from a regulatory moratorium loophole and monopoly protection the FDA will save hundreds of thousands more lives than any denial of novel therapies for rare diseases might cause if granted on the basis of compassion. Even if the drug subsequently fails after post-marketing surveillance, it contributes to future progress. It is time for the public to insist that the FDA and Congress submit to a dose of common sense, and move beyond repeated half-hearted failed attempts and embrace a future of enhanced public health and safety. Unquestionably there will a high expense to implement an effective pharmaceutical safety and efficacy program based on objective science. The cost savings to the consumer, insurance, government, industry, and public at large will more than offset this expense.

The authors have no financial conflicts of interest to report.

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