

The Kethical Dilemma

Fall 2010

KECK GRADUATE INSTITUTE
of Applied Life Sciences

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Ethics Committee Semester Recap

The EC has doubled in size from last year to this year. We are pleased with the growth & have organized our efforts into three distinct areas, which we've made significant progress in!

Newsletter. This Fall 2010 edition marks the sixth issue of the *Kethical Dilemma* since its launch in October 2009. We've focused attention toward enhancing the content of our pieces. In the process, we are pleased to welcome first year writers and to include returning student writers.

Ethics Initiatives. The November 17th discussion with David Sadava brought to light recent scandals surrounding data fudging in the world of science. About 15 students and Dr. Sadava discussed the surprising prevalence of altering test

results and the serious implications it can have in the world of health care. Attendees also debated the causes of unethical behavior and how societal pressures and norms come into play.

Future Events to look forward to include:

- January - a student "Ethics" Debate collaborating with the public speaking club (food, wine)
- Mid-Spring -Professional/Academic Debate surrounding the ethics of Biotechnology, to include representatives from the Claremont Colleges as well as industry professionals.
- April - Friday Keynote Speaker
- Next Semester: More lunch discussions with faculty experts surrounding current topics related to business ethics and social responsibility .

Procedures. This EC took on this initiative after the 2009 ratification of the Honor Code, which was also written by the EC.

Last week, Adam Calvert held focus groups with faculty, staff, and students to determine each group's perspectives in relation to KGI's academic & disciplinary procedures. The Procedures subcommittee will make recommendations to modify academic disciplinary procedures, but will devote focus to conduct-related disciplinary procedures and the promotion of the Honor Code in the coming semester.



Letter from the Editor

By Michelle Pesce

Dear KD Readers,

It is with excitement that we launch the first newsletter of the school year! This year, we've aimed toward producing solid, in-depth pieces that illustrate questionable practices or thought-provoking scenarios in the life sciences industry. The writers have purposefully aimed to discuss controversial topics that are a reality of the industry. In the article, "Consider the Source," first and second year MBS students share their opposing viewpoints on vaccines derived from aborted fetuses. In this issue, we cover topics regarding overseas pharmaceutical bribery, narcolepsy drugs that have the potential for abuse, as well as clinical trials which involve near-death participants. We hope that you enjoy our researched articles, and we welcome feedback and suggestions.

Happy reading! - MP

NARCOLEPSY DRUG DENIED FOR FIBROMYALGIA USE

By Susan Alfs

Currently, Jazz Pharmaceuticals has the drug Xyrem (sodium oxybate) on the market for narcolepsy patients who experience cataplexy, but now is seeking its approval for treatment of fibromyalgia (9). However, the FDA did not approve its use for fibromyalgia and has required more testing from Jazz Pharmaceuticals (4). The reasoning behind the FDA's decision is not completely known at this time. One possible theory is concern over the potential for its misuse, since sodium oxybate is the active ingredient, which is also known as gamma hydroxybutyrate (aka GHB, the date rape drug).

As a disclaimer, there are obviously many reasons the FDA could have taken into consideration when it decided to reject Xyrem use for fibromyalgia, but the safety issue seems to be the most likely concern. There are also several classes of narcolepsy drugs available on the market, including amphetamines (methylphenidate, dextroamphetamine, methamphetamine, and pemoline), tricyclics (imipramine, desipramine, clomipramine, and protriptyline) and selective serotonin reuptake inhibitors (fluoxetine and sertraline) (6). All of these drugs have the possibility of side effects, developing tolerance with extended use, and misuse. Since there have been no other favorable alternatives for narcolepsy, and narcolepsy is often difficult to treat, the FDA may have been willing to allow these drugs to be approved despite the risks. Also, Xyrem was seen as particularly useful in narcolepsy patients who experienced cataplexy (sudden onset of REM and loss of muscle control while awake) when other medications did not work (9). The question of why the fibromyalgia application was treated differently still remains.

Fibromyalgia is a widespread disease with 5 million Americans currently affected, and there are already several drugs on the market for it. The FDA has ap-

proved drugs for fibromyalgia from Pfizer (Lyrica), Eli Lilly (Cymbalta), and Forest Laboratories/Cypress Bioscience (Savella), as well as similar drugs used to treat narcolepsy such as tricyclics and selective serotonin reuptake inhibitors (2). However, Jazz claims that there is still an unmet need for fibromyalgia drugs, which is true because many of the currently prescribed drugs do not work for some patients. It is interesting to note that many of the same drugs used to treat narcolepsy (which have significant risks and side effects) are also used in fibromyalgia; the FDA has deemed the release of tricyclics and selective serotonin reuptake inhibitors to a larger market acceptable, but not sodium oxybate.



The results of the FDA's decision could have an impact on a variety of stakeholders, including fibromyalgia patients, narcolepsy patients, Jazz Pharmaceuticals, and those who would misuse Xyrem. If Jazz decides not to do the additional testing needed for approval, they may decide to raise the price of Xyrem for narcolepsy patients, which costs \$20,000/year (4). Decision makers at Jazz have the right to change their strategy and decide not to pursue the fibromyalgia application of the drug, and they also are able to determine their pricing strategy. Though the FDA made the decision to try to protect consumers, they may have caused the unintended consequence of burdening narcolepsy patients with increased medical costs.

The FDA assesses the risks of drugs based on the "composite profile of the drug's chemistry, pharmacology, clinical manifestations, similarity to other drugs in

a class, and the potential for public health risks following introduction of the drug to the general population" (5). The FDA wants to make sure of the safe use of Xyrem by limiting its availability, yet it is already out on the market for narcolepsy (7). Since Xyrem is an orphan drug, it has not caused a widespread problem (3). However, there is misuse data, including ten cases of Xyrem abuse, one death, and two instances of sexual assault in six years (8). The conclusion of two studies states that this is a low incidence of abuse compared to other drugs (8),(1). These infractions have occurred even though many safety checks designed to limit access are in place, such as Schedule III designation and distribution from a centralized pharmacy. Even if security were tightened further, it would not completely eliminate risk (8).

The FDA's decision gives the impression that the Xyrem's benefits for fibromyalgia patients do not outweigh the risk of abuse, which contradicts the conclusions of the study that stated the risks were typical (7). The FDA may tolerate that 26,000 narcolepsy patients have access to Xyrem prescriptions, and that only a fraction of the 5 million fibromyalgia patients may use Xyrem. However, the FDA views Xyrem as unacceptable since it would greatly increase the availability of the drug to those who would misuse it (8).

From another angle, it seems that the FDA has had to deal with pharmaceutical companies using somewhat risky drugs for both narcolepsy (a small market) and fibromyalgia (a large market) before, without the size of the market being a deciding factor. In other words, it must be that Xyrem's side effects were risky enough that this expansion of use would be unsafe. Ultimately, it is Jazz Pharmaceutical's duty to prove the safety of Xyrem to the FDA; with the information given, the FDA decided that the public health risk was too great if Xyrem were released to a larger market (5).

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BRIBERY & THE PHARMACEUTICAL INDUSTRY

By Clare Xu

A recent Wall Street Journal article declares “Drug Firms Face Bribery Probe” and conjures images of shady backroom dealings that accelerate drug sales and approvals overseas. The story describes a massive investigation across the pharmaceutical industry seeking to uncover potential violations of a 1977 anti-bribery act (8). The article implicates international firms such as Merck & Co., Bristol-Myers Squibb, and GlaxoSmith-Kline in bribery allegations—but prosecution alone is not a mark of wrongdoing.

The headline casts the pharmaceutical industry in an unfair light, insinuating guilt by leveraging public perceptions of Big Pharma as profit-mongers under the guise of life-savers. However, Big Pharma is not necessarily doling out payments abroad to buy off health sector workers and hasten clinical trials. On the contrary, pharmaceutical companies have exhibited a level of transparency that indicates that anti-corruption mechanisms are in place. Many have self-reported and have publicly disclosed that they are under investigation and are complying with U.S. law enforcement and regulatory agencies.

The investigation signifies a trend towards increasingly aggressive efforts by the U.S. Department of Justice (DOJ) and the Securities Exchange Commission to enforce the Foreign Corrupt Practices Act (FCPA), which proscribes bribery overseas. The FCPA’s anti-bribery provision has jurisdiction over any company with stocks in the U.S. and prohibits “the payment or promise of anything of value” to a foreign official for obtaining or retaining business (9). Outside the United States, “nearly every aspect of the approval, manufacture, import, export, pricing, sale and marketing of a drug product may involve a foreign official,” according to the DOJ (2).

The highly regulated pharmaceutical industry has heightened exposure to corruption risk since it deals with thousands of doctors, clinicians, joint venture partners, and third parties from foreign gov-

ernments on a daily basis. The latter are considered “foreign officials” under the FCPA because they are employed by the government or by state-owned hospitals. These interactions represent infinite opportunities to breach the FCPA.

Potentially corrupt payments may involve kickbacks, charitable donations, research grants, as well as speaking fees and hospitality (e.g. meals and all-expenses paid travel) (4). FCPA violations include paying sales agents to pass commissions to doctors, paying hospital committees to approve drug purchases, or paying regulators to win drug approvals (8). The FCPA exempts facilitation payments which only grease the wheels of business and expedite obligatory duties (1).

As pharmaceutical companies continue to outsource business, the FCPA becomes more relevant. According to the Department of Health and Human Services, up to 80% of drugs and biologics approved for sale in the U.S. involved at least one foreign clinical trial (5). Overall, 40-65% of clinical trials for FDA-regulated products were completed outside the US and nearly one-third of total industry revenues were from foreign sales (\$103.4 billion) (8). The DOJ and SEC must monitor the integrity of companies abroad to ensure that improper payments did not influence the reliability of clinical trials.

Because the FCPA is important, the U.S. has prioritized anti-corruption efforts, escalated sanctions, and dedicated resources towards FCPA crackdown within the DOJ, SEC, and FBI. Companies face fines of up to \$2 million as well as suspension and debarment for violations. Since 1998, the DOJ has collected over \$2 billion in bribery-related fines (6). Over 150 federal anti-bribery investigations are in progress.

To stay clear of the line of fire, senior management in pharmaceutical companies must develop FCPA training, education and awareness programs. Financial, technical, and clinical processes must be monitored to identify risks and prevent



enterprise corruption; due diligence of foreign business partners is a must (3,7). Additionally, firms must be periodically audited to ensure FCPA compliance at all organizational levels.

Although Big Pharma is held to the anti-bribery provisions of the FCPA, no laws prohibit gifts or payments for the purpose of obtaining business within the U.S. — the equivalent of a bribe under the FCPA. Though U.S. anti-corruption efforts have set a worldwide benchmark, the latter calls to attention marketing practices used to influence drug sales on the home front. According to a New York Times article, companies can legally hire doctors as consultants to market drugs to health professionals at medical gatherings, as long as they are not paid directly to prescribe products (2). Pharmaceutical firms can legally wine and dine clients to push products within the U.S.

Conflicting messages between anti-bribery measures abroad and at home set a double standard for pharmaceutical companies. The ethical guidelines behind international and domestic anti-corruption laws do not run parallel. For example, hospitality to influence drug purchasing is an outright violation of the FCPA in non-U.S. markets, but is a widespread tactic at home. Why is it that when a foreign official is involved, hospitality morphs into bribery? Perhaps interactions between pharmaceutical companies and health care systems in the U.S. should be subject to the same kind of regulatory scrutiny. At the very least, the Justice Department should draw a line between wining and dining and something more sinister.

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CONSIDER THE SOURCE:

THE MEASLES, MUMPS, & RUBELLA (MMR) VACCINE

Merck's MMR vaccine is manufactured from cell lines derived from an aborted rubella infected fetus. A patient who required the vaccine was concerned with the vaccine's manufacture due to their religious affiliation, and hesitated to be administered the vaccine. Is the use of the vaccine questionable?

THE BENEFITS OF IMMUNITY – View 1

By Richard Head

The fact that the rubella vaccine has been derived from human fetal cell lines has proven quite controversial. However when examined objectively, a large number of the worries associated with the current vaccine can be dispelled. In fact, the manufacturing, distribution and use of this vaccine are completely ethical and free from any immoral complicity. Understanding the history behind the vaccine is instrumental in realizing its continued importance.

In the wake of the United States rubella epidemic of 1964 and 1965, researchers scrambled to develop an attenuated rubella vaccine to prevent the devastation caused by the virus. The epidemic resulted in 6,250 fetal losses as well as 2,100 infant deaths/stillbirths (5). During the epidemic, 5,000 abortions were performed as a consequence of a maternal rubella infection during pregnancy (5). Various cells lines were developed, but only one showed promise. This cell line, RA 27/3, cultured from human diploid fibroblast cells, proved to be the best therapeutic option as it limited side effects and obtained attenuation at low temperatures. This provided for a low virulence level *in vivo* increasing the safety of the vaccine (2). These fibroblast cells were obtained from the tissue of an aborted fetus who had suffered from a congenital rubella infection.

At the time, many doctors strongly recommended abortions to families upon the determination of a congenital rubella infection (2). An infection during development frequently resulted in deafness, cataracts, and congenital heart disease (1). Serious cases often triggered mental retardation and developmental problems throughout the child's life (1). Loss of the pregnancy was a serious risk to both the mother and the unborn child, and abortions were often recommended to mitigate the risk to the mother. The use of tissue from these aborted fetuses was instrumental in the development of a vaccine to prevent the need for future abortions.

RA 27/3 became the standard of care in the United States a decade after its release in Europe in 1970. The late adoption was a direct result of the FDA's irrational fear that human-derived cell lines may contain some unknown contaminating agent (2).

RESPONSIBLE VACCINATION – View 2

By Marc Pollack

There is little doubt as to the importance of vaccines in public health. However, the necessity to have vaccines does not, and should not preclude the fact that vaccines can be and are made in an unethical fashion. Vaccines made with fetal cells, like the MMR vaccines, are unethically produced specifically because they are utilized for personal gain rather than for public health purposes alone. These vaccines also mire us in the past, preventing us from pursuing new sources of vaccine production that have become available since their inception.

The history behind the creation of the rubella vaccine is one of necessity. A rubella epidemic was rampant, and the loss of infants and fetuses to the epidemic provided a unique reason to manufacture the vaccine in any way possible. A vaccine was unavailable, and human fetal cells provided a simpler and more accessible opportunity to create a widely available vaccine with fewer side effects than other options that were available.

That necessity, however, has passed. There is no question that rubella, as well as mumps and measles, still presents a public health concern to our society, but the production of the vaccine has turned from absolute requirement to a continuous source of revenue. Due to low disease prevalence, we no longer have the absolute necessity to manufacture this product. These fetal cells are still being used to create the all-important vaccine, despite the fact that it is no longer the tremendous health risk that it once was.

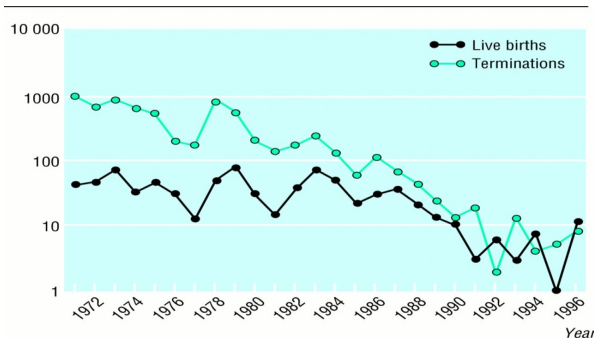
Rabbit kidney cells can now be used to create the vaccine, and have been commonly used as a standard of vaccination for rubella in Japan since 1977 (1). The reason they were not seen as a possibility before is because animal tests did not produce a significant amount of antibodies, though this was proven later to be the result of the normal body temperature of animals such as rabbits being too high to obtain optimal virus titer (2). This method didn't exist until after the epidemic had subsided, and now that the method is available, we should consider moving beyond the use of fetal cells. The other main concern is side effects, though the majority of those side effects are minor beyond allergic responses (3). Given that so many other vaccines

THE BENEFITS OF IMMUNITY

Ironically, RA 27/3 has since become the standard of reference for fully characterized cells free from contamination (2). RA 27/3 quickly became the preferred cell line, as it did not have the side effects associated with vaccines derived from duck embryos and dog kidneys. In addition, it was the only cell line that did not risk re-infection upon exposure to wild rubella strains (2).

Figure 1: Births of babies with congenital rubella (England, Scotland, and Wales) and terminations associated with rubella disease or contact (England and Wales only) after introduction of vaccine in 1970 (4).

The utilitarian perspective would suggest that maximizing the



benefit for the greatest number of people is the most morally just option. Taken from this viewpoint, it is obvious that the vaccine, despite its source, stands to benefit society as a whole. Not only will it help to prevent future cases of rubella, it also will help to preclude the incidence of families having to choose abortion in the wake of congenital infections (Figure 1). Today, the incidence of rubella has fallen to 1.78 cases per 100,000 people worldwide, thanks to the effectiveness of RA 27/3 (3). There is good reason rubella vaccination is required for children before being admitted to school. Rubella vaccination bolsters the herd immunity of the entire population and is necessary to prevent future epidemics from occurring. Discontinuing its use would risk the unmitigated spread of rubella worldwide.

Another valuable tool in evaluating the morality of such a difficult situation is the Principle of Double Effect. It allows for the determination of morality in the face of decisions involving both good and bad choices. Double Effect evaluates morally questionable situations on the basis of four criteria:

- 1) The action must be morally indifferent or good
- 2) The bad effect cannot be the means by which the good effect is achieved.
- 3) The motive must be the accomplishment of the good effect only.
- 4) The good effect must be of equal importance or greater to the bad effect.



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RESPONSIBLE VACCINATION

are produced from animal cells like this and that people experience similar side effects when taking those, this is a problem that the medical system can handle. This is a proven method for vaccine creation, distribution, and inoculation, and we are at a point where we can reevaluate the kinds of cells we use and the process by which we create this vaccine.

Use of fetal cells does bring important ethical complaints to the fore. Should we be using human tissue for profit? A wide variety of options have become available by employing such models for human cells as CHO cells. Expanding knowledge about their use and the use of other mammalian cells has provided multiple avenues to vaccine development. These cells are only utilized because it is simple and well-established; it's something companies are used to employing. Since this method for creating the vaccine is not currently theirs (it has yet to be licensed in the U.S. by any major pharmaceutical company)(4), companies ignore it and stick to what they have and know best. Only the monetary loss is preventing any sort of shift to the use of other types of cells. Should cells given without the consent (fetal cells) of the provider be able to be utilized for this purpose? These concerns, as well as others, cause a number of people to avoid getting their children these vaccines. They view it as morally wrong to utilize these cells in such a way, especially when other options exist. This creates further public health concerns by creating a larger population that is vulnerable to the rubella virus, effectively negating the impact of vaccines for a large portion of the population.

I would argue that this is bad from multiple perspectives, not least among them being the utilitarian one. A large portion of the population suffers from the lack of other available options being provided. Moreover, from a Kantian perspective, this is extremely reprehensible. This perspective, unlike the utilitarian one, assesses whether or not the action was done for moral reasons rather than whether the end result itself is moral (5). I would argue that the use of these cells for monetary gains is, by its very nature, for personal gain and not aimed at a moral imperative. Merck dominates the US and European markets, with sales of \$265 million in 2003 representing 79% of the overall market (6). Merck has generated a process by which they can produce the most effective and highly productive vaccines for the creation of the vaccine, and that is good enough for them. The fact that this newer vaccine is not widely available reveals a distinctly immoral impetus.

The Principle of Double Effect further proves my point. This is "a set of ethical criteria for evaluating the permissibility of acting when one's otherwise legitimate act will also cause an effect one would normally be obliged to avoid" (7). To be clear: we are not arguing between vaccinating and not vaccinating. We are instead talking about whether vaccinations created from fetal cells in particular are ethical or not.

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THE BENEFITS OF IMMUNITY

Utilizing the Principle of Double Effect to evaluate the morality behind rubella vaccination reveals the act to be completely ethical under the given framework. The good effect, the rubella vaccine, must be defined in relation to the bad effect, benefiting from the outcome of abortion, from which it is achieved. The first condition of Double Effect is met by the act of vaccination. The rubella vaccine is inherently good as it provides for immunity within the individual as well as bolstering the herd immunity of the entire population. It is true that the vaccine cell line was obtained from tissue harvested from an aborted fetus. However, the abortion was not performed for the purposes of the vaccine, thus satisfying the second condition. The third condition concerns the motive behind the development of the vaccine. Since the vaccine was developed in order to prevent future cases of rubella and avert the need for abortions, the third condition is met. Finally, the good vastly outweighs the bad in this situation as the tragic circumstances of a few families have provided for the safety of countless individuals who benefit from the vaccine.

Parents need not worry about moral complicity when determining whether or not to have their children vaccinated. In fact, concerned parents should be educated on the history and safety of the RA 27/3 vaccine. A new vaccine would take time to develop and satisfy regulatory specifications required by the FDA. Vaccines from non-human cell lines often run the risk of serious side effects as well. While the source of the rubella vaccine has been mired in controversy, its effectiveness in mitigating the spread of rubella is unparalleled.

No vaccine has since been developed that has been as efficacious as RA 27/3. Parents can take solace in the countless lives the RA 27/3 vaccine has saved after its development. While controversial, the abortions that led to the development of the vaccine were not a means to an end. It is far past time that we turn the page and accept the good that has come out of such a terrible situation.

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2. Plotkin, S. A. (2006). The history of rubella and rubella vaccination leading to elimination *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 43 Suppl 3, S164-8.
3. Progress toward control of rubella and prevention of congenital rubella syndrome -- worldwide, 2009 Retrieved 11/15/2010, 2010, from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5940a4.htm>.
4. Tookey, P. A., & Peckham, C. S. (1999). Surveillance of congenital rubella in Great Britain, 1971-96 *BMJ (Clinical Research Ed.)*, 318(7186), 769-770.
5. Zimmerman, R. K. (2004). Ethical analyses of vaccines grown in human cell strains derived from abortion: Arguments and internet search *Vaccine*, 22(31-32), 4238-4244.

RESPONSIBLE VACCINATION

When we look at this principle, we must compare the good effect of producing a vaccine with this type of cells with the bad effect of utilizing these cells for the purpose.

- 1) While the end product is certainly a moral good, the action by which it was created is neither morally indifferent nor good.
- 2) The use of these cells is certainly a bad effect because of the misuse of human tissue, and therefore the means itself is ethically suspect.
- 3) Since these are being sold for a profit, the motive can hardly be seen as only providing a good effect.
- 4) And, finally, the utilization of fetal cells towards a process that does not even require them creates no equitable importance between their sacrifice and the end result.

The pervading belief of companies like Merck is that there is no need to worry about moral complicity when it comes to these vaccinations. I would say otherwise. Many of these parents have every right to feel that their children should receive vaccines manufactured from non-human cells, and should feel rightly betrayed that they do not. While the Catholic Church's stance may be accepting, that does not mean that each individual inside and outside that church will be so accepting. Nor is this controversy new – HeLa cells, which were taken from a cancer patient in the early 1950's and have been used as an immortal cell line ever since, have generated similar controversy. Those cells were utilized without any notification of her or her family, and the debates that have resulted from their use have revealed serious ethical concerns. Despite all the medical contributions those cells have provided, it is deeply troubling that these cells were used in such a way without express permission. Our medical system is capable of producing this vaccine through methods that would invite no controversy, providing a life-saving preventative medication that everyone would be willing to give to their children. Certainly, there are concerns about using animal cells. However, the fact that companies who create these vaccines merely sit on their laurels and avoid advancing the technology of vaccine creation into other cell lines is reason enough for our medical system to move on.

Sources on *Supplement* page.

POLL

Are the patient's concerns (described on page 4) regarding the MMR vaccine valid?

Vote at <http://spreadsheets.google.com/a/students.kgi.edu/viewform?formkey=dGtDZmxqQmlNY1h4LURRX3Zpc0RvSWc6MQ>

- Yes, because you must consider the vaccine's source, and abortion is wrong
- Yes, because patients should consider their moral qualms in medical decisions
- No, because the vaccine saves lives of its recipients as well as others in the community
- No, because fetuses are not yet humans
- Not Sure

CONSIDER THE SOURCE

Supplement

U.S. Produced Vaccines from Aborted Cell Lines

Disease	Vaccine Name	Manufacturer	Cell line (fetal)
Polio	Poliovax	Aventis-Pasteur	MRC-5
Rabies	Imovax	Aventis-Pasteur	MRC-5
Hepatitis A	Havrix	Merck & Co.	MRC-5
Hepatitis A	Vaqta	Glaxo/SmithKline	MRC-5
Hepatitis A-B Combo	Twinrix	Glaxo/SmithKline	MRC-5
Smallpox	Acambis 1000	Acambis	MRC-5
Chickenpox	Varivax	Merck & Co.	MRC-5 / WI-38
Measels, Mumps, Rubella	MMR II	Merck & Co.	WI-38
Mumps-Rubella	Biavax II	Merck & Co.	WI-38
Measles-Rubella	MR-VAX	Merck & Co.	WI-38
Rubella only	Meruvax II	Merck & Co.	WI-38
Shingles	Zostavax	Merck & Co.	MRC-5 / WI-38

U.S. Produced Alternative Vaccines

(There are no U.S. alternatives for Chickenpox, Rubella, Hepatitis-A)

Disease	Vaccine Name	Manufacturer	Cell line
Polio	IPOL	Aventis-Pasteur	Monkey kidney
Mumps	Mumpsvax	Merck & Co.	Chick embryo
Measles	Attenuvax	Merck & Co.	Chick embryo
Rabies	RabAvert	Chiron Therapeutics	Chick embryo
Smallpox	Acambis 2000	Acambis-Baxter	Monkey Kidney
Hepatitis B	Engerix, Comvax	GlaxoSmithKline, Merck & Co	Yeast

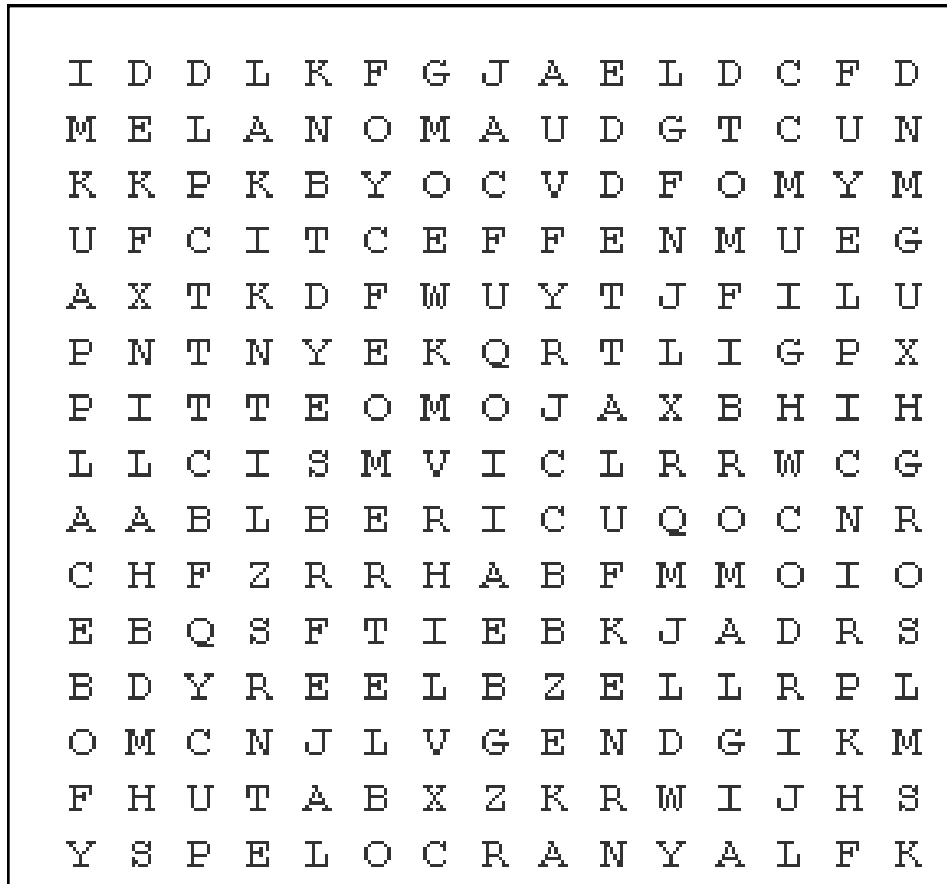
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Wordsearch

By Vinoudini Boj



ANTIBRIBERY

CONTROVERSY

DEBARMENT

EFFECT

EPIDEMIC

FDA

FIBROMALGIA

MELANOMA

NARCOLEPSY

PLACEBO

PRINCIPLE

RUBELLA

UNETHICAL



TARGETED GENE THERAPY: A DOSE OF HOPE?

By Sri Ramya Maddilate

Imagine you are suffering from terminal melanoma cancer and there is a new clinical discovery that is presently undergoing controlled clinical trials. Would you participate in the trial knowing that the chance of getting the life-saving drug instead of a placebo is only 50 percent? Would you permit a computer assigning random lottery to decide your fate? This is exactly the heart of the controversy surrounding the new melanoma drug PLX4302.

PLX4032 is a novel, oral and highly targeted drug that inhibits the BRAF (B raf protein gene) mutation which occurs in 50 percent of the melanoma cases. Plexikon, a California-based personalized medicine pharmaceutical company, is developing the drug along with the pharmaceutical giant, Roche. During Phase I and II clinical trials, the drug has demonstrated remarkable efficacy in almost all the melanoma patients. While the standard chemotherapy using dacarbazine has only slowed the tumor growth in 15 percent of the patients, PLX4032, on the other hand, actually halted tumor growth in 81 percent of patients treated with the drug (1).

This drug has proven efficacious in treating critically ill patients, even those who might be on the verge of death. A few oncologists have suggested that conducting a trial demonstrating the effect of PLX4302 on these sick patients would actually expedite the approval process by the FDA. This expedited approval is important because more patients can get the drug sooner as it shows such a tremendous benefit, but Roche fears that this might restrict the approval of the drug only to a narrow population (1). The surest way to get approval from the FDA for a broader market is to conduct a controlled trial. Roche is looking for an advantage to market its drug as a survival-prolonging agent, unlike the other competitor drugs in the market. So it has recently announced its intention to conduct a controlled clinical trial in order to get full-fledged approval from the FDA to market it to a wider population. Almost 680 patients will be included in this trial, with 50 percent of them subjected to placebo or dacarbazine drug therapy. Certain inclusion criteria for this trial include positive BRAF mutation, Stage IIIC or IV metastatic melanoma and treatment naïve (no prior anti-cancer therapy). This trial is expected to be completed by March 2014 (2).

Roche has a choice here. It could have expedited the whole process to get the drug sooner into the market for a small but really needy population. Instead, Roche choose to do a controlled clinical trial to gain large market size, delaying the process by another four years. However, terminal stage melanoma cancer patients do not have four more years to live; in fact, some of them might have only four more months to survive. Isn't it the responsibility of the FDA and Roche, to ensure the availability of the drug to these patients, especially

when the drug is working in 81 percent of the cases?

The doctors who are handling these melanoma patients in the Roche's trial knew that they are condemning patients who could actually be helped by PLX4032 by subjecting them to placebo treatment, and making their condition even worse. In fact, a couple of patients who have been administered standard chemotherapy died during this trial due to lack of appropriate treatment. This knowledge has evoked an agonized response among patients and family members who have had a chance to size up the odds. In response to this, doctors are trying to look for other trials that could help the worsening patients from the chemotherapy group of the Roche trial (1).

If PLX4032 helps these critically ill patients to live for a few more months, don't they deserve that drug? There is enough scientific data to prove the efficacy of this drug from phase I and phase II trials (1) (2). This drug gives a ray of hope to these patients to live, and it is being taken away from them through these controlled trials. Is it ethical to put a critically ill patient under a controlled trial when he or she is clearly in need of a life-saving drug to live longer? I am not arguing that controlled trials are unethical, and I strongly believe that they are important to determine the safety and efficacy of the drug



before it is approved. However, under exceptional cases like terminal stage melanoma patients who have tried all the options to improve their health condition without success, there is clearly a need to get access to this new and only drug which could help them live a little longer.

Very rarely do science, biology and clinical development totally gel and offer a new hope and promise to patients and the physicians treating them, and there are many obstacles for bringing that miracle drug from bench to the market and accessible to all the needy patients.

In my opinion, Roche and the regulatory agencies involved can be a little more flexible and provide the PLX4032 drug to the terminally ill population prior to conducting phase III studies on a larger population. If this drug is the one and only shot for terminal melanoma patients to live a little longer, then why not let them live?

Perhaps the current system can be modified in a way that aligns the interests of drug companies and terminally ill patients but still satisfies the FDA. Beginning in 1987, the FDA authorized a "Compassionate Use" policy of allowing seriously ill patients to buy an unapproved drug that shows promise when no other treatments are available (3). Patients may qualify under one of two categories: 1) expanded access programs, which are only offered during later stages of clinical trials; and 2) single-patient access. A drug company has to agree to provide the drug to the patient, but this is problematic for companies because any drug failure substantially increases their regulatory, legal, and reputational risks. Thus, the program is not used often, and although a drug company may have a good reason for denying a patient into this program, it cannot necessarily reveal its full rationale publicly.

Continued on page 8

TARGETED GENE THERAPY (cont'd)

In cases where the drug is likely to benefit the patient, one possible solution might be for the FDA to recognize a program wherein these patients sign a legal contract which specifies the level of compensation to the company, mandates non-disclosure, and provides iron-clad legal protection to the company from any liability whatsoever. The record would then be sealed so as to preserve the clinical trial success rates, and any failure in these patients could not be used against the company under any circumstance. Such protections might encourage companies to provide drugs to patients who could benefit from the drug, without compromising the drug's prospects or the company's strategic position. Roche can consider special programs like this in collaboration with the FDA to ensure the availability of PLX4032 to these terminal stage melanoma patients.

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MEET YOUR KGI ETHICS COMMITTEE

Class of 2011

Michelle Pesce, 2nd Year Ethics & Judicial Chair

(Albuquerque, NM), Bioprocessing

EC foci: Newsletter Chair, Procedures

I joined the EC because: an ethical framework is vital for implementing decisions in the pharmaceutical industry. A formal ethics education isn't necessary, but awareness around the topic is.

Adam Calvert (Redmond, WA), Business of Bioscience

EC focus: Procedures Chair

I joined the EC because: the committee provides a strong platform to push forward important initiatives at KGI.

Li Liang (Orange County, CA), Bioprocessing

EC focus: Ethics Initiatives

I joined the EC because: I believe in using what I have experienced attending KGI to guide the next class in resolving their ethical concerns.

Sri Ramya Maddilate (Andhra Pradesh, India), Business

EC focus: Newsletter

I joined the EC because: I am interested in ethics because it is omnipresent and it is important to promote the awareness of bioscience ethical issues among the KGI student community.

Marc Pollack (Ventura, CA), Pharmaceutical Discov. & Devel.

EC focus: Ethics Initiatives, Newsletter

I joined the EC because: it provides us the ability to critically analyze the way in which our school views the actions of ourselves and classmates. I don't believe there's any reasonable standards that can be set up for every school, and I enjoy the process of creating and sustaining ethical boundaries.

Yash Rane (Mumbai, India), Business

EC foci: Procedures, Newsletter

I joined the EC because: I wanted to be the part of the foundational work in constituting the Code of Ethics which will help to build a framework for future decision making process at KGI in maintaining the integrity of every individual towards our organization. In a more broad term, it's an opportunity for me to repay KGI in a very small way.

Chandana Thorat (Mumbai, India), Business & Clin/Reg. Affairs

EC foci: Ethics Initiatives, Newsletter

I joined the EC: to understand the ethical issues and concerns arising at different levels, from the school classroom to the business office and in turn make balanced, well informed decisions to better serve the community.

Class of 2012

Megan Hill, 1st Year Ethics & Judicial Chair

(St. Louis, MO), Business

EC focus: Ethics Initiatives Chair

I joined the EC because: it is (or should be) at the root of all that we do.

Susan Alfs (Los Gatos, CA), Bioprocessing

EC foci: Ethics Initiatives, Newsletter

I joined the EC because: I want to encourage dialogue about the bigger issues in biotechnology.

Vinoudini Boj (Ooty, India), Bioprocessing

EC focus: Procedures

I joined the EC because: the honor code at KGI triggered my interest in ethics. So I would like explore the ethical issues at KGI and help pull in strong -focus among fellow classmates.

Richard Head (Louisville, KY), Pharm. Discovery & Devel.

EC foci: Ethics Initiatives, Newsletter

I joined the EC because: all too often we get caught up in life and lose perspective on what really matters. I see ethics as a means to stay centered and contribute my best to society.

Wendy Milling (Federal Way, WA), Bioprocessing

EC focus: Newsletter Editor

I joined the EC because: ethics is a system of principles that guides your choices in life. I see ethics as empowering, rather than a stale list of rules and prohibitions.

Mimi Nguyen (Fountain Valley, CA), Clinical/Regulatory Aff.

EC foci: Newsletter, Procedures

I joined the EC because: it's an important aspect of our careers that is too often glossed over. I hope to help the KGI community become more informed of the ethical considerations in the biotechnology industry.

Clare Xu (Fremont, CA), Bioprocessing

EC focus: Newsletter

I joined the EC because: ethics is a framework to distinguish right from wrong in the grey space where there are no written codes to guide moral action.

Profiles assembled by Mimi Nguyen, MBS 2012.

