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The Successful Negotiator

CASE STUDY
OMNIGESIC

FOR PREVIEW PURPOSES ONLY

Prepared by

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Cast of Characters

Dr. Emmanuel Tibbett ..... NIH Senior Researcher

Dr. John Hargreaves ..... Johns Hopkins – academic researcher

Cyclonics Research Lab ..... Biotech company first selected for Omnigesics project

Champion Pharmaceuticals ..... Pharmaceutical company, joined Cyclonics in the development of Omnigesic

Allied Surgical ..... Developer of epidural pump

Dr. Ira M. Minke ..... Cyclonics – Chief of R&D

Dr. Janet Stone ..... Cyclonics – VP Clinical Development

Dr. Zwelinger ..... Purdue Team leader

Dr. Fairmont ..... Expert speaker at Advisory Committee

Case Study
Omnigesic

Introduction

The events in this case are based on real ones. The case has been prepared as a basis for group discussion, not to illustrate the correct or incorrect way to conduct these activities. The usage of Purdue and Johns Hopkins is not meant in any way to suggest they were involved in this case. The names are used only to make the case easier to read.

Background

Control of neuropathic pain syndromes remains a mystery. While a wide variety of conditions can damage nerves both within and without the spinal cord, the resulting pain syndromes are among the most challenging in medicine. Neuropathic pain can be burning, shooting, lancing, stabbing, constant, fleeting, or a dull constant companion to a life of disability. Physicians have tried heat, exercise, rest, psychotherapy, steroid injections, long acting anesthetics, destruction of the pain pathways, and little has worked. Opioid analgesics and non-steroidal analgesics are of help, but do not provide acceptable relief in many cases and are never wholly satisfactory.

Dr. Emanuel Tibbitt, a senior researcher at the NIH, has studied neuropathic pain for over ten years, focusing on the "phantom limb" pain that can occur after amputations, often in diabetic subjects. He has developed an animal model of phantom limb that reliably produces hyperalgesia in the distribution of the sensory nerve of the rat forelimb, and has been working on various therapies. The animal model allows him to test many possible therapies quickly, and he has developed a theory that both a source of painful stimuli, and damage to the small "C" fibers of the peripheral nerve and root ganglia are needed to cause neuropathic pain.

Dr. John Hargreave, an academic researcher at Johns Hopkins, is a biochemist investigating the role of neurotransmitter regulation in the tonic responses to stimuli of the spinal cord. He too studies neuropathic pain, but only because he has found that human patients with these syndromes had unusually high levels of neural peptides in the CSF. He met Dr. Tibbitt at a pain symposium, and as a result, he accepted the loan

of some of his rats, and learned that there was a new class of serotonergic neural peptides that acted in concert with the normal levels of serotonin in certain pathways to modify the "set point" for pain in the ganglia and spinal cord. If the capacity of the nerves to produce these peptides was blocked, and a low grade irritant was injected under the skin, his rats developed as bad a "phantom limb" syndrome as those studied by Dr. Tibbitt, and had the same abnormalities of spinal chemistry.

As neither Dr. Hargreave nor Dr. Tibbitt could take their discovery any farther without help, the Director of the Institute, and the Office of Intellectual Property Management at Hopkins jointly decided to advertise for a commercial partner to help them develop this theory into a useful therapy. They prepared a CRADA, a collaborative research and development agreement, and in short order they had three applicants. They were:

Cyclonics Research Laboratories is a small biotech firm that has been in existence for six years. The company was founded by several senior people who left one of the major firms in the late 1980s. They have an excellent reputation and are highly thought of. They offer to use their contacts and proven ability to support pharmaceutical development to find a series of test compounds and to develop the animal models into robust pre-clinical screening tools.

Champion Pharmaceuticals is a moderately sized pharmaceutical firm that has made its reputation as the developer of new dosage forms for old drugs. They are experts at parsimonious (cheap) drug development strategies, and have a world class reputation for their line of opioid and opioid-NSAID combination products. They are also known as a very aggressive company in their dealings with both other pharmaceutical firms and the FDA. They have come under pressure from a major European competitor, and need a new drug, (preferably something that will wow the neurologists) to retain their market. They suggest trying new dosage forms of existing short acting serotonergic agents. They are confident that they can get an effective agent approved.

Alpha Neuron is a private molecular genetics venture capital firm owned by a former department head from Johns Hopkins. He is personally known to both Dr. Tibbitts and Dr. Hargreaves and suggests that his firm is uniquely qualified to develop a new technology for altering the genetic structure of peripheral nerves. He has developed a way to add genetic material to a herpes virus, infect the ganglion, and

carry the genetic material to the nerve cell by that viral infection. He proposes isolating the gene to produce the deficient peptides, and replacing them by gene therapy.

Pre-Clinical Development

The first task was to select a commercial partner. As expected, both Dr. Tibbitts and Dr. Hargreaves were mesmerized by the vision of gene injection therapy, while their institutional representatives were much more taken with the good business savvy and track record of Champion Pharmaceuticals. Finally, after much argument, Cyclonics Research Laboratories was given the contract because they were willing to look at new compounds (pleased the researchers) and had a track record of success (pleased the managers).

They proved a capable and savvy research establishment, and were able to obtain a number of compounds that were available for purchase. They took the rodent model, and in a matter of months transformed it from a quirky research tool that took hundreds of hours of technician time per rat to a useful and robust screening test. With a battery of possible compounds and a good model, in about nine months they had identified three or four possible compounds. Two of these proved to be too toxic for consideration, but the third was a potential goldmine.

Beta-synapsine is a serotonergic partial agonist that had been tested in the seventies as a possible anti-depressant in man, but proved to have little effect on major depression in two clinical trials. Given to the pain-ridden rodents, however, it is a miracle drug. The animals double their activity, use the damaged limb over 500% more than controls, gain weight, and both the researchers agree that as best as they can determine, the characteristic spinal cord biochemical pathology is gone after three weeks of treatment with the drug.

All parties are ecstatic. The drug works in both of the rodent models, has no acute toxicity until given in five to ten times the proposed dose, and the rights to the compound are available for a reasonable amount from the original firm, (that has not a clue that their drug is anything but a research tool sought by some researchers from NIH). They also agree to hand over several lots they still have in the freezer. Ira M. Minke, the chief of R&D for Cyclonics calls a good friend who is a medical officer for the FDA. Ira is assured that if a drug has already been taken into man, there is little

resistance to additional human study from the FDA. Ira's FDA friend is excited about the research idea, and urges him to get the drug into man as soon as possible. Reassured, Cyclonics bites the bullet, buys the compound, and files an Investigational New Drug Amendment (IND) to the FDA requesting a Phase I study in man in a limited number of inpatients.

The IND is refused and a clinical hold placed on development. The FDA chemist cites several serious deficiencies in the proposal (the synthesis uses several proven carcinogens which remain in the final product in unacceptable amounts), the pharmacologist cites a series of experiments performed with a close analog of the compound that produces serious brain injury in rats, and the medical officer is very uncomfortable in testing the drug in patients without pharmacokinetic and ascending dose tolerance trials in healthy volunteers. Cyclonics receives a call from the division director informing them that the protocol is on clinical hold, and calling them in for a meeting. She indicates that he formal letter should arrive within the next several days.

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c. Should the company take this to the Ombudsman?

d. What other options are available?

e. What could the company have done to prevent this situation? What can we learn from this experience?

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The FDA staff take the issue to an advisory committee meeting, and it is a real media circus. The patient advocates end up screaming at the academic neurologists, and the agency staff are severely criticized in the media for what is perceived as excessive conservatism. The academic neuroscientists also criticize the agency in the scientific press, claiming that there is not enough safety data to support human studies. The activists behave very badly toward the agency staff, burning the Division Director in effigy and throwing decomposing animal brains at the building for the benefit of TV. After almost six months delay, the agency agreed to lift the clinical hold for limited study of the drug in healthy volunteers, provided that a number of new animal tests are done and new drug, free of carcinogens, is synthesized by modern methods.

Phase I – continued

Cyclonics conducts phase I studies in volunteer college students, and shows that the kinetics of the drug are different in man and rats (rats have ten-fold higher blood levels and prove much more sensitive to drug than humans). They also conduct a pilot clinical pharmacology study of the effect of the drug on cold pressor (ice water immersion) experimental pain. The results were equivocal, suggesting some analgesic effects, but the normal volunteer subjects reported dysphoric side effects at very low doses following intravenous administration. The results are so poor that Cyclonics chooses to call a meeting to consider backing out of the CRADA. This outrages Dr. Tibbitt, who has been experimenting with epidural administration, and who has data suggesting that the drug is almost twenty times more potent given via the epidural route than given by the IV route.

Discussion Point #2

a. Should the issue of the clinical hold have been taken to the advisory committee?

b. Were any other options available?

c. Was the company correct in not taking this to the Clinical Hold Review Committee?

Phase II

Cyclonics does continue in the CRADA, but agrees to work with a new commercial partner under a revised CRADA. Champion Pharmaceuticals is still interested, enters into a second CRADA, bringing a burst of new energy and considerable expertise in dosage form development. A joint Cyclonics/Champion project team is organized. As the Cyclonics Director of Regulatory Affairs you are appointed as the regulatory person on this committee. Within a year Champion has an epidural formulation, has completed initial animal testing for safety, and are ready to go into Phase II/III testing in patients. Having learned from their earlier problems with the agency, Cyclonics and Champion request a meeting with the review team at the agency to plan out the clinical program.

At that meeting, the agency staff reiterated their concern about the risk of neurotoxicity, reinforced by new concerns about neuraxial administration by epidural administration. In addition, the pharmacologist expressed concern that the reproductive toxicity studies done in the original application had not looked at the more sensitive behavioral measures now being used and actively discussed in the scientific press. There was a long and involved discussion, and it appeared that the clear opinion of the agency staff was that women of childbearing potential and children be excluded from the studies, but only until the animal reproductive and developmental work was done. Champion agrees.

Champion developed a small, but excellent, portfolio of efficacy trials. They study the drug in epidural administration and by intravenous administration to patients with a variety of neuropathic pain syndromes. The epidural results were very favorable. Beta-Synapsine, now named "Omnigesic", was much more effective than placebo in tolerated doses when given by epidural administration, but was not tolerated in effective doses when given intravenously. Fortuitously, a third firm, Allied Surgical Equipment, has developed an implanted epidural pump, under review by the FDA as an implantable device. The pump was tested in animals and a limited number of patients and the results were even better than with the transcutaneous epidural results in the clinical trials. Discussions with the Center for Devices suggest that there will be no problem using the new pump with the drug.

NDA Submission

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Champion does an exceptional job of working the data into an NDA, which was submitted less than two years from the start of Phase II. Much to the surprise of the sponsor, the review division in the Center for drugs refuses to file the NDA, citing the following deficiencies:

a. Lack of controlled trials of the drug used with the proposed device.

b. Inadequate study of the drug in women and children.

c. Lack of adequate pediatric experience for labeling and no request for delay or waiver of PREA requirements

The refusal to file gets out in the trade and financial press, and seriously hurts Champion stock. The development team is angry over the "arbitrary" behavior on the part of the FDA. You call the project manager, and learn that there is a much bigger problem. The new medical officer is an experienced reviewer, but has a history of conflict with Champion, and specifically their VP of Clinical Affairs. The FDA reviewer has worked in industry and has clashed with the VP when they were both working on the same project. This FDA reviewer is quoted as saying that Champion

does a poor job of demonstrating the safety of their products and relies on lawyers rather than science when developing drugs. This is going to be a problem.

In a very difficult meeting, you report the essence of your conversation to the joint development team. The Champion V.P. admits that he and the reviewers have known each other for years and have never gotten along. However, he points out "Our personal relationship should not affect how he views this compound. We have something special here, and he is doing what he accuses me of doing. He has no scientific reason for the action he's taking, so he's making this a personal issue – the science is on our side."

You suggest that you call the Project Manager and schedule a meeting with the Division, an informal conference, as required under 21CFR314.101, if you want to file even over the Division's RTF. But the V.P. says "No, we can't let him get away with this type of behavior. We should take this directly to the ombudsman." After extended discussion, it is agreed to take that step against your recommendation. There is also a strong argument to file the NDA over the objections of the review division, and you point out that in order to have the NDA accepted, you must hold the required informal meeting with the Division. Everybody agrees, however, to have a second meeting before a final decision on either issue is made.

Discussion Point # 3

You are the Director of Regulatory Affairs. You are preparing for this meeting in which you will decide if you are going to the Ombudsman and to file the NDA over the objections of the review division.

a. Should the company go to the ombudsman? Why?

b. What other options are available?

c. Should they file the NDA over the objections of the division?

d. Do you think the company is doing the right thing?

Under the PDUFA (Review) Clock

The company decides to meet with the Ombudsman. Representing the company are Drs. Minke and Stone and the Director of Regulatory Affairs. Several staff members represent the office of the Ombudsman. They indicate they will look into the matter and get back to the company as quickly as possible.

A representative of the ombudsman's office meets with the reviewer and the Division Director. She learns that the reviewer is very upset at the possibility of having to accept the application. He states that he has learned from previous experience that Champion just cannot be trusted. He says Champion makes promises and then doesn't live up to them, preferring to force a dispute that is smoothed over by the agency management. He brings forward as proof a prior product he reviewed where the company was able to convince the Division Director to approve it over his objection.

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The agency staffstart their review, and the medical officer requests that the sponsor format the data from the clinical trial into his preferred data management system. This format is foreign to the sponsor, and will cost about $500,000 in consultant's fees and take four months, but Champion agrees. The data is delivered on time, and the review progresses nicely for a while. The sponsor asks when the Advisory Committee meeting will be held, and is told it will not be till the spring. Champion has just finished planning for this when they are called and told that there is a sudden opening this fall. This is less than 30 days away, given the lag time to submit a package to the advisory committee. Champion works hard, and gets a set of presentations lined up, submits everything on time to the agency¸ only to be told that the agency will be asking Dr. Fairmont, a major spokesman and consultant for a company sponsoring a competitive chronic pain treatment to serve as an expert consultant advising the FDA. The company protests but to no avail. Dr. Fairmont is very clear about his scientific and financial relationship with the competitor. After a great deal of discussion and review within FDA, he is granted a waiver and allowed to present in the open session because his special expertise is needed by the committee.

The date for the advisory committee meeting arrives, and the agency staff are very helpful in setting up the agenda. Dr. Fairmont, the outside expert, refuses to provide

any material for the package, saying he will just speak at the session. The meeting takes place, and Champion presents an overview of the safety of the product. Dr. Fairmont stands up, and presents data on an unpublished study in six volunteers that shows biochemical evidence of early neural injury in patients receiving about 150% of the upper limit of the recommended dose by intra-spinal infusion. He advises that the drug is not well understood enough to approve. The clinical research staff from Champion protest that bringing new data that has not been reviewed is not proper. Dr. Fairmont replies that the study is still ongoing, and this is an interim look at data just available. The committee agrees that a decision is premature, and makes no recommendation, positive or negative.

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Fifteen months after filing, after many false starts, Omnigesic was approved for use with the device, although a nasty black box warning was put on the label warning against intra-spinal use.

Final Discussion Item

In the course of this IND and NDA, over thirty meetings were held between the sponsor, the academic researchers, and the FDA. In each of those meetings each side claimed that they were responding to the situation in the only reasonable way. You are an independent observer of this case.

a. Is there anything the company could have done differently at the second advisory committee meeting?

b. Is there anything the agency should have done at that time?

c. What constituencies do Champion and Cyclonics have to satisfy?

d. What constituencies do the FDA staff answer to?

e. What could both parties have done differently to improve the process in this case?