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Commentary

Who "Lost" Opioids?

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Google "opioid abuse deterrence" and you'll find a lot of hits from lawyers and elected officials. What you won't find is a lot of expert thinking from the FDA.

That needs to change.

FDA Commissioner Hamburg's March 13, 2014 testimony in front of the Senate HELP Committee) hopefully represent a more aggressive stance by the agency. That's good. But there needs to be more. The FDA must be the leading voice on the issue of abuse deterrence and the safe use of opioids.

At present, politicians and pundits (not to mention trial lawyers) own the conversation. They're the ones talking about it. They're the ones the media goes to when they write about it. Have a look at a sampling of the press coverage surrounding Zohydro and see who's quoted and what they're saying.

The struggle over control of the opioid abuse deterrence story is, shall say, not going the right way for the FDA.

The Commissioner got it right when she testified (per Zohydro), "We recognize that this is a powerful drug, but we also believe that if appropriately used, it serves an important and unique niche with respect to pain medication and it meets the standards for safety and efficacy."

In short—not all opioids are the same and not all patients respond to all opioids in the same way. Further, it's important to remember that "safe" doesn't mean 100% safe. Never has. Never will. Not for any medicine. It's always about the benefit/risk balance.

This is not a new topic. Americans woke up the morning after the Vioxx recall and were amazed to discover that drugs have risks. Good lord. Who let that happen! Avandia, in that respect, was Son of Vioxx. And, like any sequel, new actors were brought in to spice up the story. Now it's about opioids.

Relative safety is an important conversation. It's an opportunity for the FDA to help educate the public about the *safe use of drugs*.

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The foundational proposition of the FDA's "Safe Use" initiative is that the way to make a drug "safer" is to better educate prescriber, dispenser, and user about the product. And nowhere is "safe use" a more important issue than opioids.

Dr. Hamburg's testimony continued, "It doesn't do any good to label something as abuse deterrent if it isn't actually abuse deterrent, and right now, unfortunately, the technology is poor."

As with safety, "abuse deterrent" doesn't mean that an opioid can't be abused. "AD" doesn't mean "100% abuse deterrent" just as "safe" doesn't mean 100% safe.

As the saying goes, everything you read in the paper is true except for those things you know about personally. Such is the case for the drug safety imbroglio currently surrounding opioids.

The FDA must take the lead. And that means more than finessing the label. It means working with the providers of Continuing Medical Education (CME) to develop better curricula. It means more targeted Risk Evaluation and Mitigation Strategies (REMS). It means enhanced and validated reporting tools for post-marketing surveillance. It means using that data for better social science in developing tools that can assist prescribers in determining which patients are likely to abuse. "Abuse deterrence" isn't just a formulation question—it's a systems question.

One of the most promising of the FDA's initiatives on abuse deterrence is a study (to be conducted by the National Institute for Pharmaceutical Technology and Education) to evaluate opioid product formulations and in vitro performance characteristics for solid and oral dosages.

The study will investigate the effect of physiochemical properties of the active ingredient, excipient, composition, and manufacturing technology of an opioid product on potential manipulation of the active ingredient for abuse. The study is projected to take at least two years to complete—and it is not likely the FDA would issue any guidance (draft or otherwise) in the interim. This doesn't mean the agency "isn't doing anything," but "inaction to an important issue" is how many will nonetheless view it.

Unfortunately complex systems make for bad media coverage, while simplistic, dramatic demagoguing makes for sexier headlines. And when Bloomberg reporter Drew Armstrong notes that "FDA pain drug czar Bob Rappaport has already said the agency would consider jerking Zohydro from the market if an abuse-resistant version become available," it reinforces the erroneous concept of "100% abuse deterrence."[1] Dr. Rappaport understands this. The general public does not.

As the saying goes, everything you read about in the news is true—except for those things you know personally. Case in point: coverage of the FDA's advisory committee on Zohydro.

At an FDA advisory committee, the agency is asked to defend its scientific thinking in public, before a panel of experts who can dissect results, challenge conclusions, and ensure no clinical stone goes unturned. Seldom reported, however, is that advisory committee votes are recommendations. They aren't binding on the FDA.

An analysis of advisory committee recommendations compared to agency actions shows FDA followed committee advice 74% of the time. Interestingly, the agency overruled "no" votes only three times: (*Tarceva* for maintenance therapy in lung cancer, *Avastin* for breast cancer, and *Micardis* to lower blood pressure.) Since their approval, these medicines have saved, extended, and improved hundreds of thousands of lives.

So, what about the Zohydro decision? The soundbite is that the vote was against approval of the drug. That's true. But what the general public doesn't know is that, by a vote of 11-2, the experts affirmed that there was no evidence to suggest Zohydro had greater abuse or addiction potential than any other opioid.

When the committee voted, the aforementioned Dr. Bob Rappaport (Director of the FDA's Division of Anesthesia, Analgesia, and Addiction), asked members to explain their votes. All but two said that while Zohydro had met their requirements for approval, their votes were meant to call greater attention to the agency's regulation of opioids in general—not Zohydro specifically.

The FDA decided to approve Zohydro based on the agency's judgment (and the advisory committee's concordance) that the medicine is safe and effective. But the FDA also heeded the expert panel's advice for better *post-approval* regulation of opioids. Shortly before Zohydro's approval, the agency strengthened opioid labeling and post marketing requirements to address the concerns raised by the advisory committee.

There's an apt Japanese proverb that bears repeating, "Don't fix the blame. Fix the problem." Unfortunately, the recent bashing of opioids (and the FDA's regulatory decision-making and oversight thereof) isn't helping. It's time for the grown-ups to step forward and take charge of the debate on drug safety.

Former Canadian Prime Minister Pierre Trudeau once said, "There's no place for the state in the bedrooms of the nation." But what's the appropriate place for the state in our nation's pharmacies and medicine chests—particularly for opioids?

Until now, the FDA had said the drugs were appropriate for the treatment of "moderate-to-severe" pain. The new class label drops the word "moderate" and says it should be used only to manage "pain severe enough to require daily, around-the clock, long-term treatment." Additionally, FDA is adding a boxed warning on the risk of neonatal opioid withdrawal syndrome.

Manufacturers must now conduct one or more post-marketing studies to quantitatively estimate the risks of misuse, abuse, addiction, overdose and death associated with long-term use, as well as a clinical trial to evaluate the risk of developing increased sensitivity to pain with long-term use of extended-release and long-acting opioids. Companies also must conduct a study of "doctor/pharmacy shopping"—a practice in which patients visit multiple doctors and pharmacies to obtain prescriptions—and whether it is "suggestive of misuse, abuse and/or addiction." The FDA also wants companies to work together on the development of post-marketing studies. But is the agency willing to lead? And, if so, are they willing to commit the time and resources required for a serious effort?

Once the FDA's labeling changes are finalized, the agency has said it will modify the class-wide REMS for extended-release and long-acting opioids. The REMS, which the agency approved in 2012, requires companies to make educational programs available to prescribers at no or nominal cost but does not require prescribers to participate and does not include a prescriber registry.

What about Prescription Drug Monitoring Programs (PDMP) and the intended and unintended consequences thereof.

How wide a net should PDMPs cast before they begin to have the unintended consequence of restricting legitimate patient access? To infinity and beyond may make for good soundbites, but makes no practical sense. Most patient-centered thought leaders and patient advocated believe PDMPs should include Schedules 2-4.

What about e-standards for inter-operability with electronic health records? Big Data is certainly part of the answer. Knowledge is Power.

This raises the prospect of doing something that Indiana started doing with its PDMP a couple of years ago—and that a lot of other states want to do. The Hoosier State made it possible for prescribers to communicate

1 http://www.bloomberg.com/news/2014-03-12/purdue-pill-may-force-zogenix-s-rival-drug-off-market.html?cmpid=yhoo

with other prescribers about patients—so, if prescriber B sees a patient and discovers that Prescriber A has prescribed before, B can contact A and make arrangements for which one of them is going to follow the patient. Notes also can be left behind for other providers, for instance, if an ER doc gets a doctor shopper, he can leave a note about it so others are forewarned.

What about pharmacists? What's their role? Should they have broader access to patient data? Beyond being deputized by the DEA, the pharmacy community must be able to play a more appropriate role as a healthcare professional.

Beyond the debate over whether the FDA should insist that all generics be abuse deterrent (and the related IP debate), how should PDMPs instruct physicians and pharmacists? And what about formularies? Can we trust physicians to make the right call? Do all patients need abuse deterrent formulation? And, if not, what are the decision criteria? What about dose and duration limitations?

What about the issues surrounding opioid *misuse*—at present the poor public health stepchild of *abuse*? And how can better physician education defer or deter the prevalent "opioids first" prescribing philosophy of many practitioners?

In the United States, the use of opioids as first-line treatment for chronic pain conditions doesn't follow either label indications or guideline recommendations. 52% of patients diagnosed with Osteoarthritis receive an opioid pain medicine as first line treatment as do 43% of patients diagnosed with Fibromyalgia and 42% of patients with Diabetic Peripheral Neuropathy.[2] Payers often implement barriers to the use of branded, on-label non-opioid pain medicines, relegating these treatments to second line options. The result is a gateway to abuse and addiction.

This places both education (of the CME variety) and best practices (developed not just by PDMPs but also by physicians, pharmacists, and patient organizations) front and center. What about REMS training? And what about more precise criteria for what "pain specialist" or "pain clinic" even mean? As the saying goes, "if you can't measure it, then it doesn't count."

What about take-back programs? Should they only be limited to opioids? And who should pay for them?

Lastly, amercement. On a state-by-state level, does the punishment fit the crime? Should there be national standards on criminal and civil penalties?

Many tough questions—but they deserve thoughtful and timely answers. It's time for a focused national dialogue that recognizes the need for effective oversight through the use of Big Data and broader constituent alliances.

Joshua Lederberg, the Nobel Prize Laureate once observed that the failure of regulatory, legal and political institutions to integrate scientific advances into risk selection and assessment was the most important barrier to improved public health.

Lederberg noted that in the absence of such changes, "the precedents affecting the long-term rationale of social policy will be set, not on the basis of well-debated principles, but on the accidents of the first advertised examples."

Policies and regulations that seek to limit risk are often shaped by the immediate fear of sensational events. This perspective is commonly called "The Precautionary Principle" which in various forms asserts that unless innovators can demonstrate that a new technology is risk free, it should be not allowed into the marketplace. Moreover, any product that could possibly be dangerous at any level should be strictly and severely regulated.

But precaution is not always safer than the alternatives.

Some current examples of precaution and the public health:

- The National Action Plan for Adverse Drug Event Prevention, announced in a September 4, 2013 Federal Register notice, outlines a comprehensive strategy to reduce AEDs for opioids. Much of the research actions called for by the plan seem designed to decrease prescribing. For instance, the plan calls for research by CDC, NIH and, public-private collaborations to look into adopting adjunctive and behavioral modalities to augment and reduce opioids use for chronic pain;
- Upscheduling and the relabeling of medicines to treat depression, diabetes, chronic and acute pain;
- And, finally, the role of tamper-resistant technologies in the appropriate management of pain medicines (both innovator and generic).

On April 3rd, 2014 the agency's approved EVZIO™ (naloxone hydrochloride injection) for the emergency treatment of known or suspected opioid overdose. Smartly, the FDA used the approval to speak, more broadly, to the topic. In the immortal words of Don Draper, "*If you don't like* what is being said, then *change* the *conversation*.

2 IMS data

During the stakeholder teleconference the Commissioner laid it all on the table. It turns out that the FDA is doing a lot to mitigate opioid risk after all! Most importantly, they are doing so while understanding the need to ensure appropriate access for the tens of millions of Americans suffering from chronic pain.

She got specific:

Combatting the serious public health problem of misuse, abuse, addiction and overdose from opioid analgesics is a high priority. Since 2001 the FDA has taken a number of actions designed to help address prescription opioid abuse and to encourage the development of new drug treatments for pain. These actions include:

Revising the labeling for opioid medications to foster their safe and appropriate use, including recent changes to the indications and safety warnings of extended-release and long-acting opioids.

Requiring that manufacturers conduct studies of the safety of long-term use of prescription opioids.

Improving appropriate prescribing by physicians and use by patients through educational materials required as a part of a risk mitigation strategy for extended-release and long-acting opioids.

Using the agency's expedited review programs to advance development of new non-opioid medications to treat pain with the goal of bringing new non- or less-abusable products to market.

Working with other federal agencies and scientists to advance our understanding of the mechanisms for pain and how to treat it, including the search for new non-opioid medications for pain.

Recommending that hydrocodone-containing combination products have additional restrictions on their use by rescheduling them from Schedule III to Schedule II.

Strengthening surveillance efforts to actively monitor the changing nature of prescription opioid abuse and to identify emerging issues.

And, importantly, encouraging the development of medications to treat opioid abuse, such as buprenorphine for use in medication-assisted treatment, and to reverse opioid overdoses, such as naloxone.

Not all of these actions are without negative unintended consequences (upscheduling impacts appropriate access), but it's a pretty powerful list.

The Commissioner returned again and again to the role the FDA must play in facilitating physician education, not only through labeling language but physician education. She specifically mentioned CME and working to develop (with a broad constituency) validated tools for physicians to use in determining which patients may be more prone to slide into abuse so they can choose their therapeutic recommendations more precisely.

"It all comes back to provider education," she said. Amen.

That's not regulatory mission creep; it's the appropriate application of the agency's Safe Use of Drugs initiative. The way you make a drug "safer" is to ensure that it is used by the right patient in the proper manner.

Importantly, the Commissioner regularly referred not to "abuse" but to "misuse and abuse." That's more than a rhetorical flourish since it recognizes that misuse is a gateway to abuse.

Provider education—the Hamburg Manifesto.

The take away message was loud and clear—misuse and abuse of opioids is a serious issue that must be addressed in an appropriate manner.

It's also important to consider the DEA's "Thug Regulation" strategy that results in a decline in appropriate patient access; an increase in regulatory time and cost and, ultimately, a decline in innovation.

The California Medical Association has received reports from physicians that Walgreens pharmacists are refusing to fill controlled substances prescriptions without additional information from the prescriber.

Per dictates from the DEA, Walgreen's pharmacists are now demanding that physicians provide information on diagnosis, ICD-9 codes, expected length of therapy and previous medications tried and failed.

In other words, tighter restrictions for patients who really need the medications, more paperwork for physicians and a heavier workload for pharmacists. Abusers and criminals rarely follow regulations.

When you have a hammer, every problem looks like a nail. The DEA sees opioid abuse and seeks to minimize access to them. That's a law enforcement solution. They mean well—but are behaving like a bull in a china shop

Arbitrarily limiting choice is not generally associated with the Scientific Method.

Should regulation be shaped by factors other than science or should advances in medicine and digital information be used to right-size regulation, reduce the excessive reductionism that leads to regulatory overreaction and promote resilience rather than ever increasing restrictions?

Consider the program recently instituted by CVS (and detailed in a recent *New England Journal of Medicine* perspective piece[3]) where, via the use of "Big Data" the chain pharmacy identified "outlier prescribers" and took appropriate and responsible actions.

The DEA's attempt to deputize pharmacists on the one hand and the CVS program on the other raise some interesting questions:

- What will the role of the 21st century pharmacist be in improving drug safety and medication adherence via more proactive (and remunerated) patient education?
- How can pharmacists become better integrated (beyond Med Guides) into the FDA's Safe Use of Medicines initiative?
- When will pharmacy synchronization programs really kick into gear, and how will states help to jump-start these important initiatives?

To paraphrase the American political scientist Aaron Wildavsky, we need a strategy of resilience based on experience. We must learn from adverse consequences in order to develop a capacity to advance the public health. Variability is the key to survival.

According to the CDC in 2008, there were 14,800 opioid overdose deaths. Half of those, the CDC has claimed, involved opioids and other illicit substances, whether it's cocaine or heroin, or alcohol. They also mentioned that alcohol was involved in many of those deaths but they don't actually tell us the numbers. So conservatively, half or 7,400 deaths occurred in 2008 from opioid overdose. The same year from CDC's own statistics, there were 36,500 suicides. There also were 24,000 alcohol-induced deaths and that doesn't count other related alcohol deaths like drunk driving. The bottom line is that the opioid numbers do not even come up in the CDC's list of the top 15 causes of death of Americans

It's important to add to this "epidemic" perspective, the fact that people suffering fromchronic pain are under-served by existing therapies. A recent IOM report that was issued in June of 2011 found that 100 million Americans are now living with chronic pain. That's a third of the U.S. population. Ten million of those have pain so severe that they are disabled by the pain. The report also said that pain costs the U.S. economy about 600 billion dollars a year in lost productivity and health-care cost.

The vast majority of people who use opioids do so legally and safely. A subset, approximately four percent use these medications illegally. In fact, from 2010 to 2011, the number of Americans misusing and abusing opioid medications *declined* from 4.6% to 4.2%.

And the FDA's Zohydro decision was "controversial?" Really?

What ever happened to "politics has no role at the FDA?"

Joe Manchin (D, WVA) introduced a bill to overturn the FDA's approval of the opioid Zohydro ER. That certainly *sounds* like legislating science.

As a part of his rationale, Senator Manchin noted that the agency approved the drug last year over the objections of an advisory committee that had voted 11-2 to recommend rejection of the drug.

Yes, Senator, that's why it's called an *advisory* committee. Would he make such votesbinding on the agency? That's a pretty radical shift in regulatory policy. Alas, Senator Manchin isn't alone in his well-meaning but misguided attempts to legislate science. Senator Charles Schumer (D, NY) is urging Health and Human Services Secretary Kathleen Sebelius "to overturn the government's approval of a new powerful prescription opioid, Zohydro ER" (hydrocodone), "until it has been made abuse-proof."

According to reports, Schumer "believed there was a 'decent chance' that" Sebelius would revoke the FDA approval.

In addition to Senator Manchin's call for legislation and Senator Schumer's call for Secretarial interference, this careful balance is also being called into question by 28 state attorneys general who, in a letter to FDA Commissioner Margaret Hamburg, ask the agency to "reconsider its controversial approval of the powerful new narcotic painkiller known as Zohydro." The attorneys general are concerned that the medicinelacks "an abuse-limiting formula." And Massachusetts Governor Deval Patrick wants to ban Zohydro from the medicine chests of the Bay State.

Was the approval "controversial?" Well, it depends what you mean by "controversial." It's controversial because the issue of opioid abuse is controversial. And that's an important difference. Nobody said the FDA's job was easy.

Whatever your position on the issue of opioids, the proper venue for this decision is not the office of the Secretary of HHS or the halls of Congress or the courts—but rather the office of the FDA Commissioner.

Rather than dealing with the problem of abuse with sledgehammer solutions, Senators' Manchin and

3 Mitch Betses, R.Ph., and Troyen Brennan, M.D., M.P.H, "Abusive Prescribing of Controlled Substances," *New England Journal of Medicine*, August 21, 2013 DOI: 10.1056/NEJMp1308222

Schumer, and the various state AGs should focus on potential solutions such as:

- The role of the 21st century pharmacist in improving drug safety and medication adherence via more proactive and remunerated patient education? How can pharmacists become better integrated beyond Med Guides into the FDA's Safe Use of Medicines initiative? When will pharmacy synchronization really kick into gear, and how will states help to jump-start these important initiatives?
- Government and legislative initiatives such as the Stop Act (H.R. 486), which focuses on tamper-deterrent formulations and the continued development of those. Also, Senate Bill 1277 (sponsored by Senator Barbara Boxer, D/CA) which would establish a commission to bring all of the stakeholders together to have discussions about how to approach this issue so that law enforcement, providers, patients, and pharma can debate the issues and reach common ground.
- The appropriate role of tamper-resistant technologies. They are part of the solution, but they're not the *whole* solution. We need to develop policy options that focus on the prescriber/patient relationship, and a professional assessment of what's the risk involving this patient. Is the patient is going to tamper with the medication and potentially expose themselves or others to some danger. We have to do a better job (via CME and other methods) of training physicians and other prescribers on how to do these kinds of assessments.

In "Personalized Medicine and Responsible Access to Pain Medication" (a white paper based on the Center for Medicine in the Public Interest's September 2013 Capital Hill conference), Dr. Douglas Throckmorton, CDER's Deputy Director, for Regulatory Programs and the FDA's point person on opioids, writes,

> *We understand that for the millions of Americans experiencing an acute medical need or living with chronic pain, opioids, when prescribed appropriately, can allow patients to manage their pain as well as significantly improve their quality of life. However, we have also become increasingly concerned about the abuse and misuse of opioids. We are challenged with determining how to best balance the need to ensure continued access to patients who need these medications while addressing concerns about abuse and misuse.*

The FDA must walk a difficult public health tightrope, balancing patient need, medication safety, and (in the case of opioids), the dangers of abuse. And, most importantly, we need to keep the needs of patients front and center.

Commentary

GM tea: The need of the hour to reclaim India's leading position in the global tea market

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TO THE EDITOR

India had been the top tea producing nation for over a century, but relinquished that position to China in 2004. After domination of the global tea market for about 170 years, India now faces rising competition, which it has not been able to combat well and has thus slipped to fourth position.[1] There has been a particularly sharp decline in India's market share in the global tea export since the late 1980s as evidenced from the steady wane of 20.86% in 1986 to 12.34% in 2008. Also, there is an excess supply but not sufficient demand for Indian tea to boost profit percentage.[2,3] Countries which had been long-standing customers of Indian tea like USSR and UK have drastically reduced import of tea from India, while tea production in India grew by about 250% since 1947 (255 million kg) and in 2007 (950 million kg).[4] India's tea production increased at a 3-year annual average of 0.3 per cent to 988 million kg in 2011. The global oversupply of tea increased from 78,000 tonnes in 2010 to 111,000 tonnes in 2011 while the annual consumption of 4,300 million kg was predicted in 2012—this indicated an extremely small cushion against potential supply disruption.[5]

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A global economic slump, weaker global growth outlook, rising tea prices, and a sharp decline in coffee prices coupled with a faster-growing coffee market which adversely affected tea consumption in Europe, resulted in marginal decline in India's tea exports, from 193 million kgs to 180 million kgs in 2012. Exports declined at a three-year compounded average growth rate (CAGR) of 1.7 per cent during 2009-11. India's exports to Iran, a major consumer of Indian tea, were also seen to decline in 2012 because of US and EU sanctions. Hence, growth in tea supply was expected to be globally low during 2012-13, following the marginal increase in surplus during 2011. Tea output in 2012 was predicted to decline in both India and Kenya, and increase only by 4-5 million kg in Sri Lanka. World tea consumption was also forecast to increase at a lower rate of 2.9 per cent in 2012 as par the IMaCs report. Though India's tea consumption increased 2.3 per cent in 2011, growth forecast was predicted to be marginally lower at 2.2 per cent in 2012 because of slowing economic growth and increase in prices of tea and milk.[5]

India's tea production came down 11.4 per cent in the first five months of 2012. Production experienced a downward trend from October 2011, with especially severe declines around March-April 2012. While production in North India declined to a 12.2 per cent, production in South India was down by 10.2 per cent. Overall, the domestic production was forecast to decline to around 950 million kg in 2012, according to the IMaCS report on Indian tea industry. Based on the forecast of lower increase in supply, the market surplus was

also expected to decline to around 70,000 tonnes in 2012. Although the market could return to higher surplus during 2013 in line with a slightly faster rise in production than in consumption, concerns about supply disruptions were still present.[6]

The decline in India's market share in the global tea market due to a decrease in tea production and also due to reduced quality is also seen to be affected by a few internal factors. Extensive use of hazardous fertilizers and pesticides, increase in cost of production due to climate change, soil fertility, poor agricultural practices are some of the major factors. In North India, production was affected adversely by prolonged winter in 2011-12. Similarly, in South India, a prolonged dry spell in Tamil Nadu and Kerala saw a marked decline in tea production. The unabated depletion of organic matter and nutrients also lead to significant decline of soil fertility and hence to a decrease in the production of tea. However, effective agricultural practices to combat this are scarce and practiced only among a few well-educated tea growers.[6]

The problems plaguing the Indian tea industry can be solved only through proper implementation of the latest biotechnological technologies which are already being well-researched in R&D laboratories across the nation. India boasts of a R&D network of nearly three hundred national laboratories and about an equal number of universities. The national laboratories operate under various departments or agencies of the Government of India, notably the Council of Scientific and Industrial Research (CSIR), the Indian Council of Agricultural Research (ICAR), the Indian Council of Medical Research (ICMR), the Department of Science and Technology (DST) and the Department of Biotechnology (DBT), among others. All of these institutions have state-of-the-art research facilities and stellar scientific research is performed under strict regulation and stringent quality control measures. However these research findings, though novel and significant enough to be published in high-impact journals are yet to find their implementation in practical agriculture. Genetic engineering technologies can be used for the production of genetically modified (GM) crops—in this case, tea plants, which would be drought-resistant, pesticide-resistant, insect-resistant, and have higher yield with reduced need of fertilizers. However, it is seen that adherence to age-old methods of tea growers and a skeptic attitude to adopt any new scientific technology are making it nearly impossible to combat the challenges that natural calamities or man-made situations present to the growth of the tea industry in India.

However, the Prime Minister has himself made a statement that the government should not succumb to "unscientific prejudices" against genetically modified (GM) crops. Anti-GM activists who oppose even

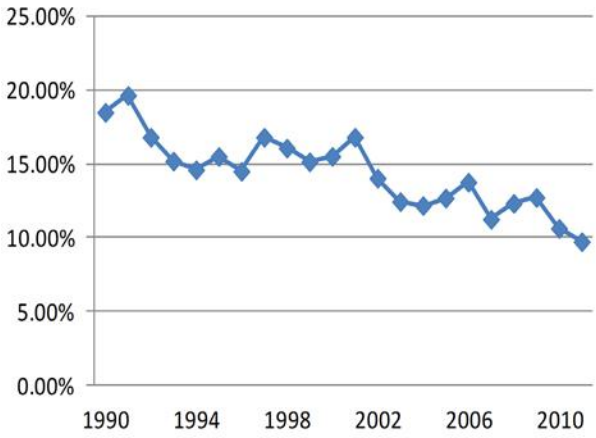

Figure 1: Indian share of global tea exports[2,3]

scientific field trials of genetically engineered crops have been met with a firm response by the Prime Minister with the declaration that his government remained committed "to promoting the use of these new technologies for agricultural development".[7] This public comment from the Prime Minister may signal a change in stance of both a reluctant government and skeptical tea growers in co-operating and benefiting from new age technology like genetic engineering.

In keeping with a dedicated approach to promoting even further R&D to tackle agricultural woes, the government has announced an extension of weighted deduction of 200 percent on expenditure on in-house R&D facilities for five years, starting 3st March 2012. There is also proposed weighted deduction of 150 per cent in agricultural extensions- so that Biotech companies in India are motivated strongly to invest in the agri-biotech segment to increase crop yields. Further, the government has sanctioned a research grant of Rs 350 crore (US$ 66 billion) for Agri-universities, of which Rs 100 crore (US$ 18.8 billion) has already been sanctioned for the Kerala agri-university. This funding is a move to aid 1,500 scientists across the country to work on various seed research programmes to simultaneously improve the productivity of crops while lowering the use of pesticides. Agriculture contributes to 14 per cent of the GDP, and is one of the most important contributors to the overall economy—not to mention one of the most necessary too. Hence, wise and effective investments to increase the agricultural output of the country will, without doubt, have a positive impact on the economy in the long term.[8]

Among the achievements of India in R&D till now is the success in decoding the genome information of rice chromosome 11 and the filing of six patents related to the mass production of bio-control agents/bio pesticides. Further, the total culture repository at the National

Centre for Cell Science has reached 1,161 samples after the addition of 34 new cell lines.[8]

The biotechnology sector in India is expected to generate revenue of US $11.6 billion by 2017, growing at a compound annual growth rate (CAGR) of 22 per cent, according to a recent report by Ernst & Young (E&Y). Revenue from biotech exports reached US$ 2.2 billion in FY13, accounting for more than half (51 per cent) of total industry revenues. During FY05 and FY13, revenue from exports increased at a CAGR of 25.1 per cent to US$ 2.2 billion from US$ 0.4 billion. The key growth drivers of the US $4.3 billion industry include strong domestic demand for Biotech products, growth in contract services, focus on R&D initiatives and strong government support for the sector.[8]

With a keen and helpful Government at the helm, dedicated and brilliant scientists at work and eager investors at hand, the use of advanced scientific technologies-specially genetic engineering to produce GM tea, will aid and ensure the return of Indian tea to the coveted leading position in the world tea market. All that is required of present tea-growers is less dependence on age-old methods of tea cultivation, and willing participation in trials of new-age technologies that are designed and conceived through dedicated R&D of tea production.

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Article

What makes a happy team? Data from 5 years' entrepreneurship teaching suggests that working style is a major determinant of team contentment

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ABSTRACT

I report on five years' testing of what makes a happy team, using students in a Bioscience Entrepreneurship Masters programme at Cambridge University as a test-bed. I looked at measures of personality (using the IPIP test for the Big Five personality characteristics) and a measure of work style derived from the time of submission of work that I term Deadline Brinkmanship. I find that teams selected to have a similar working style are generally happier working together than those selected by other criteria. Entrepreneurial activity is not significantly correlated with psychological characteristics in this study, but is slightly correlated with working style and the willingness to accept a "good enough" result now rather than an ideal result in the future. I suggest that it may be useful for a nascent entrepreneurial team to work together on an important, deadline-driven task before committing to a new venture to test for work style compatability.

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Keywords: founding team; startup; personality; Big five; work style

INTRODUCTION

What makes a good, a happy, or a successful entrepreneurial team? Many of us wish we knew, both for our own use and for educating others. Despite the media focus on the heroic lone entrepreneur, almost all businesses are actually created by teams,[1] and identifying how to build successful teams is therefore of substantial importance to business literature and economic policy. There is a wide range of research and advice on how to build the team for a new venture[2-8] and on team motivation.[9-12] Clearly, a start-up management team needs a range of skills and capabilities to manage, grow, finance and exit their company.[3,4,13] A diverse experience is usually helpful[14], and specific skills are essential, although prior track record of success, while always cited as a leading factor in attracting investment, is not actually that valuable a predictor of future success.[5,15,16] The standard investor mantra is that a good, investable management team covers the key skills needed to grow and exit the business. There is actually strong evidence that venture investors do not invest in such teams, but rather invest in teams that have previously shown they can create a successful business, and then replace them[17, 18]. However these managing teams do not necessarily represent *founding* teams.

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As Nelson says, "Every firm exists because some founding person or group of persons made the decision to establish a firm and then acted on that decision."[19] The terms new venture team, founding team, and entrepreneurial team are often used nearly interchangeably for those founding persons. However the demands on what Forster called the 'Founding Partnership', the group of people who come together to define and create a new enterprise,[20] are quite different from those on the team that then builds and runs the enterprise. The founding team rarely has all the skills that management theory and investor rhetoric says are needed for management of a start-up, but this is not a predictor of future failure (see Figure 1). Rather, the founding team is characterised by the willingness and ability to work together for a long time to develop the new business idea until it is ready to receive the skilled management it will ultimately require.

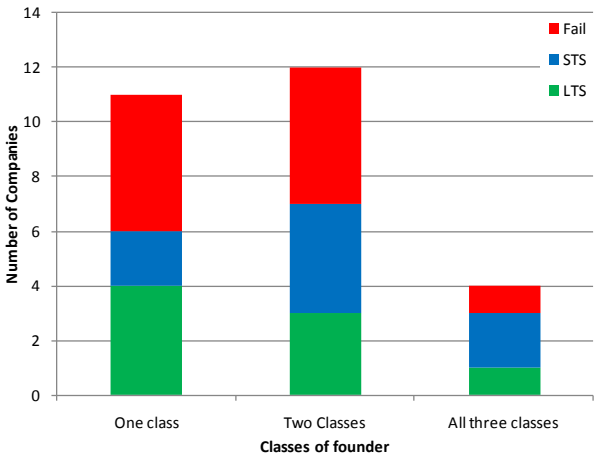

Figure 1: Skill set completeness in UK biotechnology companies

The founding teams of 27 UK biotechnology companies, founded between 2005 and 2012, were categorized on whether each member brought science/technology, business/marketing/selling, or financial skills to the company. A founding member could bring more than one skill set. X axis: number of these classes represented in the founding team. Y axis: number of company founding teams. Companies are classified as Long Term Successful (LTS) if they had raised several rounds of finance, achieved break-even in sales or exited, Short Term Successful (STS) if they had achieved their immediate business goals (usually raise one round of finance or close one major deal), or Failed (Fail) if they did not raise any finance or complete any initial sales or deals. Note that, of the 16 "successful" companies, 6 no longer existed as independent entities in Jan 2014 and had lost their initial (seed or Series A) investors some or all of their invested money. There is no statistical difference between the one, two and three-function teams (Chi squared statistic for testing the null hypothesis that LTS, STS and Fail are not significantly different between one- two- and three-class sets = 1.69 – critical value for p=0.05 for 4 degrees of freedom = 9.49, null hypothesis not rejected.)

The Founding Partnership needs to define the business they are going to build, a process that involves many iterations of planning preliminary business ideas (that usually turn out to be unworkable) in order to reach a potentially workable and convincing business plan.[21] The ability to do this successfully is a Dynamic Capability in the terminology of Resource Based Valuation[22]. Dynamic Capabilities are defined as

> *"the firm's processes that use resources — specifically the processes to integrate, reconfigure, gain and release resources — to match and even create market change. Dynamic capabilities this are the organizational and strategic routines by which firms achieve new resource configurations as markets emerge, collide, split, evolve and die."*[22]

The start-up is the search for a business model, not the operation of a business plan,[23,24] and because that model is not defined, the Dynamic Capabilities necessary at start-up, when there is no established firm, are functions of team dynamics, not business processes.[25,26] Thus the core of the value of a start-up is embedded in how the Founding Partnership work together. The start-up venture operates as if it were in a highly volatile market (a "high velocity environment"[27]), even if its actual market is a well-established one, because for the start-up what they are going to do next is not defined. In such an environment, flexibility and close working together are the key Capabilities, as opposed to detailed operational procedures in more established businesses. Thus team efficiency is key not only to team happiness but to success.

This deep working connection must be sustained.[23-25] A key early action for the Founding Partnership is raising money, which takes substantial time — the amount of time spent *failing* to gain investment is obviously hard to define, but can run to years. For a small, first time investee company that is *successful* in raising investment, the average time in UK biotechnology successfully to close the investment deal *after* they have produced an "investment-ready" business plan is around 9 months (Figure 2). During this time the Founding Partnership must work hard together, for free. This aspect of founding a new enterprise is usually skated over in case histories, which focus on initiating events and the business opportunity and not the long, hard slog to get from one to the other (for examples of such narratives, see refs[28,29]). During this time, the team must be happy to work together and trust each other: trust is a key determinant of success in early start-ups[30].

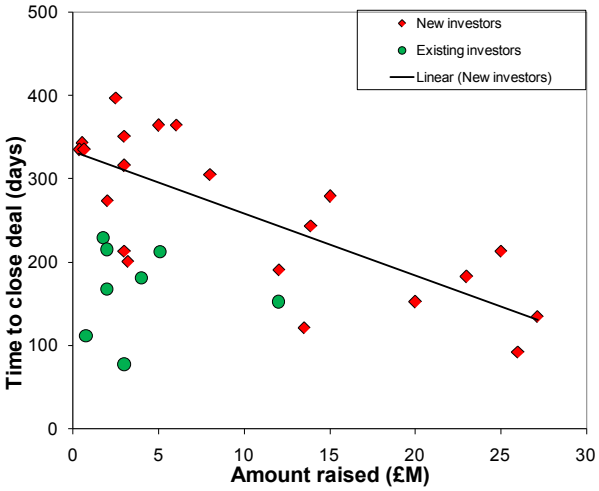

Figure 2: Time needed to raise investment

Time from sending out an investment ready business plan to agreeing Heads of Terms on an investment in that plan, for UK biotechnology companies. Data gathered by the author from confidential discussions with 32 UK biotech companies 2005 – 2010. "New Investor"– investment in a round where at least 1/3 of the shares were acquired by an investor not an existing shareholder in the investee company. 'Existing investor' – investment in a round where >2/3 of the shareholders were already shareholders in the company. Solid line – least squares best fit to "New Investors" data points.

What triggers the entrepreneurial journey is need, ambition, and that poorly defined thing "entrepreneurship". But what makes them keep on doing it, and not go back to the "day job"? In ten years' teaching on the University of Cambridge Masters in Bioscience Enterprise (MBE) programme,[i] I have been involved in discussions with over 250 students about founding teams' history and characteristics. In theory the entrepreneur is ambitious, confident, risk-averse, extrovert, and completely focussed on commercial success.[30] Class studies, visiting speakers and site visits have provided a wide range of examples of the entrepreneurial journey. The founders' personal experiences vary from the classic view summarised above to successful founders who apparently fitted none of the standard models of a new venture team. Intrigued by this, I have probed the question of what features of a Founding Partnership might enable them to work together during that pre-incorporation stage of the entrepreneurial journey, i.e. what makes them a happy team even if they are not ultimately a successful one. I have also made some limited observations on their entrepreneurial propensities as well. I hope in a decade to be able to provide a retrospective report on what characteristics subsequently lead the study participants to entrepreneurial *success*[ii].

METHODS

The student group

The majority of the results below are from students of the MBE course from years 2008/9 thru 2012/13, with some additional data on personality and entrepreneurship from 2013/14. Average student age was 25.7 years (Standard deviation 3.86 years) for the 137 men, 26.2 years (SD=6.09) for the 116 women. The students came from 33 different countries, with UK (59 students), non-UK EU countries (35 students), USA (38 students), India (20 students), and China (11 students) the most highly represented regions. The module in which these tests were done was run during the autumn term (October through December), and concerned start-up company creation and finance. The various exercises therefore supported teaching goals on team formation in this module. The students interact very intensely from the start of the course, contributing to "workplace" socialization:[31,32] as a result none of the team members were 'newbies' or 'outsiders' when these studies were conducted.

The non-student group

As an 'outgroup' for the personality tests, I also e-mailed the test form to ~100 non-students involved in the Cambridge area biotechnology cluster, and received 37 responses. A summary of this group is provided in Table 1.

Group preferences and personality profiles

Group preferences were collected by written, anonymous comments at the end of the course, as described below. 'Big Five' personality characteristics were constructed from a 100-question International Personality Item Pool (IPIP) questionnaire originally developed by Prof. Tom Buchannon at the University of Westminster, UK (www.buchanan.org.uk). The questionnaire was administered at the start of the term to students and by e-mail in March 2009 to non-student volunteers.

i http://www.ceb.cam.ac.uk/pages/masters-in-bioscience-enterprise-programme.html

ii If I can define success, and am still alive.

Table 1: Non-student participants in the IPIP personality survey

Type of participant	Number	
	Male	Female
Scientist / technologist	5	1
SME Exec	3	0
Consultant / professional services (SME/sole trader)	5	3
Consultant / professional services (large company)	3	2
Biz dev exec (including TTO)	2	1
Own start-up (other than professional services)	5	1
VC/finance	6	0

Personal data and permissions

Data has been collected from students on the University of Cambridge *Masters in Bioscience Enterprise* programme and by questionnaires sent to ex-students and to Cambridge area professionals. Test subjects were asked to fill in the forms in person or by e-mail. It was made clear to all of the student participants that the exercises were not linked in any way to course assessment. A small fraction of the students chose not to fill in the questionnaires, or were not present when questionnaires were administered, or failed to follow the instructions and so produced invalid responses. Feedback on the scores and analysis were provided back to the individual only, and not made available to anyone else (with the exception of the author's test scores, which he is happy to share).

Group assignments (see *The Big Five personality traits*, below) were done according to the study design, unless a student had a strong objection to working with another student, in which case their wishes were respected. Across the course students were assigned to groups in such as way that every student worked with as many fellow students as possible, so the studies reported here did not affect their degree experience or outcome.

Entrepreneurship

A criterion of acceptance into the MBE course is that students show evidence that they have been 'entrepreneurial' in some sense. I therefore defined 'entrepreneurial' activities very narrowly as any activity where the individual was a founding member of a new enterprise (whether for-profit or non-profit) that was set up outside their current institution (whether school, university or employment), set up without substantial *prior* commitment of resources by others (such as grants or investment), and with substantial investment of time or other resources on the founders' part. Examples of 'entrepreneurial' activities include setting up a new company, setting up a new charity, launching an independent publication. Examples of non-entrepreneurial activity (under this restrictive definition) are heading the formation of a new group within a company, leading a university organization, or organizing a student expedition. By adopting this restricted definition I avoided the requirement to make value judgements about the level of risk, initiative and personal investment needed in a wide range of disparate activities from students from many countries.

This definition does not take into account whether the entrepreneurial activity was a success. The point of this study was to analyse founding parnerships, and not the many factors (most of which are out of the control of the founding team) that can affect outcome.

Other data

Other data have been collected by the author over the last 10 years from interviews with biotechnology companies and their founders, primarily in the UK.

Data availability

The IPIP questionnaire, calculation spreadsheet and summary personality data from which this paper was derived can be downloaded as an Excel spreadsheet from www.rufus-scientific.com/grouppersonality/index.html. No individual data or data identifying individuals is in this data set.

RESULTS

The Big Five personality traits

As this study is about team personality rather than team skill, I have used two measures of personality: the Big Five personality traits (as measured by the IPIP questionnaire) and a workstyle measure (described below).

The Big Five personality dimensions are widely used as descriptors of underlying personality traits.[33,34] Terminology differs slightly between studies: the terms used here are:

- Extraversion: outgoing, social, seeking stimulation from the company of others vs

quiet, solitary, preferring small groups or individual pursuits
- Agreeableness: trusting, compassionate, empathic vs suspicious, un-empathic, less concerned with others
- Conscientiousness: efficient, liking completion, detail-orientated, self-disciplined vs relaxed, easy-going
- Emotional stability: able to cope with adverse emotions, not prone to emotional extremes, good impulse control vs 'moody', subject to substantial changes in affect and motivation
- Intellect or Imagination: curious, interested in new ideas and experiences, preference for novelty vs prefers the predictable.

These are as much a reflection of someone's self-image as an absolute measure of some neurological activity. However the Big Five are generally accepted as features of people's core psychology that reflect how they behave in a variety of situations. They are also reasonably stable over time: as an illustration, I have taken my own test six times over 5 years, and the scores remained very consistent (Extraversion 50 (standard deviation of 6 results over 5 years = 3.3), Agreeableness 51 (σ = 1.9), Conscientiousness 74 (σ = 4.4), Emotional Stability 31 (σ = 2.8), Intellect or Imagination 95 (σ = 1.4) (c.f. Figure 5).

The International Personality Item Pool is a scientific collaboratory for personality difference tests, and I have used one of their tests essentially unaltered to develop a profile for this study (see *Methods*, above). Note that the numbers generated by the test are relative for each characteristic of personality, and can *only* be used to compare different individuals or groups for one character. If someone has an Extraversion score of 70 and an Intellect and Imagination score of 80, it does not mean that they are more intellectual than extrovert. It only means that they are more extravert than someone with an Extraversion score of 60, and have less of the Intellect and Imagination score than someone with a score on Intellect and Imagination of 90.

Work style

My other probe for personality is not formalised in the psychology literature as far as I know, but reflects what is a common observation among anyone trying to get someone else to complete a task, from doing their schoolwork to writing their shareholder reports. Some people send in work well in advance, some only at the last minute. I therefore devised a simple measure of what I describe as Deadline Brinkmanship (DB). As part of their assessment, students were asked to write two or three (depending on the syllabus for the year) short analyses on case studies (typically 300 words) to be submitted by e-mail by the start of the next session 2-4 days' after the task was set. Sessions started at 9am. The case studies were then discussed during the session, and the student scripts marked and commented on afterwards. I recorded the time the e-mail was sent by each student, and (solely for the purposes of this study, and without using the data for any other purpose) rank ordered the students according to when their e-mailed submission arrived. Figure 3 shows the distribution of submission times for three years. There is a wide distribution of times, from submission two days before the deadline to 10 minutes before the session started. Obviously there are many reasons why someone sends an e-mail at a particular time. For example, there is a clear dip in submissions between 3 and 7 hours before the 9am deadline, which is between 3am and 7am, when the students would reasonably be expected to be asleep or socializing. However the rank order in which students submitted their work were moderately consistent: the difference between submission rank order from one week to the next for each student averaged 4.68 places across the five years of this exercise — if work was submitted essentially at random, a difference of 8.04 places (standard deviation 1.07 places) would be expected of a group of 24 students.

DB is weakly correlated with Conscientiousness (i.e. students with higher Conscientiousness scores tended to submit their work slightly later), other personality traits showed no correlation with DB (Table 2).

Happy groups

The main focus of my study was on what made a team work well together, i.e. what made a *happy* team, rather than what made a entrepreneur, although I can address this second question as well (see *Entrepreneurs and personality*, below). It is clear that teams with members who have wildly different personality types[35] or extremely different cultural backgrounds[36] function badly. However such extremes are filtered out by the application process for a Cambridge University degree.

During the term I set the students group tasks, and put them into groups that were selected to be i) optimised for match of their DB score, ii) optimised for their match for IPIP score, or iii) optimised for some other criterion. Other criteria included the marks they gained on the first exercise, how close they sat to someone in the class, and marks on other parts of the course — preliminary studies of groups in this and other modules of the course suggested that these different criteria had an equally

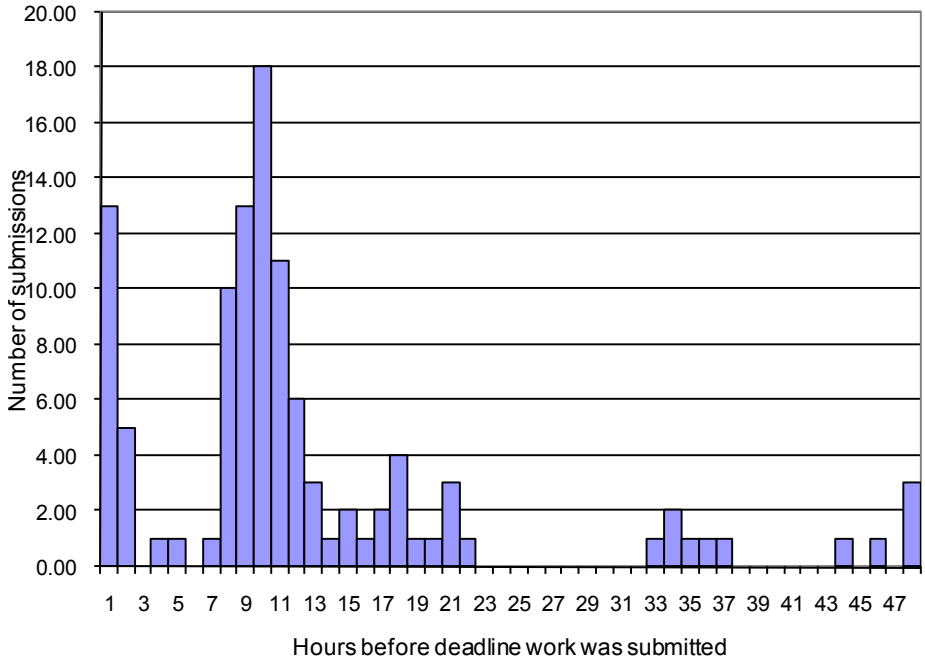

Figure 3: Time of submission of student work

Hour before the due time (09:00) when students submitted their individual written work for assessment, for 110 student work submissions between 2010 and 2012 inclusive. Y axis – number of students. X-axis: hour of submission, ie '1' = in the last hour before the deadline (08:01 to 09:00).

Table 2: Correlations between psychological measures

	Extraversion	Agreeableness	Conscientiousness	Emotional stability	Intellect or imagination
Extraversion					
Agreeableness	0.483				
Conscientiousness	-0.013	0.120			
Emotional stability	0.302	0.351	0.058		
Intellect or imagination	0.249	0.030	0.180	-0.005	
Deadline Brinkmanship (students only)	-0.085	-0.090	0.311	-0.229	0.165

small effect on group preference (not shown). I did not tell the students the criteria used for putting into groups until the end of the term. At the end of the term I asked for them to anonymously indicate which group they had enjoyed working with most and which group least, *disregarding* the task the group had to perform.

The result of group preferences are shown in Figure 4. The data is fairly noisy, as the design of the questionnaire as well as the course syllabus (and hence the tasks the groups had to perform) changed each year, and obviously the syllabus had to take precedence over the requirements of this study. It is also notable that the answers are non-commutative — sometimes students stated on their written replies that they preferred A to B, B to C and C to A. However it is clear that groups selected on the basis of DB were preferred over those selected on non-personality-based selections, and groups selected on the basis of DB are disliked least. Figure 4 hint that groups selected by DB are preferred to those selected by IPIP, but the data on this is not conclusive.

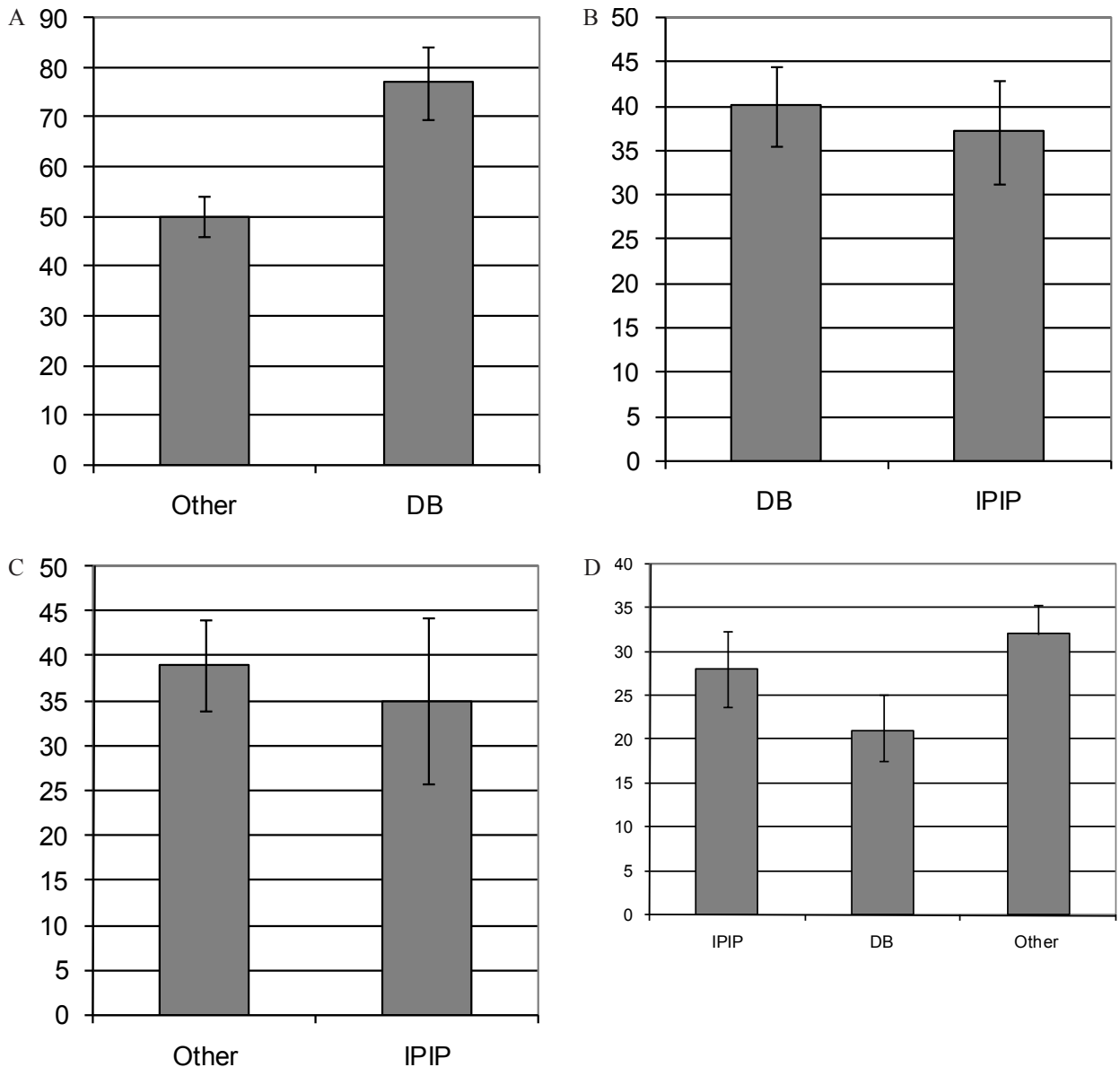

Figure 4: Group preferences for groups selected by different criteria

Stated preferences for working in groups selected by different criteria. Y axes: numbers of students stating a preference. (Note that the totals are not the same for each section, as not all students stated a preference for one group over another). A to C: summary of statement as to which group they preferred. A: Preferred groups selected for compatible Deadline Brinkmanship versus groups selected by other criteria not including IPIP scores. B: Preferred groups selected by Deadline Brinkmanship vs groups selected by IPIP scores. C: Preferred groups selected by IPIP profile vs groups selected by other criteria not including DB. D: Which group did the student dislike most?

Entrepreneurs and personality

Whether there is really an 'entrepreneurial personality' is controversial. This study was not primarily aimed at identifying entrepreneurs but exploring teams, but I also collected data from the students on whether they had shown entrepreneurial traits before the course and whether those who graduated before 2013 had done anything entrepreneurial after graduating. I defined 'entrepreneurial' very narrowly, as described in *Entrepreneurship*, above, so as to have as consistent a definition across the varied nationalities and background of the student group as was practical.

I compared the IPIP personality scores of entrepreneurial and non-entrepreneurial student groups. The results in Figure 5 show clearly that there is no significant

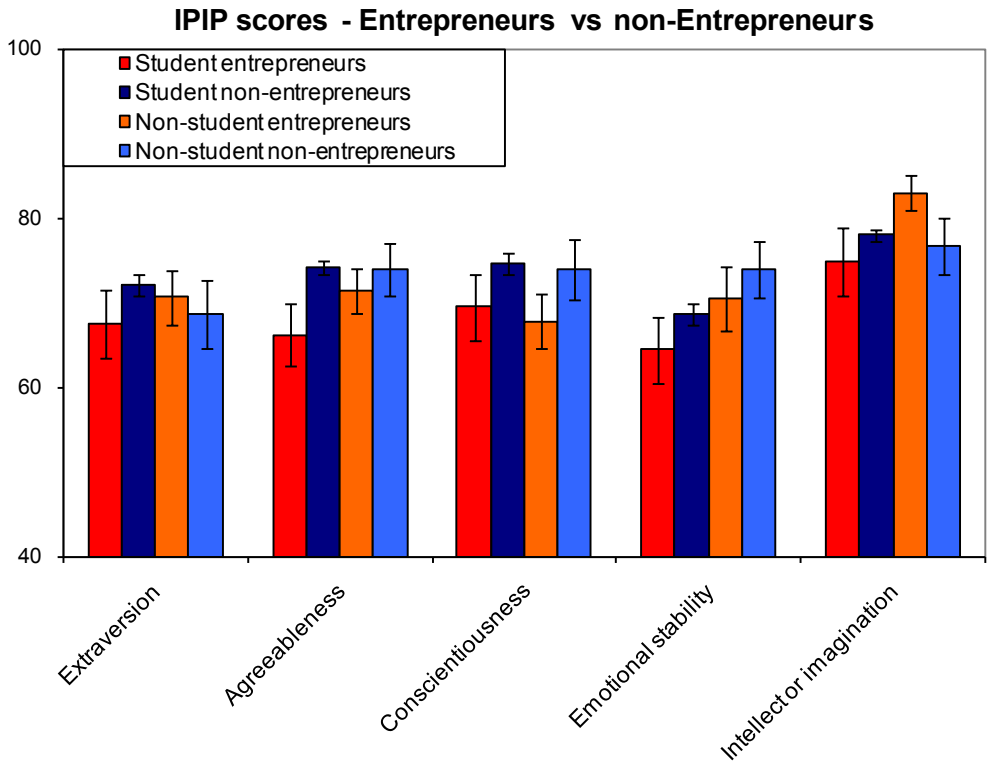

Figure 5: IPIP characteristics of entrepreneurs

IPIP characteristics of 125 students and 36 non-students from the Cambridge biocluster. I divided people into 'Entrepreneurs' and 'Non-entrepreneurs' based on whether they had started a new, independent enterprise at their own risk (See 'Entrepreneurship'). Y axis: raw scores on the IPIP 'Big Five' personality dimension test. X axis, 'Big Five' personality categories. Error bars = Standard Error of the Mean. See text for details.

difference between entrepreneurs and others in this group. As a control I also asked a number of people involved in the biotechnology industry in the Cambridge area to fill in the IPIP form as well: they also showed no strong difference between entrepreneurs and non-entrepreneurs, other than that entrepreneurs are marginally less conscientious. The students, especially those who had entrepreneurial experience, also seemed to be more nervous than the non-students, which in the employment climate over the period 2008 to 2013 is understandable. It is tempting to see the pooled set of entrepreneurs as being less conscientious and more anxious than non-entrepreneurs as a whole, but this is of marginal statistical significance.

There is no significant difference in age between entrepreneurial and non-entrepreneurial students (Entrepreneurial average age = 26.2 years, σ = 5.31, non-entrepreneurial = 24.3 years, σ = 3.55). I did not ask non-students their age.

With one exception, this is consistent with a range of other studies on the personality profile of entrepreneurs. Extraversion is generally unrelated to attempted or successful entrepreneurial activity,[21,37,38] although a few studies find enterprising individuals to be more extravert.[39] Agreeableness in founding teams may[37] or may not[21,39] be correlated with venture success. Some studies have found that entrepreneurs score higher on emotional stability than non-entrepreneurs,[40,41] which the results in Figure 5 do not support, and in fact weakly contradict.

Interestingly, however, the entrepreneurs scored significantly higher on the Deadline Brinkmanship score (i.e. handed in their individual, assessed work significantly later) than non-entrepreneur students (Figure 6). I also ran a version of the betting game described by Shiv et al[42]: in summary, students flipped a coin up to 20 times, losing 1 point at each 'tails' and gaining 1.5 points at each 'heads'. They could stop at any time before 20 throws if they wanted. The student with the most points won £20. This test of risk aversion illustrates that people often stop playing after a run of good or bad luck, even though statistically it is best to keep playing for all 20 throws. Unexpectedly, entrepreneurial students seemed to be more likely to stop playing before the end (Table 3), although the results were far from statistically significant.

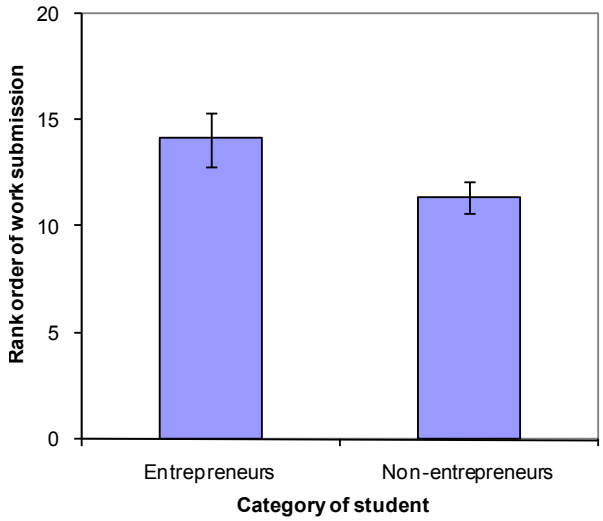

Figure 6: Deadline Brinkmanship score and entrepreneurship

Average rank order in which students handed in individual work to a deadline ("Deadline Brinkmanship) for students classified as 'Entrepreneurial' vs 'Non-entrepreneurial'. Error bars = Standard Error of the Mean.

Table 3: Risk game results

	Complete	Stopped
Entrepreneurs	7	6
Non-entrepreneurs	25	12

Risk game results. Students were asked to throw a coin 20 times, with a final score depending on the number of heads thrown. At any point they could chose to stop. The reward was biased towards continuing to throw the coin. Shown are how many students threw for the complete 20 throws ("Complete") or stopped early ("Stopped") for students classified as entrepreneurial or not according the criteria in 'Entrepreneurship'. Chi squared test of the hypothesis that there is no difference between Entrepreneurs and non-entrepreneurs as to whether they completed the run of 20 throws or stopped early =0.786, critical value for one degree of freedom for p=0.05 is 3.84, so the null hypothesis that there is no difference between entrepreneurs and non-entrepreneurs is not rejected.

CONCLUSION

This is a relatively weakly powered set of observations. Better experiments would have tested the students on four or five submission tasks to measure DB, and group preferences for at least 6 tasks for groups selected for minimal and maximal in-group differences in DB, IPIP scores and another characteristic (probably marks in previous assessments). Attempting to do this however would have distorted the curriculum for the degree, and so would not have been ethical.

This study addresses the under-explored period of new venture formation between the entrepreneurial decision to pursue a business idea and its execution. I do not address what motivates the entrepreneur to start, or stick with, an enterprise: the complex nature of such motivation has been discussed extensively elsewhere (see discussions and references in refs[9,10,12,32, 43]). What I address here is, once the decision to start is taken, what might help to keep the team together until that first success point is reached?

The Big Five personality traits seems unrelated to how well groups worked together, which is consistent with weak and inconsistent correlations of Big Five personality traits in the literature to entrepreneurship. The measure of workstyle that I have called Deadline Brinkmanship is better correlated with both happy team working, and with entrepreneurship. This is perhaps unexpected. Forming a biotech start-up does involve a range of deadlines: patents must be filed and prosecuted on time, presentations prepared for specific meetings, web site and other material launched for fixed conference and meeting dates and so on. However such tasks are a minority of the work that the Founding Partnership must do. To an extent the correlations with entrepreneurship reported here are all consistent with the idea that entrepreneurs accept a "last minute, good enough" approach. However the 'Deadline Brinkmanship' measure is also a useful pedagogical measure to show teams how working style can affect team dynamics, and to happy teams that can stick together through foundation and start-up phases.

More than anything else, that will help show you whether you will be happy to work together on the long and perilous course to a successful enterprise. Working together on an important task with a fixed deadline may be a useful test for any Founding Partnership to see probe how happy they might be working together on the long path ahead of them.

ACKNOWLEDGEMENTS

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Article

Ethical, legal, and regulatory issues regarding the study and use of medications in pregnant women

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ABSTRACT

Despite the prevalence of off-label drug prescriptions for pregnant women, little attention is paid to the ethical, legal, and regulatory issues regarding this practice. This paper discusses some of these key issues relevant to the practice of off-label medication use by women during pregnancy.

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INTRODUCTION

The Thalidomide tragedy of the 1950s and 1960s is one of the most notorious cases of how dire the outcome can be when pregnant women consume a drug that is untested on pregnant women. While the FDA never approved thalidomide for use in the United States, it was marketed in other countries to treat nausea in pregnant women despite never having been tested for safety on this patient population. By the 1960s, it was banned because it was found to be a teratogen and caused serious limb birth defects in an estimated 8,000 to 12,000 babies.[1] Most of these babies were in West Germany, but there were also incidents of thalidomide-induced birth defects in Egypt, Belgium, Brazil, England, Israel, Sweden, Switzerland, and the U.S.[2] The thalidomide incident launched a shift into the modern era of pharmacovigilance — one in which not only efficacy, but adverse effects, are considered during regulatory review. It also left a legacy in the clinical realm, for now it is not uncommon for pregnant women to be undertreated by their physicians for medical problems due to fear of the unknown teratogenic effects of drugs. Despite these unknown effects, drugs are still prescribed to treat pregnant women for medical conditions.

While the FDA may approve a drug for a specific indication, once the drug is approved for marketing, physicians can prescribe the drug for any reason, including for indications that are not approved by the FDA. Because of this, the lay public may not be aware that most of the drugs that are prescribed to pregnant women are not indicated for pregnant women nor are there studies to confirm the safety of a given drug during pregnancy. In 2000, a review of the Physicians' Desk Reference indicated that 40% of the drugs listed contained no advice at all regarding the use of the drug during pregnancy.[3] Of the drugs that did mention "pregnancy," less than half were classified in accordance with FDA pregnancy category ratings. Given how prevalent drug use is during pregnancy, there is very little information on long-term safety of drugs, much less information on the teratogenicity of most drugs.

Every year, more than 4 million women become pregnant and give birth.[4] Despite these numbers, pregnant women are a marginalized subpopulation of the adult population when it comes to clinical research and data. It is true that pregnant women do not bear the burden of being research subjects; but because of this, they have no benefit from the disproprortionate amount of resources allocated to other groups in society. Unfortunately, pregnancy does not confer immunity from any of the chronic conditions that may affect a

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women who becomes pregnant including hypertension, diabetes, psychiatric conditions, autoimmune conditions, etc. Further, pregnant women are considered part of the immunocompromised population, making them (and their fetus) more vulnerable to infections that may need to be treated and supported with medications.

According to CDC Data & Statistics (2013), about 90% of women take at least one medication during their pregnancy (over-the-counter (OTC) and/or prescription). Regarding OTC medications, 65% of pregnant women take acetaminophen, 18% take ibuprofen, 15% take pseudoephedrine. In addition, 70% of women take at least one prescription medication during their pregnancy. With regard to prescription medications, 4.5% of women used an antidepressant before/during pregnancy, and 29.7% of women used antibiotics before/during pregnancy.[5] In addition to treating depression and infection, many pregnant women have health issues including heart disease, diabetes, psychiatric disorders, cholesterol, etc that may need to be controlled with medications.

According to Peters et al (2013), from 2000 to 2010, over 70% of FDA-approved medications had no published data on birth defect risks in humans and 98% had insufficient data to draw conclusions about the risk of birth defects. Despite the lack of published studies, many websites (which is where many women do their research) claim that certain medications are safe for pregnant women despite the lack of controlled studies to confirm safety.[6] According to Lyerly et al (2001), only 12 drugs are approved and specifically indicated for pregnant women. All of these drugs that are approved for pregnancy are specifically for gestation and birth-related situations such as nausea, vomiting, preventing congenital malformation, and labor induction.[7] None of them are indicated to treat illnesses during pregnancy such as cancer, depression, hypertension, diabetes etc. When these medications are used during pregnancy, they are prescribed by a physician for off-label use and with no FDA-approved guidance to ascertain the safety of these medications for pregnant women.

There are divergent interests at stake in this issue, including the interests of the mother, the fetus, industry, prescribing physicians and society. Pregnant mothers may have chronic conditions that require medical treatment, and it's in their interest to know which medications are safe during pregnancy since they play a primary role in safeguarding the fetus. Physicians also have an interest in knowing which drugs are safe to prescribe to their patients to help them manage their medical needs during pregnancy. Industry has an interest to be profitable and bring safe and effective drugs to market. If drug companies were required to do clinical trials for pregnant women before approval because a pregnant woman might take the medication post market, this would significantly add to the expense and time it takes to bring a drug to market. This may or may not be at odds with society's interests. On the one hand, society would benefit from knowing specific teratogenic data on a given drug because the social and monetary costs of children born with birth defects is high; however, society also would benefit from drugs being marketed at a relatively affordable price point. If every drug were required to be tested on pregnant women before being brought to market, this would significantly increase the cost of development which would be passed on to other members of society who may need the drug. On the other hand, an untested drug that is eventually found to harm fetuses when taken by pregnant women may be more vulnerable to lawsuits and litigation which would also drive up drug costs.

Pregnancy and birth are key, pivotal transition periods for women, families, and society; and safeguarding the health of mothers and babies is an important endeavor. The thalidomide tragedy, unfortunately, was not the last case in history in which a drug administered to pregnant women resulted in harm to the baby. Other drugs since thalidomide have been shown to have deleterious effects, sometimes many years after the drug was being marketed. One example that will be discussed later includes diethylstilbestrol (DES), taken by pregnant women to prevent miscarriage from 1943 to 1971. DES was shown to cause cancer in the daughters who were exposed to the drug in utero. Another example are the angiotensin–converting enzyme inhibitors used to treat hypertension. Women who used these drugs to treat hypertension in their 2nd and 3rd trimesters were more likely to give birth to babies with fatal neonatal renal issues.[8] In the case of valproic acid, use during pregnancy is associated with spina bifida as well as cardiac, craniofacial, skeletal, and limb defects.[9]

There are two major consequences that result from the inadequate safety data of drugs on pregnant women: 1) harmful drugs will injure babies and 2) uncertainty in the science may lead to judicial litigation. Every year, there are a number of babies who are born with birth defects with unknown cause. Given that many people seek to find a reason for why a tragedy occurs, drugs that were taken during the pregnancy may be the scapegoat in a lawsuit even if the drug did not cause the birth defect. This litigation effectively results in driving up the cost of the drug and may even result in the drug being taken off the market. It is not ideal for a jury of lay-people (with little scientific education) to make decisions of whether a drug is responsible for injury, especially since they often are basing these decisions on inadequate data. Even if a drug is confirmed to be harmful to a developing fetus, taking it off the market is not ideal when the drug is helping other population groups who do not include pregnant women. For example, thalidomide, despite its

notoriety as a teratogenic drug, is showing great promise as a therapeutic drug for AIDS and cancer.[10] Safety data is best ascertained in adequately-controlled studies so that a given drug can be confirmed or denied as safe for pregnant women. This would allow physicians to prescribe drugs with the appropriate knowledge of the real risks. However, obtaining safety data in pregnant humans is not without its ethical, legal, and regulatory complications — issues that will be discussed in this paper.

REGULATORY ISSUES

The FDA requirements for pregnancy and lactation labeling is found in 21 CFR Part 201. The FDA Pregnancy Category System (established in 1979) categorizes drugs into 1 of 5 categories to guide doctors in prescribing drugs to their patients. In 1997, this system was further revised in an attempt to add more useful data so that a prescribing physician would have more clinically useful information. The following summarizes the current "ABCDX" system.

Category A: Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus

Category B: No evidence of risk in humans. Either animal study shows risk, but human findings do not; or, if no adequate human studies have been performed, animal findings are negative for risk.

Category C: Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify potential risk.

Category D: Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk

Category X: Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk, which clearly outweighs any possible benefit to the patient.

According to Boothby & Doering (2001) only 3 drugs are labeled as category A and they are thyroid hormones, folic acid, and prenatal vitamins.[11] Drugs that are labeled as Category X drugs are contraindicated in pregnancy due to an established link between their use and birth defects and include drugs like warfarin, live vaccines, iodides, diethylstilbestrol, and finasteride. Boothby & Doering (2001) discuss some of the major limitations of the current system including the lack of data on drug effects in pregnant women, overemphasis on animal studies, lack of clinically practical interpretation of the "C" category of drugs (which account for more than 60% of the drugs in the Physicians' Desk Reference), and high burden of proof required to assign drugs to the "A" category. The ABCDX system also oversimplifies other aspects of pregnancy and drug exposure including timing of when the drug is exposed (first trimester, second trimester, third trimester, etc) and does not take into account the importance of gestational age or organogenesis at 31-72 day of fetal life. The current system also does not account for changes in pharmacokinetics during pregnancy that would affect drug dosage, nor does it address the safety of the drug during breastfeeding.[11]

To note, in 1999 and 2008; the FDA proposed to revise the ABCDX pregnancy labeling system.[12] As of February 2011, the Final Rule is in the writing and clearing process and has not been adopted as of today to my knowledge. The proposed rule on Pregnancy and Lactation Labeling would eliminate the ABCDX system, and in its place have a narrative that includes standardized statements that would have a one-sentence risk conclusion. For example, "Human data do not indicate that Drug X increases the overall risk of structural anomalies" and state whether this is based on human or animal data.[13]

Prior to 1993, women were largely excluded from clinical trials altogether for fear that they may become pregnant and for other reasons which had the effect of making women grossly underrepresented in biomedical research.[14] According to Charo (1993), there are several reasons for this. The first is the inherent sexism bias in which the male body is considered the norm, while the woman's body is considered more complicated than is necessary due to hormonal fluctuations and menstrual cycles — a "wildcard" because it would complicate studies to include them. The paradox of this is that the findings that are based on studying only men are then extrapolated to women as though they are the same. The second is that it makes more financial sense to exclude women because by studying just men, the data is more homogenous. If women and pregnant women were to be included, particularly in Phase 1 and Phase 2 clinical trials, the costs to bring a drug to market would significantly increase because the lack of homogenous data would require a larger study population to demonstrate efficacy. The third reason why pregnant women were excluded was that drug companies feared the liability if a drug caused harm to the fetus and resulted in birth defects.[14]

Despite the perceived complications of how drugs may affect a pregnant woman, there is industry guidance for how to proceed if a drug is discovered to be teratogenic. The FDA advises that a Risk Minimization Action Plan be developed for these drugs to minimize in utero

exposure. The FDA's guidance paper on RiskMAP suggests that RiskMAPs be designed to achieve specific objectives (such as pregnancy prevention). One such risk-management program in place is iPLEDGE, a distribution program for the drug Accutane designed to reduce the number of pregnant women taking the drug and reduce the number of unplanned pregnancies in women who are taking the drug.[15]

Due in part to the DES incident (which was experimentally prescribed to pregnant women to prevent miscarriage from 1943 to 1971) causing cancer in the daughters, in 1977 FDA disallowed fertile women from being enrolled in clinical trials in Pre-marketing Phase 1 and Phase 2 studies (studies that look for human dose-ranging and efficacy as well as teratogenic animal studies). Because of this, most drugs are approved without ever having been tested for their effects on pregnant women.[14]

In 1993 the FDA, realizing that there needed to be proper evaluation of drugs in women, changed some of its policies in an effort to include more women of childbearing age in biomedical research. Prior to this change in policy, women with "childbearing potential" were excluded from early phase clinical trials. Because pregnant women are considered a vulnerable population, and because of the potential complications of study results of having pregnant women in trials; pregnant women are still, for the most part, systematically excluded from clinical trials.[16] The exclusion from clinical trials guarantees that fetuses won't be harmed by an experimental drug, but that ultimately leaves little guidance for how doctors are able to manage disease and illness in their pregnant patients. Though the FDA made changes to encourage women entering clinical trials, women who become pregnant while enrolled are typically dropped from studies. If pregnant women are so excluded from drug development studies, how *does* the scientific and medical community obtain knowledge on the safety of drugs on pregnant women? Most of the clinical research on a drug's effect on pregnant women are obtained in post-marketing or Phase 4 studies.[17]

The following diagrams the stages of clinical drug development.

Premarketing: Phase 1, Phase 2, Phase 3
Drug approved for marketing
Postmarketing: Phase 4

One program that attempts to collect safety data on a drug's effect on pregnant women is MEDWatch. According to Kessler (1993), many health professionals don't report adverse events associated with medications to the FDA. A clinical trial before a drug is marketed may have safety data for hundreds to thousands of patients, but if there are serious adverse events that occur in one in 5000 or one in 10,000; these would be missed in those trials.[18] The other issue that can occur that is not addressed adequately in pre-market studies is the way a drug interacts with other drugs a patient may be taking. FDA actions can only work if physicians are actively reporting adverse effects. For example, in 1991, based on reports to FDA, the FDA was able to warn prescribing physicians about the dangers of using angiotensin-converting enzyme inhibitors duringn the second and third trimesters of pregnancy. The estimate is that only 1 % of serious adverse events are reported to the FDA.[19]

One reason for why the reporting is so low is that the culture of physicians reporting is not ingrained. The MedWatch program of FDA is an attempt to simplify the reporting process so that serious adverse events that are drug and medical device related can be appropriately reported in a timely way.

Another way that the effect of drugs on pregnant women is monitored is through pregnancy exposure registries. Pregnancy exposure registries are created to collect clinically relevant data that can be used on the product's labeling and to give healthcare providers useful information in treating patients during pregnancy.

FDA Pregnancy Exposure Registries are post-market, prospective , observational studies in which pregnant women enroll when they take a drug or vaccine before the outcome is known in order to obtain clinically relevant data for the drug's label. Although there are spontaneous reporting registries, there are limits because of recall bias, poor documentation, lack of control groups; so studies from exposure registries can help counteract these limitations. The FDA recommends (but does not require) a pregnancy exposure registry be established when the medical product is likely to be used during pregnancy, likely used by women of childbearing age, or it presents a special circumstance such as potential of the fetus being infected from a live, attenuated vaccines. Other cases where it may be important to establish a pregnancy exposure registry is if animal toxicology studies indicate toxic effects to the fetus based on pharmacological class, human case reports, or structure-activity relationships. In some cases, the FDA may require the company to conduct an exposure registry under an IND before approval.

ETHICAL ISSUES

Justice

One major ethical principle relevant to the issue of pregnant women and research is the concept of justice, which refers to the principle of fairness. According to Faden

(2010), there are four issues of injustice with regard to pregnant women being excluded from clinical research. Being excluded from clinical research 1) denies pregnant women the benefits of participating in research, 2) results in pregnant women's interests being underrepresented, 3) results in pregnant women carrying a disproportionate burden from research findings, and 4) disrespects pregnant women.[20] Denying pregnant women the benefits of participating in research means that these individuals are denied the possibility of new therapies and technologies that could benefit them (such is the case with AIDS). The second issue is that pregnant women's interests are underrepresented. Biomedical research receives a lot of funding and in a just society, resources should be allocated in a proportionate way. Pregnant women's interests are underrepresented, and a disproportionate amount of funding goes to support other groups. Another issue of injustice occurs because pregnant women carry a disproportionate burden from the lack of knowledge. Physicians notoriously undertreat pregnant women for fear of causing harm because of the lack of research on effects of medications on pregnant women.[16]

Respect for persons

The issue of including pregnant women in trials include the question of respect for persons and respecting the autonomy of the pregnant woman giving consent. The question may also theoretically apply to the fetus and whether the fetus (who has diminished autonomy) and cannot give consent is entitled to certain protections. This is one reason that pregnant women and women of childbearing age were have been excluded from drug trials. While this protects the woman and fetus from the burdens of research, it also denies them the benefits that these two underrepresented populations would benefit from.

Autonomy

Because the FDA prohibited formal testing of drugs on pregnant women (in Phase I and II) as a result of the DES incident and industry tends to not want the expense of formal testing of drugs on pregnant women in pre-market studies; the majority of the knowledge gained of the effects of drugs on pregnant women is gained in post-market studies. Since physicians are permitted to prescribe a drug for off-label use for pregnant women all pregnant women who consume medications are, in a sense, participating in an experiment. This violates the principle of autonomy because all pregnant women who are taking a drug become un-consenting, post-market research subjects.

LEGAL ISSUES

The litigious culture has contributed to the current state in which a pharmaceutical president once stated that "no one in his or her right mind would work on products for pregnant women because of enormous liability risks such work engenders."[21] A similar situation occurred with the vaccine industry where individuals who were injured by vaccines brought civil suits against vaccine manufacturers. In one case of a vaccine injury, the manufacturer was liable for a punitive amount at 200 times the annual revenue that the vaccine generated.[21] Not only does this work as a negative incentive for future and current manufacturers to produce vaccines, but it also makes the cost of these treatments more expensive as the cost of these lawsuits gets passed onto consumers. Nobody doubts that drugs can sometimes be responsible for serious adverse effects, and those who are severely injured should have some recourse and compensation; but legal liability over time hurts industry and results in fewer treatments being available for those who need them. In the case of the drug Bendectin, there were more than 300 lawsuits pending that claimed damages for injured babies.[22] Courts awarded punitive damages such that the drug manufacturer's insurance premiums soared to $10 million annually, a mere $3 million less than the annual revenue. After a Washington DC jury awarded $750,000 to a family, Merrell Dow withdrew the drug from the market. The result of such lawsuits is that Merrell Dow withdrew the drug from the market not because Bendectin was scientifically shown to cause birth defects but because the lawsuits resulted in Merrell Dow's insurance premiums soaring to $10 million annually, a mere $3 million less than the annual revenue.[21] One unfortunate consequence of having cases go through the court system is that a jury's decision may not necessarily be based on scientific evidence since juries are not uncommonly made up of lay people. The FDA found, after an intensive 2-day review of available data, that there was no causal link between Bendectin and birth defects though they did admit that no drug can be proven to be absolutely safe for every pregnant woman under all circumstances. Based on this, many have criticized the judicial system because a safe and efficacious medication was taken off the market for business reasons, and those who may stand to benefit from the drug no longer have access to it. Lawsuits de-incentivize drug manufacturers from making medications for pregnant women since lawsuits can make insurance costs. Lawsuits also have the effect of overall de-incentivizing

pharmaceutical companies from producing treatments for pregnant women.

Another legal issue is the conflicting standards of common law with FDA regulations. Existing legal norms exist such as state liability laws often have a higher standard than FDA standards and regulations. For example, the Supreme Courts of New Jersey and Kansas found that FDA judgments can be reevaluated by the courts in the context of civil lawsuits.[23] Because of this, pharmaceutical companies can be liable for breaching state common law duties to warn of potential side effects based on evidence that FDA had found insufficient to warrant a warning. In this case, a pharmaceutical company may be in full compliance with FDA regulatory requirements but be found liable under local tort law.

No discussion of pregnancy and drug case law would be complete without a discussion of diethylstilbesterol (DES), a drug approved by the FDA to be marketed for preventing miscarriage from 1947 to 1971 on an experimental basis and warned of that. The drug was eventually linked to a rare form of vaginal and cervical cancer in the daughters of the women who took the drug after a latency period of 10-12 years. In the Supreme Court case of Sindell v Abbot Laboratories, the plaintiff, Judith Sindell was the daughter of a woman who took DES during pregnancy. She filed suit against 11 drug companies since it was unknown which manufacturer made the precise drug (as it was a fungible, brand-interchangeable drug) that her mother ingested. At the time Sindell's mother was pregnant, there were over 200 companies that manufactured DES. In this case, the court decided to uphold a kind of liability known as market share liability in which the defendants, because they were all involved in manufacturing a fungible product that harmed the plaintiff, were responsible for a percentage of the damages equal to their market share of the product at the time the product was used.[23]

In general, when patients are allegedly injured by pharmaceutical products, they bring civil charges against pharmaceutical companies rather than prescribing physicians even if the physician prescribed the drug for off-label use. One example of this is with "fen-phen." Fen-phen was a combination of fenfluramine and phentermine, each of which were separately approved by the FDA for short –term treatment of obesity. Physicians were prescribing this combination for longer periods than what was approved and for patients who were not truly obese.[25] Despite this alleged malpractice on the physicians' part, it is the drug manufacturers who were sued by plaintiffs who claim that their heart valves were damaged from the combination. While the case of fen-phen did not specifically involve pregnant women, the precedent it sets is relevant, because plaintiff attorneys argue that pharmaceutical companies need to more actively discourage off-label prescribing. The problem here is that off-label prescribing is ubiquitous for pregnant women because there are so few drugs that are specifically indicated for pregnant women; and these situations further increase the difficulty of pregnant women receiving treatments.

CONCLUSION AND CALL FOR ACTIONS

Currently, most of the burden and liability of alleged drug injury falls on pharmaceutical companies. Bearing all the burden of liability hurts industry, which eventually hurts consumers. In the case of pregnant women, there are fewer research dollars being allocated to develop treatment drugs that are safe during pregnancy and drugs that are developed become progressively more expensive to cover the cost of litigation. Given that physicians have a right to prescribe drugs for off-label use as supported by common law, tradition, and legislation; physicians should have more responsibility in ascertaining whether a drug is safe during pregnancy. One way to accomplish this would be to develop a mandatory reporting system to report when adverse effects occur, particularly for off-label use in pregnant women. Although physicians usually aren't conducting research, if they are prescribing drugs to pregnant women for off-label manner and the drug is NOT a "Category A" drug, the use of the drug is experimental in these cases, and informed consent should be obtained so the pregnant woman is made aware that the drug she is being prescribed has not had well-controlled studies confirming safety. Pregnancy exposure registries exist for some drugs, but unless the prescribing physician informs the patient of this, the patient may not be aware of these studies they can participate in. Physicians should be required to monitor whether a drug they prescribe to a pregnant woman for off-label use is being studied and inform the patient of this so she can enroll if she chooses. Since most drugs are not tested for safety in pregnant women before they are prescribed to pregnant women, it is inevitable that eventually, some drug will show some deleterious effects when taken during pregnancy. Mandatory reporting would alert regulatory bodies to the deleterious effects sooner, rather than later so that fewer babies are harmed.

In addition, consumers should have more access to information obtained in the regulatory process. There is an astonishing amount of opaqueness in the agencies that are meant to protect the public such as the FDA, and it leads to many consumers not trusting the regulatory process. While it's relatively easy to read about the ABCDX pregnancy category system, it's more difficult to ascertain what category a particular drug has

been labeled because it's not required on the drug insert nor is it easily found on the FDA website. The common sources that consumers may turn to give contradictory information. Further, it is interesting to note that the Center for Disease Control (CDC) publishes information that directly contradicts FDA information. For example, the CDC recommends that pregnant women take the pertussis vaccine for whooping cough. The CDC says the "(Tdap vaccine) is very safe for pregnant women and their babies," yet the FDA categorizes the Tdap vaccine as a "Category C" drug which means that potential benefits may warrant the use of the vaccine in pregnant women, but there are no well-controlled studies in humans.[26,27] The conflicting information makes it even more important that pregnant women have access to the primary data so they can make an informed decision about personal risk.

The medical literature and data should be more available to pregnant women so that patients can be empowered to take a role in making informed healthcare decisions and which medications, if any, to take while they are pregnant. While controlling Type I diabetes may be extremely important during pregnancy, other health conditions have considerably more "gray" area. An example of this would be in depression. There are numerous studies showing that untreated depression can result in worse outcomes in pregnant women than the side effects of treating depression, so the patient and doctor should be able to work together to see if the level of depression a pregnant woman is experiencing meets the threshold at which it would be more advantageous to treat with medications than not.[27] Like many diseases, there are risks and benefits to treating or untreating depression during pregnancy, and pregnant women should be able to discuss these risks and benefits with their physician to decide on the best course of action for her situation.

Finally, I would like to address the issue of autonomy, a concept I believe overrides all other ethical, legal, and regulatory issues. Whether a pregnant woman is a patient or research subject, she has the right to make decisions regarding her and her baby's health. Decisions must be made with knowledge of the known (and potentially unknown) risks and benefits of any treatment considered as well as the risks and benefits of no treatment. Patients ought to have the right to see the data if they request it. Researchers, regulators, and drug developers may use scientific data to draw their conclusions; but the conclusions that are drawn are normative, and not necessarily free from the influence of culture, politics, and economics. Every treatment, even those deemed "safe," have some risks, and consumers have the right to know where the margins of safety have been delineated and to decide whether those margins of safety are within their threshold of tolerance. This is particularly important because "safe" is a highly equivocated term; so different studies, researchers, and doctors means different things when they describe something as "safe." Teratogenicity, stillbirth, and miscarriage appear to be the most common meaning when ascertaining whether a treatment is safe, but pregnant women may have a safety standard that is higher than simply not causing death and/or gross physical malformations and their right to should be honored.

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From the Classroom

The University of Colorado Digital Health Consortium Initiative: A collaborative model of education, research and service

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ABSTRACT

This article describes the initiative and actions related to establishing a Digital Health Consortium (DHC) at the University of Colorado Denver. The consortium is a part of the Center for Information Technology Innovation (CITI) in the Business School. The objective is to augment existing information systems program offerings in health information technology with the support of industry affiliates and other partners of the university. The CITI-DHC is an industry-academia led initiative with a mission to accelerate digital health transformation through education, research, and service. We illustrate the vision and plan for the consortium, that will be fulfilled with academic and industry stakeholders, and who will be engaged with the platform to support digital health care innovations through collaborations.

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1. INTRODUCTION

Digital Health or Healthcare Information Technology (HIT) is emerging as a growing area of interest for academic research, policy analysis, and business development. It brings together areas such as biomedical information, technological developments dealing with health care practice and delivery, and optimal use of health care data in support of problem solving and decision making.[1] Although the healthcare sector in the United States (US) spends more than 18% of Gross Domestic Product (GDP), leading to 3 trillion dollars,[2] persistent issues of cost, quality and efficiency of health care delivery remains a challenge.[3] With the realization that higher adoption and infusion of information technology (IT) into healthcare sector can improve the health care delivery challenges, policy makers have charted out mandates and incentives for the HIT adoption. In 2009, The HIT for Economic and Clinical Health Act (HITECH), signed as part of the American Recovery and Reinvestment Act (ARRA), provides various means to advance the use of HIT in support of both use and exchange of health information, and provides the foundation for improving care for each individual in the United States.[4] These developments also led providers to increase their efforts to put in place HIT innovations in the practices and hospitals that can create business value.

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Simultaneously, technology savvy and mobile patients are looking to reap the benefits of the transformation brought in by HIT to gain better access to their information and manage their health.

Recent developments in HIT in the US have created a significant demand for creating world-class education and training programs surrounding HIT. Arguably, IT education is not new to healthcare industry. Healthcare sectors have experienced an infusion of IT in the past with the development of radiology and computed tomography (CT) technologies in 1900's, as well as bioinformatics programs associated with human genome sequencing and IT use in clinical testing of drugs in 2000's. However, recent developments are calling for IT adoption within and across healthcare organizations, motivating providers to use IT in population management, and making information exchanges become conduits for sharing patient health data.

In summary, developments surrounding the adoption, implementation and value proposition of information technology in healthcare provides an opportunity to academic institutions to take a systemic view towards HIT and its impact on health care delivery. Since the HITECH act, huge investments in IT applications and systems by many stakeholders in health care delivery call for study of innovative health practices, conduct research into unique health care delivery models and educate a new group of health care professionals to meet the anticipated demand for new HIT career professionals. At the same time, existing physicians, nurses and hospital administrators need relevant IT education to be effective in providing care in an IT-enabled healthcare environment. Given the demand for both research and education in an academic setting, a growing number of business colleges, and, specifically those with information systems departments, are exploring participation or currently participating in HIT academic efforts. This article describes the background and rationale for establishing a consortium in advancing both research and education in developing a unique HIT program at the University of Colorado Denver (UC Denver), a large western state university (with more than 28,000 students, $400 million in grants, and over 12,000 employees).

Next section explores deeper into the digital health landscape, with the following section providing a framework for academic research and education to meet the demands of both current and new health care professionals. The fourth section describes the model of the consortium that can fulfill these demands.

2. EMERGING CHALLENGES IN DIGITAL HEALTH LANDSCAPE

The health care sector is undergoing massive transformation with the incorporation of IT at various stages of health care delivery. Besides the traditional electronic medical record systems that support internal integration of health care data, an increasing number of health care providers, payers, and consumers are using Internet and other mobile technologies to improve clinical practices across providers for greater efficiency and enhance agility within the organization to address changes in the health care market place. HIT artifacts and tools are emerging as central elements in support of this transformation and will continue to play a vital role in the financial health of the health care industry.

When market forces dictate a radical change, firms re-engineer their operational processes and organizational strategies to address the competitive needs. This includes developing new entrepreneurial business models to differentiate a firm's product or service in a market place, and intra-preneurial (within the firm) efforts to reduce costs and create value added services to customers. Manufacturing and other industry sectors have gone through such reengineering efforts in the last two decades to address global competition and technological advances. The growth of global markets for customers and labor have forced several industry sectors to become service-driven and life-cycle focused (i.e., look to addressing changing customer needs over the usage of a product or service). Some of the reengineering efforts include the use of external partner engagements (i.e., sourcing), so a firm can adapt quickly to changing customer expectations and use continual process innovations to reduce costs and create customer value. IT (especially web-based technologies) has played a key role in leveraging both external partnerships and supporting customer expectations with mobile and e-service innovations.

The environment influencing a physician (that is working either in a private practice or within a hospital as an employee) and other health care providers is expected to change due to many of the transformations discussed earlier (as shown in Figure 1) and health care organizations have to look for innovations within and across the providers to meet changing patient expectations in an evolving technology landscape for differentiation. A few examples listed below will illustrate some direction in which HIT can support the service driven approach to address patient care, and the research-education motivation relevant to the context.

In a study conducted by faculty from UC Denver, in collaboration with faculty from Oakland University and Savannah State University, synchronous video

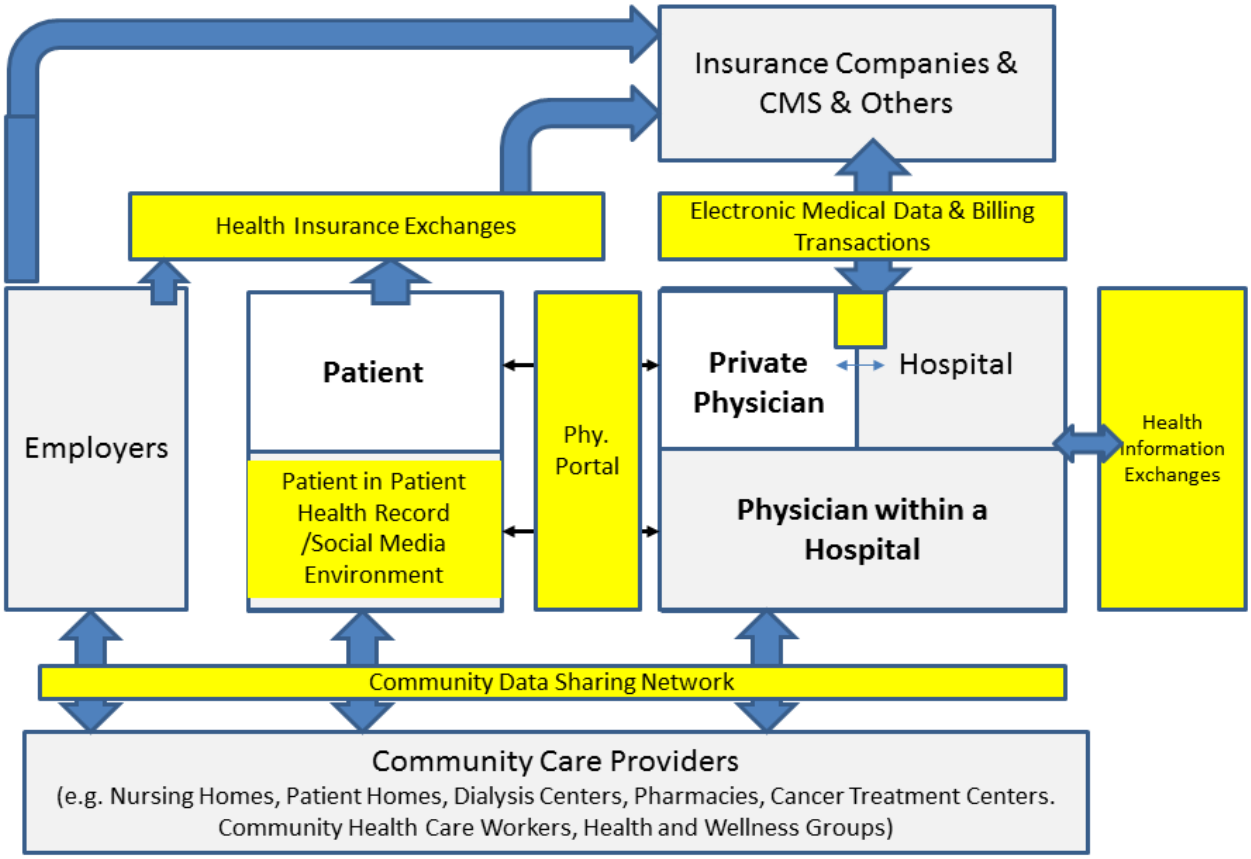

Figure 1: Framing HIT in Support of Service Driven Life Cycle Context.

communication is being designed, integrated and evaluated as part of a physician portal, so patients can interact with each other and physicians for consultation and support. This can be used to reduce costs of patients in rural areas where access to primary care physicians or specialists is limited, and can lead to new business models where insurance companies may support such physician consultation as a way to improve care: both prevention and post-discharge care.

Similarly, in another study, researchers from UC Denver and Oakland University are exploring the role of digital integration through personalized mobile communication of health information to empower patients to self-manage their chronic disease conditions, thereby improving care delivery post discharge. A third study by these researchers is looking at the way to integrate peri-operative surgical care with post-discharge care, using a myriad set of information technologies, all to support collaboration among a number of care providers both within the hospitals and outside and address challenges associated with patient readmission and satisfaction and their impact on cost.

In summary, these examples illustrate how next generation of health care leaders and managers (many of these come from the ranks of clinical practice) have to become engaged players in addressing the health care transformation by supporting innovations to:

(1) Address cost structure within a clinic in a team based operating environment by seeking new roles for nurse, nurse practitioner, physician assistant, and other staff; and using technology
(2) Allow a hospital to address patient care and post-discharge medication adherence using a multitude of community care providers by leveraging technology in collaborative care coordination
(3) Make an accountable care organization (ACO) or a health-care professional community address population health management issues such as wellness, infectious disease management, access to quality care and medication adherence, and
(4) Make exchanges become effective tools to develop new insurance products for differentiated health care needs or track patient disease patterns to address the spread of potential virus and other types of infections.

In spite of the anticipated value IT tools and artifacts can provide in support of health care, their adoption and effective use remains a persistent challenge. For example, electronic medical record (EMR) systems can help store medical records in digital format and make them accessible to both care providers and patients. They can help support improve clinical practice such as diagnosis, treatment, and medication management activities while enhancing care quality and care delivery at a reduced cost to a wider population.[5] Yet, EMR adoption has been slow.[6,7] Similarly, health information exchanges are supposed to allow portability of patient data across many providers, but are facing difficulties with their adoption and growth.[8]

Part of these adaption delays with technologies can be attributed to two specific knowledge gaps: (1) behavioral focus (organizational): lack of understanding of how IT systems can provide value to health care professionals as they address patient care, and (2) design focus (technical): a lack of understanding of complex care delivery environment with which the IT systems have to operate and provide value by those who build these systems. Bridging these knowledge gaps is the goal of the consortium being established at UC Denver. Through the collaborative efforts of academic thought leaders, system developers and health care practitioners, research and education is used to make realize that HIT indeed become a valuable asset in health care transformation. Next section provides some research and educational foundations that will be used to address this knowledge gap.

3. FOUNDATIONS FOR DIGITAL HEATH EDUCATION AND RESEARCH

Effective growth in the use of IT and its integration into health care delivery is a complex transformation and needs leadership and many internal champions with the multitude of providers in the US healthcare system. Recent reports suggest that there is a shortage of 50,000 talented and trained HIT professionals (both leaders, developers and users) in the United States;[9] with estimated 37% in clinical informatics, 28% in systems and data integration, 10% in technology and architecture support, and 9% in data statistics and analytics. In other words, while HIT development and use is increasing at a higher speed, the creation of next generation healthcare leaders and managers, who can devise strategies to successfully deploy and manage HITs at different levels of a healthcare organization, is lagging. The future HIT professionals not only need an understanding of IT in healthcare, but also the role of healthcare from an economic point of view: value based investing, strategic deployment, policy formulation to ensure privacy and security of patient data, and implementation strategies to ensure patient and professional adoption of HIT systems.

Apart from the internal challenges associated with the implementation of HIT in an organization (leadership/management, technology design and development, and user deployment), there exist several external challenges those need to be addressed through education and research. These challenges includes patient expectations in a mobile and tech-savvy population on a desire to manage their own health, changing demographics with a growing number of patients entering health care market place with little or no maturity on how to effectively use HIT in support of prevention and post-discharge medication adherence, evolving government mandates that will continue to regulate through penalties (e.g. early patient readmissions and low patient satisfaction) and incentives (e.g. cost reduction of Medicare population). In addition, with each new government mandate or regulation, insurance firms will start to look for different reimbursement models (e.g. bundled payments under accounting care organizations) and employers are looking to various premium/deductible options to reduce costs by encouraging employee use of wellness and prevention programs. In summary, besides the HIT talent gap, both the internal and external challenges are going to require hospitals, physicians and other care providers to look for innovative care delivery business models to be competitive in this evolving health care market place. This also means, academic institutions have to play a role in helping the health care providers innovate in this rapidly changing market place and educate them to meet the talent gap.

An emerging stream of literature has started to focus on the nuances associated with the research and education in HIT. For example, Chatterjee et al.[10] emphasize the role of information systems in the HIT education and provide a framework to shape a vision for HIT curriculum that leverages information systems disciplinary strengths (organizational, technical and behavioral). In an early work, Meyers and Hurley[11] provide a three-pillar framework of scientific and managerial foundations to be embedded in an education program and its relevance to entrepreneurial activities in the HIT area. Similarly, York et al.[12] note that unless business skills become an integral part of any bioscience curriculum, students will not be able to see beyond the experimental process and contribute effectively to the application of their innovation in a business context. In a recent article, Parthasarathy et al.[13] suggest that bio-medical scientists need an in-depth knowledge of core business concepts, such as finance, marketing, and legal issue to take their biotechnology offering to market and make it successful.

While scientists remain engaged with product innovation, design and development, the lack of knowledge on how it is supposed to pass the hurdles of regulatory compliance, market test, and venture funding often decides the fate of the further course regarding the product. Similarly, an increasing use of newly developed IT products in healthcare raises the demand for highly trained and business-oriented health care professionals,[14] and new or more integrated academic platforms are needed to prepare both health care professionals and researchers to meet emerging areas such as HIT design and implementation, strategies and business models.[15]

In summary, health care organizations in general and physicians, in particular, need a grand vision and systemic approach to patient care delivery that is life cycle focused (prevention, care and post-discharge care) and develop services that can leverage the skills/knowledge base of all stakeholders of health care, including those in the academic, political and social community at large. Any curriculum developed to addressing HIT talent gaps and health care innovations has to help support such a systemic approach to care delivery. The efforts at UC Denver is to establish a consortium that is aimed to not only develop a grand vision but also provide a platform to develop innovative models/pilot projects for exploration, evaluation and implementation. The experiential learning needs of students and intellectual talents of the faculty in HIT programs, in partnership with consortium members, will be used in realizing this potential. More specifically, the education and research models in support of HIT will be used to address both the leadership and management needs of both health care professionals and IT system developers. Next section will summarize how UC-Denver through this center is poised to support such a comprehensive undertaking.

4. CROSS-COLLABORATIVE PROGRAM ON DIGITAL HEALTH AT UC DENVER

UC Denver has been engaged with research and teaching with HIT for last several years. The Information Systems (IS) program at the Business School, the Anschutz Medical School, Colorado School of Public Health all offer several courses and conduct research around HIT areas. The IS program currently offers specialization in *HIT* and *eHealth and Healthcare Service Entrepreneurship* and is staffed with 10 professors and more than 10 PhD students and research assistants. The Anschutz Medical School is a world-class academic medical institution with several medical centers doing cutting edge and collaborative research in technology, prevention, diagnosis, and treatment that improves the health and well-being of the patients. The Anschutz Medical School has trained the majority of Colorado's physicians and other health care professionals. Realizing the emerging market and technology dynamics in the healthcare space, Anschutz Medical School and Business School have already started several collaborations, and are providing some innovative courses to students. For example, a recent program at the university, the Colorado Health Information Education Collaborative (Colorado HITEC), expanded and integrated existing education programs to prepare a workforce of more than 100 professionals who are capable of serving as clinical leaders, health information management and exchange specialists, and HIT sub-specialists. This expansion brought faculty and coursework from the College of Nursing, School of Medicine, School of Pharmacy, Colorado School of Public Health, School of Dental Medicine and the Business School. Further, a unique new course on biotechnology innovation and entrepreneurship and a Masters in e-Health are being offered through the Medical School. Specifically, the biotechnology innovation and entrepreneurship has the objective to help bio-entrepreneurs to achieve commercial success, thereby establishing a unique concept of using a business-centric approach to shift the bio-entrepreneur's perspectives from a product orientation to a market orientation.[13] In addition, Colorado School of Public Health is a multi-campus establishment, and is focused on issues related to public health education and research. Also, the school has focused on mobile health area—a subset of digital health—an emerging area for education, training and research. As part of this initiative, the school is offering courses as well as laboratory infrastructure for mobile health research.

4.1. Multi-entity participation through a consortium at UC Denver

While the interest in HIT has been growing exponentially in recent years, there are only a handful of schools that have recognized the need for rigorous research that is cross-disciplinary. Several major research universities have created centers that advance biomedical and health innovation efforts among students and faculty. Some of these focus specifically on the study of HIT or Digital Health. Prominent amongst them are the UCSF *Center for Digital Health Innovation*, *Vanderbilt Center for Better Health* (VCBH), *Center for IT Leadership* (CITL), Boston, MA; and *Center for Health Information and Decision Systems*, University of Maryland, College Park.

At UC Denver, the *Center for Information Technology Innovation* (CITI) has been in existence since 1999. CITI members support Information Systems (IS) at the

UC Denver Business School in myriad ways. CITI participates in community outreach, consulting, and curriculum participation. CITI members offer internships, externships, and recruiting support. CITI members include prominent Colorado businesses as both corporate sponsors and contributing members. CITI is funded entirely by these corporate members so that its mission and activities can be aligned with those of its members and the Business School. Drawing from the existing infrastructure and expertise of CITI, the *CITI-Digital Health Consortium* (CITI-DHC) was proposed to become the research and development consortium within CITI with the goal of conducting rigorous research, disseminating information, managing knowledge, and coordinating collaborations among multiple stakeholders. Through mutually beneficial partnerships, CITI-DHC will act as a focal point for thought leadership around the topic of digital health, health care information technologies, and health care decision systems; all supporting education and training of health care professionals in digital health in support of Colorado community. Furthermore, CITI-DHC extends the existing mission of CITI to create an academia-led effort with collaboration from industry and government affiliates, and accelerate digital health transformation surrounding the design, development, and integration of information technologies into the health care system.

In order to fulfill the CITI-DHC objectives, the following strategies will be pursued. First, the consortium will focus on cutting-edge research around digital health. Second, the consortium will bring information on many existing education offerings in digital health across campus, and develop new courses in response to market needs and contribute to transferring latest research into classroom. Third, an infrastructure will be developed, in collaboration with a mobile health laboratory in the existing School of Public Health at University of Colorado, to design, develop and validate digital health products and services using interdisciplinary teams. Finally, the consortium will facilitate academic, technology and health care industry interaction and knowledge exchange through annual symposia, forums, and speaker seminars.

CITI-DHC offers three sources of competitive differentiation. First, CITI-DHC is located in a business school and staffed by faculty who are experts in understanding the behavioral, organizational, and system development issues associated with introducing radical change, as seen in the health information technologies in support of healthcare sector. Such capabilities are typically absent in centers primarily staffed by medical personnel. Second, CITI-DHC is structured around a strategic-alliance/partnership model that brings experts and leading-edge thought leaders on a variety of issues related to digital health. Finally, consistent with the research and teaching mission of the UC Denver Business School, CITI-DHC faculty will continually seek to disseminate best practices to all concerned stakeholders including students, physicians, and health-care administrators, using several existing conduits that are available with the business and medical school at UC Denver. One such conduit is the Society of Physician Entrepreneurs (SOPE) (see www.sopenet.org). Dr. Arlen Meyers is the President and CEO of SOPE that has the vision is to create a global community that accelerates medical innovation to patients around the world. SOPE, with its 1200 active members will be instrumental to disseminate the research and best practice outcomes from the CITI-DHC. Thus, in summary, CITI-DHC works to accelerate advances in digital health technology implementation and use in the health care sector and study their impacts at all levels of care delivery. In the long-term, CITI-DHC will support the development of innovations in care delivery solutions that will enhance safety, improve quality, provide greater ease of improve access, increase efficiency -all leading to improved return on investment of health care dollars invested in the United States.

4.2. Business model and future plans

The CITI-DHC will be funded by industry partners, affiliate organizations and research partners. Initially, the center is funded with grant support from the University of Colorado. However, for the sustainability of the center needs support from funded research partnerships and a three-tiered membership structure: industry partners, organizational affiliates and research partners. The consortium will offer three levels of memberships with differing financial commitments (e.g., $5,000, $10,000, $15,000). Potential members may include health systems, hospitals, digital health companies, consulting companies with healthcare practices, pharmaceutical companies, and others with an interest in the application of information and decision technologies for effective health care delivery. A benefit package for different levels is being designed with all levels of membership being acknowledged on all center-generated outreach documents, websites, and presentations. In addition, members are given priority consideration for presentations and panel participation at the center-coordinated workshops, forums and conferences. In addition, a number of research verticals will be designed around HIT research, and will be managed by faculty fellows affiliated with the center. Research project sponsorships will leverage the consortium's capability as a neutral, unbiased third party and are constructed around a specific research project that the partner is interested. The project may

use PhD students and research staff with the scope of the project and deliverables defined by both the faculty director and partner.

5. CONCLUSION

This article described the Digital Health Consortium (DHC) initiative launched by the Center for Information Technology and Innovation at the University of Colorado Denver focused on digital health research, education and service activities. The intention is to encourage students, researchers and collaborators considering a foray into health information technology education and research area. Further, the program aims to offer a set of services focused on digital devices and applications, such as clinical testing of mobile apps. To achieve sustainability, the consortium has designed a benefits ladder that would be useful for both research and industry collaborators.

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Legal & Regulatory Update

USPTO guidance on patentable subject matter: Impediment to biotechnology innovation?

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ABSTRACT

In June 2013, the U.S. Supreme Court issued a unanimous decision upending more than three decades worth of established patent practice when it ruled that isolated gene sequences are no longer patentable subject matter under 35 U.S.C. Section 101. While many practitioners in the field believed that the USPTO would interpret the decision narrowly, the USPTO actually expanded the scope of the decision when it issued its guidelines for determining whether an invention satisfies Section 101. The guidelines were met with intense backlash with many arguing that they unnecessarily expanded the scope of the Supreme Court case in a way that could unduly restrict the scope of patentable subject matter, weaken the U.S. patent system, and create a disincentive to innovation. By undermining patentable subject matter in this way, the guidelines may end up harming not only the companies that patent medical innovations, but also the patients who need medical care. This article examines the guidelines and their impact on various technologies.

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INTRODUCTION

In June 2013, the U.S. Supreme Court issued a unanimous decision upending more than three decades worth of established patent practice when it ruled that isolated gene sequences are no longer patentable subject matter under 35 U.S.C. Section 101.* While many practitioners in the field believed that the USPTO would interpret the decision narrowly, the USPTO actually expanded the scope of the decision when it issued its guidelines for determining whether an invention satisfies Section 101. These guidelines may harm biotechnological innovation by rendering many technologies unpatentable. In this Article, we will examine the guidelines and their impact on various technologies.

SUPREME COURT DECISIONS REGARDING 35 U.S.C. SECTION 101

Two recent Supreme Court decisions have scrutinized the types of inventions eligible for patent protection under 35 U.S.C. Section 101. In doing so, the Court effectively uprooted decades of well-established precedent that "anything under the sun made by man" is eligible for patent protection.

In *Prometheus v. Mayo*†, for instance, the Court was asked to determine the patent eligibility of method of treatment claims that involved correlating the

* 35 U.S.C. Section 101 states, "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

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† *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 566 U.S. ___ (2012).

effectiveness of the treatment with the amount of a drug metabolite in the blood. The Supreme Court reasoned that the claims were trying to cover a "law of nature" (*i.e.*, the correlation itself), which is not "man-made" and therefore not patent-eligible under Section 101. The Court found that steps of "administering" the drug and "determining" the amount of the metabolite in the blood, *i.e.*, the steps that are performed by man, did not "add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible." Exactly what constitutes "enough" to meet the Court's standard is unclear based on the Supreme Court decision.

In *Association for Molecular Pathology (AMP) v. Myriad Genetics*‡ (also known as the "gene-patent" case), the Supreme Court was asked to decide whether "isolated" genetic sequences are patentable under Section 101. In a unanimous decision, the Supreme Court overturned more than 30 years of established biotech patent practice when it held that isolated DNA sequences are not patent-eligible. Moreover, the Supreme Court upended more than a century's worth of established patent practice in general when it held that claims directed to an "isolated XYZ substance", those at the center of the *Myriad* controversy, are no longer acceptable as a valid approach for claiming purified or isolated substances extracted from nature.§ In handing down its decision, the Supreme Court concluded that "isolation" alone does not go far enough in distinguishing isolated DNA from genomic DNA sequences found in nature. According to the Court, such claims are merely an attempt at protecting "natural phenomena". The Court did, however, find that synthetically created genetic material, such as complementary DNA (cDNA), is patent-eligible because it is not naturally occurring.

USPTO'S GUIDANCE FOR DETERMINING SUBJECT MATTER ELIGIBILITY OF CLAIMS RECITING OR INVOLVING LAWS OF NATURE, NATURAL PHENOMENA, & NATURAL PRODUCTS

Following the Supreme Court's decision, the USPTO issued a set of guidelines for examiners on March 4, 2014¶ for examiners that expanded the holdings of the *Prometheus* and *Myriad* cases to any claim involving a law of nature, natural phenomena or natural product. The guidelines will impact the USPTO's assessment of patentability of many applications currently pending in the USPTO, and may well impact the validity of many previously issued patents, especially those pertaining to the life sciences and chemistry. Not only have the guidelines undermined the established patent law framework for evaluating subject matter eligibility under Section 101, these guidelines also make the U.S. the only jurisdiction in the world where inventions, such as those claiming isolated DNA, are not patentable.

To determine whether a claim satisfies the requirements of Section 101, the guidelines provide a three-pronged test. First, the test asks whether the claim is directed to one of the four statutory categories: a process, machine, manufacture, or composition of matter. Next, the guidelines ask whether the claim is directed to one of the four judicial exceptions: an abstract idea, a law of nature/natural principle, a natural phenomenon or a natural product. Finally, if the claim is directed to a judicial exception, the guidelines state that the claim is not patentable unless the claim "as a whole recites something significantly different" than the judicial exceptions, and set forth relevant factors for making such assessment, such as reciting something that is non-naturally occurring and markedly different in structure from naturally occurring products, elements/steps in addition to the judicial exception(s) that impose meaningful limits on claim scope, and elements/steps in addition to the judicial exception(s) that include a particular machine or transformation of a particular article. Natural products that must be analyzed under the last step include, but are not limited to: chemicals derived from natural sources (e.g., antibiotics, fats, oils, petroleum derivatives, resins, toxins, etc.); foods (e.g., fruits, grains, meats and vegetables); metals and metallic compounds that exist in nature; minerals; natural materials (e.g., rocks, sands, soils); nucleic acids; organisms (e.g., bacteria, plants and multicellular animals); proteins and peptides; and other substances found in or derived from nature.

In its guidelines, the USPTO provided many examples of how to evaluate whether or not a claim satisfies the requirements of Section 101. Below are several examples demonstrating how examiners may treat claims to compositions, methods of treatment, methods of diagnosing diseases, and methods of manufacture under the guidelines.

Example A relates to a composition reciting a natural product:

‡ *Association for Molecular Pathology et al., v. Myriad Genetics, Inc.*, 569 U.S. ___ (2013).

§ *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (C.C.S.D.N.Y. 1911)

¶ USPTO, *Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products, March 4, 2014.* http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf.

Claim 2: A bacterium from the genus Pseudomonas containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway.

In this claim, both the stable energy-generating plasmids exist and the *Pseudomonas* bacteria are naturally occurring. Moreover, naturally occurring *Pseudomonas* bacteria containing a stable energy-generating plasmid and capable of degrading a single type of hydrocarbon are known in the art. According to the guidelines, the claim is found to be patent-eligible because the claim as a whole recites something significantly different than naturally occurring bacteria. Although the plasmids alone and the bacterium alone are natural products, the bacterium containing the plasmids is significantly different.

Example B relates to a method of treatment claim:

Claim 3: A method of treating colon cancer, comprising: administering a daily dose of purified amazonic acid to a patient suffering from colon cancer for a period of time from 10 days to 20 days, wherein said daily dose comprises about 0.75 to about 1.25 teaspoons of amazonic acid.

In this hypothetical, the guidelines characterize the Amazonian cherry tree as a naturally occurring tree that grows wild in the Amazon basin region of Brazil. The leaves of the Amazonian cherry tree contain a chemical that is useful in treating breast cancer. Applicant has successfully purified the cancer-fighting chemical from the leaves and has named it amazonic acid. The purified amazonic acid is structurally identical to the amazonic acid in the leaves, but a patient only needs to eat about one teaspoon of the purified acid to get the same effects as 30 pounds of the leaves. Applicant has discovered that amazonic acid is useful to treat colon cancer as well as breast cancer. According to the guidelines, the method claim is patent-eligible because the claim includes elements in addition to the judicial exception (e.g., dosage amounts, treatment period limitations) that add significantly more to the judicial exception, and thus the claim as a whole recites something significantly different than the natural product.

Example C relates to an article of manufacture that includes natural products:

Claim: A fountain-style firework comprising: (a) a sparking composition, (b) calcium chloride, (c) gunpowder, (d) a cardboard body having a first compartment containing the sparking composition and the calcium chloride and a second compartment containing the gunpowder, and (e) a plastic ignition fuse having one end extending into the second compartment and the other end extending out of the cardboard body.

In this example, the guidelines characterize the calcium chloride as a "natural product" and the gunpower as a mixture of "natural products." The guidelines explain that this claim is directed to patent-eligible subject matter "because the claim as a whole recites something significantly different than the natural products by themselves, i.e., the claim includes elements in addition to calcium chloride and gunpowder (the sparking composition, cardboard body and ignition fuse) that amount to a specific practical application of the natural products."

Example D relates to a composition reciting multiple "natural products":

Claim: An inoculant for leguminous plants comprising a plurality of selected mutually non-inhibitive strains of different species of bacteria of the genus Rhizobium, said strains being unaffected by each other in respect to their ability to fix nitrogen in the leguminous plant for which they are specific.

Rhizobium bacteria are naturally occurring nitrogen-fixing bacteria. While the prior art shows that all Rhizobium species were mutually inhibitive, the Applicant had discovered that there are particular strains that do not exert a mutually inhibitive effect on each other, and sought to patent mixtures of such strains. Following the Supreme Court's 1948 decision in *Funk Brothers*[**], the guidelines hold that this claim is not patent-eligible because "none of the natural products recited in the claim are markedly different." Rather, the guidelines explain that "[t]he specification describes that applicant has not changed the bacteria in any way, but instead has simply combined various strains of naturally occurring bacteria together." The guidelines further state that no other factors in the claim support patent-eligibility, "i.e., there is nothing in the claim other than the bacteria."

Example E also relates to a composition reciting multiple "natural products":

Claim 1: A pair of primers, the first primer having the sequence of SEQ ID NO: 1 and the second primer having the sequence of SEQ ID NO: 2.

** *Funk Brothers Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 131 (1948).

In this example, SEQ ID NOs: 1 and 2 are naturally occurring DNA sequences found on a human chromosome. According to the guidelines, this claim is not patent-eligible, because the structural difference "is not significant enough to render the isolated nucleic acid markedly different, because the genetic structure and sequence of the nucleic acid has not been altered." The guidelines further mention that the function of the recited primers is essentially identical, stating "the first and second primers have the same function as their natural counterpart DNA, i.e., to hybridize to their complementary nucleotide sequences." Interestingly enough, the guidelines fail to address the fact that primers, unlike naturally-occurring DNA, can function to amplify target DNA.

Example F relates to a method of diagnosing a disease:

> *Claim: A method for determining whether a human patient has degenerative disease X, comprising: obtaining a blood sample from a human patient; determining whether misfolded protein ABC is present in the blood sample, wherein said determining is performed by contacting the blood sample with antibody XYZ and detecting whether binding occurs between misfolded protein ABC and antibody XYZ using flow cytometry, wherein antibody XYZ binds to an epitope that is present on misfolded protein ABC but not on normal protein ABC; and diagnosing the patient as having degenerative disease X if misfolded protein ABC was determined to be present in the blood sample.*

According to the guidelines, this claim is patent-eligible because the claim as a whole recites something significantly different than the natural principle, i.e., the claim includes elements in addition to the judicial exceptions (e.g., contacting the blood sample with a specific novel antibody XYZ, and detecting binding using flow cytometry) that amount to a practical application of the natural principle.

RESPONSE TO THE GUIDELINES

The guidelines were met with intense backlash. Many argue that they unnecessarily expand the scope of the *Myriad* and *Mayo* cases in a way that could unduly restrict the scope of patentable subject matter, weaken the U.S. patent system, and create a disincentive to innovation.

As a result of the negative publicity it received, the USPTO decided to rethink its approach and agreed to host a public forum on May 9, 2014, at the USPTO headquarters in Alexandria, Virginia, to solicit feedback from organizations and individuals on its recent guidance memorandum.[††] Based on the feedback it received, the USPTO may revisit the guidelines. Moreover, the guidelines do not have the force of law. Thus, a cautious approach should be applied when relying on the guidelines.

In the meantime, however, the guidelines represent the USPTO's current thinking regarding how examiners are instructed to examine certain types of patent claims. To the extent that prosecution cannot be delayed until the revised guidelines are issued, it is helpful to have a good understanding of the guidelines, as they are likely to present hurdles for a broad range of biomedical technologies. Below are examples of rejections that have already been issued since the guidelines were announced.

STATE OF CLAIMS IN VIEW OF THE GUIDELINES

Following the release of the guidelines, many claims have been rejected as allegedly not satisfying the requirements of Section 101. Below are several examples of claim rejections that have recently been issued applying the guidelines.

Pharmaceutical Compositions:

> *A composition comprising Compound X or a fragment thereof and X % by weight of Component Y.*

According to the Examiner, since Compound X is a "natural product" and Component Y could be a "natural product", there is nothing "in addition to the judicial exceptions" that would render the overall claim patent-eligible.[‡‡]

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†† USPTO, *Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products*, March 4, 2014, http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf.

‡‡ Courtney C. Brinckerhoff, *The New USPTO Patent Eligibility Rejections Under Section 101.* PharmaPatentsBlog, published May 6, 2014, accessed http://www.pharmapatentsblog.com/2014/05/06/the-new-patent-eligibility-rejections-section-101/.

Vaccines:

A pharmaceutical composition, comprising: a peptide having an amino acid sequence that is at least 90% identical to SEQ ID NO.: 1, and a pharmaceutically acceptable carrier. [SEQ ID NO.: 1 is a naturally occurring protein or fragment thereof]

According to the Examiner, a claim directed to a vaccine is rejected because neither the peptide nor the carrier is structurally different from a natural product.

Antibodies:

An isolated polynucleotide comprising a nucleotide sequence which encodes an antibody heavy chain variable region (VH) polypeptide comprising the amino acid sequence SEQ ID NO.: 9 or SEQ ID NO.: 10, wherein an antibody comprising said VH polypeptide can specifically bind to Antigen X. [SEQ ID NO.: 9 refers to a humanized sequence and SEQ ID NO.: 10 refers to a murine sequence]

The Examiner rejected reference to SEQ ID NO.: 10 on the grounds that the murine sequence is not structurally different than the sequence found in nature. SEQ ID NO.: 9, on the other hand, satisfied the guidelines because humanized sequences are engineered.

Methods of Making

A method of making a composition comprising Compound X and Component Y, comprising providing Compound X and Component Y [at specified relative amounts].

The Examiner rejected this claim because all of the claim language relates to "natural products" and so there is nothing "in addition to the judicial exceptions" on which to base patent eligibility.[§§]

Methods of Treatment

A method of treating Disease X in a subject, comprising administering to the human the composition according to claim 1.

The Examiner rejected this claim because it is directed to a natural product and recites nothing in addition to the dosage exceptions. This method claim differs from Example B, claim 3, which includes elements in addition to the judicial exception (e.g., dosage amounts, treatment period limitations) that add significantly more to the judicial exception.

Methods of Diagnosing Disease

A method of diagnosing Disease X in an individual suspected of having disease X, comprising the steps of: a) measuring the level of expression of Genes Y and Z in a biological sample from the individual; b) comparing the level of expression of Genes Y and Z in the biological sample to the level of expression of Genes Y and Z in a control sample from an individual without Disease X, wherein a decreased level of expression of Gene Y and an increased level of expression of Gene Z in the biological sample relative to the control sample is indicative of the individual having Disease X, thereby diagnosing Disease X in the individual.

Referring to the guidelines, the Examiner rejected this claim because as a whole it was directed to a law of nature/natural principle and allegedly did not recite something "significantly different" than the law of nature/natural principle. Here, the "natural principle" is "expression of Genes Y and Z that correlate with the presence or absence of Disease X." The Examiner reasoned that the claim does not practically apply the natural principle in a significant way, but instead was drawn to conventional, routine, and well-understood method steps. Accordingly, the claims to not recite something "significantly different" than the natural principle, but rather "simply inform" the natural principle to one performing routine active method steps and do not amount to significantly more than the natural principle itself.

§§ Courtney C. Brinckerhoff, *The New USPTO Patent Eligibility Rejections Under Section 101.* PharmaPatentsBlog, published May 6, 2014, http://www.pharmapatentsblog.com/2014/05/06/the-new-patent-eligibility-rejections-section-101/.

FUTURE OF BIOTECHNOLOGICAL INNOVATION

Instead of encouraging development of biomedical inventions by promoting strong patent protection, the guidelines may create hurdles for biotechnology and pharmaceutical companies when it comes to patenting and protecting their products. Not only has USPTO guidance in view of the *Prometheus* and *Myriad* decisions unsettled the more than thirty years of established patent law framework for determining patent eligibility under Section 101, it also made the U.S. the only jurisdiction in the world to exclude whole groups of inventions that are patentable elsewhere.

The weakening of patent protection in this way could impact life sciences companies of all sizes. Established companies with marketed products may face greater competition as their ability to rely on patents to deter competitors is diminished. Startup and clinical stage companies, on the other hand, may struggle to attract the necessary financing for conducting research and development without key patents protecting their assets. As a result, many potentially life-saving technologies may never be developed. The USPTO guidelines could therefore stifle innovation because companies may choose to imitate rather than to innovate, and investors may not want to continue to fund the research and development that is required to bring products to market. Finally, contrary to public policy encouraging disclosure of patented inventions, the USPTO's guidelines may encourage secrecy as some companies may forgo seeking patent protection entirely in favor of retaining their innovations as trade secrets, where possible.

CONCLUSION

Patents in the biotechnology and pharmaceutical areas protect many important technological developments, including vaccines, drugs and diagnostic tests. As such, they are important in the development and delivery of healthcare. Over the last two years, however, the Supreme Court and now the USPTO have taken actions that threaten to diminish the value of these patents. By undermining these patents, these changes reduce incentives for discovery of new innovative medicines, which may end up harming not only the companies which patent their innovations, but also the patients who need medical care.

Legal & Regulatory Update

Staking an advantage in an AIA world: Practical patent tips for biotechnology companies

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ABSTRACT

With passage of the Leahy-Smith America Invents Act (AIA), new rules and procedures related to the application of prior art now apply to patenting under a "first-inventor-to-file" system. This article summarizes certain key prior art provisions that biotechnology companies should be aware of and details practical steps that can be implemented to help stake a competitive advantage under the new law including the use of patent liaisons, early provisional and patent application filings, and in certain circumstances, defensive publication of patentable subject matter.

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INTRODUCTION

The Leahy-Smith Invents Act, informally known as the "AIA," was signed into law September 16, 2011, and represented the first major overhaul of the United States patent system in over 60 years.[1] From opinion pieces to detailed technical analysis, an overwhelming amount of literature has already been written on the intricacies of the new law.[2] This has led to an information glut, and consequentially, many managers, CEOs, scientists and even patent counsel are left without clear directions for responding to the new law. As detailed below, however, practical steps can be taken to gain a competitive advantage in a company's intellectual property (IP) space by implementing simple steps including early patent filing, strategic defensive disclosures and the use of "patent liaisons."

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REASSESS AND ADDRESS

The most significant shift resulting from passage of the AIA altered the U.S. patent law from a first-to-invent (FTI) to a first-inventor-to-file (FIF) system. While the policy debate on the merits of this sea change show no signs of waning, beyond debate is the need for biotechnology companies to reassess their intellectual property policies and procedures from both an offensive vantage point (e.g., the filing, prosecution and enforcement of patents) and a defensive one (e.g., patent challenges and defensive disclosures).[3] A central issue relates to the AIA's provisions regarding novelty, i.e., the circumstances under which the claimed subject matter of a patent is deemed to have been already known to the public before the filing date of a patent. The AIA's novelty provisions are set forth in the Patent Law at section 102(a), which is reproduced in part below in Box A.[4]

Subject to very important but narrow exceptions, these new novelty provisions of the AIA establish a strict standard by which nearly any public disclosure of a claimed invention will obviate patentability. The exceptions, detailed in the following section 102(b), entitle the inventor to a 1-year grace period for the first public disclosure of the claimed subject matter.[5] Notably, the

Box A: 35 U.S.C. § 102(a)
(Conditions for patentability; novelty)

"A person shall be entitled to a patent *unless*—

(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention; or

(2) the claimed invention was described in a patent … or in an application for patent published … in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention."

grace period also applies to other parties' disclosures if the inventor was first to publically disclose the invention. The House Report on these new prior art laws succinctly summarizes the new reach: "Prior art will … typically include all art that publicly exists prior to the filing date, other than disclosure by the inventor within 1 year of filing."[6] Moreover, in contrast to pre-AIA law, there no longer are geographic exceptions to applicable prior art: art, as well as public use and on-sale activities, anywhere in the world can now be used.[7]

What this means practically is that if a company scientist invents something new before anyone else, but is not first to either publicly disclose or file a patent application, a competitor can obtain a patent notwithstanding the later invention date. A corporation must address this change in the law by implementing new policies, as discussed next.

FILE PATENT APPLICATIONS EARLY

Passage of the AIA led to criticism that the new patent law would provide a disadvantage to smaller companies.[8] Arguably, larger companies would have the resources to form and maintain high-throughput internal patenting and invention disclosure procedures leading to rapid filing of patent applications. Because the law no longer awards patents to the first inventor-to-file, a company with an efficient means for capturing patentable subject matter and filing a patent application could conceivably race to the Patent Office before a smaller competitor.

Smaller companies can nonetheless compete with minimal resources by instilling a corporate "publish, file or perish" mandate.[9] The goal is simple: move patentable subject matter quickly to the Patent Office, or in some cases, publish to stake an early line in the sand and capture incremental IP space. Successful implementation requires establishing in-house procedures to ensure ideas are captured early and then disclosed in usable form for drafting as a patent application or public disclosure. This requires managed oversight of the disclosure process. The goal being to decrease the lag time from the point of an inventor's conception of an idea to in-house disclosure, followed by public or Patent Office filing, with the latter preferable. Borrowing from the legislative mandate for *inter partes* review of patents, such disclosure or filing should be made with "special dispatch."[10] One relatively low-cost means for implementation involves centralizing responsibility for IP disclosure, which can be done using an IP liaison.

A CENTRAL AUTHORITY: THE INTELLECTUAL PROPERTY LIAISON

An IP liaison is so named because the post functions to facilitate a close working relationship between scientists, management, and patent counsel.[11] Moreover, the liaison will serve to ensure that inventions are properly documented, witnessed and recorded, in part by reaching out to department heads and obtaining regular updates on potential patentable subject matter. For example, the team head for a group in a particular technical field may provide a monthly update of potential new IP disclosures and developments on prior disclosures. Where new potential IP space can be captured, the liaison will then identify likely inventors and task them with the creation of an invention disclosure form (IDF) recording pertinent facts related to the scope of the invention.[12] Because the liaison is aware of disclosures among different departments, he/she can also determine whether cross-patenting is a possibility.[13]

The liaison will in turn work with patent counsel to analyze completed IDFs for patenting readiness by initiating preliminary prior art evaluations. Subsequently, the liaison will either recommend the drafting of a patent application, a defensive publication, or communicate with team heads where further research and development is needed to obtain patentability. The IP liaison's role can also be expanded to allow coordinated efforts to identify areas of virgin IP space that can be captured. Such IP space is characterized by a dearth of prior art in the technical field under study by laboratory heads.[14] Lastly, the IP liaison can serve as a repository for template invention disclosure forms and patent applications. By managing control over such forms and applications, the liaison can ensure uniformity in the disclosure and patenting process. Most

Box B: An IP Liaison can not only ensure that best practices are followed, but that patent disclosures and applications are efficiently drafted and submitted among other duties.

The IP Liaison: Roles & Responsibilities		
Point Person and Go-Between for Inventors, Department Heads, Managers and Patent Counsel	Assist in Drafting Invention Disclosure Forms (IDFs) and Patent Applications	Monitor Patent Prosecution
Monitor Department Heads Vis-à-Vis Intellectual Property Issues	Oversee Brain-Storming Sessions for Capturing IP Space	Monitor and Disseminate Patent and Prior Art Data
Maintain Template Invention Disclosure Forms (IDFs) and Patent Applications	Create and Maintain IP Databases	Perform IP Training
Ensure Best-IP Practices Compliance	Provide IP Updates on Regulatory Issues	Monitor Competitor IP and Track In-House IP Projects
Locate and Capture "Free" Patent Space in Key Technical Fields	Bolster Recognition of the Importance of IP Protection	Develop In-House IP Policy

importantly, the liaison can distribute template invention disclosure forms and employ a uniform disclosure process. This will improve efficiency in communicating with patent counsel without impacting the quality of patent applications. The various roles and responsibilities that may be assigned to an in-house IP liaison are summarized in Box B.

Under the AIA regime, patenting is now a race to the Patent Office. Optimizing the disclosure process, which can be implemented using patent liaisons, is an important step to getting there first. The suitability of various forms of disclosure under the new AIA regime is considered next.

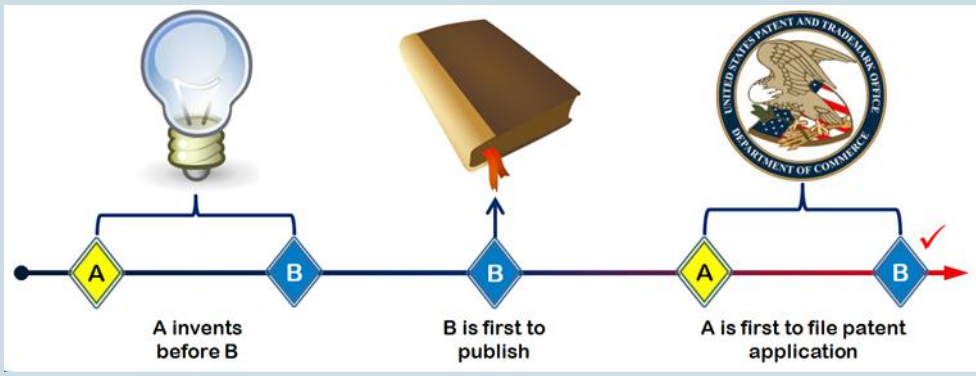
USE OF PROVISIONAL PATENT APPLICATIONS AND PUBLIC DISCLOSURES

Under the AIA, applications with a claimed invention having an effective filing date on or after March 16, 2012 are generally subject to the new framework with respect to prior art. As detailed above and codified in section 102 of the Patent Law, publications, patents, sales and uses, that are public before an applicant's effective filing date can be invalidating prior art.[15] Moreover, certain patent publications by another that are filed before the applicant's effective filing date can also be prior art. It is therefore critical that a corporation determine whether to take advantage of the one-year grace period for making prior art disclosures. This is because pre-filing disclosure can serve to overcome the earlier filing of an application to the *same* subject matter by a competitor (or other intervening prior art), as illustrated below in Box C.[16] Box C also highlights that the relative dates of invention under the AIA no longer determine the scope of applicable prior art.

Under the AIA's First Inventor-to-File rules, in the absence of pre-filing disclosure,[17] the AIA favors the first filer among multiple filings with the Patent Office toward the same invention. Thus, the effective filing date of a patent application—not the conception date of an invention—is the *sine qua non* determinative of the applicable prior art. Provisional filings provide a convenient means for helping ensure an early effective filing date. Because provisional filings are low-cost, even cash-strapped companies can stake a line in the sand.[18] Because an applicant has one year to file a final non-provisional application, an initial provisional filing can *and should* be supplemented with additional provisional filings in a rolling manner that add additional disclosure or address any issues with prior disclosures.

As an alternative to provisional patent applications, a corporation can also consider the use of other public disclosures to offset the chance that a competitor will be first-to-file. These disclosures can include the use of low-cost "grey literature"—informally published but publically available written materials (like white papers)—or press releases and tradeshow abstracts/materials. While provisional applications do not become publically accessible until after the filing of a non-provisional application and publication of that application, other public disclosures are generally immediately available.[19] A corporation will have to consider whether early public disclosure is preferable to disclosure by means of a provisional filing.[20] The former may be preferable where it is clear that patent protection is not desired; public disclosure in this case serves

Box C: Under the AIA, Inventor A loses to Inventor B despite an earlier invention date and patent filing because Inventor B was first to publish (disclose) the claimed invention.



a defensive purpose by setting forth potentially invalidating prior art. In contrast, a provisional application avoids the risk that comes with public disclosure, i.e., that the public disclosure will fail to meet an exception under the prior art provisions and become prior art to a company's own patent application. Close consultation with IP counsel on these alternatives is paramount.

MONITOR COMPETITOR PATENTING, KNOW THE PRIOR ART AND DISCLOSE

Among the key provisions of the AIA related to prior art, the AIA now provides for expanded options for pre-grant oppositions.[21] In particular, third-parties can now submit prior art from any part of the world related to a patent application within certain timeframes, as well as any statements made by the applicant to the Patent Office or before a federal court. Moreover, such submissions may include explanations of the pertinence of the prior art.

Because a corporation should include in its IP due diligence a continuing analysis of the prior art landscape related to any target or competitor technology, such materials are useful not only in the planning and prosecution of a corporation's patent applications, but may be used offensively against competitors. Defensively, early disclosure of potential prior art before the Patent Office can be used to offset the risk that the prior art will be used successfully by a competitor in a pre-grant filing.

INFORM, INFORM, INFORM

A sea change in patent law has occurred. But far from a one-off event, continued changes are on the horizon as the Patent Office and the courts begin interpreting and implementing the law to actual patent cases. This article has provided some practical advice with respect to a small subset of the new AIA law. A corporation should ensure that its employees are continuously informed and updated on patent law developments, and that its scientists adhere to good patent disclosure practices. Implementation of a patent liaison and appreciation of the role of prior art under the AIA is one solid step in the right direction. Continued vigilance and early patent application filing is the next.

ENDNOTES

1. Leahy-Smith America Invents Act, H.R. 1249 (112th Congress, First Session), enacted (President Obama) 16 September 2011, available online at http://www.gpo.gov/ fdsys/ pkg/ PLAW-112publ29/content-detail.html (accessed 24 February 2014).
2. *See, e.g.,* American Intellectual Property Law Association (2012) Summary of the America Invents Act. http://www.aipla.org/advocacy/congress/aia/Pages/summary.aspx, accessed 26 February 2014 (providing a succinct summary of key provisions); Uthaman, S., Lu, D., and Kowalski, T. (2012) Post-grant review: The good, the bad and the ugly for biotechnology companies. Journal of Commercial Biotechnology 18(1): 97–99 (discussing new opposition procedures); Intellectual Property Owners Association (2011) Comparison of Selected Sections of Pre-AIA and AIA U.S. Patent Law https://www.ipo.org/wp-content/ uploads/ 2013/ 03 /Patent_ Reform_ Chart_ Comparison_ of_ AIA_ and_ Pre-AIA_ Laws_FINAL.pdf, accessed 26 February 2014.

3. *See, e.g.,* Fox, J. (2011) America Invents Act receives cautious welcome. Nature Biotechnology. 29: 953–954; Rondeaue, G. (2011) "America Invents Act" patent law overhaul: the benefits and the drawbacks. Lexology. 17 November. http://www.lexology.com /library/detail.aspx?g=5f772592-7ac2-41bc-becb-d3ff5c8ed192, accessed 26 February 2014.
4. The full text of Title 35 of the United States Code (U.S.C.), Section (§) 102 (enacted 2012) is available online at http://www.law.cornell.edu/uscode/text/35/102?qt-us_code_tabs=0 (accessed 26 February 2014).
5. *See* 35 U.S.C. § 102(b) (setting forth exceptions for disclosures made 1 year or less before the effective filing date of the claimed invention and for disclosures appearing in applications and patents).
6. Commonly owned disclosures, i.e., subject matter disclosed in the published application or patent and the claimed invention were owned by or subject to an obligation of assignment to the same person, made within a U.S. patent, patent application, or PCT application are also excepted as prior art.
7. It is not yet clear whether private use and on-sale activities may be considered prior art "available to the public" under the new § 102. *See* 35 U.S.C. § 102(a).
8. *See, e.g.,* Rao N. (2013) Opinion: AIA Does Not Discriminate. The Scientist. 21 August. http://www.the-scientist.com/?articles.view/articleNo/37133/title/Opinion--AIA-Does-Not-Discriminate/, accessed 26 February 2014 (arguing that the AIA does *not* discriminates against academics and small biotech firms).
9. The "paradox of large organisations," in which companies with great assets are successfully out-competed by smaller and newer companies has been previously described, and suggests it is managerial efficiency and not assets, that determine winners in the marketplace. *See* Luke Johnston (2011) The biggest groups are ill with inefficiency. Financial Times. 5 April. http://www.ft.com/intl/cms/s/0/863409bc-5fca-11e0-a718-00144feab49a.html#axzz2uMzj3yLQ, accessed 25 February 2014
10. *See* 35 U.S.C. § 305 (Conduct of reexamination proceedings).
11. *See* Knight, J. (2013) Patent strategy for researchers and research managers, 3rd ed. Chichester, West Sussex, U.K.: John Wiley at ch. 3 (discussing use of patent liaisons).
12. Some have argued that practices under the pre-AIA world related to documentation of an invention's conception and reduction-to-practice are of lesser import now that a first-inventor-to-file system has been implemented. Nonetheless, good practices should still be adhered to for use in potential derivation proceedings and to ensure that the scope of an invention is accurately and quickly translated into a fulsome patent application. *See, e.g.,* Lu, D., Kowalkski, T., Uthaman, S. (2012) Are laboratory notebooks necessary in a first inventor to file world? Journal of Commercial Biotechnology. 18(3): 67–68.
13. For example, one department may have ideas relating to improved gene amplification techniques, and another department may have ideas relating to improved gene silencing techniques. The IP liaison can help determine whether potential IP space can be captured involving a combination of those techniques. The resulting combination patents are more likely to survive prior art challenges where a motivation to combine those techniques has not been previously demonstrated or suggested.
14. *See e.g.,* Rzucidlo, G. and Miller, S. (2008) Aggressive Intellectual Property Strategies. In Friedman, Y. (ed.) Best Practices in Biotechnology Business Development, ed. Yali Friedman, US: Logos Press, pp. 61–80 (discussing the use of strategic patenting to capture free IP space).
15. The "effective filing date" of a claimed invention is defined to be the earlier of the actual filing date of a nonprovisional application and the date to which the nonprovisional application claimed domestic benefit or foreign priority of another application describing the claimed subject matter. *See* AIA Frequently Asked Questions (2013). USPTO, 30 October. http://www.uspto.gov/aia_implementation/faqs_first_inventor.jsp, accessed 26 February 2014.
16. *See* 35 U.S.C. § 102(b)(2)(B) (setting forth that as to a later filed application, an earlier-filed application or patent is not prior art under § 102(a) if the inventor(s) of the later filed application publically disclosed the claimed invention within the 1-year grace period and prior to the effective filing date of the earlier filed application). Importantly, patent counsel should be consulted when considering a pre-filing disclosure because such disclosures can have other consequences such as affecting patenting rights in foreign jurisdictions or serving as prior art against a company's own later filed patent applications where a disclosure does not meet a prior art exception.
17. Importantly, the grace period does not apply where the difference between the subject matter in the prior art disclosure that is relied upon under 35 USC § 102(a) and the publically disclosed subject matter of the inventor are different (*even if the difference is trivial or obvious*).

18. Such filings should be as complete as possible to ensure that later claimed subject matter will be entitled to the earlier effective filing date.

19. *See* 35 U.S.C. § 122 (Confidential status of applications; publication of patent applications).

20. Disclosures should be made carefully and with the advice of counsel, as the prior art exceptions under 35 U.S.C. § 102(a) do not apply where the disclosure of the prior art and the subject matter relied upon under § 102(a) is not identical. Otherwise, a defensive publication by a company may inadvertently become prior art to a company's own patent application!

21. *See, e.g., supra,* Uthaman (2012) Post-grant review: The good, the bad and the ugly for biotechnology companies.

Legal & Regulatory Update

EU Legal & regulatory update – June 2014

ABSTRACT

UK and European content is compiled and written by Bird & Bird LLP, an international law firm which advises Life Sciences clients on:

- licensing intellectual property and know-how
- R&D agreements and other commercial contracts
- clinical trials
- regulatory issues
- risk management
- private equity, venture capital, joint ventures, strategic alliances, mergers & acquisitions and stock exchange listings
- patent & trade mark litigation
- data protection
- EU & competition law
- product liability

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This section is intended to be a synopsis of recent legal developments and is not intended to be exhaustive. If any issue referred to in this section is to be relied on, specific advice should be sought.

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GENERAL COURT OVERRULES EUROPEAN COMMISSION ON ORPHACOL MARKETING AUTHORISATION

Facts

Article 10a of EU Directive 2001/83/EC, as amended, provides a route by which an applicant seeking marketing authorisation for a medicinal product can secure such an authorisation without the need to submit pre-clinical data and clinical trial data as to safety and efficacy, or to cross reference (after expiry of the period of regulatory data protection) an existing marketing authorisation for the same active substance based on such data. Article 10a requires that the applicant:

> *"demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the [EU] for at least 10 years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I".*

It goes on to provide that "[in] that event, the test and trial results are to be replaced by appropriate scientific literature".

Laboratoires CTRS had sought a centralised marketing authorisation under the Article 10a route for its medicinal product Orphacol (cholic acid), used to treat two rare, but serious liver disorders. Cholic acid had not previously received a marketing authorisation in the

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European Union. Despite a recommendation from the relevant standing committee of the European Medicines Agency that a marketing authorisation be granted in respect of Orphacol, after seeking unsuccessfully to pressure the standing committee into changing its opinion, the European Commission eventually adopted an implementing decision refusing a marketing authorisation, as it took the view that there was no legal basis for granting such an authorisation in this case.

Decision

On July 4 2013 the General Court upheld an appeal by Laboratoires CTRS seeking to annul the European Commission's decision. In so doing, the court rejected all three reasons advanced by the European Commission in reaching its decision.

First, the European Commission asserted that the well-established medicinal use of cholic acid had not been proved, arguing that its use as a hospital preparation between 1993 and 2007 was insufficiently systematic and well documented to prove well-established medicinal use over a period exceeding 10 years. In support of this, it argued that "hospital preparations" are not covered by Directive 2001/83/EC. However, the court held that these are covered by Article 5(1), which subsequently relieves certain medicinal products from the provisions of the directive, such as the need to secure a marketing authorisation, where these are:

> *"supplied in response to a bona fide unsolicited order, formulated in accordance with the specification of an authorised health care professional and for use by an individual patient under his direct personal responsibility".*

The European Commission's second argument was that it was inconsistent with the well-established medicinal use route for Laboratoires CTRS to have been able to rely on "exceptional circumstances" as a reason for not providing comprehensive data on safety and efficacy, as is allowed by Article 22 of Directive 2001/83/EC where the applicant can show that it is unable to do so for "objective, verifiable reasons". The court also rejected this argument, noting that nothing in the legislation precludes the simultaneous application of the concepts of "well-established medicinal use" and "exceptional circumstances"; the court observed that Laboratoires CTRS had "objective, verifiable reasons" in the rareness of the disorders in question and in ethical considerations. Indeed, the conditions that Orphacol was used to treat were sufficiently rare for it to have secured designation as an orphan medical product.

Finally, the European Commission argued that the grant of such a marketing authorisation would undermine the objectives of the EU Paediatric Regulation (1901/2206) and the protection of innovation. As to the second point, the court held that this had not been presented in the European Commission's decision as a free-standing ground for refusing to grant the marketing authorisation, but merely as a remark. As to the first point, the court noted that Article 9 of the Paediatric Regulation specifically excludes applications under the well-established medicinal use route from the relevant requirements of the regulation. Thus, the court also rejected this third line of argument.

Comment

This decision represents a setback for the European Commission in its attempts to limit the scope of the well-established medicinal use route for securing marketing authorisation for a medicinal product. The European Commission has in the past successfully sought to limit reliance on the well-established medicinal use route in cases where it has been used in an attempt to circumvent the regulatory data protection afforded to new active substances which have already received marketing authorisation. An example of this is the Plavix case in Germany, as a result of which the European Commission threatened proceedings against Germany for allowing such circumvention to take place; however, the European Commission did not then proceed, presumably because it received satisfactory assurances from the German authorities that their practice had changed. However, the Orphacol case is different and concerns an active substance that had not previously received a marketing authorisation in the European Union. It is clear that by extending its hostility to the well-established medicinal use route to this different situation, the European Commission has overreached itself.

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PROMOTING EARLY ACCESS TO NEW MEDICINES — BUILDING AN "ADAPTIVE LICENSING" FRAMEWORK

Adaptive licensing

Referred to by various terms (staggered approval, managed entry, progressive authorisation), "adaptive

licensing" is a departure from the traditional approach to authorising new medicinal products. Under the current system, the initial grant of a marketing authorisation (MA) tends to be regarded as a "magic moment", at which point the medicine is suddenly held to be safe and efficacious. The "adaptive licensing" (AL) approach embraces the reality that, due to restricted patient exposure during clinical trials, it is often not until the post-marketing phase that information on the benefit-risk profile of the product as used "in real life" is obtained, and that there are certain situations in which a degree of acknowledged uncertainty over the benefit-risk profile of a product at the time of initial MA may be acceptable to regulators, patients and payers alike. Given this, medicines regulators have been discussing developing the concept of AL, namely, a prospectively planned, flexible approach to licensing whereby an initial, limited MA is granted (often for a "niche" indication/restricted patient population) based on limited data. Prospectively planned extensions of the MA, following iterative phases of data gathering and regulatory evaluation, follow. The hope is that, as well as providing patients with timely access to new medicines for treating serious conditions with unmet medical needs, AL will also help to address the fact that the number of newly approved drugs per year has remained flat in recent years (as increasing demands in terms of the amount of up-front data required to bring a new drug to market necessitates increased investment to match the scale, duration and complexity of clinical trials required). The AL approach will allow products onto the market based on smaller scale trials in limited indication(s)/patient population(s).

For now, the AL approach is founded on various existing mechanisms (discussed below) which are already in place to ensure that the regulatory framework is able to promote the assessment and approval of medicines to treat currently unmet medicinal needs, making them available to patients as soon as possible. AL seeks to balance timely access to new authorised treatments with the need to have enough data for a robust risk/benefit profile assessment. In the European Medicine Agency's "Road Map to 2015", it is emphasised that "AL should not lead to reducing evidentiary requirements for first-time marketing authorisation".

The European Medicines Agency (EMA) has now announced that it is seeking candidate medicines to enter a pilot scheme to investigate the application of the AL approach in the context of medicines currently in development. Although already much debated, this is the first formal step by EU regulators towards introducing a specific AL approach to getting selected products onto the market.

From the current licensing framework to AL

The current medicines regulatory framework does recognise that MA applicants will not always be able to produce full dossiers of robust clinical data at the time of MA application. In the interests of making authorised products available to patients in need, the legislation already provides for mechanisms to address this issue, allowing authorisation in a variety of special circumstances where there is sufficient justification. For example, a "conditional" MA (valid for one year and renewable) may be granted where there is scientific data to demonstrate a positive benefit-risk profile for the medicinal product (pending confirmation) but the clinical part of the dossier is incomplete. The product must meet certain criteria. Specific obligations (with a timetable for completion of further studies) are attached to the MA and the aim is to convert the authorisation to a "normal" MA in due course, depending on the outcome of those studies. An "exceptional circumstances" authorisation also provides a route to MA (again with specific obligations attached and based on annual reassessment of the benefit-risk profile), but in situations where it is unlikely that a full data package will ever be obtained (where the indication is very rare, where comprehensive information cannot be provided "in the present state of scientific knowledge" or where it is contrary to generally accepted principles of medical ethics to collect such information).

Pre-authorisation "compassionate use" schemes and the increasing emphasis on post-authorisation pharmacovigilance through follow-on trials, patient registries, risk minimisation plans and other schemes, also illustrate a shift in thinking away from the traditional binary unapproved/approved paradigm towards viewing the initial authorisation of a product more as just a formal step in a progressively managed product development and monitoring programme.

For the time being, AL will use the regulatory approaches available within the existing framework (including scientific advice, centralised compassionate use and the other mechanisms described above, particularly conditional marketing authorisation and risk management plans). However, some stakeholders see this new approach as possibly transforming the licensing landscape to become the standard approach to authorising new medicines; it may well be that legislative changes (strengthening these existing mechanisms and addressing other issues) will be required for full implementation to succeed.

The EMA's AL pilot scheme and beyond

In seeking candidates for its pilot scheme, the EMA has asked industry to identify suitable experimental medicines currently in the early stages of clinical development (normally prior to the initiation of confirmatory studies i.e. during or prior to phase II, although this can be considered case-by-case). Significant coordination and buy-in among all stakeholders will be needed to make AL work well, so the pilot scheme will involve all those with a role in determining patient access, including health technology assessment bodies, organisations issuing clinical treatment guidelines and patient organisations. The informal discussions will take place in a "safe harbour" environment to allow for open discussion of the pros and cons of all options in confidence, without commitment from either side; the rules of engagement are currently being developed.

Under AL, the aim is to adapt the MA as information on the benefits and risks of the product evolves and undergoes regulatory assessment. AL may not be applied to all drugs in the same manner; a product for use in treating a serious or life-threatening illness where there is an unmet medical need and promise of high added clinical value for patients may require considerably less data for an initial authorisation than would be required for a new product to treat a disease for which there is already a range of treatments. The specifics of the pathway are likely to vary on a case-by-case basis and to differ from one product to another and from one therapeutic area to another. This pilot scheme aims to assess how future AL pathways might be designed for different products and indications, as well as highlighting any potential problems that might arise. For a fully developed AL framework to succeed, regulators may need new authorities to allow them to implement wide use of restrictions on the terms of the MA and prescribing surveillance.

The possibility of a means of reducing the overall costs of developing new products, by allowing better informed decisions on product viability to be made earlier in the development process, should be attractive to industry, although it is likely that a number of issues will need to be addressed if AL is to succeed; for example, the current reward and incentive structures are designed to work in the context of the traditional "all-population" authorisation and promotion approach and these may need to be re-examined. The EMA notes that the European Commission will examine the legal and policy aspects of AL as the scheme progresses.

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ARE MY TECHNOLOGY TRANSFERS READY FOR THE NEW TTBER AND THE UPC?

In this contribution, we highlight two developments that shall impact technology transfers:

1. On May 1, 2014, the revised EU block exemption regulation for technology transfer agreements, the so-called *TTBER*, entered into force,[1] together with the new guidelines for technology transfer agreements (*TT-Guidelines*).[2] They bring important changes for future and existing technology license agreements.[3]
2. As matters stand, it may be expected that by the end of 2015, the Unitary Patent Package will take effect. This package will bring a Unitary Patent and a Unified Patent Court, with new challenges and opportunities, which one should consider when conducting technology transfers that comprise patent (application(s)), including future and existing patent license agreements.

Both developments may warrant that parties adapt their policies concerning technology transfers and that they review their existing licensing agreements.

The revised TTBER and TT-Guidelines

Introduction

Together with Article 101 of the Treaty on the Functioning of the European Union ("*TFEU*"), the TTBER in combination with the TT-Guidelines provide the core competition law framework for licensing agreements relating to

1 Commission Regulation (EU) No 316/2014 of 21 March 2014 on the application of Article 101(3) of the Treaty on the Functioning of the European Union to categories of technology transfer agreements (OJ L93, 28.3.2014, p. 17-23).

2 Communication from the Commission 2014/C89/03, Guidelines on the application of Article 101 of the Treaty on the Functioning of the European Union to technology transfer agreements (OJ C89, 28.3.2014, p. 3-51).

3 New TTBER: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.093.01.0017.01.ENG; new TT-Guidelines: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:C:2014:089:TOC#C_2014089EN.01000301.doc; press-release: http://europa.eu/rapid/press-release_IP-14-299_en.htm

technology and is therefore of particular importance for companies in technology driven sectors like life sciences.

Article 101(1) TFEU prohibits as incompatible with the internal market "[..] *all agreements between undertakings, decisions by associations of undertakings and concerted practices which may affect trade between Member States and which have as their object or effect the prevention, restriction or distortion of competition within the internal market* [..]". Pursuant to Article 101(2) TFEU, such agreements shall be automatically void, and also competition authorities such as the European Commission, the Dutch Authority for Consumers and Markets and the Bundeskartellamt can decide to investigate the contracts and impose fines if the contracts show a consistent violation of the TTBER without there being an objective justification.

However, Article 101(3) TFEU allows that the rule of Article 101(1) is declared inapplicable in the case of any such agreement, decision and concerted practice, or categories thereof,

> *"which contributes to improving the production or distribution of goods or to promoting technical or economic progress, while allowing consumers a fair share of the resulting benefit, and which does not: (a) impose on the undertakings concerned restrictions which are not indispensable to the attainment of these objectives; (b) afford such undertakings the possibility of eliminating competition in respect of a substantial part of the products in question."*

This is where, for technology licensing agreements,[4] the TTBER and TT-Guidelines come into play. In accordance with Article 101(3) TFEU, the TTBER provides that the prohibition of Article 101(1) TFEU shall not apply to technology transfer agreements. After all, such agreements will normally improve economic efficiency and be pro-competitive as they can reduce duplication of R&D, strengthen the incentive for the initial R&D, spur incremental innovation, facilitate diffusion and generate product market competition.[5] However, this is not a general exemption. Supplemented by the TT-Guidelines, the TTBER formulates a series of criteria for, and limitations to the "safe harbour" that the TTBER provides.

4 The TTBER does not apply to licensing in the context of R&D agreements. For this, a separate EU block exemption regulation is in place. Same goes for licensing in the context of specialisation agreements. Also excluded from the scope are agreements that merely have the purpose of reproducing and distributing software copyright protected products, and agreements to set up technology pools.

5 See Recital 4 of the new TTBER.

The previous TTBER[6] and TT-Guidelines[7] have been in place since 2004, and they were due to expire on 30 April 2014. Therefore, preparations were commenced for a revision of both instruments. This comprised two public consultation rounds issues by the European Commission. The first consultation was started in 2011, and invited interested parties to communicate their experiences with the existing framework.[8] The second was held in 2013, and served to obtain comments concerning a proposal by the Commission for a revised package comprising a new TTBER and new TT-Guidelines.[9] On 21 March 2014, the Commission adopted the new TTBER and new TT-Guidelines, and per 1 May 2014, they have replaced the old TTBER and TT-Guidelines.

The new TTBER and TT-Guidelines contains some important changes, deviating from the former framework. The most significant changes relate to the following:

- Passive sales restriction;
- Grant back obligations;
- Non-challenge clauses.

Passive sales restriction

Under the new TTBER, the restriction on passive sales will only be allowed when the licensor grants an exclusive license. Absent such exclusivity, each passive sales restriction is considered to be a so-called "hard core restriction", and hence will not be allowed. Under the old TTBER, there was an exemption which allowed a licensor to restrict passive sales for a period of two years for those situations where a licensee was offered a new and exclusive territory or customer group (in license agreements concluded between non-competitors). Please note that the new TT-Guidelines provide for a further explanation to this restriction by considering the fact that a passive sales restriction can be justified if the licensee needs to do significant investments in marketing, promotion and/or production (TT-Guidelines, § 126).

> *"Where substantial investments by the licensee are necessary to start up and develop a new market,*

6 Commission Regulation (EC) No 772/2004 of 27 April 2004 on the application of Article 81(3) of the Treaty to categories of technology transfer agreements (OJ L 123, 27.4.2004, p. 11).

7 Commission Notice 2004/C 101/02, Guidelines on the application of Article 81 of the EC Treaty to technology transfer agreements (OJ C101, 27.4.2004, p. 2-42)

8 http://ec.europa.eu/competition/consultations/2012_technology_transfer/index_en.html

9 http://ec.europa.eu/competition/consultations/2013_technology_transfer/index_en.html. Bird & Bird LLP has filed a submission in the public consultation.

restrictions of passive sales by other licensees into such a territory or to such a customer group fall outside Article 101(1) for the period necessary for the licensee to recoup those investments. In most cases a period of up to two years from the date on which the contract product was first put on the market in the exclusive territory by the licensee in question or sold to its exclusive customer group would be considered sufficient for the licensee to recoup the investments made. However, in an individual case a longer period of protection for the licensee might be necessary in order for the licensee to recoup the costs incurred."

Restriction of automatic grant back obligation

Another topic that has been subject to changes concerns clauses obligating the licensee to transfer to the licensor ownership or grant to him an exclusive license for any improvements to the licensed technology. Whereas the former TTBER exempted contractual obligations for grant back of rights concerning improvements that are *non-severable* from the licensed technology (i.e. improvements that cannot be exploited without infringing the licensed technology), under the new regulation even this exception shall be waived. The European Commission explains in the new TT Guidelines (para. 129) why this further restriction would be necessary.

"An exclusive grant back is defined as a grant back which prevents the licensee (which is the innovator and licensor of the improvement in this case) from exploiting the improvement (either for its own production or for licensing out to third parties). This is the case both where the improvement concerns the same application as the licensed technology and where the licensee develops new applications of the licensed technology. According to Article 5(1)(a) such obligations are not covered by the block exemption."

A result of this limitation on imposing automatic grant backs is that the licensor will be linked to the licensee for the duration of the licensed technology, and that he will be restricted in the possibility to exploit its own technology to the fullest. This threat may have the counter-productive adverse effect that the licensor will keep his technology to himself in order to avoid the licensee making improvements to it, as these will not be automatically transferred or exclusively licensed back to the licensor.

What remains allowed under the new TTBER is a contractual obligation for the licensee to grant back to the licensor on a *non-exclusive* basis.

Non-challenge clause

Another important change of approach relates to termination clauses in the event of validity attacks. Under the old TTBER it was allowed to terminate the license agreement if the licensee challenged the validity of one or more of the licensed IP-rights. The block exemption for this type of termination clause in the current TTBER will be waived and replaced by a more strict case-by-case approach for termination clauses in non-exclusive license agreements. Only termination clauses in exclusive licenses will remain under the automatic block exemption; specific rules apply to know-how licenses.

The rationale of this change has been laid down in paragraph 134 of the new TT-Guidelines:

"The reason for excluding non-challenge clauses from the scope of the block exemption is the fact that licensees are normally in the best position to determine whether or not an intellectual property right is invalid. In the interest of undistorted competition and in accordance with the principles underlying the protection of intellectual property, invalid intellectual property rights should be eliminated. Invalid intellectual property stifles innovation rather than promoting it."

Safe harbour for patent pools

The Commission acknowledges the pro-competitive effects of patent pools, in particular in the context of standardization, and providing "safe harbour" rules for patent pools in the revised section of the TT Guidelines. This chapter in the new TT-Guidelines is very helpful, but should be read in combination with the chapter on Standardisation in the Guidelines for horizontal cooperation agreements.[10]

Settlement agreements

The Commission's experience in the effects of settlement agreements on competition is reflected in a revised chapter in the TT-Guidelines.

Effect

The new TTBER and TT-Guidelines took effect on 1 May 2014, and they will have to be applied in respect of any technology transfer agreement concluded as from that date. Further, technology transfer agreements that have been concluded up until 30 April 2014, and that are in

10 Guidelines on the applicability of Article 101 of the Treaty on the Functioning of the European Union to horizontal co-operation agreements, OJ, C11/1, 14.2011.

compliance with the old TTBER, will remain exempted under that until 30 April 2015. However, this is only a one year transitional period. As from 1 May 2015, they must also comply with the new framework provided by the new TTBER and new TT-Guidelines.

It may be added hereto that the (new) framework will only apply if it concerns licensing agreements which are not intra-group, i.e., with a third party outside the group structure. This means that if a holding company licenses its technology to one of its subsidiaries in which it exercises sole control, or if subsidiaries conclude license agreements with each other, this is considered as an intra-group license agreement. The competition rules only apply on agreements or concerted practices outside the group structure and hence, if intra-group license agreements are concluded these will not be covered by the new (and old!) TTBER.

The unitary patent package

As matters stand, it may be expected that by the end of 2015, the Unitary Patent Package will take effect. This will be the biggest change in the last 40 years of patent law in Europe, i.e. since the introduction of the European patent. Briefly put, the Unitary Patent Package consists of:

a. the creation of a European patent with unitary effect ("*Unitary Patent*") by way of an enhanced cooperation of all EU Member States except for Spain, Italy and Croatia.[11] For this, two EU regulations have been adopted on 17 December 2012: EU Regulation No. 1257/2012, which serves to create the unitary patent protection system as such, and Council Regulation No. 1260/2012, which sets out the legal framework for the applicable translation arrangement.
b. the creation of a Unified Patent Court ("*UPC*"). For this, an intergovernmental Agreement on a Unified Patent Court ("*UPC Agreement*"), which also sets out the (basic) rules for the UPC, has been signed by 25 EU Member States (i.e. all EU Member States except for Spain, Poland and Croatia).[12]

The above mentioned date of entry into effect of the Unitary Patent Package is not carved in stone, if only because many practical preparations still need to be completed, but there is little doubt that the new system will become a reality in the not too distant future. In this context, it is noted that the system will come into force as soon as *thirteen* Contracting EU Member States, including the United Kingdom, Germany and France, have ratified the UPC Agreement[13]. So far, Austria and France have ratified, and Belgium and Malta have completed the ratification procedure.

The Unitary Patent

The Unitary Patent will come as an alternative to already existing forms of patent protection, i.e. the traditional European patent, which is (argued to form) a bundle of national patent rights, and national patents[14]. Note, however, that the Unitary Patent will only be available in part of the jurisdictions where one can obtain a traditional European patent. For the other jurisdictions protection through a traditional European patent (or national patents) will still be necessary.

The Unitary Patent will undergo the same examination procedure as traditional European patents, be it that *ultimo* one month after the date of publication of the mention of the grant of the patent, the patentee can "upgrade" the European patent to a Unitary Patent by requesting the unitary effect to be registered in the register for unitary patent protection. As a consequence, the patent will — with retroactive effect — have unitary effect in all participating EU Member States where it has unitary effect, i.e. in those which have at the date of registration ratified the UPC Agreement. This means that in those EU Member States it shall provide uniform protection and that it shall have equal effect.[15] It shall confer on the patentee the right to prevent any third party from infringing his exclusive rights throughout the territories of these EU Member States,[16] and the scope of that right and its limitations shall therefore be uniform.[17] Further, in these EU Member States the patent may only be limited, transferred or revoked, or lapse, in respect of

11 Croatia has entered the EU after the adoption of the two regulations. Spain, Italy and Croatia are free to participate in the cooperation if/when they deem fit.

12 The UPC's Rules of Procedure, which finely detail the procedural rules to be applied by the court, are still in draft form (16th), but adoption thereof is expected within relatively soon.

13 See Article 18(2) of EU regulation 1257/2012, as well as Article 89 UPC Agreement.

14 A requirement for Unitary Patents is, however, that it has been granted with the same set of claims in respect of all participating EU Member States (Art. 3(1) of EU regulation 1257/2012).

15 Article 3(2), first para of EU regulation 1257/2012.

16 Article 5(1) of EU regulation 1257/2012.

17 Article 5(2) of EU regulation 1257/2012.

all of them[18]. (Licenses may of course be concluded in respect of the whole or part of the territories of the participating Member States.[19])

The maintenance fees of a Unitary Patent are still to be determined, but it is expected that they will be as high as the fees of a traditional European patent designating 4-5 contracting states.

The Unified Patent Court

The UPC will be a specialized patent court, composed of specialized patent judges. It will consist of a court in the first instance, made up of three types of divisions (Central, Regional and Local), hosted by a variety of contracting EU Member States,[20] and a court of appeal with seat in Luxembourg. It will serve as the exclusive *"one stop shop"* for a variety of actions concerning Unitary Patents, including infringement, declaration of non-infringement, and revocation actions. Given the UPC's exclusive jurisdiction, such actions cannot be instituted with national courts.

It is noted that the UPC's exclusive jurisdiction is not limited to Unitary Patents: in as far as it concerns the territories of the contracting EU Member States, this will also count for any traditional European patent, unless it is *opted-out* from the UPC's jurisdiction, as well as for any Supplementary Protection Certificate (SPC) that is based on a Unitary Patent or on a European patent that has not been opted out. Unitary Patents (and SPCs based thereon) cannot be opted out.

Traditional European patents and European patent applications can — at least for a transitional period of 7 years — be opted out from the jurisdiction of the UPC, unless an action concerning the patent has already been brought before the UPC.[21] The opt out shall be for the life of the European patent or application, including the time after expiry, lapse or withdrawal, and it shall cover all designations owned by the proprietor(s) in question.[22] Interestingly, an opt-out can also be *withdrawn* by the patentee, unless an action has already been brought before a national court.[23]

Judgments of the UPC will have effect in all contracting EU Member States, and shall have effect regarding the patent as a whole. The advantage hereof is obvious: one will only need a single decision from the UPC, to put an end to pan-European infringements, contrary to the current situation where patentees have to seek injunctive relief before a multitude of national courts. However, the flipside of the coin is that the patentee can lose big: he may also lose its infringement case, or even its patent for all contracting EU Member States.

Technology transfers that comprise patent (application(s))

European patent portfolio management and enforcement strategies will have to be reviewed in the wake of the new system. However, also in technology transfers involving patents, patent applications or SPCs, whether by assignment, acquisition or licensing, one will have to take due account hereof, for instance when doing the due diligence.

Particularly in sectors like the life sciences, the value of a transaction is dependent on the value of the know-how and IP that goes with it. For the value of the IP, it is not only important that the patent portfolio covers the (to be) exploited technology and potential competitive technologies, and so for a sufficiently remaining period to recoup the investments and make a decent profit, but also that it is suitably strong to deter, and if necessary to successfully litigate against competitors. Having a

18 Article 3(2), second para of EU regulation 1257/2012.

19 Article 3(2), third para of EU regulation 1257/2012.

20 The Central Division will have branches in London, Paris and Munich (case-distribution depending on type of technology). Regional Divisions can be set up in cooperation by at least two contracting EU Member States, and Local Divisions can be set up by single Member States. As matters stand — this is still in progress — there will be a Nordic-Baltic Regional Division, formed by Estonia, Latvia, Lithuania and Sweden, and perhaps one or two additional Regional Divisions (including a South-Eastern Regional Division), but the majority of those contracting EU Member State with an interest in forming a division will most likely decide to host a Local Division.

21 Article 83(3) UPC Agreement.

22 See the Note to Rule 5 of the *draft* Rules of Procedure (16th). Further, it is noted that Article 83 of the UPC Agreement is not entirely clear on the opt-out arrangement, and even open for multiple interpretations. For this reason, the Preparatory Committee of the UPC has on 29 January 2014 adopted its (first) Interpretative Note, i.e. on the consequences of the interpretation of Article 83. Herein, the Preparatory Committee concludes "[..] *that if an application for a European patent, a European patent or a Supplementary Protection Certificate that has been issued for a product protected by a European Patent is opted out (or during the transitional period the case is brought before a national court), the Agreement no longer applies to the application for a European patent, the European patent or the Supplementary Protection Certificate concerned. As a consequence the competent national court would have to apply the applicable national law.*"

23 Article 83(4) UPC Agreement.

Unitary Patent, or the prospect thereof, may well have an effect on the value. In principle, this could be an upward effect, because of the unitary character and the fact that it can be enforced on a pan-European basis through a single specialized patent court (the UPC). However, having all eggs in one basket also poses the aforementioned risk of losing big, and certainly in respect of patents with a weaker validity or scope, having a Unitary Patent may not impact positively on IP value. The same goes for SPCs based thereon, for European patents that are not opted-out (unless an opt-out is still possible), and for SPCs based on such not opted out European patents. Also, there are various parties in the Life Sciences who at least for the first years of the UPC want to opt-out their European "crown-jewel" patents and SPCs, if only because they first want to see how the UPC will assess patent and SPC cases.

Therefore, also in view of technology transfers involving patents, patent applications or SPCs, proprietors should carefully consider how they should protect their inventions in Europe, through Unitary Patents, traditional European patents (and opt them out) or through national patents. Ideally, this assessment is done on a case-by-case basis, and timely before the system goes live, be it of course whilst taking account of the costs of such an exercise (and those of the Unitary Patent). Those who are interested in obtaining rights through such technology transfers may want to consider all of this when conducting their due diligence.

Another issue to be taken into account is that under Article 47(2) UPC Agreement, the holder of an *exclusive* licence in respect of a patent shall be entitled[24] to bring actions before the UPC under the same circumstances as the patent proprietor, provided that the patent proprietor is given prior notice. Only in cases where the licensing agreement provides otherwise, will this not be the case. Indeed, this corresponds to statutory rules in certain European jurisdictions, but in other European jurisdictions, such as for instance the Netherlands, only the patentee is in principle entitled to seek relief.

Further, pursuant to Article 47(3) UPC Agreement the holder of a *non-exclusive* licence shall not be entitled to bring actions before the Court, unless the patent proprietor is given prior notice and in so far as expressly permitted by the licence agreement.

For the patentee, who wants to be in control of the institution of court proceedings with the UPC, this is something to be taken into account when negotiating future agreements. Also, he may need to review his existing exclusive licensing agreements, and re-negotiate a provision stipulating that only he shall be entitled to bring actions before the UPC.

Also, in view of maintaining a certain degree of control over the institution by third parties of declaration of non-infringement proceedings, he may want to take similar steps in respect of the entitlement to respond to third party applications in writing for a written acknowledgment of non-infringement. After all, a refusal or failure to respond, by the patentee *or* the licensee, is a requirement for the third party to institute a declaration of non-infringement action with the UPC.

The non-exclusive licensee should, on the other hand, be aware that under the UPC Agreement, he shall only be entitled to bring actions before the UPC, if — apart from giving prior notice to the patentee — he is expressly permitted to do so in the licensing agreement.

Moreover in general, professionals who advise their clients in respect of licensing agreements, should always take due account of the above when Unitary Patents or traditional European patents are potentially involved.

In this respect, it is added that in such licensing agreements, whether to be concluded or already in place, parties may also wish to make clear arrangements in respect of decisions concerning the filing of a request for unitary effect (see above), and the filing of opt-out requests and the withdrawal thereof.

Conclusion

Both the new TTBER and the upcoming Unitary Patent Package give good reason to review existing technology transfer policies, and the criteria that are formulated in the relevant agreements; however not only in respect of future deals, but also in respect of existing agreements. Certainly if there is a need to review existing patent licensing agreements on compliance with the new TTBER, and even re-negotiating them, then this would seem a sensible moment to also review (and if necessary re-negotiate) the terms that potentially impact on the position of, and control over court proceedings before the UPC.

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The Netherlands

DEVELOPMENTS IN PUBLICATION OF CLINICAL TRIAL DATA BY THE EUROPEAN MEDICINES AGENCY

The EMA has announced a final round of targeted consultations with key stakeholders on its draft policy on proactive publication of clinical trial data. The policy

24 Not exclusively: under the UPC, the patentee remains entitled as well.

seeks to balance the commitment to provide the widest possible access to data with the need to protect personal data and legitimate commercial confidential information. The Agency has been releasing clinical trial reports on request once the decision-making phase of the marketing authorisation process has been completed since November 2010 as part of its access to documents policy. It is now moving towards proactive publication of clinical trial data and has published for consultation a draft policy on proactive publication of clinical trial data in June 2013. The consultation was open for 3 months during which the EMA has received over 1,000 comments. The policy was then discussed at the EMA's Management Meeting in March 2014.

Now the final fine-tuning consultations will take place at the beginning of May 2014 and will focus on the principles for the possible pre-publication redaction of the clinical trial study reports in order to protect data containing commercially confidential information. Another objective is to clarify how the data owners will be consulted before publication of clinical study reports. The policy is expected to be presented to the EMA's Management Board for endorsement in June 2014.

The clinical data policy is part of the EMA's transparency initiative intended to encourage trust and confidence in the system. It runs parallel to other initiatives in the EU to increase transparency of clinical trials, in particular the new Clinical Trials Regulation which received a strong vote in favour in the European Parliament on 2 April 2014 and is expected to come into force in mid-2016.

At the same time, AbbVie has withdrawn both its court cases brought against the Agency concerning access to clinical trial data. The cases concern requests by third parties for access to AbbVie's clinical trial reports submitted to the EMA. The EMA has initially refused access on the grounds that it would undermine AbbVie's commercial interests. However, it decided to release the data following a complaint to the European Ombudsman who concluded that the reports did not contain commercially confidential information and recommended that the information be disclosed. AbbVie applied to the General Court to annul the Agency's decision to release the information. It also made an application for a preliminary injunction to prevent disclosure pending a final decision, which was granted in April 2013. Following the successful appeal to the CJEU by the Agency, the preliminary injunction was set aside and AbbVie has asked the EMA to consider a new set of redacted documents. The EMA considered that the very limited redactions proposed by AbbVie were consistent with the Agency's redaction practices and had no significant impact on the readability of the reports. The EMA has therefore accepted the new documents.

Another court case brought by InterMune against the EMA challenging a decision to grant access to clinical study reports is still ongoing.

Polina Lanckriet
Lyon

Book Review

India's Healthcare Industry: Innovation in delivery, financing, and manufacturing

Lawton Robert Burns (Ed.)

Cambridge University Press, 2014. Hardcover, 610 pages, $125.00. ISBN 978-1107044371

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India's Healthcare Industry seeks to synthesize broad elements of India's healthcare sector to provide a system-wide perspective to stakeholders on a range of issues that may fall outside the borders of individual circumscribed areas of interest. This book also tries to address two related issues (1) how India may meet rising demands and heightened consumer expectations for healthcare in line with increasing economic growth and (2) how India's domestic companies are faring in competition with multinationals. The title of this book suggests a comprehensive review of innovative developments in India's Healthcare sector and this weighty volume — 580 pages including endnotes and index — does not disappoint. This reviewer found the book to be quite a good read, in addition to being very helpful to gain a system-wide perspective on the present system and ongoing challenges.

The book consists of chapters contributed by healthcare industry experts, with an impressive number of chapters written by the editor Lawton Robert Burns who displays an encyclopedic understanding of India's sprawling healthcare industry. The book is well organized and the division of Sections and related Chapters provide a good roadmap for readers with a particular interest:

- Section I provides an introduction and overview on India's Healthcare System together with suggested innovative responses to urgent challenges and an overview of the value chain;
- Section II focuses on Providers — physicians, hospitals, medical tourism, and a case studies on the Aravind Eye Care System, the L.V. Prasad Eye Institute, ad Vaatslya Healthcare as a model for rural healthcare delivery;
- Section III focuses on healthcare financing and related Private Equity opportunities in India; and,
- Section IV addresses different manufacturing sectors — pharmaceuticals, biotechnology, and medical devices and offers and essay on balancing access and innovation in developing countries (for the most part not specific to India).

Organizationally, end-notes are provided following each chapter and a separate List of Figures, following the Table of Contents, provides additional navigational support for the reader. Overall, Burns and other contributing authors tell a compelling story and make effective use of tables so that the empirical data does not overwhelm or exhaust the reader. Here too, the diagrams and tables are well-placed to illustrate India's relative strengths and immediate challenges.

The strength of this book lies in its development as part of a Wharton School of Business course entitled: "Innovation in the Indian Healthcare Industry," where the course content was develope by Wharton faculty and students in collaboration with the Indian industry experts. The resulting materials have been edited and published now as an encyclopedia of the Indian healthcare sector. Some areas are covered in greater detail than others, though. Background and current challenges relating to education, training and staffing of physicians and organization of India's hospital sector are provided in great detail, as is the issue of Medical Tourism.

Other areas appear to have been given less comprehensive analysis. With regard to the pharmaceutical sector, for example, the book provides little more than an overview on leading players and historical events, and does not attempt to address India's challenges to implement the World Trade Organization (WTO) Agreement on Trade Related Intellectual Property Rights and to

balance the interests of domestic manufacturers, multinational companies, and patients. Given the economic, social and political importance of the Indian pharmaceutical sector, this is surprising. Over the last 18 months in particular, we have seen an increasingly impact of India's industrial policy relating to patents for pharmaceutical products on American and European companies, becoming a trade irritant and affecting India's bio-pharma investment climate. In the biotechnology chapter, scant attention is given to the important issue of access to early capital for funding of innovation intensive life science enterprises, a priority issue for the Department of Biotechnology within the Ministry of Science and Technology. Although these gaps are disappointing, they are perhaps to be expected in a book that provides a comprehensive survey of the healthcare landscape in India — a Goliath task in itself.

More troubling is the absence of a chapter focused on India's *Ayurveda*, *Yoga* & Naturopathy, *Unani*, Siddha and Homoeopathy (*AYUSH*) systems of traditional medicine that require improved documentation and standardization to meet ongoing challenges for India's rural populations that remain out of the reach of allopathic healthcare resources and reliant on poorly regulated AYUSH systems. China has demonstrated that standardization and quality control can promote successful and effective traditional medicine services and products domestically and for export.

One other important gap is the absence of discussion of India's ongoing regulatory challenges relating to both Good Manufacturing Practices (GMP) and Good Clinical Practices (GCP). Persistent GMP issues are affecting India's leading pharmaceutical manufacturers access to the important US generics market — most recently in the case of Ranbaxy this has been a major driver of the proposed merger with Sun Pharma. Similarly, GCP issues have derailed India's formerly thriving clinical research sector over the past year, where Indian and foreign pharmaceutical companies alike have colluded with regulators and academic institutions to game the system. While recognizing the general regulator weaknesses in the national and state-based healthcare regulatory system, the absence of an in-depth discussion of India's regulatory challenges relating to manufacturing, clinical research and drug approval is a significant weakness in the book that should be addressed in a future edition.

More broadly, in addition to providing an accurate overview of the disparate elements of India's healthcare sector, the editor/author Lawton Robert Burns, identifies islands of excellence and areas where innovative solutions may be applied to mitigate ongoing healthcare challenges in Section I of the book. These discussions add value to the book, as do the three case studies provided in Section II, relating to successful low-cost models for healthcare delivery. India's Healthcare Industry is a very useful reference text for anyone seeking a general system-wide understanding of the Indian healthcare sector, with particular focus on the issues of physician education, training and staffing, the hospital sector and medical tourism.

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Conference Report

Four perspectives on business model evolution in synthetic biology

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Keywords: synthetic biology; business model

INTRODUCTION

Back in 2010 in these same pages, managing editor, Yali Friedman asked: Is the biotechnology industry ready for a new business model?[1]

Historically, the industry had three models, the fully integrated life science company (or FILCO), the platform company, and the hybrid. The FILCO model is best characterized by Amgen and Genentech, early biotech pioneers that built large vertically integrated companies.

The platform company developed a technology platform–a tool, equipment, or software—licensed it out or sold it. This business model is similar to technology platform companies, where a firm develops a technology that can be sold to other research and development firms or is split up and sold off piecemeal, ultimately generating more total value. In the 2010 OECD Workshop on the Outlook of Industrial Biotechnology, platform companies were also categorized as service providers.

The hybrid model combined product development with a technology platform that could be sold or licensed to others. This model was especially popular in the years leading up to and after 2000, and could be best characterized by Human Genome Sciences and Millennium.

Since biotechnology is a young industry, funding sources change, and corporate interest wax and wane, new business models emerge without necessarily replacing the older ones. Most recently, the biotechnology industry is beginning to, according to Ryan Bethencourt of Berkeley Biolabs, "benefit from a digitization of biology, the maker movement, quantified self, grinders/transhumanists, crowdsourcing… a resurgence in local production technologies like 3D printers… biotech equipment at 1/10th to 1/1000th the cost"[2] and cheap outsourcing.

Is the business of biotechnology on the verge of radical disruption? To find out, we interviewed the CEOs of three synthetic biology companies and a futurist in biological technologies to find out.

Tim Fell: Synthace is an applied synthetic biology company focused on making valuable chemicals and biologics cheaper and faster than existing companies. We create and capture value by being more efficient and decreasing the cost of goods.

At the moment, we are making known molecules and we're not doing research into novel chemicals. That will come in the future.

Jamie Bacher: Pareto Biotechnologies utilizes a specific polyketide pathway and related technologies to develop new designer molecules. Our first products will be high-value chemicals. As the technology develops we are looking to other areas as well.

Omri Amirav Drory: Genome Compiler is focused on developing software for the engineering of biology. People can use our design software on our website to design, build and test biologically engineered products. People can buy their DNA and bioinformatics directly from the software. Our model is designed to bring products to market faster.

1 Friedman, Yali. "Time for a New Business Model?" Journal of Commercial Biotechnology (2010) **16,** 1-2. doi:10.1057/jcb.2009.33

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2 Bethencourt, Ryan. Biotech's Cambrian Era. BioCoder, Fall 2013. Accessed at http://programming.oreilly.com/2013/10/biotechs-cambrian-era.html

Andrew Hessel: Autodesk has a long history of offering stand-alone 3D design software running on desktops or servers. Over the past ten years, the company moved many of its products to the cloud. Today, we offer a wide variety of powerful design tools and applications that are available online, via an Internet browser. We support the idea that software should be easy to connect to, easy to use and are actively working to democratize technology. Now, we're using that approach in the development of software tools for biotechnology and nanotechnology.

JOCB: Could you describe your current business model?

Tim Fell: Synthace is primarily pursuing a licensing model where we engineer microorganisms and bioprocesses to produce a specific chemical. We develop those strains within partnerships where our partners will either use and/or sell the products they produce. Our ideal partner brings scale-up expertise and a route to market, but also shares their intimate knowledge of the specialty chemical industry because without such information it can be a challenge to understand the pain in the marketplace and which products to target.

Jamie Bacher: We have a technology—a platform—that's very broad. We will use our technology to develop valuable products with partners, that they can quickly move to market, then leverage the technology development that goes into those products to fuel additional technology developments and additional products. Where a lot of other companies backed into this strategy, we are going forward with it.

I think of the model as an expanded Elon Musk model because he not only founded Tesla but Space-X. The Tesla model was to sell a high-end roadster to a very small market then to use that funding to develop a family sedan that you can sell to everyone. The model allowed for rapid feedback from the marketplace and is a model that is more analogous to a software or web development company using lean principles.

The parallel for biotechnology is that we sell high-valued products like flavors, fragrances, or cosmetics and use the funding from those to develop and refine a technology platform. Pareto is going after high-value products first, where we can do 20 percent of the technology development and get 80 percent of the output value. The Musk model is to then leverage that into commodity chemicals (the family sedan) or into therapeutics (the rocket).

Omri Amirav Drory: We are a startup, so our business model will likely change. Right now, our core business is focused on developing the software on our website. People have access to it as a software-as-a-service (SaaS) and customers can pay for the full software package. They can just pay as they go or they can pay only for features that they want. In addition we offer a marketplace where people can share and buy DNA and other services.

JOCB: What are some challenges faced by synthetic biology companies?

Tim Fell: There seems to be a revolution brewing as we start to further professionalize, standardize and digitize the biotechnology industry. Biotechnology's biggest challenge is that it is still very artisanal. We are now further along in bringing engineering principles to the field, in being able to create more complex bio-organisms faster, and in scaling up production, but there is still much work to do. This type of transition occurred in most other industries a long time ago, biotechnology has taken bizarrely longer.

Jamie Bacher: For companies that are young and small like Pareto, one challenge is how much you outsource versus how many people you hire since that will have a real effect on your company culture. Having been at several startups, I understand that culture is hugely important and not to be underestimated. It's something every company has to figure out for themselves. In other words, at what point are you trading off efficiency for culture building, at what point are you trading efficiency for building in-house capabilities that in the long run might not be that important for you?

Omri Amirav Drory: The biggest challenge is market maturity. Genetic engineering is not a new market. In the U.S., it's estimated at $350 billion with PWC conservatively estimating the global biotechnology market will be $1.2 trillion by 2020. Synthetic biology or the use of synthetic DNA very much depends on the price of DNA, which has been decreasing rapidly. Today, the price of DNA synthesis is around 25 to 30 cents per base pair. In the next year or two, we will see an infection point where people will move from traditional PCR-based cloning towards the use of digital tools and synthetic DNA. They will outsource most DNA synthesis and construction. People will do more designing and testing, and less construction.

Andrew Hessel: The rate-limiting step for biotechnology is manual work at the lab bench and software tools that accurately connect to bench research. At Autodesk, the Bio/Nano/ Programmable Matter group is developing

powerful software tools that can take big data as an input and also directly connect to robust printing tools. Today, 3D printing tools are available for a variety of materials including living cells and even DNA. As laboratory hardware and software become more integrated, the rate-limiting step will disappear quickly.

JOCB: What are some emerging opportunities or innovative ideas in the synthetic biology industry?

Andrew Hessel: The one that I love sharing is Glowing Plant. It is not that expensive to make the genes that will make something glow. Doing that work in the plants has gotten easier. The founders of Glowing Plant wanted to make an ornamental glowing plant and found the existing regulations allowed it. They didn't have much money, so they ran a Kickstarter campaign. Kickstarter served as a focus group for them and not only showed there was a market for glowing plants, but helped them raise almost a half million dollars.

Omri Amirav Drory: We started the Glowing Plant project that raised half a million dollars on Kickstarter in 2013. One of our European users, a DIY hacker wanted to make a glowing plant and built different designs on our platform. He didn't press the "Buy" option on the web site because he didn't have the money to pay the few thousand dollars for the DNA. We thought why not do that because it's feasible and done dynamically. The science isn't new.

The experience shows you don't have to be in academia or in industry to start a biotechnology company. You can be a couple of kids from California, build it online, crowdsource the funding, then built it. I met Anthony Evan, the project lead at Singularity University. Kyle Taylor, the Chief Scientific Officer, studied plant biology in Stanford. Genome Compiler gave the two of them a lot of support. The result caught the imagination of a lot of people and caused a lot of uproar. Now, they are trying to commercialize the technology. Genome Compiler has other, similar projects in the pipeline.

JOCB: What business models do you see emerging?

Andrew Hessel: There are a few. Glowing Plant is one of the best examples to date in the startup space. I see another model emerging for cancer. We know today that once you've been diagnosed with cancer it never really goes away. The oncologists take their best shot, and then the waiting game begins.

A more logical way, particularly with early detection, might be to treat cancer continuously, starting by killing the weakest cells and just keep knocking them back, the way you might prune a tree or a bush. Managed this way, cancer might never reach a point where it crashes major organ systems. This would require customized medicines, programmable for each cancer, that are easy to update if the cancer develops resistance. Computer-generated synthetic oncolytic (cancer-busting) viruses are one possibility.

A treatment model that provides a steady stream of targeted drugs personalized to individuals and their cancer is like Netflix, a subscription business, where you subscribe to a process rather than just purchase one single drug.

Another business model is more familiar: advertising. About seven or eight years ago, I pointed out that if you put genetic code (such as "ATGGCATA…" and so on) into a Google search, you got no result whatsoever. That surprised me. Why didn't it tell me if it matched a known gene, genome, or marker?

I expect that as more people get their genome and microbiome sequenced, Google and other groups will match my results to products or services linked to that information. The mix of bacteria in my mouth might determine which toothpaste I might want to buy, or my skin type the soap or shampoo. I expect to see this type of genetic marketing to begin appearing very soon.

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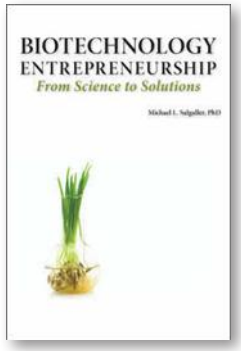

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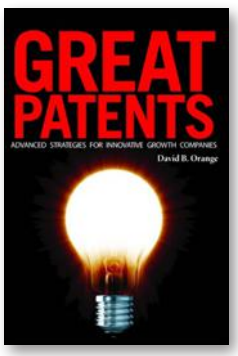

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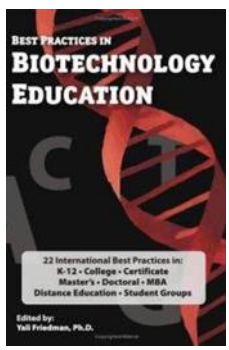

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