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Contents

Commentary

Combating a Global Pandemic of Weak, Adulterated, and Fake Drugs

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ABSTRACT

Whether it's willful counterfeiting, sloppy manufacturing processes, or neglectful handing of drugs in the global supply chain, recent studies suggest the problem of weakened, adulterated, and fake drugs is a growing global issue with deadly consequences. In Africa, the lack of access to innovative drugs makes the population vulnerable to counterfeits and inefficacious copies of medicines that are much needed. This humanitarian crisis rests on policymakers' steadfastness in each country to ensure the authenticity of the drug supply. Among the steps that should be taken is the restriction of the sale of drugs to pharmacies and hospitals and the prohibition of their sale through street vendors and open markets. There is also an urgent need for post-importation testing to ensure drugs actually contain their active ingredients in adequate strength before they are sold. These are necessary parts of a needed comprehensive approach to combating the importation of counterfeit, weakened, and adulterated drugs. Countries have it within their power to protect their populations, ensure the integrity of medications, and restore trust in their healthcare systems.

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Keywords: falsified drugs; Good Laboratory Practices; regulation

In Sub-Saharan Africa, the deaths of an estimated 122,350 children under the age of five in 2013 involved the use of poor-quality drugs to treat malaria. That represents a small part of the global toll from pharmaceutical products that are not what they appear to be.

Whether it's willful counterfeiting, sloppy manufacturing processes, or neglectful handing of drugs in the global supply chain, recent studies suggest the problem of weakened, adulterated, and fake drugs is a growing global issue with deadly consequences. Beyond the harm they do to the patients who use them, these so-called "falsified medicines" as dubbed by a recent special journal supplement by The American Journal of Tropical Medicine and Hygiene, undermine trust of the health system and carry an economic toll as well.

It's difficult to quantify the problem because falsified drugs often go undetected due to weak or absent regulatory systems in some parts of the world, or assumptions by doctors that when a treatment fails it was merely not the right drug for the particular patient rather than questioning whether the drug used by the patient was of the formulation and strength assumed. An introduction to the journal's special supplement[1] estimates criminals generate $75 billion in annual illegal revenue through the sale of falsified drugs. Seven quality studies covered in the supplement examined 16,800 samples of drugs to treat malaria, tuberculosis, bacterial infections, and leishmaniasis that were tested for quality. Those various studies found between 9 percent and 41 percent failed to meet quality specifications. Quality issues are a serious problem even among World Health Organization accredited drug manufacturers.

Similar studies have produced similar results. In 2012, the U.S. National Institutes of Health found that more than one-third of the malaria drugs in 21 Sub-Saharan African countries failed a chemical analysis test

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1 http://www.ajtmh.org/content/92/6_Suppl/2.full.pdf+html?sid=4d17bcce-0181-41d6-bd72-24e02af9d689

because they were either expired or poorly made. Some 20 percent of the drugs were outright counterfeits.

This is a problem that is by no means limited to Africa. Of the more than 11,700 incidents of counterfeit drugs globally in 2014 examined by the Pharmaceutical Security Institute, a non-profit established by international drugmakers, it found the highest incidence were in China, India, Pakistan, the United States, and Japan. But in low- and middle-income countries the problem is particularly concerning because it threatens to undo progress made against deadly diseases such as malaria, AIDS, and tuberculosis. The use of adulterated antibiotics also threatens to worsen the problem of resistant bacteria, thereby broadening the toll from substandard drugs beyond the people who use them.

The U.N. Office on Drugs and Crime notes that criminal groups take advantage of gaps in the legal and regulatory frameworks, weaknesses in capacity, and the lack of enforcement. "The prospect of the comparatively low risk of detection and prosecution in relation to the potential income make the production and trafficking in fraudulent medicines an attractive commodity to criminal groups, who conduct their activities with little regard to the physical and financial detriment, if not the exploitation, of others," the organization says. Jim Thomson, co-founder of the European Alliance for Access to Safe Medicines in 2009 told the London newspaper The Daily Star that "major league" narcotics dealers were turning to counterfeit pharmaceuticals because they carried greater profits with far smaller risks. He said a kilo of the active ingredient for Viagra yielded about 2,000 times more profit than cocaine.

With an increasingly complex global supply chain, the problem requires a broad and coordinated effort to combat. This includes public education efforts, increased surveillance, the use of technology to track and trace the chain of custody, as well as verify the authenticity of products. It is also essential that tougher legislation is enacted and enforced to make the penalties against counterfeiting fit the seriousness of the crime. "Where existing laws are not enforced crime is perpetuated as criminals are not afraid of being arrested and prosecuted," says the World Health Organization. "Lenient punishments for offences tend to encourage criminal activities such as medicines' counterfeiting, particularly when the penalties for counterfeiting non-medicinal products are more severe."

In Africa, the lack of access to innovative drugs makes the population vulnerable to counterfeits and inefficacious copies of medicines that are much needed. This humanitarian crisis rests on policymakers' steadfastness in each country to ensure the authenticity of the drug supply. It is incumbent on them to implement regulations to put a halt to it.

Of the 191 member states of the WHO, about 20 percent have well developed drug regulation. Of the remaining member states, about half implement drug regulation at varying levels of development and operational capacity, the organization says. The remaining 30 percent have no drug regulation in place or a very limited capacity that hardly functions. "Inadequate, ineffective or weak drug regulatory control could promote unregulated importation, manufacture, and distribution of drugs, leading to the proliferation of counterfeit drugs in the national market," WHO says.

Among the steps that should be taken is the restriction of the sale of drugs to pharmacies and hospitals and the prohibition of their sale through street vendors and open markets. Registered distributors should be the only source of supply to pharmacies and hospitals, and these distributors should be monitored and inspected by regulatory authorities.

In Africa, there is an urgent need for public-private partnership to work with ministry of health authorities to implement an effective Good Laboratory Practices so samples of drugs coming into a country can be tested. Post-importation testing should be conducted to ensure drugs actually contain their active ingredients in adequate strength before they are sold.

These are necessary parts of a needed comprehensive approach to combating the importation of counterfeit, weakened, and adulterated drugs. It is not financially prohibitive, but requires political will, and the right equipment and training. Countries have it within their power to protect their populations, ensure the integrity of medications, and restore trust in their healthcare systems.

Commentary

The Globetrotting Regulator

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I am putting in a lot of miles on behalf of international regulatory fraternity.

Like Johnny Cash said, "I've been everywhere" — or at least it seems that way. Recently I've visited with government health officials in China (both PRC and ROC), the Philippines, Malaysia, Egypt, Algeria, Saudi Arabia, Jordan, the United Arab Emirates, Kuwait, Russia, Brazil, Colombia, South Africa, Indonesia, Kenya, and many other points in-between. And the only thing that's grown more than my frequent flyer miles is my respect and admiration for those over-worked and under-appreciated civil servants toiling on the front lines of medicines regulation.

It's a global fraternity of dedicated (and generally under-paid) healthcare and health policy professionals devoted to ensuring timely access to innovative medicines and quality generics drugs.

But, just as in similar Western agencies (USFDA, EMA, Health Canada, etc.), "doing the right thing" is often a battle of evolving regulatory science, tight resources, competing priorities … and politics.

There are many languages, priorities, pressures, and impediments (social, political, cultural) to consider, but one thing everyone agrees on is that quality counts. But what does "quality" mean – and does it mean the same thing from nation to nation, product to product, and for both innovator and generic medicines? The good news is there's general agreement that lower levels of quality for lower cost items aren't acceptable. But the bad news is that there are gaps and asymmetries in how "quality" is both defined (through the licensing process) and maintained (via pharmacovigilance practices).

Can there be a floor and a ceiling for global drug safety and quality? Even as we embrace differential pricing, should we allow some countries to have lower standards than others "based on local situations?" Can one man's ceiling be another man's floor? Can a substandard medicine ever be considered "safe and effective?"

Aristotle said, "Quality is not an act, it is a habit." Habits are learned and improve with iterative learning and experience. And nowhere is that more evidently manifested than through the many and variable methodologies for generic medicines licensing and pharmacovigilance practices. From paper-only certification of bioequivalence testing and questionable API and excipient sourcing, the safety, effectiveness, and quality of some products are, to be generous, questionable.

Is this the fault of regulators; of unscrupulous purveyors of knowingly substandard products; of shortsighted, overly aggressive pricing and reimbursement authorities? It depends. While there are many different and important avenues of investigation, the most urgent are the asymmetries of how quality is defined, measured, and maintained. That which gets measured, gets done.

National 21st century pharmacovigilance practices must take into consideration the realities of funding, staff levels, training programs, and existing regulatory authority. Increasing regulatory budgets is problematic. Should licensing agencies consider user fees for post-market bioequivalence testing of critical dose and narrow therapeutic index drugs? That's a contentious proposition–but agency funding is an often over-looked 800-pound gorilla in the room and deserves to be seriously discussed and openly debated.

Another uneven issue is that of transparency. While regulatory standards are undeniably an issue of domestic sovereignty, shouldn't there be transparency as to how any given nation defines quality? "Approved" means one thing in the context of the MHRA, the USFDA, and Health Canada (to choose only a few "gold standard" examples), but how can we measure the regulatory competencies of other national systems? Is that the responsibility of the historically opaque WHO? What about regional arbiters? Should there be "reference regulatory systems" as there are reference nations for pricing decisions? And how would this impact the concept of regulatory reciprocity?

And then there's the danger of regulatory imperialism. Expecting other nations with less experience and

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resources to "harmonize" with the USFDA or the EMA isn't the right approach. Rather we should seek regulatory convergence, because that gives us a pathway to improvement – with the first step being the identification of specific process asymmetries that can be addressed and corrected. Just as every nation has it's own unique culture and cuisine, so too must it design it's own regulatory philosophy and structure. It's not about replicating the USFDA or the EMA – it's about converging towards best practices.

Two of the most important health advances of the past 200 years are public sanitation and a clean water supply. Those achievements helped to control as many public health scourges as medical interventions helped eradicate. In our globalized healthcare environment of SARS, Avian Flu, and Ebola, it's important to remember that a rising tide floats all boats.

Working together to raise the regulatory performance of all nations will help all nations create sound foundations to address a multitude of regulatory dilemmas such the manufacturing of biosimilars, the control of API and excipient quality, pharmacovigilance and, yes, even counterfeiting.

Whether it's in Cairo, or Amman, Riyadh, Brasilia, Kuala Lumpur, Dubai, Beijing, Bogota, Pretoria, Nairobi, or White Oak – a regulator's work is never done. Global regulatory fraternity is essential to success. It's about building capacity through collaboration.

Difficult? Surely. But, as Winston Churchill reminds us, "A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty."

And at the top of the list is quality.

Without quality, safety and effectiveness are nonstarters. Without quality, healthcare spending is not just wasteful – but harmful. Without quality it's al about price without any consideration for value. Without quality, regulation is a sham.

Consider the Middle East and North Africa. In April 2015 I spent three fascinating days in Sharm El Sheikh, Egypt at the Second Arab Conference on Food & Drugs.

Delegates from the Levant to Morocco had a lot to say and share. The fundamental take-away was that the Arab world is serious about coordinating their efforts in healthcare in general and in regulatory affairs specifically. "Convergence" and "harmonization" were the two key words of the event.

(The Middle East/North Africa Region – MENA – consists of 22 nations – but just 2% of global pharmaceutical sales.)

I was honored to present a plenary address on "Advancing Medicines Quality via New Strategies in Bioequivalence Regulations, Pharmacovigilance Practices, and the Identification and Management of Substandard Pharmaceutical Events," as well as chair the event's panel on pharmacovigilance, sharing the panel with governmental thought leaders such as Dr. Amina Tebba (Morocco), Dr. Amr Saad (Egypt), Dr. Emad Munsour (Qatar), and leading global policy experts Dr. Hisham Aljadhey (King Saud University), and Michael Deats (WHO). I also participated on a panel discussing the urgency of IP, as well as another on biosimilars – specifically the vexing debate over nomenclature, physician notification, and therapeutic substitution.

With healthcare policy (as with life in general) – wherever you go, there you are.

Much of the conversation centered on controlling costs – specifically pharmaceutical costs – without the appropriate balance of time spent on the pennywise/pound foolish consequences of many of these policies. The IP panel tried to add balance to that debate by strongly presenting facts and figures on the value of innovation.

Dr. Rasha Ziada (Egyptian Ministry of Health) made the important point that if a pricing authority doesn't take outcomes into consideration, it will lead to overall price distortions. Amen. And Dr. Ola Ghaleb (Ministry of Health, United Arab Emirates), spoke about the UAE's strategy of performance-based risk-sharing arrangements – but also how politics can derail any decision-making process. Her honesty was refreshing. Net/Net – Outcomes is now capitalized and bolded in the international lexicon of healthcare policy.

While many of the presenters discussed the value of sharing pharmacoeconomic data across borders, there was not a counterbalancing discussion of the value of sharing clinical data for approvals and outcomes-based decision-making processes. But there was certainly an effort (both on many of the panels as well as during the breaks and after hours) to stress the urgency of this agenda. The good news is that many speakers (sometimes in passing and other times passionately) made the point that it mustn't just be about "getting the lowest price," but also appropriately pricing the most clinically effective treatments. Bravo.

Delegates agreed the conference was useful – but that action is required. In short – talk is cheap. My feeling (speaking privately with senior government officials from many of these nations) is that there is serious momentum for change (and even reinvention). But only time will tell.

As Deming said, "Change is not required. Survival is not mandatory."

At the closing plenary session came "The Sharm El Sheikh Declaration" that called for:

- Strengthening drug post-marketing regulation through the establishment and

activation of pharmacovigilance centers, while working on workforce qualifying and training.
- Urging Arab countries to invest in training inspectors of pharmaceutical factories to raise the quality of the inspection process and ensuring the application of current good manufacturing practice (cGMP).
- Urging Arab countries to authorize bioequivalence studies and ensuring that they conform to the technical requirements of Good Clinical Practice (GCP) through regular inspection visits.
- Urging international drugs regulatory authorities in the Arab world to activate drug post-marketing monitoring programs through establishing pharmacovigilance centers and equip them with trained pharmacists and doctors.

(Pleased and proud to say that many of these recommendations came from the conference panel I chaired on pharmacovigilance.)

In May 2015 my regulatory travels took me to Asia. In Jakarta I met with senior hospitalists to discuss the impact of Indonesia's new legislation (designed to provide universal access to healthcare) and its impact on both the quality of medicines available and a physicians right to choose both therapy and brand. Senior healthcare leaders are concerned that, by insisting the lowest priced product be used, suboptimal outcomes will increase for those patients unable to access private healthcare. They recognize that a system that provides broader access to low quality care is not a victory. Bioequivalent does not equal identical. Biosimilar does not equal identical. Quality should not be negotiable. The stakes are high.

Next up was the Javanese capital of Yogyakarta for a symposium on pharmacovigilance held by Ahmad Dahlan University. A senior Ministry of Health official shared the fact that, for a nation of 250+ million, there are but 10 people focused on pharmacovigilance. Talk about the Java Jive! She spoke of the need to develop better risk-based assessment protocols and more aggressive information sharing with other nations in the region (adverse events, bioequivalence test results, API and excipient quality inspections, etc.). Quality is a team effort.

Meetings in Hanoi and Ho Chi Minh City focused on quality with a more specific focus on the need for more regular bioequivalence testing using patients under treatment (as opposed to healthy volunteers) in order to better understand the uptick in Substandard Pharmaceutical Events (SPEs). SPEs occur when a product does not perform as expected—perhaps because of API or excipient issues. SPEs can arise because of an issue related to therapeutic interchangeability. In Vietnam they are beginning to understand and appreciate that Small is the new Big. The need to focus on individual patient outcomes and on long-term care rather than short-term cost.

The last stop on my Asian tour was Taipei, where I had the opportunity to speak to a colloquium of oncologists. Their fear and frustration was similarly directed towards a government healthcare program that mandates the use of lowest cost products. Nowhere does this cause greater angst and anger than with healthcare professionals treating patients with cancer. The unintended therapeutic consequences caused by short-term, price-driven government policies on quality and clinical outcomes cannot be underestimated. Those on the front lines (physicians and pharmacists) understand this – as do patients. Recognizing there is a problem is the first step towards solving it.

What have I learned? Many things, but most importantly that medicines regulation – regardless of language or location – isn't just a job, it's a personal public health mission.

And so home again, home again, jiggity jig to an American healthcare system debating many of the same issues – bioequivalence, biosimilarity, interchangeability, physician notification, substandard pharmaceutical events, patient/physician/pharmacist education, the price/value equation, short-term savings vs. long-term patient outcomes.

It's a small world after all.

Commentary

Off-Label on the Table

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The headline in the Washington Post reads, *"FDA proposes to let drug companies undermine official safety warnings,"* but that is misleading at best and a downright error at worst.

Alas, this isn't a case of a bad headline written by an editor. Here's how the article begins:

"The Food and Drug Administration is proposing to allow pharmaceutical companies to undermine official safety warnings in sales presentations to customers."

For starters, that's not true. What the draft guidance addresses is the ability of pharmaceutical companies to present research published in peer-reviewed journals that goes beyond the information provided in the FDA label. That does not undermine anything. In fact, the reverse is true, it adds to scientifically acceptable, often cutting-edge information. And knowledge is power in pursuit of the public health.

Specifically, under the proposal, FDA would not "object to the distribution of new risk information that rebuts, mitigates, or refines risk information in the approved labeling." The studies must be "well-designed" and "at least as informative as the data sources" that the FDA used in generating the official warning.

Knowledge is power in pursuit of the public health. Further, this language makes it clear that the FDA retains the right to object when such information *does not* meet this standard. It is by no means a Katy-bar-the door exercise. And since there is no definite "standard," FDA actions will be carefully watched. CDER's Office of Medical Policy currently lacks a permanent director. When that slot is filled, this is a key issue that person will need to prioritize.

Sid Wolfe of Public Citizen offers the expected broadside that the proposal, "seriously undermines FDA authority." Balderdash. What it does is affirm that the FDA does not regulate the practice of medicine and that there are finite limits to the agency's powers relative to "regulated speech."

It also raises an important issue – there's a difference between off-label communications and off-label marketing – and it's more than a finesse. It's one of those 800-pound gorilla issues we've been pussyfooting around for too long. And now, at long last with the FDA appropriately leading the charge, it's time for a serious conversation.

The first thing to point out is that this agency action preempts attempts to legislate similar outcomes. According to the House Energy & Commerce Committee's 21st Century Cures Initiative white paper:

Communication about how certain treatments are working in certain patients is happening through a multitude of media around the globe. These conversations between and among doctors, patients, researchers, and scientists in academia and industry should be facilitated. This includes the free flow of data, research, and results related to what a therapy or combination of therapies does or does not do well and in what types of patients.

As PhRMA has said in the past, some of the regulations and guidances of the Food and Drug Administration (FDA) have a more direct impact on patient care than others. The FDA's restrictions on biopharmaceutical companies' ability to share authoritative, regulated data about prescription medicines limits healthcare professionals' access to information that can help them make informed decisions based on their patients' individual healthcare needs and preferences.

Biopharmaceutical companies have the most complete and up-to-date information about the medicines that they research, develop and manufacture for use by patients. However, companies are often unable to proactively share valuable information about their medicines, especially for information that is not contained in the FDA-approved prescribing information (the package insert you often receive with a prescription), with physicians and other healthcare providers.

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The new FDA draft guidance opens the door for companies to share truthful, scientifically accurate, and data-driven information with healthcare professionals to inform treatment decisions. Some examples of this kind of information include:

- **Observational data and "real world evidence"** – Information on the safety and effectiveness of medicines taken from medical records based on actual use of approved medicines.
- **Sub-population data –** Information on the safety and effectiveness of medicines in sub-populations including gender and race. Such information can help healthcare professionals tailor their treatment to meet the needs of individual patients.
- **Observational and comparative data** – Information from the use of a medicine outside of randomized clinical trials, especially comparisons between two or more therapies.
- **Pharmacoeconomic information** – Healthcare economic data and information on the economic value of medicines can improve the efficiency of patient care.
- **Information on medically accepted alternative uses of medicines** – Information on new uses of approved medicines that are listed in major compendia and/or routinely reimbursed by the federal government and major payers. As the National Cancer Institute states, "Often, usual care for a specific type or stage of cancer includes the off-label use of one or more drugs."[1] Healthcare professionals help patients by applying new uses of approved drugs in "every specialty of medicine."[2] When patients are being prescribed medicines off-label, they deserve to know that their healthcare professionals have the latest information on these uses.

There is distinction between off-label communications and off-label marketing. And it is a distinction with a difference. Off-label marketing means sharing information with the intent to impact sales. Off-label communications means sharing information to improve and advance the public health. One well-known moniker for off-label communications is "the free and fair dissemination of scientific data." The new FDA action clearly is directed at off-label communications. Another way to look at it is that "communications = education" and "marketing = sales."

Facts do not cease to exist because they are ignored. And this is an issue with a lot of history – with only a small piece making it into the reporting of this week's FDA announcement. Let's look at the record.

According to a 2011 notice in the Federal Register:

> *The Food and Drug Administration (FDA) is announcing the establishment of a docket to assist with our evaluation of our policies on communications and activities related to off-label uses of marketed products, as well as communications and activities related to use of products that are not yet legally marketed for any use, we would like to obtain comments and information related to scientific exchange. FDA is interested in obtaining comments and information regarding scientific exchange about both unapproved new uses of products already legally marketed ("off-label" use) and use of products not yet legally marketed for any use.*

And the issue of "scientific exchange" comes front and center. According to the FR notice, *To assist with our evaluation of our policies on communications and activities related to off-label uses of marketed products, as well as communications and activities related to use of products that are not yet legally marketed for any use, we would like to obtain comments and information related to scientific exchange.*

The FR notice puts this request into perspective:

> *On July 5, 2011, a citizen petition was submitted by Ropes & Gray and Sidley Austin LLP on behalf of seven product manufacturers (Petitioners): Allergan, Inc.; Eli Lilly and Co.; Johnson & Johnson; Novartis Pharmaceuticals Corp.; Novo Nordisk, Inc.; Pfizer, Inc.; and sanofi-aventis U.S. LLC under 21 CFR 10.30. The citizen petition requested that FDA clarify its policies for drug products and devices governing certain communications and activities related to off-label uses of marketed products and use of products that are not yet legally marketed for any use. Specifically, the petition requests clarification in the following areas:*
>
> 1. *Manufacturer responses to unsolicited requests;*
> 2. *Scientific exchange;*
> 3. *Interactions with formulary committees, payers, and similar entities; and*
> 4. *Dissemination of third-party clinical practice guidelines.*

For some time, FDA has been considering these issues and is currently evaluating our policies on sponsor or investigator communications and activities related to off-label uses of marketed products and use of products that are not yet legally marketed for any use. We have been considering what actions to take in the areas specified by the petitioners with respect to manufacturer responses to unsolicited requests; interactions with formulary committees, payors, and similar entities; and the dissemination of third-party clinical practice guidelines.

Specifically, the FDA asks:

- *How should FDA define scientific exchange?*
- *What types of activities fall under scientific exchange?*
- *What types of activities do not fall under scientific exchange?*
- *Are there particular types and quality of data that may indicate that an activity is, or is not, scientific exchange?*
- *In what types of forums does scientific exchange typically occur? Should the use of certain forums be given particular significance in determining whether an activity is scientific exchange or an activity that promotes the drug or device? If so, which forums?*
- *What are the distinctions between scientific exchange and promotion? What are the boundaries between scientific exchange and promotion?*
- *Generally, who are the speakers involved in scientific exchange, and who is the audience for their communications?*
- *Should the identity of the participants (either speakers or audience) be given particular significance in determining whether an activity is scientific exchange or an activity that promotes the drug or device? If so, which participants would be indicative of scientific exchange and which would be indicative of promotion?*
- *How do companies generally separate scientific roles and promotional roles within their corporate structures?*
- *How should the Agency treat scientific exchange concerning off-label uses of already approved drugs and new uses of legally marketed devices? Please address whether there should be any distinctions between communications regarding uses under FDA-regulated investigation (to support potential approval) and communications regarding uses that are not under express FDA-regulated investigation.*
- *How should the Agency treat scientific exchange concerning use of products that are not yet legally marketed (that is, products that cannot be legally distributed for any use outside of an FDA- or institutional review board (IRB)-approved clinical trial)?*
- *Should investigational new drugs and investigational devices be treated the same with respect to scientific exchange? Why or why not?*
- *Under 21 CFR 812.7(b), an investigational device is considered to be "commercialized" if the price charged for it is more than is necessary to recover the costs of manufacture, research, development, and handling. Similarly, FDA considers charging a price for an investigational drug that exceeds that permitted under its regulations (generally limited to cost recovery) to constitute "commercialization" of the drug (see 74 FR 40872 at 40890, August 13, 2009; 52 FR 19466 at 19467). What other actions indicate the commercialization of drug and/or device products? If there are differences in the steps taken to commercialize drug products and the steps taken to commercialize device products, either before or after approval, please explain these differences.*

And it's not just PhRMA – patient groups have weighed in as well. Some examples:

NORD:

At the same time, the government severely restricts what drug companies can say about new research and about off-label uses, thus cutting off information from the most knowledgeable sources. The Congress should seek new policies that permit drug companies to share appropriate information without fear of enforcement action.

OVARIAN CANCER NATIONAL ALLIANCE

In ovarian cancer, as in many oncology settings, patients receive "off-label" therapies, which are legal and often part of practice guidelines. Access to these therapies is critical to providing patients with the best possible care...

The Alliance is deeply concerned that these revisions will chill off-label use of drugs and the dissemination of scientific information about non-approved uses. We strongly urge FDA to reconsider these changes and remove any language that may curb patient access to medically-accepted and life-saving medications.

AND FROM BIO:

Current law deals with the important question of providing payers and others with meaningful information regarding the pharmacoeconomic benefits of medicines. However, implementation of Section 114 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) has undermined innovators' ability to meet requests for such information. The committee could evaluate how this important provision could be implemented in a less restrictive way to allow manufacturers to discuss more fully the value to the healthcare system of their innovations.

More broadly, provision of other truthful and non-misleading information to providers, payers, and patients also should not be impeded by unnecessary and cumbersome regulatory restrictions or requirements. Such approaches hinder users of medicines from accessing information that can help them use the medicines most effectively.

Much food for thought here, but two things in particular to mention:

* This is not an "out-of-the-blue" action by the FDA.
* It's not just about communications with physicians – but also with payer formulary committees.

To address concerns that FDA regulations were limiting the dissemination of outcomes research, Congress added Section 114 (in 1997) to set a new, **less stringent standard** applicable to promotional dissemination of health care economic information to MCO formulary committees: "competent and reliable scientific evidence."

But as Bob Temple commented, FDAMA 114 is "an interesting section, and its not entirely simple to figure out what's included and what's not included.

No kidding.

Even though there is no FDA guidance to explain the agency's understanding of "competent and reliable scientific evidence," PhRMA developed a draft guidance, which was submitted to the FDA in June 1998. In its draft, PhRMA sought input from the International Society for Pharmacoeconomics and Outcomes Research, the Society for Medical Decision Making, the Academy of Managed Care Pharmacy, the American Pharmaceutical Association, and other groups.

In its submission to the FDA, PhRMA explained the history behind Section 114 and proposed guidance on the following terms used in the new law:

- Health care economic information.
- Managed care or other similar organizations.
- Formulary committee or other similar entity.
- Directly related to an approved indication.
- Competent and reliable scientific evidence.

The PhRMA proposal took an approach to interpretation consistent with Congress's intent that Section 114 would increase the dissemination of outcomes research information by product manufacturers to MCOs. PhRMA concluded that the term "health care economic information" should include all forms of economic analysis so the guidance could adapt to new and evolving outcomes research methods.

One of the phrases in Section 114 that is difficult to interpret is that promotion must involve a claim that "directly relates to an indication approved [by the FDA]." In the draft guidance, PhRMA proposed that extrapolation from data included on labeling would be appropriate at least under the following circumstances: from duration of use in labeling to actual duration of use found in pharmacy databases, from dosages included in labeling to actual dosages found in pharmacy databases, and from controlled trial settings to actual practice settings.

The standard set by Section 114, "competent and reliable scientific evidence," is the same standard used by the Federal Trade Commission (FTC) when assessing the adequacy of substantiation for manufacturer claims involving OTC drugs and products affecting environmental health. That standard requires transparency of methods and use of methods accepted by experts in the field. In its proposal, PhRMA recommended that the FDA follow long-established FTC interpretation of the competent and reliable scientific evidence standard.

The full FR Notice on "Communications and Activities Related to Off-Label Uses of Marketed Products

and Use of Products Not Yet Legally Marketed; Request for Information and Comments" can be found at http://www.gpo.gov/fdsys/pkg/FR-2011-12-28/pdf/2011-33188.pdf.

In October 2012, PhRMA issued a white paper, asking the FDA for guidance on the supporting evidence drug companies need for the health care economic data they send to formulary managers should specifically allow for use of a range of data sources, not limited to adequate and well-controlled clinical trials.

The white paper urges the agency to develop formal regulatory guidance on Sec. 114 of the FDA Modernization Act of 1997, which allows drug companies to proactively disseminate health care economic information to formulary committees within certain limitations.

The white paper outlines a number of data elements that should satisfy the competent and reliable scientific evidence standard. They include: methods for establishing economic costs and consequences that are widely accepted by experts in the field using a clear, pre-defined study protocol; an "accurate and balanced assessment of the economic consequences of a drug therapy, consistent with the current weight of credible evidence"; a representative study population; and information that allows the reader to determine how the research was conducted.

PhRMA recommends that FDA allow the competent and reliable standard to be satisfied with data obtained through a number of different methods, including observational study designs, database reviews and other economic modeling techniques. "There should be no pre-specified number or type of study required to substantiate a claim."

For example, "a claim that a drug is more cost-effective than a competing drug may be made where the cost savings are due to reduced resource utilization resulting from improved efficacy outcomes, decreased administration or monitoring costs, or where the difference in cost is due to the drug causing fewer adverse events, as long as these differences are supported by competent and reliable evidence."

PhRMA argues that FDA should not consider such a statement a comparative clinical claim, which would trigger the "substantial evidence" requirement involving clinical trials.

Companies should be permitted to disseminate data on the "real world" economic implications of a therapy on health outcomes, according to the white paper. For example, "if a manufacturer conducts a competent and reliable study investigating the impact of a drug indicated for the treatment of diabetes mellitus on costs associated with cardiovascular care, the manufacturer should be permitted to proactively disseminate such data to appropriate audiences."

For industry, the new FDA guidance opens up tremendous potential for enhanced (but restrained and responsible) sharing of important scientific data. The key question is, do the opportunities outweigh the risks? There are a few ways to approach this.

There's the First Amendment question. Did the *Caronia Philharmonia* impact the way FDA views off-label promotion within the context of the free-and-fair dissemination of scientific data? It was certainly a part of the cogitation process.

An extreme way to look at it is that, in a post-*Caronia* world, some pharmaceutical companies may no longer feel obligated to seek FDA approval for new indications, since they can openly "promote" them without fear of prosecution. This is a flawed argument. Indications of the on-label variety have many benefits—not the least of which is reimbursement. But such negative unintended consequences are important to discuss and consider. Any company that chose this route would be acting in a highly irresponsible manner, putting promotion before the public health. The recent FDA action makes this a relatively implausible route.

In other words, the FDA's action advances the public health by accelerating the free-and-fair dissemination of scientific data while maintaining appropriate regulatory oversight of communications behavior.

That's the FDA doing its job both protecting and advancing the public health. Bravo.

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2. Christopher M. Wittich, et; al., Ten Common Questions (and Their Answers) About Off-label Drug Use, Mayo Clinic Proceedings, available at http://www.mayoclinicproceedings.org/article/S0025-6196(12)00683-0/fulltext#sec3.

Commentary

A 'Genetically Engineered' Label: Way More Expensive Than You Think

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ABSTRACT

Pseudo-controversy continues to rage over whether foods from plants and animals genetically engineered with the newest molecular techniques should have to be labeled as such. The battles, fought in the media, state legislatures, referendum issues, and in federal courts, have been largely fomented and funded by the organic agriculture and food industries. All but one of the proposals to require labeling in the United States have failed, and that exception is being challenged in a federal court . In spite of these failures and the fact that mandatory labeling fails every test –scientific, economic, legal and common-sense–the true believers soldier on.

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Pseudo-controversy continues to rage over whether foods from plants and animals genetically engineered with the newest molecular techniques should have to be labeled as such. The battles, fought in the media, state legislatures, referendum issues, and in federal courts, have been largely fomented and funded by the organic agriculture and food industries. All but one of the proposals to require labeling in the United States have failed, and that exception is being challenged in a federal court.[1] In spite of these failures and the fact that mandatory labeling fails every test[2]–scientific, economic, legal and common-sense–the true believers soldier on.

One of the less obvious but more egregious claims made by pro-labelling groups is that the costs of mandatory labeling would be minimal. In the run-up to referendum issues on labeling in the November 2014 elections in Colorado and Oregon, for example, Consumers Union, a product-testing and advocacy group, released an analysis[3] it had commissioned on the costs of mandatory labeling of genetically engineered (GE) foods which claimed that the median cost of labeling would be "$2.30 per person per year," with a broad range of estimates, "from $0.32 to $15.01."

This analysis is an example of getting the wrong answer by making the wrong assumptions. Approaching the labeling question as the FDA did in its study of the impact of nutritional labeling was fundamentally misguided. Costs associated with nutritional labeling requirements do indeed incur a relatively small one-time cost, essentially from the reprinting of packaging to conform to regulators' new requirements; but the labeling of genetically engineered ingredients is far more complicated, fraught with difficulties and expensive. In short, GE ingredient and nutritional labelling are very different because GE crops would need to be kept strictly segregated in order to ensure that labeling regulations are complied with and to avoid or minimize the potential for liability due to cross-contamination (even if the effects are wholly inconsequential).

The expense associated with GE labeling is primarily a function of two cost elements: (1) the productivity-driven difference between the cost of production of GE and non-GE production systems (the GE crop tends to be cheaper than the non-GE alternative); and (2) the costs involved in delivering certified non-GE products

1 http://www.usatoday.com/story/news/nation/2014/06/12/lawsuit-challenges-vermonts-gmo-labeling-law/10402301/

2 http://www.forbes.com/sites/henrymiller/2013/10/09/mandatory-labeling-of-genetically-engineered-foods-deserves-a-warning-label-of-its-own/

3 https://consumersunion.org/wp-content/uploads/2014/09/GMO_labeling_cost_findings_Exe_Summ.pdf

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to the market (which includes the nominal cost of changing the labels on both products that contain GE ingredients as well as on those that do not).

Those two primary cost elements are in turn affected by several factors, many of which are related to supply and demand:

- *the cost of production/supply differential* is driven by the impact of the technology, which is a function of factors such as pest, weed, or drought pressure—if the GE trait is pest-resistance, herbicide-tolerance or drought-tolerance, respectively; the level of effectiveness of conventional pest/weed control or drought alleviation strategies compared to the GE alternative; the costs of inputs (herbicides, insecticides, fuel, seed) for production; and the availability (supply) of GE versus non-GE products. Evidence from 18 years of widespread cultivation of GE crops around the world shows that GE crops are more productive and cheaper to produce than non-GE alternatives.[4]
- *the costs of delivering certified non-GE products* to users who wish to avoid GE ingredients depend on factors such as the specifications set by food manufacturers and retailers—for example, whether they want certified supplies to contain less GE than, say, 1% or 0.1%. This is crucial because the tighter (lower) the specification, the higher the cost.
- *the availability of certified non-GE products* (which can vary on both an annual and seasonal basis) and the level of aggregate demand for such products.
- the extent to which the avoidance of GE ingredients is applied to highly processed "derived" products, food processing aids and animal products. Related issues include, for example, whether material related to the process of genetic modification can be detected in the final product (it is unlikely in soybean oil or sugar from sugarbeets, for example); meat, milk and eggs, where the issue is whether animals have been raised on non-GE feed, or to products derived from and using processing aids obtained from GE derived micro-organisms (e.g., recombinant DNA-derived chymosin in cheese production).

  If a GE ingredient-avoidance policy is extended to these types of products—typically where the GE content typically is not detectable, this will add further costs, mainly because strict raw material traceability and supply chain auditing systems will be required to ensure product (non-GE) authenticity.

The evolution of markets in places like the EU where GE ingredient labelling has been mandatory for many years shows that—contrary to the stated intentions of labeling initiatives (viz., to offer greater choice)—consumers are the principal losers, with less choice and higher prices in the short term, and less innovation in the long-term.

Contrary to some inexpert, simplistic and flawed analyses, mandatory labeling of GE products is a complex and potentially costly undertaking. And in the end, it's neither necessary nor advantageous to consumers.

Evidence from markets where GE ingredient labeling has been required suggests that most food manufacturers and retailers will initiate GE-ingredient avoidance policies because they are typically concerned about threats to their brand or name, a perceived risk of bad PR fomented by anti-GE lobby groups (manifested by demonstrations against products labeled as containing GE ingredients, social media campaigns, etc.), and can be easily influenced by a small number of "customers" demanding they stock certified non-GE products.

Consider, for example, that food production behemoths like General Mills and Post Foods were stampeded by activists[5] into reformulating their iconic Cheerios and Grape Nuts cereals, respectively, to be non-GE, and then were confounded by the Law of Unintended Consequences[6]—namely, needing to eliminate certain added vitamins from their products because they couldn't obtain these from sources certified to be non-GE. This is an example of how a manufacturer trying to meet a perceived consumer demand (i.e., for a certified non-GE product) ends up supplying both a more expensive and inferior product—inferior in having reduced nutrients (vitamins). This situation has been called a "regrettable substitution."[7]

If consumers are offered a genuine choice of certified non-GE products alongside essentially the same products containing GE ingredients, most will likely

4 http://dx.doi.org/10.4161/gmcr.28098

5 http://www.wsj.com/articles/SB10001424052702304049704579320311512770326

6 http://www.npr.org/blogs/thesalt/2014/12/05/368248812/why-did-vitamins-disappear-from-non-gmo-breakfast-cereal

7 http://www.tandfonline.com/doi/full/10.1080/13698575.2014.969687#tabModule

buy the less expensive, GE one because the issue of GE ingredients in food is not important (or at least, not as important as price) to a majority of consumers. A minority (likely small) will buy the more expensive, certified non-GE product.

However, the marketplace rarely operates so straightforwardly. Food manufacturers don't want to perform separate product runs and segregate processing and packing, because this adds cost. And at the retail level, because shelf space in supermarkets is limited, managers don't want shelves filled with three choices of virtually identical products–viz., conventional, containing GE; certified non-GE; and organic. This means that, as has happened in the EU, many U.S. food manufacturers would likely adopt a policy of GE avoidance, insisting that all supplies are certified non-GE, or else switch to crop ingredients where GE technology is not currently available, such as from soybean oil to sunflower oil.

In this way, given the current milieu, mandatory labeling gives rise not to more consumer choice in the marketplace, but to *less*, with consumers often having access only to either certified non-GE or organic products–both of which are more expensive than the unavailable GE alternative.

This scenario plays into the hands of the organic sector because it makes the now "conventional" (i.e., certified non-GE) alternative more expensive, narrowing the price differential with organic and reducing the availability of the cheapest alternative (i.e., GE-containing products). The organic sector thereby hopes to attract consumers who switch to organic because there is less of a price differential between the organic product and the GE-free "conventional" one.

The promotion of mandatory GE food ingredient labeling fits very well with the underlying marketing strategy of the organic sector. As exposed by Academics Review[8], a science-oriented nonprofit organization of academic experts, "consumers have spent hundreds of billion dollars purchasing premium-priced organic food products based on false or misleading perceptions about comparative product food safety, nutrition and health attributes," and that this is due to "a widespread organic and natural products industry pattern of research-informed and intentionally-deceptive marketing and paid advocacy."

Mandatory labeling of GE foods is a subtle but integral part of this "black marketing" campaign, because by increasing fear, suspicion and doubt among consumers, it is likely to result in more of them pressuring retailers and food manufacturers for what they perceive is more "choice" in the form of greater availability of certified non-GE products.

If the food industry and retailers comply with such demands, the constraints on supply chains, processing costs and shelf space could result in:

- the stocking of organic as the alternative to GE—thus increasing organic sales, if the retailer did not previously sell an organic alternative;
- food manufacturers shifting to organic ingredients, because they should, by definition, be GE-free, eliminating the need to establish a whole new supply chain system to provide a certified non-GE alternative;
- using only non-GE-certified supplies of ingredients and products (instead of GE-derived ones), which increases the cost of what would be the only alternative to organic—and which would have the effect of making organic more attractive to some consumers because of the lower price differential;
- possible legal liability for inadvertent (and inconsequential) errors in labeling;
- a financial bonanza for companies that provide GE testing in the supply chain.

8 http://academicsreview.org/wp-content/uploads/2014/04/AR_Organic-Marketing-Report_Print.pdf

Article

Cannabis-Derived Pharmaceuticals

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ABSTRACT

Cannabis, commonly known as marijuana, weed or pot, is a natural product derived from the Cannabis sativa plant. It has been used medicinally for thousands of years. Recent legislation allowing the use of medical marijuana in over 23 US states has spurred interest in developing pharmaceutical-derived Cannabis products to treat a variety of clinical indications ranging from pain relief to epilepsy. Many products are in late stage clinical development in the US and elsewhere. This article reviews the medicinal properties of Cannabis and describes pharmaceutical-derived Cannabis products that are currently being developed for theUS market.

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INTRODUCTION

Cannabis, commonly known as marijuana, weed or pot, is a natural product derived from the *Cannabis sativa* plant. It has been used medicinally for thousands of years in China, India, The Middle East and in the West through much of the 19th century.[1,2] Anecdotally, and in the medical literature, *Cannabis* has been recommended as a treatment for numerous diseases including pain, arthritis, glaucoma, neurological disorders including epilepsy, multiple sclerosis (MS) and Parkinson's disease and diabetes and a variety of ailments including loss of appetite, anxiety, nausea and vomiting and menstrual cramps.[3,4]

The plethora of therapeutic benefits offered by *Cannabis* has largely been attributed to a class of naturally-occurring, plant-derived terpenophenolic compounds known as phytocannabinoids.[5,6] Inhalation (smoking and vaporization) and ingestion are the most common routes of administration of *Cannabis* products but other routes including rectal, sublingual, transdermal, ophthalmic, intrathecal and intravenous routes have been used.[7]

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In addition to the phytocannabinoids, endogenous or endocannabinoids that are produced by the body have been identified and characterized. Endocannabinoids are thought to modulate or play a regulatory role in a variety of physiological processing including appetite, pain-sensation, mood, memory, inflammation, insulin sensitivity and fat and energy metabolism.[8,9] Finally, a number of synthetic cannabinoids (mimetics of naturally-occurring endocannabinoids) have been developed to better understand cannabinoid receptor biology/function/selectivity and, also, as possible treatments for a variety of therapeutic indications including pain management, inflammation, cancer and neurodegenerative diseases.[9]

MECHANISM OF ACTION

Cannabinoids (endogenous, synthetic and phytocannabinoids) are thought to exert their physiological effects by interacting with CB1 and CB2, G-coupled protein cannabinoid receptors that are widely distributed and found throughout the body.[10-13]

CB1 receptors which constitute the most prevalent neurotransmitter system in the brain and central nervous systems (CNS) are primarily found in basal ganglia, hippocampus and cerebellum.[10,11] In contrast, CB2 receptors are found almost exclusively on cells of the immune system including T and B cells and mainly appear in

tissues when there is cellular pathology. CB1 receptors are thought to be involved in the effects of *Cannabis* on appetite, mood motor function and neurocognition[12,14] whereas CB2 receptors appear to be responsible for mediating the anti-inflammatory and analgesic effects of *Cannabis*.[15-18]

Recent studies showed that certain cannabinoids such as CBD interact with the transient receptor potential vanilloid channels of the endovanilloid system, e.g, capsaicin receptors that are thought to modulate neuropathic pain and were recently shown to be involved in bone growth.[19-21] Also, other studies suggest that cannabinoids may exert therapeutic their effects by targeting α3 glycine receptors, stimulating PPARγ receptor activity, increasing intracellular Ca^2 and antagonizing GPR55 receptors.[22,23] The mechanisms of action of cannabinoids for a variety of clinical indications including chronic pain, cancer, and multiple sclerosis (MS) has been extensively reviewed elsewhere.[5,17,24,25,26-29]

PHARMACOLOGICALLY-ACTIVE PHYTOCANNABINOIDS

To date, over 60 cannabinoids unique to *Cannabis* have been identified, including the most psychoactive cannabinoid, Δ-9-tetrahydrocannabinol commonly referred to as THC. Other medically- relevant and well characterized cannabinoids include; Δ-9–tetrahydrocannabivarin (THCV), cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC) cannabinol (CBN) and cannabidivarin (CBDV); with THC, CBD and CBN being the most abundant phytocannabinoids (Table 1).[30]

THC is the main active cannabinoid in *Cannabis* and is primarily responsible for its psychoactive properties. It was the first cannabinoid to be isolated and identified (1964) in *Cannabis* resin and flowers.[31] The concentration of THC found in *Cannabis* and its extracts can vary based on plant variety, cultivation techniques and type of preparation. Pure THC can be derived from natural sources (extraction from cannabis plants) or produced synthetically.[32] The molecule acts as a partial agonist of CB1 receptors found in the CNS and CB2 receptors found on immune cells.[32]

While THC exhibits potent anti-inflammatory and anti-emetic properties, its development as a therapeutic drug treatment has been hindered by its accompanying psychotropic effects. Nevertheless, in the past, dronabinol (Marinol™) a synthetic THC and nabilone (Cesamet™) a synthetic THC-mimetic received FDA approval as appetite stimulants and treatments for chemotherapy induced nausea and vomiting (CINV).[7] However, neither drug is widely prescribed. Finally, possible development of tolerance to THC could limit the long term clinical and therapeutic uses of the molecule.

Δ-9-tetrahydrocannabivarin (THCV) is a relatively abundant non-psychoactive phytocannabinoid present in *Cannabis*.[33] THCV is a CB1 receptor antagonist and a partial agonist for CB2 receptors. Several studies showed that THCV has anti-convulsive effects in animal models and that it may be useful as a treatment for epilepsy and other CNS diseases.[33-35]

Cannabidiol (CBD) is the major non-psychotropic cannabinoid found in *Cannabis*. It has been found to possess anti-epileptic, anti-inflammatory, anti-emetic, muscle relaxing, anxiolytic, neuroprotective and antipsychotic activity and reduces the psychoactive effects of THC.[36,22,23] Unlike THC, the mode of action of CBD is not fully understood and it is thought to act via non-CB1 receptor mechanisms because it has low affinity for CB1 and CB2 receptors.[35] Recent studies suggest that CBD may exert its action by targeting α3 glycine receptors, stimulating PPARγ receptor activity, increasing intracellular Ca^2 and antagonizing GPR55 receptors.[22,23] Other studies suggest that CBD may be a CB1 receptor antagonist[37] and may also exerts its effects by stimulating the vanilloid receptor type 1 (VR_1) with efficacy similar to that of capsaicin.[20,21,38] Also, CBD is thought to inhibit the degradation of the endocannabinoid anandamide[38] and may interfere with THC metabolism.[39] CBD is being evaluated as a possible treatment for epilepsy[40], schizophrenia[41] and for its anti-tumorigenic effects.[42]

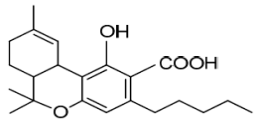
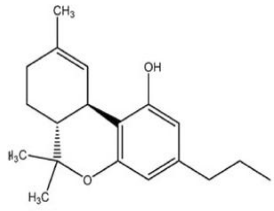
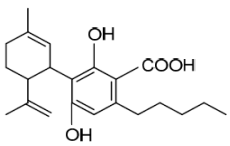
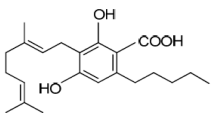
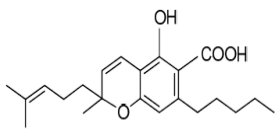
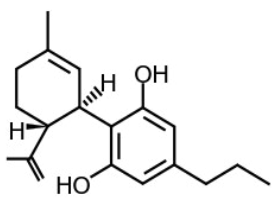
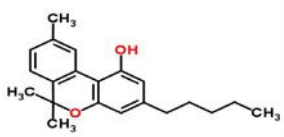
Cannabigerol (CBG) is another non-psychoactive phytocannabinoid found in *Cannabis* and the chemical precursor of THC and CBD. CBG has been reported to relieve intraocular pressure and possesses anti-inflammatory properties.[43-45] The molecule has also been reported to have anti-convulsive effects but these effects have yet to be substantiated.[46] CBG is being evaluated as a possible treatment for multiple sclerosis and inflammatory bowel disease.[45,47]

Another non-psychoactive cannabinoid found in *Cannabis* with possible therapeutic benefits is cannabichromene (CBC). CBC is thought to possess analgesic and anti-inflammatory activity.[48,49] Other studies suggest that CBC may also possess some neuroprotective effects.[34,49]

Cannabidivarin (CBDV) is a non-psychotropic homolog of CBD. CBDV is actively being developed as a therapeutic to treat epilepsy and convulsions because of its previously observed anti-convulsive and anti-epileptic activities in animal models.[34,35,50] CBDV has been reported to act via CB2 cannabinoid receptors-dependent mechanisms but direct CB2 receptor binding has yet to be demonstrated.[50,51]

Cannabinol (CBN) is a weak psychoactive cannabinoid found only in trace amounts in *Cannabis*[52]

Table 1: Pharmacologically active phytocannabinoids

Name	Abbreviation	Structure	Physiologic Effects	Therapeutic Indication(s)
Δ-9 tetrahydrocannabinol	THC		Psychoactive, mild analgesic, anti-emetic, appetite stimulant neuroprotective, reduces neuroinflammation and stimulates neurogenesis	Pain, Nausea, Nutritional wasting, Cancer
Δ-9-tetrahydrocannabivarin	THCV		Non-psychoactive, anti-convulsant, anti-inflammatory,	Epilepsy and other CNS disorders hepatic ischemia
Cannabidiol	CBD		Non-psychoactive, relieves convulsion, inflammation, anxiety and nausea	Schizophrenia, epilepsy, cancer
Cannabigerol	CBG		Non-psychoactive, relieves intraocular pressure, anti-inflammatory, neuroprotective, anti-emetic	Multiple Sclerosis, Glaucoma and inflammatory bowel disease
Cannabichromene	CBC		Non-psychoactive, anti inflammatory and analgesic effects	Pain, Cancer
Cannabidivarin	CBDV		Non-psychoactive,anti-convulsive, anti-inflammatory	Epilepsy
Cannabinol	CBN		Weakly psychoactive (degradation product of THC), immunosuppressant activity, anticonvulsive	Epilepsy

It is mostly a degradation product (metabolite) of THC.[53] Studies suggest that CBN acts as a weak agonist of CB1 receptors and has a higher affinity for CB2 receptors albeit lower than the affinity of THC for CB2 receptors.[54,55] Because CBN is a partially-selective agonist of CB2 receptors it may possess possible anti-inflammatory and immunosuppressant therapeutic effects.

CLINICAL EFFECTS

Over the past decade, despite a challenging legal and regulatory landscape, a surprising number of clinical studies have been conducted with *Cannabis* and cannabinoids for a variety of therapeutic indications.[7,28,56,57] The main areas of clinical research include chronic non-cancer pain, neurological diseases including MS and epilepsy,[28,29,57,58] and oncology including analgesia, anorexia, chemotherapy-induced nausea and vomiting (CINV).[5,7,27,42,59]

A systematic review of 18 randomized controlled clinical trials for chronic non-cancer pain conducted since 2003 revealed that smoked cannabis, cannabis extracts (oromucosal spray) and orally-administered synthetic THC (nabilone and dronabinol) had modest analgesic effects (compared with placebo) on 766 participants with chronic, neuropathic or acute non-cancer pain.[57] The databases that were searched to conduct this retrospective study included PubMed, Em base, CINAHL (EBSCO, PsycInfo, The Cochrane Library (Wiley) ISI Web of Science, ABI Inform (Proquest), Academic Search Premier, Clinical Trials.gov , Trials Central.org and clinical trial sites for Eli Lilly, GlaxoSmithKline, OALster (OCLCC) and Google Scholar.[46] However, the small number of participants, short trial durations and modest efficacy caused the authors to suggest that additional clinical trials will be necessary to conclusively determine the effects of cannabinoids on chronic pain management. To that end, there are currently 11 late-stage US clinical trials in progress to assess the effects of smoked/ vaporized *Cannabis* (6) and cannabis extracts (6) on neuropathic and chronic pain (Table 3). However, it is important to note, that GW Pharma's Sativex® a cannabis extract containing 1:1 ratios of THC: CBD (that is delivered via oromucosal spray) has been approved outside the US as a treatment for chronic neuropathic and cancer-related pain.[60,61]

The immunomodulatory properties of cannabinoids suggested that they might be therapeutically useful in MS which is generally believed to be an autoimmune neurological disease. Based on a search of the PubMed database, 37 controlled clinical trials involving 1300 patients were conducted from 2005 to 2009 to assess the effects of *Cannabis,* cannabis extracts and synthetic THC on MS and MS-related muscle spasticity and pain.[56] The results of these studies showed that cannabis extracts containing different ratios of THC and CBD (Cannador® 2:1 and Sativex® 1;1), as well as THC and nabilone can improve MS-related symptoms of spasticity, pain and urinary incontinence.[56] Additional clinical studies led to the approval of Sativex® in 27 countries (not the US) as a treatment for MS spasticity.[58] At present, in the US, there are 15 late stage clinical trials in progress that are evaluating smoked/vaporized cannabis (2) and Sativex® (13) as treatments for MS and MS-related spasticity, pain and urinary incontinence (Table 3).

More recently, there have been reports that cannabis extracts with high concentrations of CBD may be effective anti-convulsants for children suffering from severe forms of uncontrollable epilepsy known as Dravet Syndrome and Lennox-Gastaut.[40,62] Four, early randomized, placebo-controlled clinical studies conducted between 1978-1990 involving 48 patients with epilepsy found that daily treatment with 200-300 mg of CBD for up to 4 months was safe and well tolerated.[52] The databases that were searched to conduct the study included the Cochrane Epilepsy Group Specialized Register (9 September 2013), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2013, Issue 8), MEDLINE (Ovid) (9 September 2013), ISI Web of Knowledge (9 September 2013), CINAHL (EBSCOhost) (9 September 2013), and ClinicalTrials.gov (9 September 2013). However the small number of patients and short trial duration were not sufficient to draw any conclusions about CBD's efficacy.[63] More recently, GW pharma's Epidiolex, a liquid formulation of highly purified *Cannabis*-derived CBD was granted Orphan Drug Designation by FDA as a treatment for Dravet and Lennox-Gastaut syndromes and other pediatric epilepsy syndrome.[64] Currently, there are 7 mid to late stage clinical trials underway to evaluated Epidiolex's anti-epileptic properties (Table 3).

In the 1970s, purified and synthetic cannabinoids were being evaluated as palliative treatments for cancer related symptoms.[65] This led to the early approval of dronabinol and nabilone as treatments for CINV but their use has not been extended to treat cancer-related pain or wasting (although dronabinol is approved in the US as an appetite stimulant for patients with weight loss from HIV/AIDS). Interestingly, inhaled *Cannabis*, and extracts containing THC and CBD have been clinically found to be more effective in treating cancer-related neuropathic pain than placebo[66] but their effectiveness compared with conventional pain medications is uncertain.[7] Nevertheless, Sativex® is an approved treatment for cancer-related pain in 27 countries outside of the US. Four clinical trials are underway in the

US to determine the effects on Sativex® on advanced cancer pain and chemotherapy induced neuropathic pain (Table 3).

One of the earliest recognized clinical indications for cannabinoids was CINV. A 1988 prospective open label trial found that inhaled cannabis effectively controlled nausea and vomiting in 78% of 56 patients who had inadequate control of nausea and vomiting with conventional anti-emetics.[7] Also, a later report that evaluated 30 trials and over 1300 participants determined that nabilone and dronabinol were more effective than conventional anti-emetics in controlling acute CINV.[67]

There is a growing body of evidence that cannabinoids *exhibit* anti-tumor and cancer – fighting effects.[7,57] Numerous studies have demonstrated inhibition of tumor growth *in vitro* and in a variety of animal models of disease for cancer including glioblastoma, breast, prostate, thyroid, colon, skin, pancreatic, leukemia and lymphoma.[68] The exact mechanism by which cannabinoids exert their anti-tumor effects is thought to occur via suppression of proliferative cell signaling pathways, inhibition of angiogenesis (blood vessel formation) and cell migration, stimulation of apoptosis (programmed cell death) and induction of autophagy (intracellular degradation).[68,69] Interestingly, cannabinoid receptors CB1 and CB2 have been found in higher concentrations on tumor cells than on surrounding normal tissue for a variety of cancers.[70,71] Also, several studies suggest that cannabinoids may selectively inhibit tumor cell growth and proliferation while sparing normal tissue.[59,68] Although cannabinoids exhibit possible anti-tumor effects, only a single Phase 1 clinical trial that assessed the safety and efficacy of THC in 9 patients with treatment refractory glioblastoma mutliforme has been published.[65] However, at present, there are two (2) Phase 2 clinical trials underway (Table 3) to assess the effect of cannabis extracts on solid tumor growth (CBD) and glioblastoma (Sativex®).

Finally, there are a number of mid to late clinical trials underway in the US to assess the effects of cannabis extracts and cannabinoids on other therapeutic indications including Huntington's Disease, ulcerative colitis, Crohn's disease, schizophrenia and graft vs. host disease (Table 3).

COMMERCIALIZING *CANNABIS*-DERIVED PRODUCTS

The current regulatory and legal environments for *Cannabis*-derived products is extremely difficult and fraught with numerous challenges. For example, in the US, *Cannabis* and products derived from it (including hemp) are federally classified as Schedule I drugs according to the US Controlled Substances Act. This means that *Cannabis* and its products have been deemed to have "no currently accepted medical use in treatment in the US" (heroin and LSD are also schedule I drugs), are harmful and consequently, are illegal. Not surprisingly, its Schedule 1 classification has seriously hindered *Cannabis* research in the US and made it extremely challenging for drug companies developing *Cannabis*-derived pharmaceutical products. However, over the past decade or so, 34 states including the District of Columbia have enacted legislation that permits some form of *Cannabis* consumption for medical purposes. Yet, despite this, *Cannabis* and products derived from it remain illegal at the federal level and interstate transport (even between states where medical marijuana has been legalized) is illegal and criminally punishable.

The confusion regarding *Cannabis* use at the state and federal levels has given rise to two distinct types of companies that are attempting to commercialize *Cannabis* and products derived from it. The first of these are commonly referred to as medical marijuana or medical *Cannabis* companies. Typically, products from these companies are botanical extracts or actual plant materials derived from specific *Cannabis* strains with anecdotally-reported medicinal properties that can be topically applied, ingested, smoked or vaporized. Patients require a "prescription" from a state-licensed physician to obtain medical marijuana and it can only be used in states that permit consumption of *Cannabis* for medical purposes. It is important to note, that while a prescription is required for medical *Cannabis* use, these products do not require human clinical testing for safety, tolerability and efficacy (like other prescription drugs) prior to their sale in states where medical marijuana is legal.

In contrast with medical marijuana companies, biopharmaceutical companies including GW Pharma, Kannalife, Aphios and others (Table 1) are committed to developing *Cannabis*-derived pharmaceuticals using conventional US Food and Drug Administration regulatory approval pathways. UK-based GW Pharma is the clear leader in *Cannabis*-derived pharmaceutical space—its flagship product Sativex®, a plant extract, has been approved as a treatment for cancer-related pain and MS spasticity in 27 countries outside the US. In April 2014, FDA granted Sativex® Fast Track designation for the treatment of pain in patients with advanced cancer who experience inadequate analgesia during optimized chronic opioid therapy.[64] Sativex® is currently in US Phase 3 clinical trials for this indication (Table 3). Most of the other companies developing *Cannabis*-derived pharmaceuticals (extracts or individual cannabinoids) are in pre-clinical development or very early stage clinical trials (Table 2).

Table 2: Companies developing *Cannabis*-based therapeutics

Company	Product	Properties	Indication(s)	Stage of Development
AbbVie	Marinol® (dronabinol)	Synthetic Δ-9-THC	Chemotherapy-induced nausea/vomiting (CINV); MS neuropathic pain; HIV/AIDS appetite stimulate	FDA-approved for nausea and vomiting associated CINV (1985) when other anti-emetics fail and appetite stimulant for HIV/AIDS patients(1992) Approved in Denmark for multiple sclerosis neuropathic pain (2003)
Valeant Pharmaceuticals International Inc	Cesamet® (nabilone)	Synthetic Δ-9-THC	Management of nausea/vomiting	Approved in Canada (1982); now available in US and UK
GW Pharma	Sativex® (naviximols)	Mixture of extracts of cannabis plant containing two cannabinoids in 1:1 ratio, Δ-9-THC and CBD (cannabidiol) in 50% alcoholic solution; oro-mucosal delivery (mouth spray)	Neurologic and cancer-related pain; Spasticity in patients with MS	Approved in 27 countries outside US; US Phase III trials for cancer pain/MS muscle spasticity; granted FDA Fast Track designation
	Epidiolex®	CBD (cannabidiol) liquid extract from genetically-defined cannabis strain	Orphan pediatric epilepsy; Dravet Syndrome and Lennox-Gastaut syndrome	Early clinical development; granted FDA orphan drug status
	GWP42003	Not disclosed	Ulcerative colitis	Phase 2a
	GWP42004	Not disclosed	Type 2 diabetes	Phase 2b
	GWP42006	Cannabidivarin (CBDV)	Adult epilepsy	Phase 1
Society for Clinical Research (Germany)	Cannador®	Oral capsule containing whole plant extract with standardized THC:CBD ratio of 2:1	Muscle stiffness; MS spasticity/pain; cachexia in cancer patients, post-operative pain management	Phase 1/2
Kannalife	Not named	Cannabis extract/semi-synthetic CBD (cannabidiol)	Hepatic Encephalopathy	Preclinical; Seeking orphan drug designation for clinical development
Aphios	APH-080	Liposomal formulation of Δ-9-THC	CINV; Appetite stimulant for HIV and cancer patients	Preclinical
	APH-1305	CBG (cannabigerol) liposomal-oral delivery	MS & other neuroinflammatory neurodegenerative disorders	Preclinical

Table 2: Continued

Company	Product	Properties	Indication(s)	Stage of Development
Cannabis Sciences	CS-S/BCC-1	CBN (cannabinol) enriched extracts	Oncology	Preclinical
	CS-TATI-1	Plant extract	Kaposi Sarcoma	Preclinical
	TBN	CBN (cannabinol) plus other cannabinoids	Anxiety, sleep disorders, Alzheimers disease	R&D
Medical Marijuana Sciences	TBN	CBD (cannabidiol) extracts plus microencapsulation technology	Brain and pancreatic cancer	R&D

Regulatory and Commercialization Hurdles

While the business case for developing pharmaceutical *Cannabis*-derived products is a sound one, the time and costs associated with commercializing these products is certain to be greater than those associated with medical marijuana. This is because medical marijuana can be prescribed and sold in states (where it is legal) without scientific review or human clinical testing. And, while FDA has signaled a willingness to review new drug applications for *Cannabis*-derived pharmaceuticals, the agency has yet to issue definitive guidance for regulatory approval of these products. Consequently, the actual costs, regulatory requirements and time required for FDA approval for *Cannabis*-derived products are difficult to gauge at the present time. Nevertheless, garnering FDA approval for *Cannabis*-derived pharmaceuticals may offer several competitive advantages as compared with medical marijuana products that currently dominate the US market.

First, the average cost per patient of Sativex® to treat MS spasticity in countries where it is approved has been estimated to be roughly $16,000.[72] Several studies have suggested,[72,73] that the high price of Sativex® will make it unlikely to be considered cost effective by regulators in countries with government-mandated national formularies like the UK, Ireland and Australia. However, this should not be an impediment for the US market because the US federal government does not set drug prices nor determines formulary placement. Moreover, medical marijuana is currently an out-of-pocket expense for patients whereas newly FDA approved *Cannabis*-derived products are likely to be reimbursed at rates similar to those of synthetic cannabinoids such as dronabinol and nabilone.

Second, unlike medical marijuana (which as previously stated is a Schedule 1 drug), FDA approved *Cannabis*-based pharmaceuticals like dronabinol and nabilone have been classified or reclassified as Schedule 2 (opioids) or Schedule 3 (codeine) drugs. Federal regulators are likely to apply the same scheduling criteria to the next generation of FDA-approved *Cannabis*-derived pharmaceuticals like Sativex® and others. Rescheduling will effectively allow these products to compete with medical marijuana because unlike medical marijuana—which is legal in certain states and cannot be transported across state borders because of Federal law—FDA-approved *Cannabis*-derived pharmaceuticals can be legally prescribed, sold and used in all 50 US states and US territories.

Finally, and perhaps most importantly, physicians may be inclined to prescribe FDA-approved *Cannabis* drugs rather than medical marijuana because the approved products have been medically evaluated in human clinical trials and officially deemed to be safe, effective treatments for specific clincial indications. In contrast, questions or suspicions regarding medical marijuana's safety, effectiveness and quality are likely to linger until industry best practices are clearly established and adopted.

MEDICAL AND TECHNICAL CHALLENGES

In addition to legal and regulatory challenges, there are technical and manufacturing issues that must also be addressed before *Cannabis*-derived pharmaceuticals can be successfully commercialized. First, substantial financial investment in infrastructure, equipment and production facilities will be required to breed and grow different *Cannabis* strains to obtain appropriate chemical compositions and extracts to treat specific therapeutic indications. Industry experts contend that this investment must include research on

Table 3 Current clinical trials for Cannabis-derived pharmaceuticals

Product	Sponsor	Therapeutic Indication	Study Title	Phase	ClinTrial.gov Identifier
Cannabis	University of California, Davis Center for Medicinal *Cannabis* Research, VA Northern California Healthcare System	Neuropathic pain, mlutiple sclerosis, spinal cord injury	Effects of Vaporized Marijuana on Neuropathic Pain	2	NCT01037088
Cannabis	University of California, Davis VA Northern California Healthcare System University of California Davis, National Institute of Drug Abuse	Spinal cord injury pain	Vaporized Cannabis and Spinal Cord Injury Pain	2	NCT01555983
Cannabis	Center for Medicinal *Cannabis* Research	Diabetic neuropathy	Efficacy of Inhaled Cannabis in Diabetic Painful Peripheral Neuropathy	2	NCT00781001
Cannabis	Center for Medicinal *Cannabis* Research	Neuropathic pain	Effects of Smoked Marijuana on Neuropathic Pain	2	NCT00254761
Cannabis	Center for Medicinal *Cannabis* Research	HIV-associated distal, sensory-predominant polyneurophathy (DSPN)	Medicinal Cannabis for Painful HIV Neuropathy	2	NCT00255580
Cannabis	Center for Medicinal *Cannabis* Research	Pain, hyperalgesia	Analgesic Efficacy of Smoked Cannabis	2	NCT00241579
Cannabis vs. dronabinol, Marinol or THC	University of California, Davis, National Multiple Sclerosis Society	Multiple Sclerosis spasticity	Cannabis for Spasticity in Multiple Sclerosis	2	NCT00682929
Cannabis	Center for Medicinal *Cannabis* Research	Multiple Sclerosis spasticity	Short-Term Effects of Medicinal Cannabis Therapy on Spasticity in Multiple Sclerosis	2	NCT00248378
Sativex®	GW Pharma	Cancer pain	A Study of Sativex® for Pain Relief in Patients With Advanced Malignancy (SPRAY)	3	NCT00674609
Sativex®	GW Pharma	Cancer pain	Study to Compare the Safety and Tolerability of Sativex® in Patients With Cancer Related Pain	3	NCT00675948

Sativex®	GW Pharma; Otsuka Pharmaceuticals	Advanced persistent cancer pain	Sativex® for Relieving Persistent Pain in Patients With Advanced Cancer (SPRAY III)	3	NCT01361607
Sativex®	Capital District Health Authority Canada	Neuropathic pain associated with chemotherapy	Sativex for Treatment of Chemotherapy Induced Neuropathic Pain	3	NCT00872144
Sativex®	GW Pharma	Peripheral neuropathy	A Study of Sativex® for Pain Relief of Peripheral Neuropathic Pain, Associated With Allodynia	3	NCT00710554
Sativex®	GW Pharma	Neuropathic pain	A Study to Compare the Safety and Tolerability of Sativex® in Patients With Neuropathic Pain	3	NCT00713323
Sativex®	GW Pharma	Neuropathic pain management	A Study to Determine the Maintenance of Effect After Long-term Treatment of Sativex® in Subjects With Neuropathic Pain	3	NCT00713817
Sativex®	GW Pharma	Diabetic neuropathic pain	A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy	3	NCT00710424
Sativex®	GW Pharma	Spinal cord injury pain	A Study of Cannabis Based Medicine Extracts and Placebo in Patients With Pain Due to Spinal Cord Injury	3	NCT01606202
Sativex® vs. THC	GW Pharma	Brachial plexus injury pain	A Study to Compare Sublingual Cannabis Based Medicine Extracts With Placebo to Treat Brachial Plexus Injury Pain	3	NCT01606189
Sativex®	GW Pharma	Central neuropathic pain due to Multiple Sclerosis	A Study of Sativex in the Treatment of Central Neuropathic Pain Due to Multiple Sclerosis	3	NCT01604265
Sativex®	GW Pharma	Central neuropathic pain due to Multiple Sclerosis	Sativex Versus Placebo When Added to Existing Treatment for Central Neuropathic Pain in MS	3	NCT00391079
Sativex®	GW Pharma	Multiple Sclerosis, pain, spasticity	A Study of the Long-term Safety of Sativex Use	3	NCT01606137

Table 3. Continued

Product	Sponsor	Therapeutic Indication	Study Title	Phase	ClinTrial.gov Identifier
Sativex® vs. THC	GW Pharma	Pain; Multiple Sclerosis	A Study to Evaluate the Effects of Cannabis Based Medicine in Patients With Pain of Neurological Origin	3	NCT01606176
Sativex®	GW Pharma	Multiple Sclerosis	Neurophysiological Study of Sativex in Multiple Sclerosis (MS) Spasticity (NS-MSS)	3	NCT01538225
Sativex®	GW Pharma	Multiple Sclerosis	An Study to Investigate the Efficacy of Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) in Multiple Sclerosis	3	NCT01610713
Sativex®	GW Pharma	Multiple Sclerosis	An Investigation of Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) in Multiple Sclerosis Patients	3	NCT01610700
Sativex®	GW Pharma	Multiple Sclerosis spasticity	A Study of Sativex® for Relief of Spasticity in Subjects With Multiple Sclerosis	3	NCT00711646
Sativex®	GW Pharma	Multiple Sclerosis spasticity	A Study of the Safety and Effectiveness of Sativex®, for the Relief of Symptoms of Spasticity in Subjects, From Phase B, With Multiple Sclerosis (MS)	3	NCT00681538
Sativex®	GW Pharma	Multiple Sclerosis spasticity	Evaluate the Maintenance of Effect After Long-term Treatment With Sativex® in Subjects With Symptoms of Spasticity Due to Multiple Sclerosis	3	NCT00702468
Sativex®	GW Pharma	Multiple Sclerosis spasticity	A Study to Evaluate the Efficacy of Sativex in Relieving Symptoms of Spasticity Due to Multiple Sclerosis	3	NCT01599234

Sativex®	GW Pharma	Multiple Sclerosis spasticity	A Randomized Study of Sativex on Cognitive Function and Mood: Multiple Sclerosis Patients	4	NCT01964547
Sativex®	GW Pharma	Multiple Sclerosis Detrusor over activity	A Parallel Group Study to Compare Sativex® With Placebo in the Treatment of Detrusor Overactivity in Patients With Multiple Sclerosis	3	NCT00678795
Sativex®	GW Pharma	Huntington's Disease	Neuroprotection by Cannabinoids in Huntington's Disease	2	NCT01502046
Sativex® plus Temozolomide	GW Pharma	Cancer	A Safety Study of Sativex in Combination With Dose-intense Temozolomide in Patients With Recurrent Glioblastoma	2	NCT01812603
Epidiolex (GWP42003-P)	GW Pharma	Epilepsy, Dravet or Lennox-Gastaut Syndromes	An Open Label Extension Study of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet or Lennox-Gastaut Syndromes	3	NCT02224573
Epidiolex (GWP42003-P)	GW Pharma	Epilepsy, Dravet Syndrome	A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome	3	NCT02224703
Epidiolex (GWP42003-P)	GW Pharma	Epilepsy, Lennox-Gastaut Seizures	A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults	3	NCT02224560
Epidiolex (GWP42003-P)	GW Pharma	Epilepsy, Lennox-Gastaut Seizures	A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults	3	NCT02224690
Cannabidiol (CBD)	GW Pharma Fancea 66 Foundation	Sturge-Weber Syndrome	Cannabidiol Expanded Access Study in Medically Refractory Sturge-Weber Syndrome	2	NCT02332655
GWP42003	GW Pharma	Schizophrenia or related psychotic disorder	A Study of GWP42003 as Adjunctive Therapy in the First Line Treatment of Schizophrenia or Related Psychotic Disorder	2	NCT02006628
Cannabidiol (CBD)	Meir Medical Center	Ulcerative Colitis	Cannabidiol for Inflammatory Bowel Disease	2	NCT01037322

Table 3. Continued

Product	Sponsor	Therapeutic Indication	Study Title	Phase	ClinTrial.gov Identifier
Cannabinol (CBD) and THC	Meir Medical Center	Crohn's Disease	Combined THC and CBD Drops for Treatment of Crohn's Disease	2	NCT01826188
Cannabidiol (CBD)	Hadassah Medical Organization	Solid Tumors	A Study: Pure CBD as Single-agent for Solid Tumor	2	NCT02255292
Cannabidiol (CBD)	Rabin Medical Center	Graft vs. Host Disease	Safety and Efficacy of Cannabidiol for Grade I/II Acute Graft Versus Host Disease (GVHD) After Allogeneic Stem Cell Transplantation	2	NCT01596075

strain construction, cannabinoid concentrations at different stages of plant growth/harvest times and yield improvements. Also, included in infrastructure costs is applying Current Good Manufacturing Practices (CGMPs) to plant growth, extraction processes, formulation and manufacture of *Cannabis*-derived pharmaceuticals which will guarantee product safety, efficacy and quality. Interestingly, crop failure (not having a redundancy of supply) is a serious issue that all commercial entities in the medical *Cannabis* industry must address and contend with to meet commercial demand.

Second, the route of delivery and dosing regimens for *Cannabis*-based pharmaceuticals for specific indications will be vitally important. While smoking/vaporizing *Cannabis* is currently the most obvious method to deliver desired therapeutic effects,[7] it may not be the most effective to maximize its therapeutic benefits for different indications and individual patients. Over the past few years, there has been a growing interest in exploring oral, oromucosal, topical and sustained release delivery of *Cannabis*-derived pharmaceutical depending upon the therapeutic indication of interest.[74,75]

Finally, safeguards must be put into place to ensure protection against misuse, fraud and abuse of *Cannabis*-derived pharmaceuticals by healthcare providers and patients. The development of novel metered dose devices to deliver these products will help to limit misuse and abuse.

A WAY FORWARD?

Surveys conducted in the 1990s[76] and 2000s[77] found that between 30% and 54% of internists and oncologists were interested in offering cannabis as a therapeutic option for their patients. Yet, despite this, the surveys showed that many physicians were concerned about the legality of making medical cannabis recommendations or writing prescriptions regardless of state laws.[7] Also, the existing confusion about the legality/criminality of *Cannabis*-derived products is certain to have an effect on the behavior of insurers and third party payers. At this point, it is not clear whether or not payers will place *Cannabis*-derived pharmaceuticals on their formularies and reimburse patients who use them. Alternatively, it is possible that insurers may reimburse patients who use FDA-approved *Cannabis* products but continue to treat medical marijuana as an out-of-pocket expense for patients who use it.

The legal patchwork for *Cannabis* that has evolved over time in the US suggests that *Cannabis*-derived products may only be available in the states that have legalized their use. Consequently, companies developing

Cannabis-based pharmaceuticals may have to duplicate commercial operations in states where medical *Cannabis* is legal and underwrite multiple product launches in individual states because interstate transport of these products is illegal. This would be extremely costly (driving up product prices) and also decrease patient access to products that address unmet medical needs. To that point, most companies developing *Cannabis*-derived pharmaceuticals believe that rescheduling of these products from Schedule 1 drugs to Schedule 2 or 3 would obviate these concerns. Others contend that legalization at the federal level will be necessary for the US *Cannabis* market to grow to its full potential.

Finally, because *Cannabis*-derived pharmaceuticals represent a new class of therapeutics, patient and healthcare provider education will be vital to successfully commercialize them. Put simply, if physicians don't understand *Cannabis*-derived pharmaceuticals and are not convinced of product safety and efficacy, then, they will be reluctant to write prescriptions for these products. Nevertheless, the burgeoning popular demand for medical marijuana suggests that commercializing *Cannabis*-derived pharmaceuticals will help to address rising unmet medical needs for a variety of life-altering clinical indications including cancer, neurological disorders and chronic pain.

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Article

Venture Capitalists as Gatekeepers for Biotechnological Innovation

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ABSTRACT

Venture capitalists (VCs) aim at trade sales as a preferred exit-strategy for biotechnology companies they invest in. Therefore, VCs pay close attention to the wishes of larger (bio)pharmaceutical acquirers. In this paper we explore VCs' behavior and strategies by analyzing the technology fields and therapeutic areas in which they are invested most and which yield the highest relative returns by means of trade sales. The data show that VCs are by far most invested in oncology and this is also an area in which relatively high returns are realized. Regarding other areas, VCs could balance their average investment valuations more in correspondence with what acquirers are willing to pay. In addition, VCs have predictive insight in the types of technologies that do well and they seem to employ a strategy focused on both short-term and long-term success. They are investing most in small molecule drugs and protein/peptide therapeutics, which both yield high returns, followed by DNA/RNA technologies which underlie the possibilities of personalized medicine. We conclude that VCs act as technological gatekeepers because they are predicting long-term cure and care macro-trends.

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Keywords: venture capital; biotechnology; trade sales; innovation

INTRODUCTION

Venture Capital (VC) is the primary source of funding for biotechnology ventures, with annual VC financing of biotechnology quadrupling in ten years from $2 billion in 1999 to $8 billion in 2008.[1,2] Since this 2008 high, annual VC financing has been relatively stable at $5.5 billion.[2]

From an investor's perspective biotechnology start-ups are considered to be high-risk investments.[3] On the flipside, VC firms can reap returns of five to ten times their initial investment when portfolio companies are successful, as measured by an initial public offering (IPO) or a trade sale (i.e. acquisition).[4] In light of recent merger and acquisition (M&A) trends in the (bio)pharmaceutical industry related to innovation deficits and the productivity paradox,[5,6] most biotechnology companies are currently built with a trade sale in mind as a preferred exit.[7] Not surprisingly, venture capitalists (VCs) pay close attention to the wants and needs of larger (bio)pharmaceutical firms.[7] However, the taste of big pharma can change over time – even within the average three to five years between investment and exit. For this reason, when it comes to investment decisions and valuations, VCs rely on their own intuition and market intelligence, in addition to the declared wants and needs of big pharma.

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In a sense VCs are the drivers for technological change within a given industry, and the biotechnology industry in particular. They act as "technological gatekeepers, accelerating the process of technological change".[8] By their investment decision-making, VCs set the tone for the entire life sciences market, essentially generating the supply of innovation to big pharma and the market in general. Considering multiple factors influencing investment decisions, it is imperative for both investors and bio-entrepreneurs to gain insight in global biotechnology investment strategies. Not only for deciding whether or not to get involved in new life sciences opportunities, but also to use this information in negotiating company valuations, business planning and raising capital.

Therefore, this paper aims to distill global investment strategies of VCs by analyzing the distribution and extent of investments with respect to therapeutic areas and technology fields. Furthermore, these areas and fields are analyzed in terms of exit potential and relative returns on investment (ROI), which are based on trade sale multiples.

The aim is to explore the therapeutic areas and technology fields in which VCs are invested most and whether that corresponds to where they realize the highest relative returns. Therefore, a total of 2,639 life sciences companies receiving VC backing between 1999 and 2013 are analyzed to identify the most popular areas and fields for investment and acquisition. In addition, the average investment amounts and average trade sale transaction values are analyzed by technology field and therapeutic area of the lead product(s) to gain insights in investments and show what acquirers are willing to pay for different types of companies. Finally, the average trade sale multiples are calculated in order to evaluate relative success rates of VC investments per technology field and therapeutic area. From the results an overall investment strategy is interpreted that is useful to investors and entrepreneurs in considering their engagement in new life sciences opportunities.

METHODOLOGY

An initial dataset was developed, containing early-stage investments in life sciences ventures between 1999 and 2013 based on data extracted from ThomsonReuters' SDC Platinum VentureXpert database (official database of the National Venture Capital Association; NVCA). A total of 2,639 dataset entries were analyzed individually to determine the companies' main technology field and therapeutic area focus. Subsequently, medical technology/devices (medtech) companies and service-oriented companies were excluded from the dataset, resulting in a total of 1,217 small molecule and biotechnology ventures that received their first investment round between 1999 and 2013. Of those 212 companies were acquired later on and for these, additional data on transaction details have been gathered from the ThomsonReuters' SDC Platinum VentureXpert M&A database and news reports, to calculate the average trade sale values and multiples.

Biotechnology fields

Based on 21 exploratory interviews with VCs and literature,[9,10] a classification of technology fields is used. The categorization of individual companies is based on in-database and online company descriptions as well as companies' lead products in development. In addition, the Cooperative Patent Classification (CPC) codes were analyzed, if available and as provided by Espacenet (worldwide.espacenet.com), of respective companies' patents to verify our categorization. First medical technology (devices), small molecule drugs, and biotechnology are separated. Medical technology companies are excluded from further analysis and Biotechnology is further categorized in biotechnology fields (DNA/RNA; Proteins/peptides; Cell/tissue engineering; Gene/RNA vectors; Targeting/delivery; Bioinformatics; Nanobiotechnology; and Glycobiotechnology), depending on the technology used for the respective company's lead product(s) (Table 1). Note that some companies may focus on combinations of technologies, so the illustrated data will add up to more than 100% of actual funding.

Therapeutic areas

Based on the WHO ICD-10, literature,[7] and declared investment interests in 21 exploratory interviews with VCs, a full range of therapeutic areas is used for analysis. Again the classification of backed companies was based on their lead product(s) in development. Ultimately the 15 most invested areas are included in the analysis. Note that some companies may focus on different indications and therapeutic areas simultaneously, so the illustrated data will add up to more than 100% of actual funding.

Limitations

While our analysis aimed to be a systematic, bias-free, review of life sciences VC investments and average trade sale multiples, several limitations apply. First, our dataset is in essence a data sample as we are unable to ensure that the collection of relevant data is 100% complete. While we are confident that the large majority of early stage life sciences investments is included in our dataset, we

Table 1: Overview of Biotechnology fields

Biotechnology Field	Biotechnology Subfield
DNA/RNA Technologies	
	Genomics/pharmacogenomics
	Gene probes/DNA markers
	Genetic engineering
	DNA/RNA sequencing/ synthesis/ amplification
	RNAi/siRNA (inhibiting gene function)
	Gene expression profiling/Antisense technology
Proteins/peptides and other large molecules	
	Engineering of proteins and peptides/ recombinant proteins
	Proteomics
	(Monoclonal) Antibodies
	Subunit/VLP vaccines
	Protein isolation and purification
	Peptide/protein sequencing/ synthesis
	Signalling Analysis (of cytokines, chemokines, transcription factors, cell cycle proteins, and neurotransmitters)
Cell and tissue engineering technologies	
	Cell therapy (including Immunotherapy)
	Tissue engineering (including tissue scaffolds and biomedical engineering)
	Cellular fusion
	Embryo manipulation
Gene and RNA vector technologies	
	Gene therapy
	DNA vaccines
	Viral vectors
Drug targeting/delivery technologies	
	Proteins
	Liposomes
	Micelles/dendrimers
	Inorganic/biodegradable
	Nanostructures
Bioinformatics (ICT applications in life sciences)	
	Construction of databases on genomes
	Modelling complex biological processes (including systems biology)
Nanobiotechnology	
Glycobiotechnology	

Based on 21 exploratory interviews with venture capitalists and literature. [9,10]

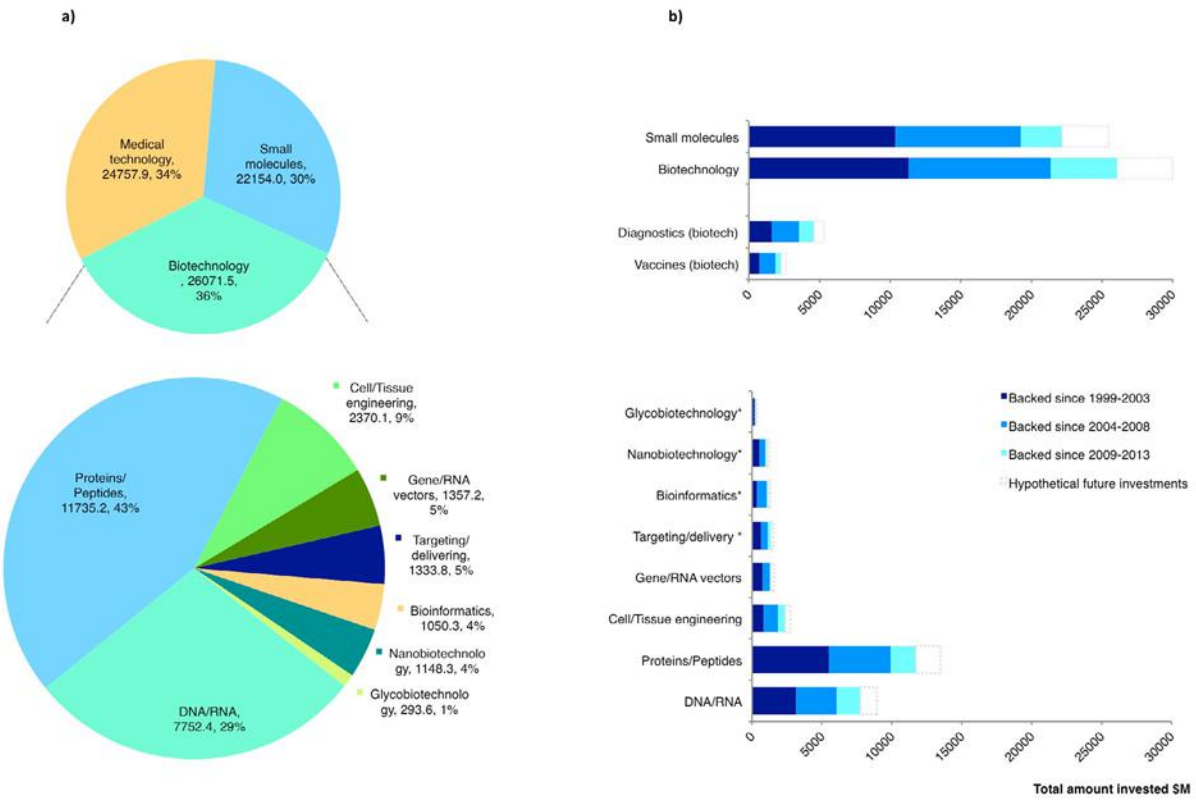

Figure 1: VC investments ($M) per technology field and per biotechnology subfield (a); and VC investments ($M) per technology field and date of first round
Note: Hypothetical future investments are included, as a subset of companies backed since 2009–2013 will most likely receive later-stage financing in the near future. For illustration purposes, an estimated 15% is added. This percentage is based on average later-stage funding of companies initially backed in previous periods.
Source: ThomsonReuters' SDC Platinum VentureXpert Database, company websites, worldwide.espacenet.com

cannot claim a 100% coverage of all deals, as the search criteria might have excluded deals that should have been included or the ThomsonReuters SDC Platinum VentureXpert database, which is based on self-reported data, might not include all existing deals. Second, the categorization process was conducted using several indicators to assess technology fields and therapeutic areas, namely lead products and programs, company websites and profiles, and CPC codes. Although two researchers conducted this process separately, some cases are still open to interpretation and for others limited information was available. Nevertheless, we are confident that most VC backed companies were categorized correctly. Third, of approximately 37% of trade sales, transaction values were not disclosed. Therefore, the average trade sale valuations as used for the analysis are also based on a sample of trade sales and we do not claim to cover 100% of all existing data. Fourth, the dataset included global data, and differences between geographic regions were not analyzed. Such differences may provide additional insights and could be an avenue of further research. Finally, this study does not aim at uncovering absolute returns for VCs in biotechnology as we focus on trade sales as successful exits and do not include losses or other gains VCs have made with their investments. Further research may attempt to reveal general results of VC investments in biotechnology. However, this paper aims at comparing general VC investments in technology fields and therapeutic areas with realized trade sale multiples in those fields and areas.

RESULTS

The majority of backed companies concerned medtech companies (965) followed by biotechnology companies (813) and small molecule drug companies (456). VC financing, however, is almost equally distributed

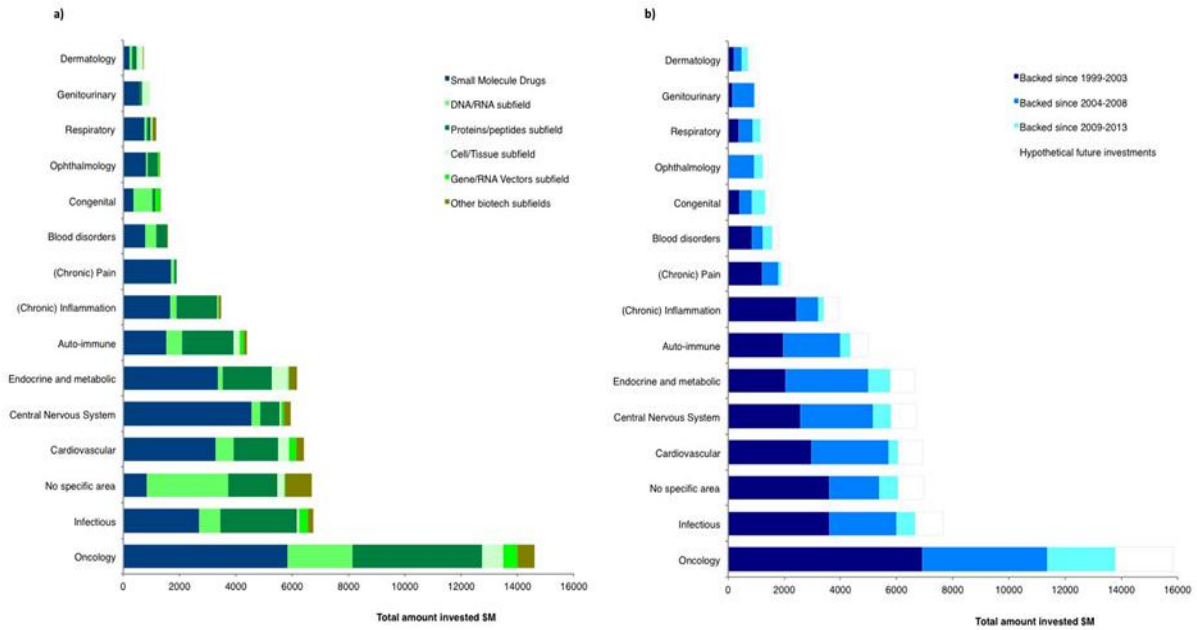

Figure 2: VC investments ($M) per therapeutic area and technology field (a); and VC investments ($M) per therapeutic area and date of first round (b)
Note: Hypothetical future investments are included, as a subset of companies backed since 2009–2013 will most likely receive later-stage financing in the near future. For illustration purposes, an estimated 15% is added. This percentage is based on average later-stage funding of companies initially backed in previous periods.
Source: ThomsonReuters' SDC Platinum VentureXpert Database, company websites

over these three fields of technology, with biotechnology taking the upper hand (36%). Thus, small molecule drug companies receive the highest average investment per company ($48.6 million), followed by biotechnology companies ($32 million) and medtech companies ($25.7 million). The total amount of $26 billion invested in biotechnology is distributed among several biotechnology fields as specified in Table 1.

Technology fields

As shown in Figure 1, almost half (43%) of VC investments in biotechnology has been invested in companies focusing on proteins/peptides, which include products and technologies such as recombinant proteins, monoclonal antibodies, recombinant subunit and virus like particle (VLP) vaccines, peptide therapeutics, engineered enzymes, and proteomics. Subsequently, 29% has been invested in DNA/RNA technologies mainly involving genomics and pharmacogenomics; gene probes and DNA markers; sequencing, synthesis and amplification of DNA/RNA, RNAi and siRNA gene regulation therapeutics; and gene profiling and antisense technology. Following these two subfields, which are undoubtedly most popular, 9% of VC financing of biotechnology companies involved cell/tissue engineering technologies, which include (stem) cell therapy (immunotherapy); tissue engineering; cellular fusion and embryo manipulation. Thereafter, 5% concerned gene/RNA vector technologies, involving gene therapy; vector vaccines and DNA vaccines. Another 5% has been invested in drug targeting and delivery (encapsulation) technologies using proteins; liposomes; micelles/dendrimers; inorganic, biodegradable structures; and nanostructures. As such there is overlap with nanobiotechnology, in which 4% of VC biotechnology funds has been invested. The remaining 5% was invested in bioinformatics (4%), involving IT as a basis for new diagnostics and therapeutics; and glycobiotechnology (1%), which involves the synthesis of glycolipids and glycoproteins. Moreover, 21% of backed biotechnology companies focused on molecular diagnostics technologies, mostly within the subfield of DNA/RNA. In total $4,6 billion has been invested in biotechnology related diagnostics companies (Figure 1).

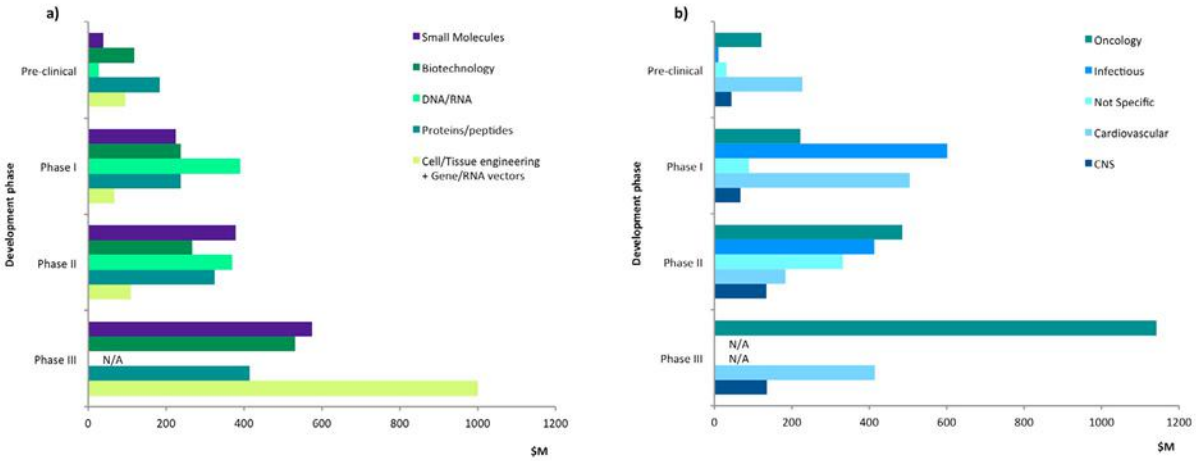

Figure 3: Average trade sale prices ($M) per therapeutic area (a) and per technology field (b), for each phase in clinical development
Source: ThomsonReuters' SDC Platinum VentureXpert and M&A Databases, company websites, clinicaltrials.gov

Therapeutic areas

Figure 2 shows that 29% ($13.8 billion) of all small molecule and biotechnology investments have been in companies that focused on oncology, making it by far the most invested therapeutic area (Figure 2). The following five most invested areas are infectious diseases ($6.7 billion), platform technologies, defined as 'no specific area' ($6 billion), cardiovascular diseases ($6 billion), central nervous system (CNS) indications ($5.8 billion), and endocrine and metabolic diseases ($5.8 billion).

Not surprisingly, small molecule drugs are mostly invested in when targeted on a specific disease area and not often when developed as platforms (Figure 2a). They are mostly focused on CNS, pain, oncology, endocrine and metabolic diseases, and cardiovascular diseases. However, it seems that different biotechnology subfields are used for a wide variety of therapeutic areas (Figure 2a). Proteins/peptides are developed mostly for treating oncology, infectious diseases, inflammation, auto-immune diseases, and endocrine and metabolic diseases, while DNA/RNA includes many discovery and diagnostics technologies, which seem to be mainly developed for oncology, platforms, and for congenital diseases. Furthermore, cell therapy and cell/tissue engineering is used most for oncology and endocrine and metabolic diseases, while gene therapy and vectors are mainly focused on oncology, infectious diseases, cardiovascular diseases, and auto-immune diseases. This data seem quite accurate considering advances such as immune cell modifications (cell therapy/immunotherapy) to treat cancer and the use of vector- and DNA vaccines for infectious diseases.[11, 12, 13]

Trade Sales

As IPOs and more so trade sales are the most important denominators for success from an investor's perspective the dataset includes which companies went public and which ones have been acquired. Of the 1,217 small molecule and biotechnology companies backed between 1999 and 2013, 212 have been acquired and 132 went public. Of those that were acquired, subsequent data was collected on the transaction values, if disclosed, and the clinical development phase of the respective company's lead product. This data was collected from ThomsonReuters' SDC Platinum M&A database (thomsonreuters.com/sdc-platinum), clinicaltrials.gov, company websites and additional webscraping of business websites (e.g. businessweek.com). Average trade sale transaction values are plotted per development phase for different therapeutic areas and technology fields (Figure 3).

The average trade sale valuations of companies in different development phases vary amongst therapeutic areas and technology fields, suggesting different risk profiles. Strikingly, trade sale valuations of oncology focused companies increase substantially with each development phase, whereas those of cardiovascular diseases or CNS show different patterns. In figure 3b, the complexity of newer technology fields (e.g. cell therapy and gene therapy) is represented by relatively low trade sale valuations of such companies up until phase III clinical trials. Yet, when phase III is reached, the value of such companies increases substantially, illustrated by the acquisition of Biovex by Amgen in 2011. Small molecule drugs, however, as a more classical technology field, show a more predictable and stable path as average trade sale

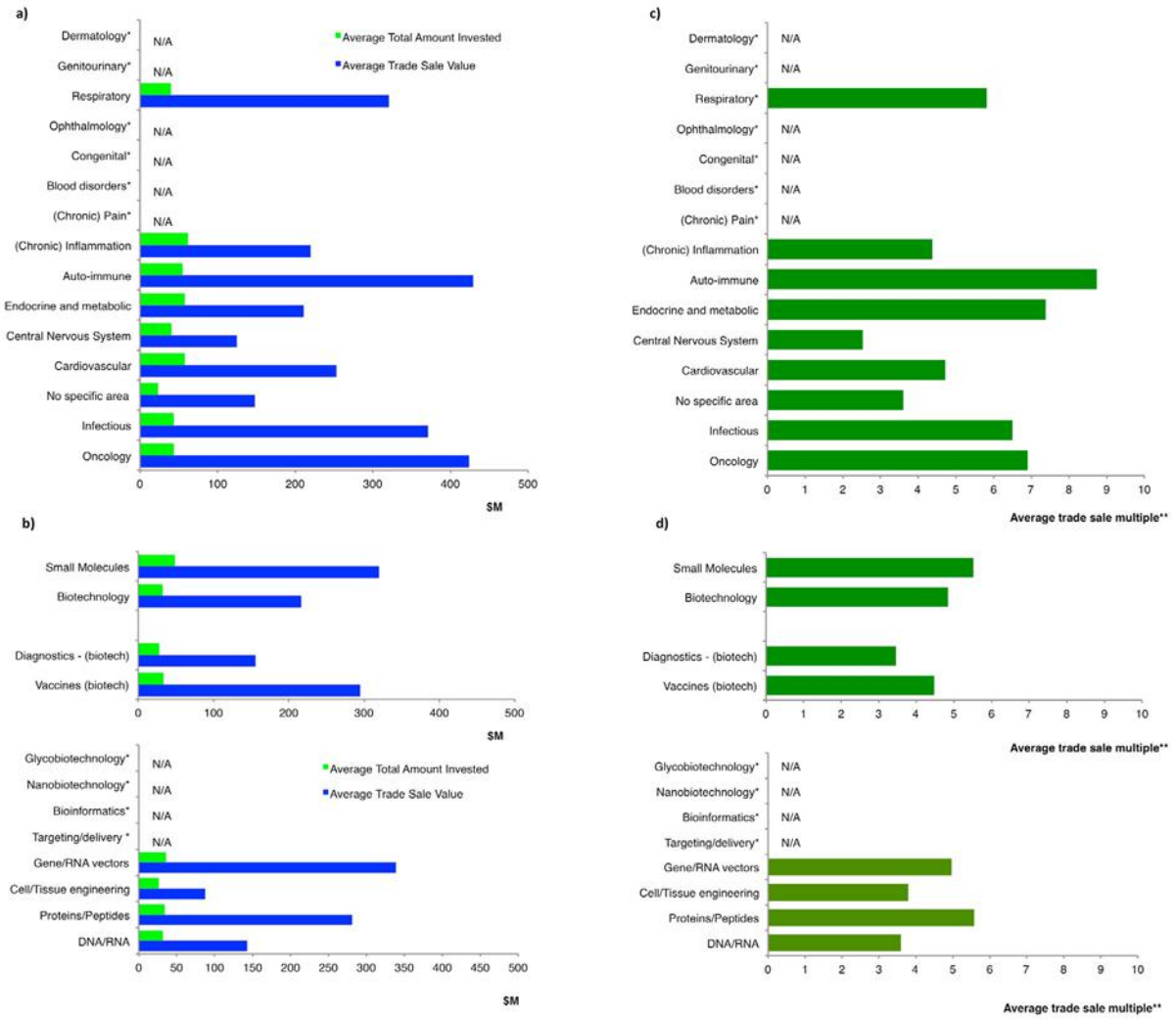

Figure 4: Average trade sale price ($M) and average total investment amount ($M) per therapeutic area (a) and per technology field (b); and average trade sale multiples per therapeutic area (c) and per technology field (d)
** Too few or no trade sales to calculate appropriate average (N/A).*
*** Trade sale multiple = (Trade sale value)/(Total amount invested in acquired company).*
Source: ThomsonReuters' SDC Platinum VentureXpert and M&A Databases

valuations of small molecule drug companies increase more gradually with each development phase. The same holds true for proteins/peptides.

Deal values and Multiples

Arguably, there are various ways to evaluate the success of individual investments and of investments over categories. In order to review patterns between where VCs invest the most and where they earn the most, the average trade sale values and the average total amounts invested in companies are evaluated per therapeutic area (Figure 4a) and technology field (Figure 4b). In addition, for the VC backed companies in our dataset that have been acquired, the trade sale multiple was calculated for each individual acquisition to determine the average trade sale multiples, again per therapeutic area (Figure 4c) and technology field (Figure 4d).

As shown in Figure 4a, average trade sale transaction values are highest for auto-immune diseases ($430 million) and oncology ($424 million), followed by infectious diseases ($371 million). Interestingly, this top three of therapeutic areas for acquirers is different from the top three areas based on average VC investment values. Per company VCs have invested most, on average, in (chronic) inflammation ($62 million), endocrine and metabolic diseases ($58 million), and cardiovascular

diseases ($58 million). Auto-immune diseases comes fourth for VCs with an average total investment amount per company of $55 million, while it seems to be the first area for acquirers. Moreover, average trade sale transaction values for different therapeutic areas seem to have a much wider range (from $125 million to $430 million) than the average total VC investments per therapeutic area ($40 million for CNS to $62 million for inflammation).

The average multiples, however, are highest for auto-immune diseases (8.7), endocrine and metabolic diseases (7.4), oncology (6.9), and infectious diseases (6.5). Of these the first two are also in the top four of areas that receive the highest average investments from VCs. The second highest multiple has been realized in endocrine and metabolic diseases, while the difference between average VC investment and average trade sale value for this area is not very large ($58 million versus $211 million). This suggests that the successful exits have come from relatively lower investments in this area. For all other areas, the average trade sale multiples are quite consistent with the average trade sale values, confirming little differentiation of average VC investments with regards to therapeutic areas.

For the technology fields, an overall difference in average VC investments is shown between biotechnology ($32 million) and small molecule drugs ($49 million). The biotechnology subfields subsequently range between $26 million for cell/tissue engineering to $36 million for gene/RNA vectors, with $32 million for DNA/RNA and $34 million for proteins/peptides in between. This suggests that VCs undoubtedly expect most from the technology field of small molecule drugs, especially when also considering the total amount invested in this field (30% of all funds; Figure 1). Although high expectations for this field are justified by the corresponding average trade sale value ($320 million) and multiple (5.5), similar trade sale multiples have been realized for the biotechnology subfields proteins/peptides ($282 million; 5.6) and gene/RNA vectors ($339 million; 5.0). The average trade sale values for the subfields DNA/RNA and cell/tissue engineering are much lower ($143 million and $87 million respectively). However, the average multiples for these fields are relatively close (3.6 and 3.8), suggesting that the successful trade sales resulted from relatively lower investments in these fields. This is especially true for the DNA/RNA subfield, considering the average VC investments in this field ($32 million), which is the same as the average for the entire biotechnology field. Moreover, the total amount invested in DNA/RNA technologies is high (29% of all biotechnology investments) relative to what big pharma is willing to pay for these technologies. This suggests a notable interest of VCs in the DNA/RNA technology subfield.

The average multiples in the technology fields as shown in Figure 4d show less variation (4–6) than those in the therapeutic areas (3–9; Figure 4c). VCs, thus, seem to be better at anticipating returns within technology fields and adjusting their investment allocation accordingly, than doing the same for the various therapeutic areas.

CONCLUSIONS

We conclude that VCs act as technological gatekeepers because they are predicting long-term cure and care macro-trends. They have predictive insight in the types of technologies that do well. However, in terms of therapeutic areas, VCs can balance their average investment valuations more in correspondence with what big pharma is willing to pay. We set out to distill global investment strategies of VCs by analyzing the distribution and extent of investments with respect to technology fields and therapeutic areas. It seems that VCs employ a strategy focused on both short-term and long-term success. On the one hand they play it safe, minimizing risk by investing most in small molecules and proteins. On the other hand, they are investing heavily in DNA/RNA technologies, which as a field seem to be underperforming (Figure 4b, 4d). As VCs and bio-entrepreneurs build for big pharma, the blockbuster business model directly affects new venture financing by VCs for the short term. However, VCs are also rebelliously investing for long-term cure and care macro-trends, as they invest in biotechnologies that underlie the possibilities of personalized medicine.

For therapeutic areas, a discrepancy between variation in average VC investment amounts and variation of average trade sale transaction values is illustrated by an imbalance in average multiples (3–9). Acquirers seem to attach greater importance to differentiating between therapeutic areas than VCs do, resulting in unnecessary overinvestment in one area versus potential underinvestment in another. As VCs are essentially building for big pharma,[7] they, their investors and bio-entrepreneurs would benefit from a portfolio balanced more in correspondence with what pharma is willing to pay. Doing this can in turn lead to more predictability and consistency of average multiples over the therapeutic areas. However, success ratios between therapeutic areas may be more susceptible to rapid changes than technology fields, making prediction difficult. Many VCs might therefore be investing quite opportunistically with less distinction per therapeutic area.

With regards to technology fields, there seems to be a macro investment strategy that appears to focus both on short-term and long-term success. For the short-term, VCs are investing heavily in small molecule drug

companies with a relatively higher average investment valuation. In addition, within biotechnology they are investing most in the proteins/peptides subfield (43% of all biotechnology investments), while keeping their average investments relatively low. This conservative risk-averse strategy corresponds with pharma's blockbuster business model as small molecules and proteins/peptides are the only type of products that can become blockbusters (in the form of new molecular entities and biologicals).[14] This strategy has resulted in average multiples of around 5.5 for both these technology fields. However, VCs have invested less in the gene/RNA vectors field, while there have been some tremendous recent successes in this field.

In addition to the conservative investment strategy tailored to pharma's business model, VCs have also invested a large proportion (29%) of biotechnology funds in the DNA/RNA technology field. The DNA/RNA field includes the technologies required for realizing the potential of personalized medicine, which has been claimed to be the future of medicine, promising to significantly increase the quality of healthcare.[15,16,17] Here, we find evidence that despite the low average multiple and average trade sale valuation for this field, VCs are embracing their role as technological gatekeepers.[8] They are investing in this field and thereby the future, while a proven business model for personalized medicine that could be equally lucrative as the blockbuster model is still lacking now.

For other investors and VCs with less experience investing in life sciences, a similar investment strategy is recommended. Moreover, we believe it to be wise to evaluate the therapeutic areas new ventures are focusing on, with respect to both an appropriate match with technology types and relative ROI rates. It is however noteworthy that VCs evaluate companies on a case-by-case basis and employ strict criteria for their investments (e.g. competition, regulations, reimbursement, management team, financials) irrespective of therapeutic areas or technology fields. Notwithstanding, oncology, infectious diseases and auto-immune diseases seem to be the most interesting therapeutic areas to invest in, considering investment amounts, average trade sale valuations and average multiples.

In the current investment climate, bio-entrepreneurs can increase chances of being funded by combining a focus on radical innovation within technology fields with blockbuster potential with a focus on therapeutic areas where investors can realize relatively high multiples. When developing technologies underlying personalized medicine and diagnostics, where the blockbuster model is not applicable, it is imperative that entrepreneurs focus on business models for generating income during (early) development stages, ensuring survival whilst cure and care macro-trends continue towards a personalized and patient-centered approach.

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From the Board Room

BioTime's bid to end age-related disease: A look at CEO Michael West's Vision

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ABSTRACT

The regenerative medicine space is one that is set to explode with considerable innovation and profitability for shrewd biotechnologists. I had the opportunity to speak with Michael West, PhD., CEO of BioTime (BTX) and found a man passionate about regenerative medicine and of course passionate about his role in its future. In this conversation I learned of West's vision, which I think provides some powerful clues as to areas of future growth in the biotech sector. He points to three scientific advances that make this vision actualizable. First, sequencing technology that allows us to perform RNA sequencing for around 300 dollars or less, second the common and reversible molecular basis for age-related diseases, and finally industrial scaling of pure cell lines like the ones manufactured by BTX. Let's look at the three enabling technologies that West touched on and examine how they are being utilized to achieve West's vision within BTX and others involved in the anti-aging revolution.

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Keywords: BioTime; corporate vision; anti-aging; longevity

Michael West's BioTime (BTX) is born of his initial passion for treating age-related disease that he feels companies like Geron lost; he was a founder of GRN and CEO at Advanced Cell Technology (ACTC) before BTX.[1] "It's going to be an exciting next 5 years," he says, speaking about his company, its growth potential and the field of regenerative medicine. For Dr. West, BTX is another company with the same aim as his first (Geron) which is a passion for restoring youth to the elderly by focusing on aging and age related disease. "My vision," West states, "was that there ought to be a company that focused uniquely on the challenges of age-related disease." Geron strayed from his vision, West claims, and it was one of the reasons he parted ways with the company he founded in 1990 after 8 years. "The vision is to find some of the most strategic areas that we can apply our modern understanding of aging and regenerative medicine and use it to repair chronic degenerative diseases for which medicines are ineffective." This vision is solidified in three biotechnological advances; low cost sequencing, molecular mechanism reversal and cell line scalability.

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LOW COST SEQUENCING AND BIG DATA

The cost of DNA and RNA sequencing has decreased dramatically in the past 20 years. "We used to sequence DNA using Maxam-Gilbert sequencing doing 300 base pairs at a time; taking a week or more," says West. Two advances, one by Sanger, whereby DNA could be determined via chain-terminating inhibitors,[2] and one by Allan Maxam and Walter Gilbert, via a chemical degradation of specific bases,[3] would allow the first DNA genome, of a virus, to be sequenced in 1977. "Can you imagine how many millennia it would take to sequence every RNA in a cell (using this method)?" he asks. In the next decade rapid advancements would allow for the first semi-automated DNA sequencing machines to be produced.[3] Further advances by Craig Venter at The Institute for Genomic Research, now the J. Craig Venter institute, lead to the first genome of a bacterium,[4,5] marking the first use of the shotgun sequencing approach that Venter and the Human Genome project would use to map the human genome. The revolutions in genome sequencing

led to the so-called 'next-generation' approaches that are now numbering in the dozens of proprietary methods; with names like massively parallel signature, Ion Torrent semiconductor and DNA nanoball sequencing, that have brought the price of sequencing down toward several hundred dollars in the past couple years.[6] From West's vantage, these are the powerful tools that "far surpass what was present 15 to 20 years ago," and make his vision of an anti-aging revolution defensible. In the early 1990s at GRN, West's bioinformatics team began looking for pan-cancer markers, and found telomerase, which became the poster technology for the company for over a decade and a half. "It's expressed abnormally in over 90% of human cancers," said West. And with BTX, using updated sequencing technology, he has been looking for more pan-cancer markers. "We had some of the same scientists on this bioinformatics team," West told me, "They found collagen 10 (collagen 10 alpha 1; CAL10A1). This is a small collagen variant that's involved in the transition of cartilage to bone." CAL10A1 is found in the growth plates; lines of hypertrophic cartilage at the end of long bones, and in the bone callus, "but its silent elsewhere in the body." Except that it is produced by the stromal tissue in a high percentage of cancer. "It is one of the markers in what we call PanC-Dx," says West, developed by BioTime and subsidiary Oncocyte for the detection of various human cancers. "I haven't calculated the percentage but its somewhere near 90% anyway." The use of sequencing technologies to aid in cancer diagnosis has facilitated rapid advancement for these technologies and regenerative medicine will ultimately capitalize on these advances to treat other age-related diseases as well. The wise investor might use this knowledge to seek out early stage and publicly traded companies investing in the growth of these technologies.

REVERSIBLE MOLECULAR MECHANISMS

West believes that diseases are biological processes that can be reversed or exacerbated by genetic changes. "Nature tells us that age-related degenerative diseases have reverse mechanisms behind it," he says, "as evidenced by diseases like Progeria and Werner's syndrome, where you have these single nucleotide changes leading to osteoporosis, grey hair, cataracts, type-2 diabetes, and coronary disease." These molecular changes, West believes, share a common molecular basis that if understood could be harnessed to reverse some of the signs and disease associated with aging or perhaps even prevent them from occurring. West believes that his company can be of practical utility is aiding healthy human aging through its recently acquired OpRegen Technology and another product, which is beginning clinical trials in Israel under the BTX subsidiary; Cell Cure Neurosciences, also funded by Israeli based Teva Pharmaceutical, to counteract both forms of acute macular degeneration (AMD) through reimplanting retinal pigment epithelial cells (RPE cells).[7] "When you lose the RPE cell you can't support the neuro retina," West says. This leads to a spreading plaque of neurodegeneration known as the dry form of AMD, "You can watch these patches grow like a grass fire," he says. His solution is to bring in new RPE cells derived from pure multipotent progenitors. The wet form of AMD is the only treatable form today, accounting for only 10% of AMD and it is treated via needle injections of angiogenic inhibitors to the eye. "They dry form," says West, "arguably would be a bigger market than the 5 to 7 billion dollar market for the wet form." By incorporating new RPE cells in the area of the neural retina, BTX is hoping to reverse the molecular mechanisms responsible for this age-related disease, increasing BTX profits but reducing the overall cost of aging. In general, companies focused on the reversible molecular mechanisms of disease will discover profitable new therapeutic.

SCALABLE STEM CELL LINES

The third component in West's assault against aging comes in the form of his so called PureStem technology, currently used by BTX subsidiaries Orthocyte and Recyte. "We've got over 200 distinct human cell types in a directly scalable clonally pure form in this PureStem template," West says. His subsidiaries are focused on bringing these products to market, with Orthocyte focused on reversing joint and skeleton degeneration, and Recyte focused on providing vasculature progenitors for ischemic disease. "The really blockbuster thing," West says is their scalable progenitors to brown fat. "It is dramatically lost with age. We can make that in scalable pure manner as well." With the baby boom and surge in aging in many developed countries, West thinks that regeneration of brown fat is "going to be the largest single opportunity in regenerative medicine." Researchers have determined that brown fat is the adipose tissue that burns other fat and West and his BTX team have described their clonally pure progenitors in recent meetings. Discovered in the last five years, brown fat has been shown to produce mitogens for the beta cell call betatrophin and other adipokines; cytokines produced by fat.[8,9] In a clinical trial underway in Europe, West hopes to establish that fat can be reincorporated into the elderly and show the utility of the BTX's Hystem matrix injection system,

paving the way for future injectable cell therapies meant to combat aging. He thinks that these off-the-shelf cell lines will become more and more useful in the treatment of age related disease. What is certain however, is that the mass production of cell lines focused on the production of factors necessary to treat age-related disease will play an increasingly important role in therapeutics.

Through BTX, West hopes to consolidate biotechnology under one company to defeat aging. "The vision," he says, "is to find some of the most strategic areas that we can apply our modern understanding of aging and regenerative medicine and use it to repair chronic degenerative diseases for which medicines are ineffective." Describing BTX's recently aggressive tactics in acquisitions West says, "we wanted a commanding position in intellectual property." To that end, BTX and its subsidiaries have accumulated over six hundred patents and patent applications worldwide, including all of GRN's stem cell assets, the licensing of assets from ACT, and Singapore's ES Cell International (ESI). And West suggests that in the next five to seven years BTX will be filing patents related to the 200 clonal progenitors represented by its PureStem technology. "The goal of the company," he says, "is to be the leading source of young healthy cells to replace cells like the degenerating RPE in the back of the retina." With technical advances in sequencing technology, leading to new molecular clues to the deleterious effects of aging, West and his team intend to target disease using injectable scaffolds of pure progenitor cells to correct these defects in the elderly and he is hoping that public investors in BTX will help him do it. Primarily West's focus is to build an umbrella company with investments in multiple scientific advancements. This 'de-risking' strategy will be advantageous in keeping his group of companies profitable.

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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 companies on the full spectrum of legal and commercial issues affecting the industry:

- IP licensing & transactions
- R&D collaborations
  - Technology transfers
  - Clinical trials
- Patent & trade mark litigation
- Regulatory issues
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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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ORGANISMS NOT CAPABLE OF DEVELOPING INTO A HUMAN BEING ARE NOT HUMAN EMBRYOS

Rachel Fetches and Toby Sears, London

On 18 December 2014, the Court of Justice of the European Union (CJEU) handed down its judgment holding that an organism that was incapable of developing into a human being did not constitute a human embryo within the meaning of Directive 98/44/EC (Case C-364/13).[1] The CJEU observed that the purpose of the Directive was to regulate patentability of biotechnological inventions and not to regulate research and use of human embryos. It was a matter for the English Court to determine if human parthenotes had the inherent capacity to develop into a human being but if they did not, then they would not be a human embryo within the meaning of the Directive. Any such an organism used for industrial or commercial purposes would in principle be capable of being patented. This Judgment adopted the Opinion delivered by Advocate General Cruz Villalón on 17 July 2014 (previously reported in the January 2015 edition of the Journal of Commercial Biotechnology).

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1 Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions (OJ 1998 L 213, p. 13).

Background

In April 2013, the English High Court referred a question to the CJEU on the interpretation of Article 6(2)(c) of the Directive. The question asked whether a parthenote, which only contained pluripotent and not totipotent cells and was therefore incapable of developing into a human being, was included in the term "human embryo" under Article 6(2)(c) of the Directive. This arose from the application by International Stem Cell Corporation ("ISC") for a patent claiming methods of producing pluripotent human stem cells from parthenogenetically-activated oocytes and stem cell lines produced according to the methods and another patent claiming methods of producing synthetic corneal or corneal tissue from such pluripotent stem cells. ISC argued that the parthenotes were unable to develop into a human embryo because of genomic imprinting, although ISC acknowledged that this might be possible through extensive genetic manipulation and had amended the claims to exclude such a possibility.

Judgment

In *Brüstle* (Case C-34/10) the CJEU held that a 'human embryo' included "non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis" as they were "capable of commencing the process of development of a human being just as an embryo created by fertilisation of an ovum can do so." The CJEU noted that whereas in *Brüstle,* written observations presented to the Court stated that parthenotes did have the capacity to develop into a human being, none of the interested parties (which included a number of observations from Member States) in this case disputed that this was not correct according to current scientific knowledge.

The CJEU agreed with A-G Cruz Villalón's Opinion that in order to be classified as a 'human embryo,' a non-fertilised human ovum "must necessarily have the inherent capacity of developing into a human being." Therefore, if an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis did not, in itself, have the inherent capacity of developing into a human being, it would not constitute a 'human embryo' under the Directive.

The case will now come back before the English High Court who will consider the application of the CJEU's Judgment to ISC's patent applications.

NEW POLICY ON PUBLICATION OF CLINICAL DATA FOR MEDICINAL PRODUCTS FOR HUMAN USE

Maria-Paz Martens and Nicolas Carbonnelle, Brussels

In October 2014, a new policy on publication of clinical data for medicinal products for human use was unanimously approved by the management board of the EMA. The adoption of this policy forms an important milestone in the on-going debate on access to clinical research, data sharing and transparency.

Introduction

The new policy governs publication of clinical trial data for medicines that have received a Marketing Authorization (MA) under the centralized procedure as from 1 January 2015. Indeed, applicants for a MA routinely submit such data, composed of clinical reports and Individual Patient Data (IPD) to the EMA under the centralized marketing authorization procedure.

The new policy clarifies the extent to which the EMA will proactively publish these data and under what conditions. It deals with the main concerns relating to the concept of Commercial Confidential Information (CCI) and the protection from unfair commercial use, protecting patient confidentiality as well as the concept of raw data.

This policy is without prejudice to Regulation No 1049/2001 regarding public access to documents. The result of this is that any natural or legal person may continue to submit a request for access to documents to the EMA independently of the proactive publication mechanism established in this new EMA policy.

Importantly, the EMA developed this policy in the absence of any specific legal provision mandating that the EMA must publish such data. Hereby taking into account the views and concerns of a broad range of stakeholders (including patients, healthcare professionals, pharmaceutical industry representatives, researchers, transparency campaigners, academic and public institutions, health technology assessment bodies, and national medicines regulators) and European bodies, who all contributed actively to the development of this new policy.

Scope of the new policy

The EMA's new policy will only cover clinical data of new MA applications and Article 58 applications of Regulation (EC) No 726/2004 (medicines that are intended exclusively for markets outside the European Union) submitted to the EMA after 1 January 2015 and does not apply to clinical data that the EMA holds for applications received under the centralized procedure before that date.

For post-authorization procedures for existing centrally authorized medicinal products, the effective date will be 1 July 2015 for extension of indication and line extension applications that have been submitted as of that date.

Therefore, according to this policy, data will only start to become accessible once the final decision on a given procedure has been reached by the European Commission, which implies a timeframe of approximately 18 months.

Main features of the new policy

In accordance with the policy, the EMA will provide access to clinical reports primarily redacted by the Marketing Authorization Holder (MAH). In limited circumstances these reports may be redacted prior to publication, the objective being a publication of the documents around the time of the Commission decision granting or refusing the MA/post-authorization submission outcome.

The redaction mechanism foresees that the reports may only be subject to redaction when needed to protect specific elements which qualify as CCI. The EMA will have the final say in case of disagreement on what will be redacted, following a consultation with the MAH. Importantly, the new policy provides an extended list of documents potentially containing CCI for partial redaction.

The policy is accompanied by newly developed Terms of Use (ToU) and access rules. The Annexes of the policy contain (i) copies of the ToU, (ii) details of information contained in clinical reports that may be CCI and (iii) the process for publishing clinical reports.

Two sets of ToU are available depending on the intended use of the information contained in the clinical reports:

- Any user may have view-only access to the clinical reports for general information purposes (non-commercial, including non-commercial research purposes) following a simple and limited registration process; or
- Formally identified users to the EMA may download clinical reports solely for academic and non-commercial research purposes. These data may not be used to support a MA application or extensions or variations to a MA nor to make any unfair commercial use of the clinical reports.

A Q&A document was published together with the final policy.

Stepwise implementation of the new policy

The first stage of implementing the new policy will involve the publication of clinical data relating to clinical reports only. There will be no access to so called raw data. This will however, be reviewed by the EMA in a second phase in which various aspects in relation to IPD, including finding the most appropriate way to make IPD available in compliance with privacy and data protection laws, will be analyzed.

EU data protection regulators clarify scope of 'health data' and champion explicit consent for data processing in the context of scientific research.

Frank Simons, the Netherlands

While medical researchers find innovative ways[2] to gain valuable insights from large amounts of medical data, European data protection regulators have clarified their views[3] on the scope of the definition of personal health data and on the processing thereof in the context of historical, statistical and scientific research.

The regulators – unified in the Article 29 Working Party (the "Working Party") – wrote[4] to the European

2 http://www.bbc.co.uk/news/science-environment-31166170.

3 The Article 29 Data Protection Working Party's criteria for health data may be found at: http://ec.europa.eu/justice/data-protection/article-29/documentation/other-document/files/2015/20150205_letter_art29wp_ec_health_data_after_plenary_annex_en.pdf.

4 A copy of the letter is available at: http://ec.europa.eu/justice/data-protection/article-29/documentation/

Commission in reaction to a recent Commission consultation[5] concerning mobile health (mHealth) devices and apps, but their views have wider implications.

Health data

Pointing to the proposed definition in the draft EU Data Protection Regulation,[6] the Working Party explains that 'health data' in the context of data protection regulation is a much broader term than 'medical data'. In the Working Party's view, 'health data' includes *inter alia* 'information derived from the testing or examination of a body part or bodily substance, including biological samples' and any information about 'disease risk' and about 'the actual physiological or biomedical state of the data subject independent of its source.'

For data to qualify as 'health data,' it need not necessarily relate to 'ill health.' Whether data about a person's physiological or biomedical state is within the 'healthy' limit or not is not relevant. Moreover, in the Working Party's view, even personal data not directly related to a person's health may qualify as health data if processed with the purpose of identifying disease risks - for example as part of big data analysis of exercise habits or diet.

The broad definition of 'health data' championed by the Working Party implies that data being processed in the context of life sciences research may unexpectedly qualify as personal health data in the eyes of data protection regulators, and be subject to a stricter than usual data protection regime.

Explicit consent

In particular, the requirement for explicit consent from the data subject, commonly required for processing of health data outside the scope of the provision of healthcare to patients, may become of particular relevance in a research context.

Whereas the current EU Data Protection framework allows national legislators and regulators relative flexibility in applying a lighter regime for further processing of personal data for historical, statistical and scientific research purposes, the European Parliament has proposed to amend the new draft EU Data Protection Regulation with a strict consent requirement for such processing.

The Working Party now calls for this strict consent requirement to be also applied under the current regulatory framework for the further processing of personal health data for research purposes. In this regard the Working Party specifically expresses its concern about the introduction of the notion of a lighter data protection regime for pseudonymised data. According to the Working Party, the use of pseudonymised data is, in itself, not sufficient to justify a lighter regime.

Whether the Commission will respond to the Working Party's call, and whether the European Parliament's proposal will be included in the Data Protection Regulation is uncertain. It is clear, however, that the use of personal health data, including in the context of historical, statistical and scientific research, is on the agenda of data protection regulators.

other-document/files/2015/20150205_letter_art29wp_ec_health_data_after_plenary_en.pdf.

5 See: http://ec.europa.eu/digital-agenda/en/public-consultation-green-paper-mobile-health.

6 A copy of the draft regulation may be accessed here: http://ec.europa.eu/justice/newsroom/data-protection/news/120125_en.htm.

Conference Report

Innovation Landscape, Deal-making Strategies and Success Stories

Vasu Pestonjamasp

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The Licensing Executives Society (LES) held its 2015 Spring Meeting at the Hilton La Jolla Torrey Pines Hotel in La Jolla, CA (May 12-14, 2015).

As described on the web site of LES, "LES (USA & Canada) represents a highly diverse community of nearly 4,000 IP, business development and technology professionals that collaborate across multiple industries to create a unique networking and learning environment." Further information on LES is available at: http://www.lesusacanada.org

The Spring Meeting was attended by more than 200 professionals that represented companies, academic institutions, law firms and service providers. The event featured various panel discussions and workshops. Some highlights are provided below.

Mr. Mark Edwards (Managing Director, Bioscience Advisors Inc.) presented a Life Sciences Workshop entitled, "Re-emergence of Platform Technologies -- Gonna Party Like It's 1999." Mr. Edwards used the term "biotech" to refer to a biotechnology company and mentioned that a total of 150 biotechs have gone public in USA during the period of January 2013 through April 2015 (with 51 in 2013; 82 in 2014 and 17 in 2015; so far). The presentation also provided a recap of the 2000 biotech initial public offering (IPO) window. Mr. Edwards quoted a resource that reported that "biotech companies raised more money in 2000 than they had in the previous six years combined (A Superlative Year, Signalsmag.com 1/01)." The biotech public offerings in 2000 amounted to a total of $18.5 billon, and this topped all the public offerings in the previous 8 years (1992-1999) combined. Mr. Edwards noted that "the majority (almost 60 percent) [of 2000 Biotech IPOs]" were "platform companies rather than product companies" "(2000 IPOs Lead the M&A Charge, Signalsmag.com 8/01)." Thus platform technologies dominated the financing in 2000. Among these, 58% of the IPO biotechs were involved in genomics, proteomics/SNPs, genetics and combinatorial chemistry technologies whereas only 29% of the IPO biotechs had already developed clinical-stage drug candidates as of their IPO event. Mr. Edwards pointed out that by mid-August 2000, biotech genomic stocks were trading, on average, 99% above their IPO prices, and more than a few had tripled in value. At the end of December 2000, more than 50 public biotechs had market caps of at least $1 billion, and 20 biotechs raised over $200 million in a single financing. The options available to several biotechs were many; including construction of a manufacturing plant, expansion of clinical trials, recruitment of sales and marketing staff, or engagement in M&A.

However, the financing climate changed suddenly in 2001. As Mr. Edwards discussed, companies built on technology platforms were deemed to be not viable as businesses over the long term. Mr. Edward's presentation noted a resource at that time advised that "These companies are either going to have to acquire more like technology to enhance their share of the discovery platform or they're going to have to become drug discovery companies themselves by adding other capabilities." (Stelios Papadopoulos, SG Cowen, 8/01)."

In contrast with 2000, by July 31, 2001 the stocks of the 2000 IPO biotechs had begun trading on average, 30% below their closing prices at year-end; underperforming the market. Further, by July of 2002, the stocks of the 2000 IPO biotechs were trading, on average, 59% below their IPO prices. In July 2002, the aggregate market cap of the 2000 IPO biotechs plummeted to 51% of IPO valuations. Almost 50% of the biotechs that went IPO in 2000 got involved in M&A in 2001, and biotechs formed over 1,100 new alliances (with big pharma or other biotechs). However, in 2002, restructuring moves were initiated by some biotechs to protect cash; some publicly traded biotechs received warnings or delisting notices, and some other public biotechs filed for bankruptcy or liquidation. On the other hand, some of the best outcomes of the 2000 IPO companies have been InterMune (acquired

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by Roche for $8.3 billion); Ista Pharmaceuticals (bought by Bausch for $500 million) and Third Wave (a platform company; acquired by Hologic for $580 million). The period of 1999 to 2003 saw that key alliances provided sustainability & momentum. For example, about $2 billion were reported in aggregate payments with $82 million average, and 8.3% average effective royalty rate. On the other hand, 8 bankruptcies & liquidations and 16 firesale acquisitions were reported; the latter amounting to exit at less than 50% of IPO market cap. These transactions included genomic platforms, bioinformatics, combi chemistry platform and clinical compounds.

Mr. Edwards compared the 2014 biotech IPOs versus the biotech IPOs of 2000; with respect to the % step-up per round in terms of Series A to Series B to Series C to Series D to IPO. These have been +39%; +15%; -7% and +43% for the IPOs in 2014 whereas for the IPOs of 2000, these were +92%; +81%; +48% and +103%, respectively. Comparison of the current IPO cohort with IPOs of 2000 showed that 58% of the 2000 IPO biotechs were platform technologies whereas this fraction corresponded to 41% for the biotechs that went public on US Exchanges from January 2013 through April 2015. Mr. Edwards shared that the technology platforms of the current IPO cohort include various groups such as: (1) Small molecule discovery and design, (2) Approaches to genetic and orphan diseases, (3) Protein, antibody and vaccine discovery and design, and (4) Immunotherapy, cell and gene therapy. In contrast with the biotechs of 2000 IPO when no platforms and only 29% were in the clinic, 89% of the current IPO cohort with platforms are in clinics. Mr. Edwards discussed that there have been 41 "SEC-Filed" alliances signed since January 2012 with total announced payments to the licensor of at least $400 million, and $22.4 billion in potential payments from recent IPO cohort alliances. The examples of post-IPO acquisitions include Omthera (by AstraZeneca), Ambit (by Daiichi Sankyo) and Prosensa (by BioMarin).

Mr. Edwards concluded his presentation with the suggestion that it is better to compete for partners than for capital and that structuring alliances could be vital for a company's future.

A Workshop entitled, "Life Sciences Global Royalty Rate and Deal Terms Survey Beyond 'BIO $$ Bucks'!" featured a detailed presentation by James A. McCarthy, CLP (Corporate & Commercial Development, Licensing and Alliance Management, CorpDev Ventures). This workshop discussed a landmark global survey of royalty rates and deal terms conducted in partnership by the Life Sciences Sectors of LES USA/Canada and the LES International (LESI). The results comprised deals submitted by 200+ companies out of which 128 surveys were deemed complete for analysis. About 50% the deals were submitted by companies outside of USA and Canada. The survey is deemed useful with respect to deal terms in various therapeutic areas and geographic markets, and could be valuable in the context of early stage technologies and international deals for the present times.

Based on number of deals that were submitted for the survey, the respondents corresponded to 34% not-for-profit organizations, 7% government, 49% operating companies (of these 32% were pharmaceutical and 22% were biotech), and 10% other entities. Considering organization composition, 16% of the respondents were pharmaceutical companies (including diagnostic and drug delivery companies), 19% were biotech companies (including device companies), 20% academic institutions, 7% government , and 38% other entities. Deals data analysis showed that the most prevalent therapeutic area types were anticancer (oncology), CNS, and infectious disease. Deals involving small molecules amounted to 27% of the deals. The deal statistics regarding submitted deals showed that 61% were still in the preclinical stage of development [discovery , investigational new drug (IND) track/ pre-IND, IND filed, and pre-investigational device exemption (pre-IDE)]; 80% of deals were exclusive; 78% of deals included USA whereas 64% were considered of global type. In terms of peak annual sales, 49% of deals involved more than $US100 million. The assessment of royalty rates showed that of the 128 deals considered for the analysis, 82 deals used fixed/flat royalties, 22 employed tiered royalties, and 24 did not involve any royalty components. The average fixed royalty rate associated with the earliest stage products was about 5%. Additional inferences include potential for increase in royalties as a product matures through development, and the presence of 3 tiers as the most common structure amongst tiered royalty deals. Overall, the deals included upfront payment as the most common financial component (61%); however, sales milestones showed the greatest average and median dollar amounts. The primary valuation method used was net present value (NPV) / risk-adjusted net present value (rNPV) (45% of the deals) whereas about 32% of the deals involved the method of comparables.

Featured Luncheon Speaker Standish Fleming (Co-Founder, Forward Ventures) discussed that the pharmaceutical industry is facing innovation crisis. The key points from Mr. Fleming's presentation are described as follows. About 85% of jobs are generated through innovation. Countries that promote innovation would be expected to be global leaders. Among the factors that influence innovation, high regulation is a consideration as it can stifle innovation. The concept of innovation needs to change in that an invention without development cannot be considered innovation. In this respect, it is interesting to note that the hallmark

of 19th century was individual inventor. This changed to the hallmark being commercial lab for 20th century whereas the need for innovation marks the interest for the 21st century. Actual profits (and not simply the value of an invention on paper) are important. With respect to the trends in innovation, information technology (IT) would be important. The methods employed for financial calculations include NPV and discounted cash flow (DCF). However, these are not accurate and some risk is involved. Besides, a large fraction of innovations do not result in a product. This leads to misallocation of resources on the part of pharma. For example, in January 2012, Bristol-Myers-Squibb paid $2.5 billion for Inhibitex (focus: Hep C therapeutic); however, wrote off a significant amount in August as the deal went bad. Thus the advice for pharmaceutical companies would be that they kill more molecules quickly and that they allocate resources for only those opportunities that show promise. In addition, Mr. Fleming mentioned that patient advocacy groups are becoming important and this can be key in the innovation space. Pharma should make parallel investments in a series of companies. Unlike some other countries, USA is risk-averse and reporting of one bad case can lead to loss of data points and that this approach needs to change.

Another highlight of the event was a Plenary Session, entitled "San Diego Success Stories Roundtable," which was moderated by Bruce V. Bigelow (Editor, Xconomy San Diego) and the participants included Alex Dickinson (Illumina); Chrysa Mineo, (Receptos) and Rory Moore (CEO, EvoNexus). The panel mentioned various examples of mergers and acquisitions deals such as those between Fisher Scientific and Life Technologies; Bristol Myers Squibb and Amylin Pharmaceuticals, and Hologic and Gen-probe. In addition, the example of Aragon Pharma's acquisition by Johnson & Johnson was discussed. Other reflections by the panel included that an acquisition can make a company lose assets and people, and thus a company may not be keen on getting acquired. In terms of the understanding of diseases, not only are the biological data important, but the bioinformatics data are also very relevant.

Overall, the LES Spring Meeting provided various panel discussions, and educational and networking opportunities for licensing and other professionals. This event is expected to facilitate continued deal-making activities within the industry and academia.

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