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Opinion

The Open Insulin Project: A Case Study for 'Biohacked' Medicines

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New innovation ecosystems are emerging that challenge the complex intellectual property and regulatory landscape surrounding drug development in the United States (US). A prime example is an initiative known as the Open Insulin Project. The goal of the project is to sidestep patents and enable generic manufacturers to produce cheaper insulin. However, the US regulatory environment, not patent exclusivity, is the main barrier to insulin affordability. If the Open Insulin Project succeeds in releasing an open protocol for insulin manufacturing, follow-on work could enable a number of new insulin production ecosystems, including 'home-brewed' insulin. Regulators will need to consider how to proceed in a future where commercial pharmaceuticals remain unaffordable, but patients are empowered to produce drugs for their personal use.

Highlights

New innovation ecosystems for drug discovery and development are emerging.

Members of the 'do-it-yourself biology' community, sometimes called 'biohackers,' are contributing to this new frontier by experimenting with the development of medical treatments and devices.

An initiative known as the Open Insulin Project is working to develop a protocol for insulin production in order to sidestep intellectual property.

Follow-on work could contribute to a number of different insulin distribution structures, including 'home-brewed' insulin for personal use.

The current regulatory system is incongruous with emerging innovation ecosystems such as the Open Insulin Project.

New Innovation Ecosystems for Medicines

The current model of drug development in the US relies on a complex intellectual property and regulatory landscape, which necessitates long product development times and high costs. As the prices of many medicines continue to rise, new models of funding, research, and drug development have begun emerging as part of a novel innovation ecosystem. These include a more active role for patients and healthcare providers and an evolving emphasis on drug manufacturing at smaller scales.

On the provider side, hospitals, frustrated by the high cost and low availability of certain medications, have begun organizing to formulate plans for manufacturing their own **generic** (see Glossary) drugs [1]. Some experts have also begun discussing the possibility that health centers or pharmacies could manufacture drugs at small scales similar to **compounding** to help facilitate the realization of **personalized medicine** [2,3]. That is, one solution to the regulatory and economic challenges of precision medicine is to retool the development and production of drugs so they are as close as possible to the patient (i.e., bedside drug production for treating patients with individually tailored pharmaceuticals). Drug production in this model would be overseen by a physician for individual patients under their care [2].

Patients and concerned citizens are also taking an increasingly active role in attempts to steer drug discovery and development. **Crowdfunding** is now being used to fund health-related projects [4]. There have also been reports of tech-savvy patients hacking medical devices for improved symptom monitoring [5]. More formally, **community biolabs** (Box 1) made up of **citizen scientists** have begun developing rudimentary drug production and delivery devices. For instance, an initiative called Four Thieves Vinegar[i] released instructions for manufacturing an automated lab reactor using household materials and an epinephrine auto-injector with low-cost commodity parts. These self-described '**biohackers'** benefit from an opportune blind

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Box 1. Open Insulin, Community Biolabs, and the DIYbio Movement

The Open Insulin Project is a collaboration involving groups at community biolabs around the world. Started in 2015 by a group at Counter Culture Labs[vii] in Oakland, CA, USA, it also includes groups at ReaGent in Ghent, Belgium[viii] and BioFoundry in Sydney, Australia[iv] and recently welcomed collaborators based in Senegal, Cameroon, and Zimbabwe.

Community biolabs sprung out of the do-it-yourself biology ('DIYbio') movement, a social movement that encourages public access to and engagement in biology research for curiosity, fun, and to kick start innovative endeavors that benefit humanity[vv]. Community biolabs provide DIY biologists access to scientific equipment and training opportunities they need to pursue low budget research projects. Community biolabs are not-for-profit organizations funded by memberships, gifts, and revenues from educational activities. The first community biolab, GenSpace, was founded in 2009 in Brooklyn, NY, USA. There are now community biolabs in most major metropolitan areas in North America and Europe.

Individual community labs vary greatly in degrees of formality, scope, and purpose. Some community biolabs are overseen by highly trained scientists with a focus on education and science outreach. For instance, Denver Biolabs[vvi] is hosted by the University of Colorado in Denver and overseen by CU Denver faculty. Others, such as Counter Culture Labs, operate independent of any formal research institution.

While the press has covered cases of DIY biologists who self-experimented with unregulated therapies [6,7], these behaviors are more an exception than a rule. Most community biolabs have proactively developed biosafety best practices, including formal codes of conduct[vvii] and use of a community portal to seek biosafety guidance from experts[vviii] to help to foster a culture of responsible bio-innovation.

Companies have also been launched out of the DIYbio movement. For instance, companies like OpenTrons and Bento Bioworks are offering affordable laboratory instruments. Others like Amino Labs or The ODIN are proposing molecular biology kits for various applications from DNA extraction to genome editing. Specialized venture capital funds like IndieBio and even some mainstream incubators like YCombinator have invested in projects first prototyped in community biolabs.

spot within the regulatory framework: the FDA does not regulate online protocols for producing drugs or prototyping medical devices in the absence of a specific health claim. Nonetheless, these initiatives, as well as recent cases of entrepreneurs posting protocols for self-experimentation with unregulated treatments online [6,7], have, not surprisingly, evoked alarm among scientists and regulators[v,vi] [8].

One particularly intriguing endeavor that is ongoing within the 'do-it yourself' biology (**DIYbio**) community is an initiative called the Open Insulin Project[ii]. With a mix of computer science and biology backgrounds, the creators of the project are inspired by an **open-source** philosophy. Their goal is to increase competition in the market by developing and releasing a protocol for manufacturing off-patent insulin. However, follow-on work could theoretically lead to a number of different innovation ecosystems: (i) insulin could be 'home-brewed' individually for personal use; and/or (ii) insulin could be produced for '**magistral**' use by pharmacies, health centers, or community biolabs; and/or (iii) new methods for producing insulin that are not patent-protected could be developed, and those protocols and any associated intellectual property could be handed off to existing drug manufacturers as the project's creators intended [5]. In this regard, we discuss the Open Insulin Project as a case study of the potential risks, rewards, and legalities of 'biohacked' medicines.

Insulin is a Prohibitively Expensive Essential Medicine

Since its discovery in 1921, insulin has revolutionized the quality and quantity of life for persons with diabetes. Yet, despite its long market history, the cost of insulin has continued to rise. For example, insulin prices tripled between 2002 and 2013 [9], costing uninsured patients as much as US$400 per month [10]. In inner cities, the leading cause of diabetic ketoacidosis – a potentially fatal condition – is stopping or inconsistent insulin treatment, and cost is a major

Glossary

Bioequivalence: when there are not expected to be any significant differences between the bioactivity and bioavailability of two pharmaceuticals based on pharmacokinetic, pharmacodynamic, and *in vitro* studies, they are said to have bioequivalence.
Biohackers/biohacking: terms sometimes used to describe individuals who engage in biological research outside of formal scientific institutions and the projects they undertake.
Biologic: a pharmaceutical compound, such as a protein, that is produced by a living organism via **biomanufacturing**.
Biomanufacturing: production of biomolecules using living systems such as bacteria or cultured mammalian cells.
Biosimilar: similar to generic, a biosimilar is a biologic drug that is produced by a pharmaceutical company that was not the original developer after the relevant patents held by the original manufacturer have expired. For relevance to insulin see Box 2.
Citizen scientists: individuals who are not trained as scientists or who do not work at formal science institutions but who engage in low-budget scientific research.
Community biolabs: facilities which provide access to scientific equipment and training opportunities needed to pursue low budget biology research.
Compounding: the practice of combining, mixing, or altering an existing drug's ingredients to create medication specifically tailored for an individual patient's needs.
Crowdfunding: fundraising efforts that rely on relatively small donations from a large number of people, typically accomplished through solicitation on social media or other online platforms.
DIYbio: short for 'do-it-yourself biology.' A movement encouraging public engagement in biology research
Generic: a small molecule/chemical drug (not a biologic) that is produced by a pharmaceutical company that was not the original developer at a considerably lower price point after

reason reported for this [11]. Cited examples of health risks from high insulin costs include rationing treatments, using expired products, fasting, and even intentionally inducing diabetic ketoacidosis in order to obtain insulin from hospital emergency rooms [12,13]. While many other lifesaving medications have become available as less expensive generics, the high price of insulin is maintained in part by the small number of multinational corporations that dominate the insulin market and the complex and opaque pricing and supply chain [14].

The structure of human insulin is not patent protected, but the market has shifted to the production of genetically modified **insulin analogues,** in large part because the pharmaceutical industry has seen fit to incrementally innovate, raise the price, and phase out the old forms of insulin [10,14]. Insulin analogues are marketed as having additional benefits such as fast or long-acting properties and labeling for pediatric or pregnant patients. However, many experts argue that the originally approved human insulin is just as effective for most patients [15,16], so it is difficult to say whether patients who, because of lack of insurance and/or socio-economic inequalities [17,18], should be literally paying the price for insulin analogues when human insulin may well be as effective.

Only now, with **intellectual property** (i.e., patents) for many insulin analogues having recently expired or expiring soon [19], have **biosimilar** insulin analogues been marketed. However, there is still no inexpensive supply of insulin biosimilars for people living with diabetes in North America, and Americans are paying a steep price for the 'continued rejuvenation' of this medicine [10]. Meanwhile, at least 11 insulin biosimilars are marketed (under less stringent regulatory frameworks) at considerably lower price points in China, India, Mexico, Pakistan, Peru, and Thailand [20]. Studies comparing a handful of these biosimilars to innovator insulins showed no meaningful differences [19,20].

It is difficult for potential biosimilar manufacturers to compete in the US because the regulatory system explicitly favors existing manufacturers. First, the main purpose of clinical trials is to establish similarity to an **innovator biologic**, not clinical benefit *per se* [21,22]. This emphasis on proof-of-similarity strongly favors the pharmaceutical companies that produced the original as only they have access to the confidential manufacturing protocols.

Additionally, while competitors wishing to manufacture a biosimilar are subject to strict regulatory oversight, changes by existing manufacturers rarely require clinical trials, and the resulting biosimilar is treated as **interchangeable** [23]. This discrepancy is deemed excusable because a manufacturer that modifies its own processes is supposed to have extensive knowledge and information about the product. It is thus no surprise that the first insulin biosimilar approved in the US, Basaglar® (Box 2), was produced by Eli Lilly, which already owned 20% of the market share for insulin [24].

While generic drugs are typically 80% less expensive than the equivalent name-brand medications, Basaglar® is only 15% cheaper than the innovator biologic Lantus® [25]. The minimal cost saving associated with biosimilar insulins likely has little to do with manufacturing cost; the market value of pharmaceutical insulin is over $1000 per gram [9], while insulin costs roughly $50–75 per gram to manufacture [24]. Instead, costs are largely set by the intellectual property holders in response to the complex regulatory environment surrounding biologic drugs. Developers of biohacked insulin will thus have to navigate both intellectual property and regulatory hurdles in order to develop a more affordable model for insulin production.

the relevant patents held by the original manufacturer have expired.
Innovator: the biologic product produced by an original manufacturer which may be later manufactured as a biosimilar by a different manufacturer once the relevant patents have expired.
Insulin analogues: modified versions of the human insulin protein in which the amino acid structure has been modified in some way in order to provide clinical benefits.
Intellectual property: work products or inventions which may be protected by law (i.e., copyrights, patents, or trademarks) or may be kept confidential by the inventor to prevent them being copied (i.e., trade secrets).
Interchangeable: when a generic/biosimilar drug is deemed interchangeable, it can be freely substituted without patient or physician knowledge.
Magistral: the term magistral drug production refers to small-scale bedside manufacturing of drugs and is considered a form of compounding.
Open-source: generally referring to software, the term open-source describes information (such as source code) that is made freely available.
Personalized medicine: the tailoring of medical treatment to an individual patient's needs.
Pharmacodynamics: the relationship between the concentration of a drug and its effects.
Pharmacokinetics: how a drug moves through the body, including absorption, distribution, metabolism, and excretion.

Box 2. The Changing Insulin Regulatory Landscape

Historically, the FDA has not categorized insulin as a biologic. However, as of April 2020, insulin will be redefined and its approval managed by the Center for Biologics Evaluation and Research according to the regulatory mechanism laid out in the Affordable Care Act [24]. For simplicity, 'follow-on' or generic insulins, including Basaglar, are referred to in this manuscript as biosimilars. However, Basaglar® is not technically a biosimilar biological drug product because new versions of insulin products are currently regulated and approved under the Food, Drug, and Cosmetic Act (FD&C Act), section 505(b)(2), the new drug application (NDA) pathway [22].

The Biologics Price Competition and Innovation Act, under the Patient Protection and Affordable Care Act that was passed in 2010, created an amendment to the Public Health Service Act (PHSA) section 351(k), which will require all biosimilars (including insulin) to be regulated under PHSA section 351(k) by 2020 [2,29,30]. To make the transition, the FDA proposes to essentially 'deem' proteins already approved via New Drug Applications and Abbreviated New Drug Applications (ANDAs) as licensed biologics on March 23, 2020.

In the regulatory review process, Basaglar® was compared to the innovator insulin Lantus in two clinical trials. While it is possible that Basaglar® was subject to especially high levels of scrutiny because it is the first insulin biosimilar, Merck's LUSDUNA™ Nexvue™, the second biosimilar tentatively approved by the FDA withstanding upon resolution of a patent lawsuit, also underwent two clinical trials with over 500 patients each.

Obstacles for 'Biohacked' Insulin: Intellectual Property

Biohacked insulin will face different intellectual property barriers depending on the distribution model. If the Open Insulin Project succeeds in developing and releasing a protocol for insulin manufacturing, and that protocol is adapted for personal use (as epinephrine auto-injectors have been), intellectual property will likely not be a substantial obstacle. Personal use of 'home-brewed insulin' would not trigger any patent considerations in most European countries, as the exclusive exploitation rights granted by a patent are restricted to commercial exploitation. In Europe, a private person who builds a patented invention and/or uses a patented method in her own home for her own personal goals generally cannot infringe on a patent. The reasoning behind this is that such a situation cannot harm the patent holder. In the US, the law is stricter, and it forbids anyone from making, using, or experimenting with an invention, even when the use is not commercial, except in very limited cases [26]. Practically speaking, however, since patent infringement lawsuits are very expensive, and it is difficult to track restricted use in private, an individual would rarely, if ever, be prosecuted for using an invention in her own home. In the case of insulin, the safety ramifications of this scenario are obvious and will be discussed more thoroughly in the following sections.

Any other innovation ecosystem for insulin (e.g., 'magistral' production or technology transfer to a generic company) may run afoul of patents on the molecule and the production process, provided such patents exist. We note that there are plenty of patent applications filed for various 'next generation' insulin analogs, methods of making them, and methods of using them [27]. However, patents protecting the amino acid sequence of unmodified human insulin itself and of some recently off-patent insulin analogues are not a major barrier to the market introduction of affordable insulin. Patents protecting production methods of insulin are a more likely intellectual property obstacle.

Manufacturing is typically protected by a combination of patents and proprietary, non-patented know-how, or 'trade secrets,' which do not expire like patents. Manufacturing intellectual property includes the strain of microorganism used to biologically manufacture, or 'express,' the insulin and the specifics of the microbial fermentation process and recovery/purification of the expressed protein. Trade secrets are often used to protect non-patentable information. An insulin 'biohacker,' however, can independently uncover or stumble upon and 'acquire' a trade secret.

To the extent that third party manufacturing patents are being exploited, DIY biologists could invoke the 'Bolar' provision in order to conduct studies, research, and tests in preparation for

submitting documents for drug regulatory approval [28]. However, experimentation with patented technology, unless associated with seeking market approval, would likely be considered patent infringement. Likewise, actual production of the insulin once regulatory approval is achieved would not be covered by the Bolar provision.

Therefore, in order for biohackers to develop an insulin production method for 'home brew' for personal use, intellectual property will likely not be an issue. For magistral use or for use by a generic drug company, biohackers would have to sidestep existing patents except for those used in seeking regulatory approval. Clearly, understanding the intellectual property landscape, even for home-brew biohackers, will be important for the production of biohacked medicines. However, such ventures will encounter an even greater hurdle in the form of regulatory approval.

Obstacles for 'Biohacked' Insulin: Regulation

If the Open Insulin Project succeeds in developing a protocol for insulin production that does not infringe on any outstanding patents, the project's influence will be severely limited by the cost of regulatory approval. Regulation of biosimilars is more complex than for chemical generic drugs, and insulin, due to its long market history, has an especially convoluted regulatory footprint (Box 2).

Due to the size and complexity of biologics and the sensitivity of their manufacturing processes, achieving consistency is a major challenge. Impurities, altered structural stabilities, and differing patterns of glycosylation [19] can all potentially alter immunogenicity. Safety and therapeutic efficacy must be demonstrated using animal toxicology data, **pharmacokinetics**, **pharmacodynamics**, and most expensively for the applicant, Phase 1 and likely Phase 3 human clinical trials. Clearing these regulatory hurdles is estimated to cost between $30 and $250 million [23,24]. Even if one company absorbs the substantial cost, the same manufacturing protocol in the hands of a different company would require yet another regulatory assessment. Thus, regulatory costs create a major barrier to entry for potential biosimilar producers and necessitate high drug prices to recoup investments spent on clinical trials.

In the unlikely case that the production of DIY or magistral insulin could be considered **compounding**, then its producers would be subject to markedly less complex regulations. Drug compounding is the practice of combining, mixing, or altering an existing drug's ingredients to create medication specifically tailored for an individual patient's needs. Compounding is typically performed by small distributors and manufacturers that are permitted to market drugs under two circumstances: when a formulation, including a generic drug, requires a minor tweak to serve a tiny number of patients – those who can't swallow a pill but can take a liquid, for example, or those who are allergic to a certain inactive ingredient[iii].

In those cases, physicians have to write personalized prescriptions for individual patients, covering the change. Compounding firms are permitted to make and distribute drugs in bulk, rather than individually, only when they are declared by the FDA to be in a shortage or serving a particular clinical need. New regulatory controls were imposed on compounders under the Drug Quality and Safety Act of 2013[iv] after a deadly fungal meningitis outbreak was caused by contaminated compounded drugs sold by the now-shuttered New England Compounding Center. While compounding facilities are subject to regulatory oversight and inspection, compounded drugs are still not required to go through the time intensive and costly FDA-approval process.

The only innovation model for biohacked insulin that would not be subject to any regulation is the production of insulin for personal use. No structure exists at present for regulatory oversight of non-commercial products, and reports of self-experimentation with unregulated treatments have

begun surfacing [6,7]. The scenario of self-experimentation with unregulated insulin remains improbable, but the rising costs of this essential drug make such measures of desperation more likely. It is difficult to track or engage with persons experimenting with unregulated pharmaceuticals in their own homes, but it would be prudent for regulators to engage patients and innovators in community biolabs to design adaptive oversight that fosters an ethos of responsibility. Such an engagement should help create a more fully-informed citizenry that is empowered with more and better information about biosafety and relevant risk trade-offs.

Is There a Feasible Model for Low-Cost Biosimilar Production?

New models of insulin production that are subject to regulatory approval will likely depend on an alternative biosimilar approval process. If similarity to innovator biologics, including insulins, could be confirmed without clinical trials, the cost of development would decrease considerably. For instance, it has been demonstrated that multivariate data analysis can be used to determine comparability between biologics and biosimilars and monitor batch-to-batch variation [29]. In this case, variation between biosimilars and innovators even at different manufacturing sites was comparable to variation between batches. The only significant difference observed was in comparing data from a manufacturer with data from the National Institute of Biologics where samples had been forwarded from that manufacturer [29]. This finding suggests that cold chain management (including transport and storage) and sampling of biologics may be stronger determinants of variability than initial manufacturing.

Remarkably, a precedent has already been set for approving biosimilars without substantial new clinical data within the US. Before 2010, three 'generic' biologics (called 'follow-on biologics') were approved in the US via the Abbreviated New Drug Application (ANDA) [21]. This process relies on the safety and efficacy data of the innovator biologic and only requires evidence of **bioequivalence**. To our knowledge, no adverse effects of these drugs have been reported. The ANDA pathway thus demonstrates former confidence on the part of the FDA in the establishment of bioequivalence in the absence of clinical trials. However, after 2020, marketing and registration of biosimilars will no longer fall under the NDA/ANDA 'drug' pathway (Box 2). Whether or not bioequivalence is a sufficient marker of safety or efficacy for insulin remains to be determined.

A biosimilar regulatory structure less reliant on large clinical trials would be especially feasible in smaller-scale manufacturing. Scaling up production introduces additional opportunities for contamination, extends the cold chain, increases the number of patients exposed to a single potential biosafety event, and makes it harder to track the origin of safety issues. For instance, only when pharmacy compounding was outsourced and scaled up did it result in a major safety issue invoking the current regulations on compounding facilities [30]. Microbioreactors capable of producing small doses of biologics have already been developed by the academic community [31]. Further research could result in highly automated tools for safe and effective production of medicines at very small magistral scales.

Concluding Remarks

If the Open Insulin Project succeeds in developing and releasing a production method for human insulin, three different distribution structures are possible: (i) patients could manufacture their own insulin, (ii) insulin could be produced magisterially through community biolabs or health facilities, or (iii) the process could be picked up by an existing pharmaceutical company. Under the current regulatory environment, the third model is very unlikely to result in low-cost insulin (Figure 1). Expanding the availability of safe, affordable, off-brand insulin may thus require a revised regulatory process that enables lower-cost, decentralized production.

Outstanding Questions

What are the best methods for demonstrating bioequivalence? How well does bioequivalence relate to clinical safety/efficacy for insulin?

What are the largest remaining obstacles for small-scale biosimilar production? How might automation be used to improve the safety of biologics manufactured at magistral scales?

Because diabetes is a device-intensive condition, how might DIY models apply to other diabetic devices, such as patent-protected glucose meters and test strips?

What is the best model for introducing regulation within the DIYbio community without stifling innovation? How can certain 'biohackers' who might be resistant to regulatory oversight be encouraged to participate voluntarily in a regulatory system?

In what ways might the academic community and the DIYbio community be encouraged to interact such that academia can benefit from the unstructured creativity and innovation taking place in community biolabs in exchange for oversight and training?

	Traditional manufacturing of innovator insulin	DIYbio manufacturing of biosimilar insulin		
		Process released to pharmaceutical company for biosimilar production	Magistral production in health center or community biolab	Production for personal use
Research & development	Drug discovery in a formal research setting	Crowd-funded development of a protocol for producing off-patent insulin		
Intellectual property	Licensing and technology transfer		Some licensing likely required	Effectively none
Manufacturing workflow	Good manufacturing practice (GMP) compliant			Non–GMP complaint
Clinical trials	Conducted to determine safety & efficacy	Conducted to determine safety & possibly efficacy	None	
Regulatory approval	Extensive		Minimal	None
Production	Large scale		Small scale	Very small scale
Cold chain management	Storage and distribution		Short-term storage only	
Patients	Many		Few	One
Post-market	Extensive safety and quality control (QC) surveillance		Minimal safety and QC surveillance	None
Initial costs	$$$$	$$$	$	
Production costs	$$			$
Cost to patient	$$$$	$$$	$$	$
Safety	Considered safe		Uncertain	

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Figure 1. Comparison of Traditional and DIYbio Manufacturing Models for Insulin. Differing shades of gray are used to demonstrate differing levels of complexity, cost, and risk, where the most complex, costly, and risky are shaded darkest, and the least complex, costly, and risky are shaded lightest.

Open source information produced by DIY initiatives like the Open Insulin Project, combined with the support provided by a rapidly growing global network of community biolabs and a revised regulatory process, may create the opportunity for individual patients to access regulated medical products that they could not access before.

For insured patients, additional barriers will include prescriber and payer bias towards analogue insulin and preference for patented insulin delivery devices. For uninsured patients (10% of adults with diabetes in the US [32]), the safety risks associated with the lack of an affordable insulin supply should not be underestimated (see Outstanding Questions). It would be prudent for regulators to acknowledge and engage emerging innovation ecosystems such as community biolabs to find productive solutions that emphasize affordability without compromising safety.

Disclaimer Statement

The authors do not have any conflict of interest.

Resources

[i] www.fourthievesvinegar.org

[ii] www.openinsulin.org

[iii] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM602276.pdf

[iv] www.gpo.gov/fdsys/pkg/PLAW-113publ54/pdf/PLAW-113publ54.pdf

[v]www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm586343.htm
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[vii]www.counterculturelabs.org
[viii]www.rea.gent
[iv]www.foundry.bio
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