cb2insights

INDUSTRY **REPORT**

The Cannabis Industry Needs a Contract Research Organization (CRO)

INTRODUCTION

In an era where the race-to-market for cannabis-based medicines seems to have rested squarely on one's increased capacity to cultivate or on a slick branding strategy to market to the masses rather than clinically-validated safety and efficacy data, the medical cannabis industry has started to stall in its ability to penetrate the traditional pharmaceutical sector within nearly every regional market.

Medical cannabis continues to serve a rapidly growing patient-set, but as a medicine, it is accessed in most jurisdictions only through a narrow opening made up of specialty clinics, highly regulated dispensaries and patients being told by their primary care physicians to seek out alternative treatments on their own. It is a non-traditional pathway whereby solidified culture pushes regulation, which in turn creates an industry leaving proper research as only an afterthought. But after decades of legal frameworks coming into effect, how does the medical cannabis industry finally move from being a fringe therapy to an integrated part of comprehensive, mainstream healthcare strategies?

The answer lies in reverting back to the traditional validation process of mainstream pharmaceuticals – a method that only an extremely small group of cannabis-focused drug manufacturers have adhered to thus far.

EPIDIOLEX®, for example, a cannabis-based epilepsy medication targeted at childhood seizures and developed by GW Pharmaceuticals PLC has gone through rigorous clinical testing over the course of five years and eventually became the first all-natural CBD-based medicine approved by the US Food & Drug Administration. Since its approval in June 2018, the drug has gone on to be prescribed to more than 12,000 patients by 2,500 physicians in the US[1] and generate $86.1 million in just the third quarter of 2019 for GW Pharmaceuticals[2]. This is a massive outcome for such a slim subset of the patient population. Most large-cap Licensed Producers have yet to put up these types of revenue numbers and those LPs continue to target the patient and recreational population at-large.

Within EPIDIOLEX's development and approval process, the FDA granted GW Pharmaceuticals a 7-year orphan exclusivity on the medication and GW's patent is not set to expire until 2035[3]. This is how pharmaceuticals traditionally come to market. This is how major pharmaceutical companies gain real value. This is how a cannabis company with only a single blockbuster drug, serving only a subset of the patient population now has a $40B valuation which is a nearly 40% increase since the beginning of 2019[4].

1. http://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-plc-reports-financial-results-and-1
2. http://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-plc-reports-financial-results-and-2
3. https://www.globenewswire.com/news-release/2019/08/06/1897896/0/en/GW-Pharmaceuticals-plc-Reports-Financial-Results-and-Operational-Progress-for-the-Second-Quarter-Ended-June-30-2019.html
4. https://finance.yahoo.com/quote/GWPH/history/

At a macro level, medical cannabis has gone from drug discovery – which occurred, you know, sometime around 440 BC[1] – direct to market entry, leapfrogging the traditional drug development process which has inadvertently created a ceiling for the industry. And that ceiling has been hit. The steady resistance that comes from physicians and the mainstream medical community at-large remains the barrier to full success.

While it may be one of the world's oldest drugs, the medical industry still views cannabis as a new treatment. Even with new regulatory frameworks sweeping across the globe – over 45 countries at the time of this publishing[2]– a lack of adherence to standard drug development and approval processes continue to prevent physicians from widely embracing the drug despite increasing belief that it could unlock life-changing therapeutic benefits for their patients. This resistance is solely based on limited data and a lack of clinical trial studies which is the cornerstone of how the medical world traditionally shapes itself.

Cannabis-based therapy will undoubtedly solidify its place as a valid part of traditional medical treatment regimens. With hundreds of thousands of patients already benefiting today, that much is clear. The question remains, will licensed cannabis producers step up and adhere to customary processes that the healthcare sector demands, or will large pharmaceutical companies enter the space with those heavy processes already intact, reducing existing Licensed Producers to simply a wholesale provider to big pharma? Frankly, that is largely up to those producers that are willing to act fast and embrace the process.

1. https://www.smithsonianmag.com/smart-news/2500-year-old-chinese-cemetery-offers-earliest-physical-evidence-cannabis-smoking-180972410/

2. http://worldpopulationreview.com/countries/countries-where-weed-is-illegal/

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A REBEL *WITH* A CAUSE

The global pharmaceutical industry generates over US$1.2 trillion in sales each year[1] – a number that has nearly tripled over the past 15 years. It is a profit-rich industry despite heavy regulations and long and costly development cycles.

The cannabis industry, on the other hand, has been defiant of traditional processes, busting into the side door of the medical market focused almost solely on adhering to legal regulations rather than focusing on the conventional safety and efficacy validation processes used when bringing medicines to market.

There is no blame to be placed.

Cannabis is not a new drug. Drug discovery has perhaps seemed unnecessary. Over its centuries of prohibition, millions of people have found therapeutic benefit in cannabis which in turn has allowed it to enter the market quite easily once legal restrictions were lifted. But in skipping the traditional steps that are taken when a new drug is developed you lose the ultimate trigger for a surge in prescriptions and ultimately solidifying cannabis as a certifiable medical treatment option.

Cannabis is intrinsically a rebel. And the industry that bore out of cannabis became a rebel in and of itself. Defying tradition and paving its own way.

Timing, as always, is everything. Medical cannabis came to market at a time when there was an onslaught of capital looking for a new hype market to invest in and several large government bodies were signalling a readiness to lift strict regulations. This emboldened a medical sub-industry to come to market in a manner that did not align with traditional medical practices. And you could see that clearly play out as the industry evolved. Physicians were not immediately willing to prescribe so speciality clinics emerged. Pharmacies were not immediately willing to dispense so direct orders and dispensaries were launched. While these concessions allowed the industry to grow quickly, it inevitably created a plateau that traditional drug manufacturers don't typically experience.

Therefore, while the rebellious nature of cannabis has brought the industry to its current state, the fundamentals of healthcare are required to take medical cannabis rise to the level it can – and likely should exist at.

THE PROCESS OF DRUG DEVELOPMENT

The pharmaceutical industry spent $802 million on average for a single drug development project in 2003[2]. In 2019, that number is expected to close around $2.6 billion according to the Tufts Center for the Study of Drug Development. And time frames for a drug from discovery through to market entry continues to average around 12 years.

1. https://pharmaceuticalcommerce.com/business-and-finance/global-pharma-spending-will-hit-1-5-trillion-in-2023-says-iqvia/
2. https://www.policymed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-de.html

Costly. Lengthy. Understood.

There are over 322,000 ongoing clinical studies taking place across the globe in 209 countries according to the US National Institutes of Health[1]. That said, in the 75 years since the US Food and Drug Administration was established in 1938 up until 2013, less than 1,500 drugs in total had been approved for mass marketing[2]. And while overall macro-market growth rates in pharmaceuticals are expected to slow down from a 6.3% CAGR over the past 5 years to a 3 - 5% CAGR within the next[3], research and development pipelines are growing and success rates for new drug discoveries are expected to increase by 20%[4]. In other words, more emphasis on strong research is now set to produce a greater number of new drugs in the coming years.

The development process, while lengthy, is tried, tested and true.

1. Basic Research & Drug Discovery

In this phase, researches work to identify various chemical or biological substances on the way towards developing a drug. This is traditionally done through new information regarding a disease process, testing of compounds to find possible effects and researching existing treatments that have had unexpected effects. Once a promising compound has been found, they perform some simple testing for efficacy, toxicity and gather some preliminary information on effectiveness and safety.

2. Pre-Clinical

The next step is for researches to administer the drug to selected animal species or into cells. The drug must be shown to cause no serious harm at the doses that are required to provide the desired effect. If the results are promising and reach the acceptable safety levels, the researchers would then move to submit a Clinical Trial Application to the appropriate governing body for authorization of human participation.

3. Clinical Trial (Phase I)

This is considered “the Safety phase” which usually tests the new drug in a small group of healthy human subjects. The purpose of this phase is to determine the pharmacokinetics / pharmacological action of the new drug, find a safe range of dosing and identify adverse drug reactions.

4. Clinical Trial (Phase II)

This is considered “the Effectiveness phase” in which the drug is given to a larger group of individuals (usually several hundred) who suffer from the condition the drug is intended to help. The purpose of this phase is to gather data on the effectiveness of the drug and to further assess both the safety and ideal dosing levels.

1. https://clinicaltrials.gov/ct2/resources/trends

2. https://www.raps.org/regulatory-focus/news-articles/2014/10/how-many-drugs-has-fda-approved-in-its-entire-history-new-paper-explains

3. https://www.globenewswire.com/news-release/2017/10/10/1143791/0/en/213-84-Billion-6-3-CAGR-Expected-for-Global-Active-pharmaceutical-ingredient-market-by-2021-Zion-Market-Research.html

4. https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/2019/files/whitepapers/pharma-rd-review-2019-whitepaper.pdf

5. Clinical Trial (Phase III)

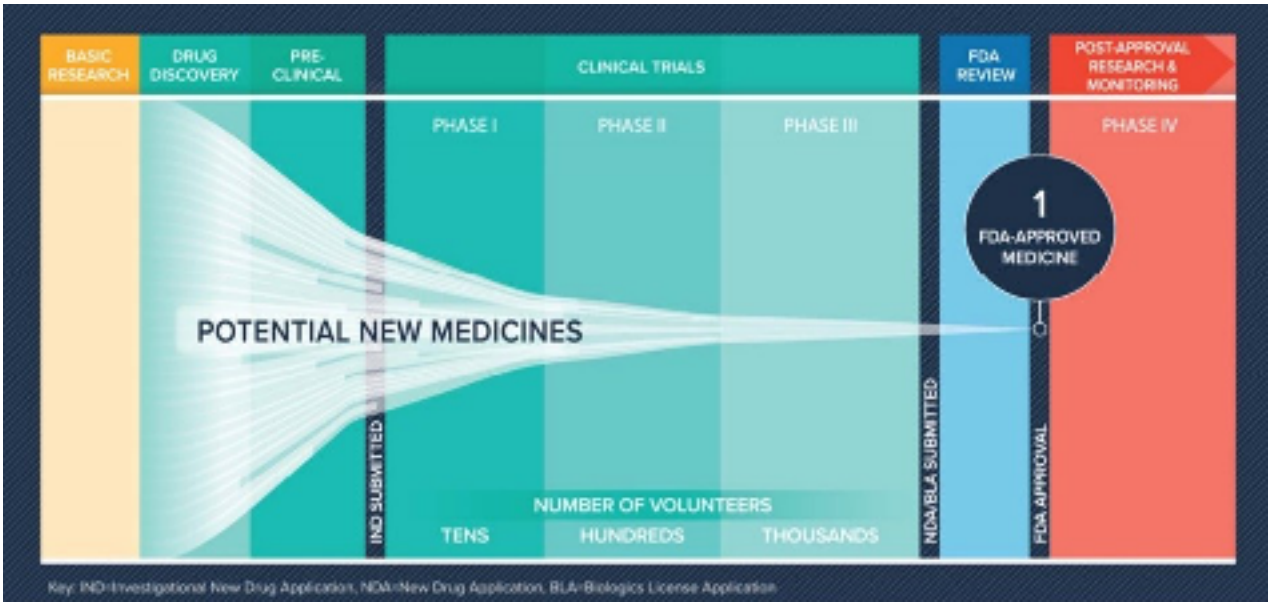
This is considered "the Confirmation phase" in which the test population size is much larger (usually in the thousands). The purpose of this phase is to confirm the drug's effectiveness, compare the drug to other, existing treatment options, monitor all side effects and gather other data that enable the drug's wider usage and for it to marketed safely.

6. FDA (or other regulatory body) Review

Should the results of the discovery process, pre-clinical phase, along with trial phases I through III show that the drug's potential therapeutic benefit outweighs any known risks, the researchers will file for approval from the regulatory body with oversight over the desired market. Datasets collected from the previous phases must be comprehensive enough for the regulatory body to assess the full safety and efficacy of the new drug. Should approval be granted, the drug would then be cleared to move to full marketing to the public for its intended purpose.

7. Post-Approval Research and Monitoring (Phase IV)

Once the new drug is in the market, researchers work to continue monitoring the drug and establishing whether it successfully holds the desired effect on the targeted population. Often times this phase can be done by outside parties including regulatory bodies, academia or other research organizations.

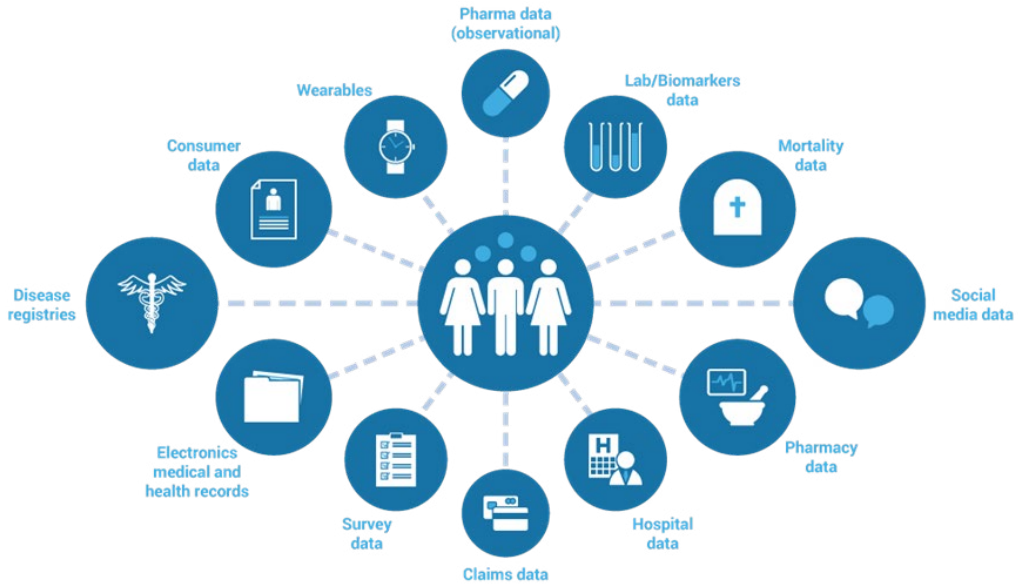


But while traditional drugs may take a lot of capital to develop, 40% of those costs are attributed to pre-trial and drug discovery. Therefore, within medical cannabis, as products are now readily available, resources in both time and financial investment can be significantly reduced. Moving a cannabis-based medicine into Phase I can be relatively easy with perhaps only a fraction of the pre-clinical stage needing to be addressed.

REAL WORLD EVEIDENCE CAN BECOME THE BRIDGE

A new push from several major healthcare oversight bodies to amplify Real World Data (RWD) and Real World Evidence (RWE) now allows for a solid bridge for an industry that has years (if not centuries) worth of data, to be able to circumvent some of the heavy burden that comes with conducting traditional clinical trials.

In late 2018 and throughout 2019, the US Federal Drug Administration released several guidance papers on how it would allow for RWE to be used to help bolster traditional clinical studies – and ultimately expedite the process. In an era defined, in large part, by data collection at countless touchpoints within the lives of consumers, the FDA recognized that there are plenty of objective data sets that exists which can augment the clinical trial process and increase the rate at which life-improving medications come to market. Below, you will find the sources that are considered to be a part of the RWD / RWE scope, which are collected from varying stakeholders on a daily basis.



(Reference for graphic: https://privacy-analytics.com/real-world-evidence/ IQVIA – Real World Evidence – Privacy Analytics)

Whether it be data collected from hospitals, physicians, patient surveys, various registries, pharmacies, etc., being able to access and then coalesce that data into meaningful insights is a key part of the new norm in the clinical trial process.

For example, if a drug developer is able to show a substantial number of patients have used a medication for a particular indication over a certain length of time through Electronic Medical Records (EMRs) under the watch of a physician and therefore can illustrate an equal level of safety findings, this could remove months (if not years) off time and reduce other costs of traditional clinical trials.

Within the medical cannabis industry, the data that exists is as broad as it is deep. This provides ample potential to leverage RWE but also can create a larger issue with understanding the strength of various data sets. Licensed Producers and other industry stakeholders will need guidance on what RWD / RWE constitutes appropriate reinforcement of otherwise lengthy and costly trials, however the right CRO can not only provide that guidance, but some can also help provide the data.

SUSTAIN SALES THROUGH VALIDATION

It has been a race for producers and retailers to illustrate pure consumer sales for the cannabis industry. Volume achievements in dispensaries has equalled positive headlines for most licenced producers. Sustaining that, however, goes against everything that the medical community stands for. Volume wins via marketing and cultivation capacity, a good medicine does not make. To win the medical cannabis war, product manufacturers are going to have to embrace validation in the traditional pharmaceutical sense of the word.

The US FDA has gone on record saying that while cannabis remains a Schedule I drug at the federal level, they are open to receiving and approving drug applications derived from cannabis-based[1] medicine that can help the population at-large so long as there is sufficient validation in its safety and efficacy[2]. There is no need to try to call their bluff when you look at GW Pharmaceutical's launch of EPIDIOLEX®.

As stated above, EPIDIOLEX is the first naturally derived cannabis-based medicine to be approved by the FDA. It has gone on to not only help over 12,000 patients but is on track to earn GW Pharmaceuticals more than $340 million in revenue on an annualized basis[3]. It is important to note that for their efforts, GW Pharma received 7 years of orphan drug exclusivity from the FDA, 10 years of exclusivity in Europe, 9 granted patents which have expiry dates up until 2035[3] and this has allowed import and sale in countries such as South Korea which otherwise have vey strict accessibility of CBD products[4].

The process can be long and arduous – no question about it. But this is how big pharma works. And whether positioning itself as a future target for a traditional pharmaceutical acquisition or to itself become the largest cannabis-based medicine producer in the world, GW Pharmaceuticals has become a $45B company with essentially a single blockbuster drug in post-market today. For context, that is

1. https://www.fda.gov/news-events/congressional-testimony/researching-potential-medical-benefits-and-risks-marijuana-07122016-07122016
2. https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd
3. https://www.newcannabisventures.com/gw-pharma-posts-cbd-drug-for-epilepsy-sales-of-86-million-in-q3/
4. http://www.koreabiomed.com/news/articleView.html?idxno=5963

about 20% of the market value of Pfizer who produces more than 10 times that in blockbuster drugs[1] and hundreds more in prescription and over-the-counter medications.

So why is GW Pharmaceuticals valued at such a high rate? Because they understand that sustainability is tied to product validation. In most markets, a cannabis 'prescription' or recommendation still leaves it up to the patient to select what brand or product strain they purchase. This leads to patients looking to try various products in a trial-and-error fashion which creates inherent disloyalty to the product manufacturer or Licensed Producer. Whereas in traditional pharmaceuticals in which a physician may prescribe a certain brand, the physician does so with reference to proven efficacy and safety validation studies and the patient is removed from holding a completely subjective decision on which medicine to choose.

GOING YOUR OWN WAY CAN HAVE SERIOUS RAMIFICATIONS

Other than resistance in prescribing cannabis-based medicines from the traditional medical ecosystem, the cannabis industry is starting to see other cracks stemming from avoidance of traditional research and validation methods over the years. While there was early push back from many regulatory bodies such as the Canadian Medical Association[2], the US Food & Drug Administration (FDA)[3], National Health Service in the UK[4], the Australian Medical Council[5] and Germany's Federal Ministry of Health[6], it hasn't been until just this past year that specific companies have been targeted by regulators who see clinical trial data as the only means to market a wellness or medical product.

On March 29, 2019, the FDA's Center for Drug Evaluation and Research released letters to three CBD manufacturers[7] stating that is it a violation to cite any health benefits without "competent and reliable scientific evidence, including, when appropriate, well-controlled human clinical studies. The FDA demanded that these companies (PotNetwork Holdings, Nutra Pure LLC and Advanced Spine and Pain LLC) remove all health-related claims from their product packaging, marketing materials and websites within 15 days. All three complied with the demand.

Then on July 22, 2019, Curaleaf became the first major Licensed Producer to receive a violation warning[8]. Similar to the CBD manufacturers listed above, the FDA demanded Curaleaf remove claims of positive health benefits from their website and other marketing materials as they were deemed "unsubstantiated" due to a lack of clinical evidence. Curaleaf also complied with the demand.

More recently, on September 18, 2019, Alternative Laboratories received a similar

1. https://investors.pfizer.com/financials/annual-reports/default.aspx
2. https://www.cbc.ca/radio/quirks/scrap-medical-weed-women-in-space-and-more-1.4636793/doctors-group-wants-to-scrap-canada-s-medical-cannabis-program-1.4636810
3. https://www.ncbi.nlm.nih.gov/books/NBK425757/
4. https://www.wired.co.uk/article/medical-cannabis-nhs-prescription
5. https://www.tga.gov.au/medicinal-cannabis-guidance-documents
6. https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/4_Pressemitteilungen/2017/2017_1/170119_02_PM_Cannabis_als_Medizin.pdf
7. https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products
8. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/curaleaf-inc-579289-07222019

warning[1]. Alternative Laboratories produces CBD-infused coffee products and CBD oils. Within their warning (as was the case with the others) the FDA cites GW Pharmaceuticals as an example of a company who followed the rules and thereby infers that in order to comply, these companies would have to submit documentation in the same manner that GW has done in order to come into compliance.

LICENSED PRODUCERS SHOULD BE PROTECTING THEIR TURF BETTER

Licensed Producers shouldn't feel entitled to leading the way for medical cannabis. According to the Cannabis Business Executive, as of June 2018, Sanofi, Pfizer, AstraZeneca and other mainstream pharmaceutical companies all had active clinical trials underway for cannabis-based medicine. Cannabis-related patents also show a similar landscape with Novartis, Abbvie, Sanofi, Merck, Bristol-Myers Squibb, Roche and others all holding upwards of a dozen cannabis-based patents. It has been estimated that medical cannabis could erode up to $4B in traditional pharmaceutical sales annually[2], so it is no wonder pharma companies are dipping their toe into the space.

Traditional pharmaceutical companies have vast resources and the knowhow to manage clinical validation of medical cannabis through traditional drug development. But they increasingly rarely go it alone. Over the past 40 years, an increasing trend began to outsource multiple stages of the drug discovery and development process. The use of Contract Research Organizations, otherwise known as CROs, gained traction due to increasing pressure on drug companies to systematically test compounds in a preclinical environment. Quintiles, which has since merged with IMS to form the industry's largest CRO, IQVIA, was formed in 1982 in order to formalize consulting work that had previously been done for pharmaceutical companies.

To increase efficiency, both in time and monetary resources, the assignment of external support in drug development began to grow. Moving from internal management of drug development to outsourcing much of the role to contract research organizations, the CRO industry not only was born, but it thrived.

THE ROLE OF A CRO

A Contract Research Organization (CRO) provides support to a pharmaceutical, biotech or other Life Sciences firm through research services. Within the CRO ecosystem, it is estimated that 50% of CROs are used for outsourced clinical study work, 27% work for biotechnology firms and the remainder for a mix of medical device manufacturers, foundations and governments[3]. The CRO market has seen a steady climb since the early 2000's and is expected to achieve total growth of more than 400% in 20 years by 2022[4].

1. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/alternative-laboratories-586947-09182019
2. https://www.healthworkscollective.com/how-medical-marijuana-industry-impacting-big-pharma/
3. https://www.thebalance.com/contract-research-organizations-cro-2663066
4. https://www.bccresearch.com/market-research/pharmaceuticals/global-market-for-contract-research-organization-cro-services.html

Over those two decades, the global pharmaceutical industry has increasingly externalized their research and development programs, leaning on CROs and Contract Manufacturing Organizations (CMOs) as an essential part of the value chain. The CRO market was valued at US$34 billion in 2018 which represents a substantial portion of the pharmaceutical industry's entire R&D spend[1]. According to the Pharmaceutical Research and Manufacturers of America, big Pharma spent more than $71 billion on R&D efforts in 2017[2]. If we use the figures above and attribute 50% of the CRO market to clinical study work, we are looking at $17 billion in 2018 being derived from pharmaceutical companies. This represents nearly 25% of the total R&D spend of pharmaceutical companies to go to CROs for their services. Now, it isn't quite as clean as that, as CROs that are focused on clinical study work can earn revenue outside of the pharmaceutical industry, such as through academia, government agencies and other organizations but majority of these CROs would generate most of their revenue from Big Pharma.

While the pharmaceutical industry tends to strengthen year-on-year, growth rates are moderate and in the past several years they have even had some reductions. This, while R&D spending continues to increase at a healthy rate. This is a clear cause and effect for the growth in the CRO market. The tightening of the pharmaceutical industry creates an even greater need to outsource R&D efforts. There remains high pressure to get new drugs swiftly through drug discovery to post-marketing and the cost efficiency of outsourcing to CROs can alleviate pressure on a firm's bottom line.

MARKET CONSOLIDATION

Over the past decade, major M&A activity within the CRO market contributed to a substantial rise in deal value within the sector. A report from GlobalData Pharma cites a more than doubling of M&A activity from 2014 to 2015 to the tune of $5.5 billion to $12 billion respectively – that number grew to $24 billion in 2016[3]. In large part, this effort has been to broaden the scope of services that a single CRO offers. Whether that is the phase of trial, the type of medication or condition the CRO handles, geographical reach or other specialty capabilities, CROs continue to find niche players to acquire in order to be a single source for any pharmaceutical R&D efforts.

In a market with strong growth and high margins, it's no wonder. In 2014, sector leader Quintiles posted annual net income of nearly $600 million[4]. Since then, further consolidation has taken place with Quintiles and IMS Health merging to form IQVIA which together posted over $1 billion in net income as of 2018[5]. In a list of the Top 20 CROs in 2015, all are still in operation but less than half remain independent.

The impact of this consolidation on the market has reduced the total number of outsourcing deals yet drastically increased the value of each deal. With a broader skill set, pharmaceutical companies may need to engage less CROs, but each deal is much

1. https://www.bccresearch.com/market-research/pharmaceuticals/global-market-for-contract-research-organization-cro-services.html
2. https://catalyst.phrma.org/phrma-member-companies-rd-investments-hit-record-high-in-2017-71.4-billion-0
3. https://resultshealthcare.com/insight/ma-trends-in-the-cro-industry/
4. https://www.sec.gov/Archives/edgar/data/1478242/000119312517046709/d321341d10k.htm
5. https://www.iqvia.com/newsroom/2019/02/iqvia-reports-fourth-quarter-and-full-year-2018-results-issues-first-quarter-and-full-year-2019-guid

richer in scope and therefore, richer in value. For example, in from 2014 to 2015, the total number of total outsourced deals decreased by 36%[1]. However, the value of those deals increased substantially by more than 76% from a total of $9.9 billion in 2014 to $17.6 billion in 2015[1].

THE PLAYERS

Today, after this increasing consolidation effort, the 9 largest CROs now comprise approximately 50% of the total market size. North America and Europe hold more than 80% of the CRO market with APAC contributing close to 15% of the overall CRO revenue – making them the third largest market share holder. These are the main players (in alphabetical order) in the market today:

Charles River Laboratories –

As the name suggests, CRL is well focused on clinical laboratory work. Though they have a wealth of service offerings, Charles River is known for its research models, safety assessments and laboratory services from early screening through to preclinical and clinical support.

Covance –

Having been purchased by LabCorp in 2015, Covance now boasts annual revenue of more than $11 billion. Considered one of the largest CROs in the industry, their focus is almost solely on oncology and specifically a move to speed up drug delivery to cancer patients.

ICON –

ICON has been a fast-growing CRO with a growth rate above that of the industry as a whole. The Company is also looking towards advancing their Real World Evidence capabilities with the acquisition of MAPI Group and poses strong competition to the larger CROs such as IQVIA.

IQVIA –

The result of a major industry merger between Quintiles and IMS, IQVIA is considered the largest CRO in the industry by way of several different metrics. With a revenue of more than $10 billion, IQVIA has spent years acquiring specialty CRO firms in order to give them a huge breadth of service offerings across any geography.

KCR –

A boutique firm with a focus on Europe, KCR has now started to move into the US. KCR approaches its research services with a high focus on people and seeking understanding on an individual patient level.

1. https://drug-dev.com/cro-market-cro-sector-sales-margins-remain-healthy/

LabCorp –

Nearly as large as IQVIA, LabCorp is another premier CRO with a broad focus across specialty areas and geographies. With a high focus on M&A activity, LabCorp has acquired more than 20 organizations over the past 10 years.

MedPace –

MedPace is considered a mid-sized CRO with a focus on drug development and devices. MedPace stands out as an organic growth firm with little to no focus on acquisitions throughout the years. They are well established and make them the topic of discussion for future acquisitions by larger players.

Parexel –

Similar in size as ICON, Parexel puts focus on lower-cost, emerging markets and works run reduced cost research support. Parexel was acquired by Pamplona (a PE firm) in 2017 which has resulted in an improved profit margin as well as overall quality of service.

Pharmaceutical Product Development (PPD) –

Operating in 48 countries around the globe, PPD is considered a premium CRO within the biotech and pharma industries. After acquiring Evidera in 2016, PPD became known for its focus on Real-World Evidence. PPD also recently acquired Synexus which has led to a new patient recruitment model which looks to identify prospective participants prior to their activity on site of a clinical trial.

PRA Health Sciences –

While it has been around for nearly 40 years, PRA went public in 2014 after its acquisition of Kohlberg Kravis Roberts and only then began to gain international attention. There is a heavy focus on Asia with PRA with Singapore and China being of top priority, though their coverage spans 85 countries around the world.

Syneos –

A large CRO, Syneos generates about $5 billion in revenue annually and maintains a broad area of focus. Proof that patient engagement is one of the most challenging aspects of CRO services, the company recently partnered with AiCure which together will work to provide better patient behaviour prediction and analysis.

MARKET OPPORTUNITY – CONTRACT RESEARCH ORGANIZATIONS (CROs)

Traditional (Historical & Forecast)

If we look at the growth of the CRO market over from 2003 through to forecasts up until 2022, we see a growth in the industry of more than 450%. Studying analysis from Business Insights, Global Data Pharma eTrack, Frost & Sullivan, Analytical Research Cognizance and Grand View Research, not only does it paint a picture of where the industry has been and is going, it is proof that this industry is steeped in quality research assessing its success.

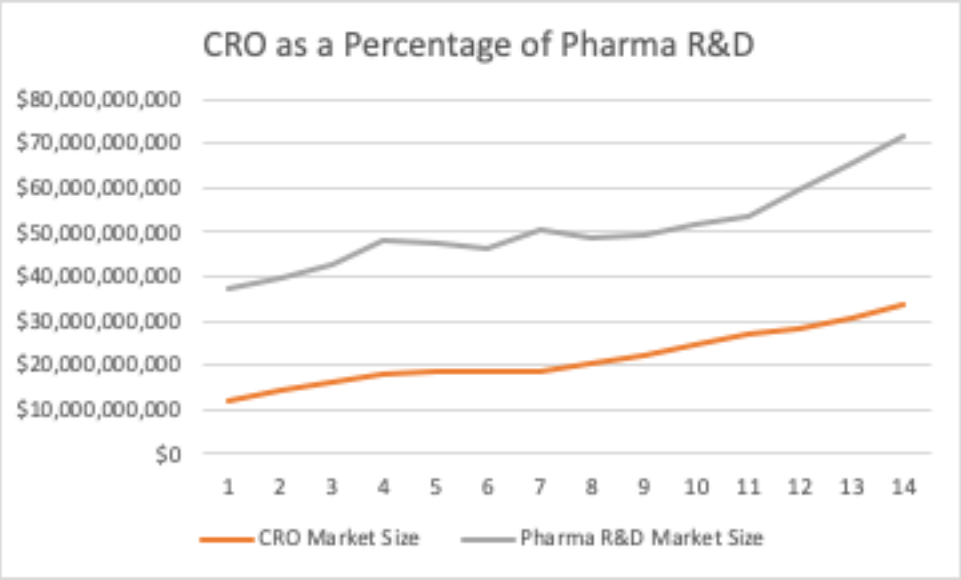
Growth in the sector has increased from $10.5 billion in 2003 to $34.5 billion in 2018. Grand View Research anticipates that to grow more than $10 billion to $45.2 billion in 2022. This growth is driven by many factors including greater industry reliance on Contract Research Organizations, increased value per contract, expansion of drug development across multiple health conditions and growth rates in emerging markets such as Asia Pacific and Latin America.

CRO as a Percentage of Pharmaceuticals

It is important to look at the percentage at which the pharmaceutical industry leverages CRO services. According to PhRMA (the Pharmaceutical Research and Manufacturers of America), the global Pharmaceutical industry spent $37 billion in R&D expenditures[1] in 2004 which nearly doubled to $71 billion in 2017[2]. When we compare this to the total CRO market size above, we see that this represents anywhere from 32% up to 51% of total R&D spend represented by the revenue of CROs, with an average of 42%. This certainly illustrates the consistent reliance on

1. https://www.pharmaceuticalprocessingworld.com/pharmaceutical-rd-expenditure-shows-significant-growth/
2. https://www.biopharmadive.com/news/phrma-research-development-spending-industry-report/529943/

outsourcing research and development efforts to contract research organizations going back over a decade.



With the medical cannabis industry leveraging a very minimal amount of this type of external support, the CRO industry within medical cannabis does not represent what is warranted if Licensed Producers and MSOs started to act like traditional pharmaceutical companies.

CRO Market Opportunity within Medical Cannabis

First, the medical cannabis industry today still represents a small market in comparison to the traditional pharmaceutical space. This is likely why major pharmaceutical companies and even traditional CROs have yet to enter the space. That said, with a forecast of over $45 billion as stated above, it still represents a significant market that is currently well underserved.

Trying to compare today's pharmaceutical industry with the current state of the medical cannabis industry is intrinsically unfair. While some regional markets are well into a decade of medical cannabis production, certifications and distribution, on a global scale it is still lagging and requires substantial change in mindset to bring it closer to becoming a valid part of the pharmaceutical industry.

Therefore, let's compare the forecast for the medical cannabis market in 2024 with the traditional pharmaceutical market in 2014. While this 10 year differential may still not make this a direct comparison, the maturity of the medical cannabis market over the next 5 years should certainly bring it substantially closer.

Using these two years, we estimate that the medical cannabis industry has the potential to represent 4.23% of the global pharmaceutical industry. This estimate can be further bolstered by understanding that medical cannabis has the potential to be a

treatment option for dozens of indications from physical ailments, mental conditions, physiological difficulties and many others – either on its own, or more likely as part of a larger treatment plan. As it has growing potential to be viewed as a valid treatment option on its own, in tandem with other traditional treatments or even as an active ingredient in mainstream pharmaceuticals, it is our belief that 4.23% is a solid estimate over the next 5 years.

Let's then take a look at the Global CRO market as a percentage of the total pharmaceutical industry – rather than strictly the pharma industry's spend on R&D, as stats on the total R&D spend in the medical cannabis space are difficult to verify.

In 2014, the CRO market size was $27 billion whereas the total pharma market was $1.05 trillion. This represents that the CRO market equated to about 2.57% of the total pharmaceutical market. If we then apply this to the forecast for the medical cannabis space of $44.4 billion, the Total Addressable Market within medical cannabis should grow to $1.14 billion.

CRO Market Opportunity / Share of Market		
Global Pharma Market Size (2014)	$1,050,000,000,000	Source: Statista
Global Medical Cannabis Market Size (2024)	$44,400,000,000	Source: Research&Markets.com
Percentage of Medical Cannabis to Pharma	4.23%	
Global CRO Market Size (in 2014)	$27,000,000,000	Source: Grand View Research
CRO as a % of total Pharma	2.57%	
Therefore, the CRO TAM within Medical Cannabis	**$1,141,714,286**	

Currently, only Licensed Producers who understand the value of clinical research have worked to start integrating CRO services into their budgets. And while over $1 billion in new market spend is on the table, it will only happen if more LPs advance their thinking outside of simply trying to cultivate and sell into mass markets and rather treat medical cannabis the way regulatory bodies want to see it – like a verifiable, true pharmaceutical. But the reverse is also true. If the forecasts of the industry hold true, and it grows to over $44 billion, that figure is certainly also reliant on a change in mindset and an embrace of the traditional protocols that have hoisted the traditional pharmaceutical industry to be valued at well over a trillion dollars.

CONCLUSION

As medical cannabis continues to show significant benefits to a growing patient set, its desire to become part of mainstream treatment will only occur once it sheds its rock and roll exterior and begins to see itself as a future part of verified, certified treatment options. It's fun to be a rebel. Cannabis has enjoyed its position as a legitimate alternative treatment option for years if not decades. But it will continue to stall in its growth opportunity if licensed producers and other cannabis providers continue to view itself and therefore act like a fringe medicine.

In traditional pharmaceuticals, the weight of clinical trials and ultimate authorization from regulatory bodies is heavy. Consuming in both time and monetary resources, as an outsider it can seem as though it barely creates a return on investment. But that is only a view from an outsider. To play in big pharma you must adhere to the decades-long regulatory processes that guide the global industry. To try to leapfrog those and exist outside of the framework will continue to keep you outside of the big returns that come with following the rules.

There are emerging companies such as GW Pharmaceuticals that recognized this from the start and are now many times greater in value than those that produce some 20X the product as an outsider. The largest licensed producers are still only valued at a fraction of GW Pharma, not because their product is in any way inferior, but because GW Pharma saw itself as a pharmaceutical company from the beginning.

Any while even the largest pharma companies rely on CROs to guide them through the regulatory process, it is those companies, like licensed producers and other cannabis manufacturers that don't think like traditional pharmaceutical companies yet that require the greatest amount of support. For those who are frustrated by the stall or even decline in cannabis valuations across the industry, you must first ask whether these companies relied solely on increasing capacity or developing slick branding strategies. Sure, Pfizer or Procter and Gamble have plenty of spend in those arenas. But what makes the large pharmaceutical companies truly successful is there understanding of drug development and regulatory processes. Something sorely missing in the medical cannabis space. Though something that can easily be gained through partnering with a Contract Research Organization.