Bringing HD Treatments to Market: The Role of Regulatory Oversight

Moving drugs from the lab bench to pharmacy shelves is no small task. In this article we delve into the role regulatory oversight plays in clinical trials and the approval of medicines for Huntington's disease.

By Dr Rachel Harding | October 21, 2024 | Edited by Dr Sarah Hernandez

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There has been a lot of buzz in the Huntington's disease (HD) space recently with multiple updates from companies testing many different drugs in the clinic. As these drugs move closer to seeking approval from the regulators, this has raised some questions. Why are some trials held in certain countries and not others? What does it matter if a company applies to the European or US regulators? How does a drug really move from being tested in a lab to being approved for sale on pharmacy shelves? We spoke with Cristina Sampaio, MD, Chief Medical Officer at the CHDI Foundation and former longtime member of CHMP, a committee that evaluates applications to the European Medicines Agency (EMA) for new drugs to be approved to be sold in the European Union (EU). Here, we get into the nitty gritty of drug regulation and find some answers to these important questions.

Getting a drug to market

After a company has been busy in the lab and has worked with different animal models to test their drug, the next step is to begin testing their drug in people in clinical trials. Clinical trials are typically divided into Phases 1, 2, and 3. As a drug progresses through these phases, more participants are dosed for longer periods of time. Each phase seeks to answer different questions about the drug being tested: Phase 1 is about what dose of the drug is safe for people; Phase 2 aims to work out if the drug is working and doing what it is designed to do while continuing to monitor safety; and Phase 3 seeks to confirm the effect of the drug, generally in a larger more diverse group of people, usually over a longer period of time, and looking out for possible side effects.

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If a drug successfully moves through all phases of theclinical trial process, the company behind the drug will then apply to the regulators for approval which would allow them to market and sell their drug. This is the ideal outcome for companies, patients, and other stakeholders as it means we have a bigger arsenal of drugs to treat different diseases and conditions. In the case of HD, we're hoping to soon have the first agency-approved, disease-modifying drug - what a thought!

Regulators – laying down the law on clinical trials and drug approvals

Testing new drugs in clinical trials is however a very risky business. Scientists do their utmost to make sure that new drugs they help develop are safe, effective, and could halt, slow, or alleviate symptoms of disease in humans, based on experiments they do in cell and animal models in the lab. However, there is always a risk that things might not go as well as everyone hoped when the drug is first given to people, with potentially very bad or disappointing outcomes, a scenario with which the HD community is unfortunately very familiar.

To work in the best interests of patient groups, it is important that all aspects of this process are carefully vetted and overseen by an independent panel of experts, from the very first people to be dosed with a drug, all the way to the final approval so that the drug can be made available. This is one of the roles the regulators play, helping to get drugs from the lab bench to the people who need them the most, the patient communities.

Most countries have drug regulatory agencies, although the scope, structure, and responsibilities of these agencies varies a lot. Regulators are responsible for ensuring the safety, efficacy, and quality of drugs, medical devices, and in some cases, other health-related products. All of these regulatory agencies serve different populations with different interests and needs, operating within different healthcare systems.

Regulators in Europe and the US

You are probably familiar with some of these regulators already – the European Medicines Agency (EMA) in the EU which is the central agency for approving and monitoring medicines across all 27 EU member states; and the Food and Drug Administration (FDA), which is responsible for regulating drugs, medical devices, and food safety, but is a federal agency representing the citizens of a single country, albeit a big one, the US.

As the FDA and EMA are currently the two big players in advancing HD drugs to market, they will be the focus of this article. The FDA and EMA are also two of the most important regulatory agencies in the world because of their global influence, scientific expertise, and high standards for drug evaluation and approval. This makes them key players in ensuring the safety, efficacy, and quality of pharmaceuticals and medical products in the global landscape of drug development.

However, it is important to note that there are many more regulators beyond those governing the US and the EU. This includes Health Canada (no points for guessing where they operate!), the National Medical Products Administration (NMPA) in China, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and the Central Drugs Standard Control Organization (CDSCO) in India.

The FDA is an end-to-end authority on drug testing and regulation in the US

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The FDA is a self-contained entity, with full control over drug approvals in the US in a very standardized process. The companies developing the drug will first file an investigational new drug (IND) application when they want to begin clinical trials. The FDA then reviews this huge dossier of information that comprises that application, detailing all of the pre-clinical data (experiments in cells and animal models) the company has worked to put together, and they then either approve it so the company to start clinical trials and begin testing their drug in people, or they don’t and things will pause.

The company might continue to have interactions with the FDA as needed and seek advice as drug development progresses through Phase 1 and Phase 2 trials. Then at the end of Phase 2 trials, all companies have to meet with the FDA and discuss plans for their Phase 3 trial. Together, this means that the FDA has a very prescriptive series of interactions with each company as they progress through the drug development pipeline. Because the FDA has been in the loop the whole way through this process, they should have the complete back story on each drug.

After the Phase 3 trial concludes, they will often privately advise companies on their potential chances of success if they were to file a new drug application (NDA), the final approval needed to bring their drug to market. This does not mean if a company files an NDA it will definitely be approved but more the opposite; that if the FDA suggests that a company NOT file for approval because the data for their drug are too weak, they will generally follow this advice.

The EU regulatory system works to serve all of its member states

In contrast to the US system, the EU system has multiple layers of organization, a reflection of the fact that it works to represent so many different countries.The EMA itself is not the regulator of clinical trials in the EU; this is controlled by each of the member states. This means that it is perfectly possible, although generally inadvisable, that the first time a drug company will interact with the EMA is when it starts the process to seek approval for its drug.

However, the EMA does offer scientific advice to companies, to support the development of new drugs. Scientific advice could be used to check with an independent body about the company's choice of endpoints (what they plan to measure and benchmark against in the trial) or the population they plan to test in, and whether this all makes sense. This service helps companies do a better job designing and running their preclinical and clinical studies. This can help ensure that they meet regulatory criteria before submitting their drug for approval, reduce the risk of failure, and streamline the drug development process.

Once clinical trials are complete, in the EU system the companies will prepare a dossier with all kinds of information about the drug they have been testing to submit to the regulators. This is a huge administrative task and a lot of work for the companies to do and can take a very long time - up to 12 or 14 months! In fact, big pharmaceutical companies like Pfizer and Novartis will have dedicated teams whose sole job is to put applications like this together. We asked Cristina about the significance of this step in the drug approval process and what this might indicate about the likelihood that a drug would be approved. She clarified that submitting this package had little to do with the merit of the application, and it is a largely administrative milestone in the drug approval timeline.

EMA approval is directed by a committee of experts

The EMA also differs from the FDA as it does not itself hold the decision-making power about whether a drug is approved. The approval instead comes from another body called the European Commission (EC). Linking the EMA and EC is the committee for medicinal products for human use (CHMP) comprised of a representative from each member state, and experts in the fields of science relevant for the application. CHMP reviews all of the

materials provided in the dossier submissions to the EMA by drug companies and gives an opinion on whether the drug should be approved to the EC. But it is the EC who makes a final decision on whether a license will be granted for a particular drug.

This is a complex process, not made any easier to understand by all the acronyms! Cristina sat on the CHMP for 13 years and is an expert on drug approval in the EU. She tells us that whereas just one faction is ultimately in charge of approvals at the FDA, there is a large and complex network of people in the EU system, making sure that the collective interests of all EU citizens are considered and represented in the process.

Once clinical trials identify drugs that will work for HD, we want those to move toward regulatory approval as quickly as possible.

Despite this diversity of perspective, the CHMP works to ensure consensus of opinion in their recommendation, and does their best to avoid a split vote, which could open the door to applicant companies exploiting possible wedge issues. In practice, this can mean that CHMP could make a recommendation for approval, but with caveats, to ensure that consensus is reached. These caveats might be about permitted dosing strategies or who can receive the drug. For example, a breast cancer drug might be approved but only for patients with a certain genetic mutation instead of all breast cancer patients.

Do all drugs follow this same approval process?

Often, this is not the end of the process and there is considered to be a Phase 4 of clinical trials, as drugs are monitored for their effect after approval. This is to make sure that in much larger populations over longer periods of time, side effects or other occurrences which were not spotted in the course of the normal clinical trial time frame can be identified and assessed.

Sometimes, if the needs of patient groups are extreme and there are no drugs available yet, drugs might be approved even before a Phase 3 trial. This was the case for a PTC Therapeutics drug for Duchenne muscular dystrophy (DMD), Translarna (ataluren), which

was conditionally approved by the EU regulators in 2014. Although the Phase 2 trial did not meet its primary endpoint, when the company sliced and diced the data, there did seem to be a somewhat promising effect in a subgroup of trial participants.

Translarna was approved by the EMA under the condition that additional data from a Phase 3 trial confirmed that the drug truly worked in the subgroup PTC had identified. Sadly, this Phase 3 trial did not reach its primary endpoint either. The application to the FDA for approval was denied and the EMA recommended the drug be withdrawn from the market. The EMA concluded that Translarna did not improve walking ability in patients sufficiently, resulting in the non-renewal of its marketing authorization in the EU. This decision was upheld despite appeals from PTC as well as from patient advocacy groups. PTC continues to seek FDA approval, but the inconsistency in clinical trial results remains a challenge for its approval.

This example demonstrates that even after agency approval, this is not the end of the road in drug regulation. However, companies with robust clinical trial data are unlikely to encounter such a turbulent back-and-forth with the regulators for approval of their drug as in this instance, especially if they're backed by positive data from a Phase 3 trial showing endpoints were met.

Why might the EMA and FDA make different decisions?

In general, the EMA tends to be more restricted in their approvals, compared with the FDA. In fact, there is a growing divide in drugs approved and available in the US that are not approved in the EU. But not all of these differences in approvals are to the benefit of people in the US.

For example, the Alzheimer's drug, Aducanumab was initially approved by the FDA in 2021 under the accelerated approval pathway. However, its approval sparked significant controversy in regards to its efficacy, as clinical trials did not provide clear evidence of a clinical benefit. This led to the company withdrawing the drug in 2022 as it was no longer commercially viable - the drug had a huge price tag and very few doctors were prescribing it. Following the withdrawal, Aducanumab became a notable example of the complexities and challenges involved in drug approvals, particularly for conditions like Alzheimer's where treatment options are severely limited.

These setbacks are indescribably disappointing for patient families. The rollercoaster of hope for those battling diseases like DMD, Alzheimer's, and certainly HD is sufficiently fraying without regulatory approvals and withdrawals of medications that these families hope will modify the course of their disease. The hope, energy, and risk associated with advancing these ineffective medications could have been better spent with additional clinical testing to ensure endpoints are met, preventing such agency withdrawals.

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Why are trials held in some countries and not others?

People from HD families have undoubtedly searched for clinical trials they may be eligible for only to be met with the disappointment that those trials aren’t taking place in their country. While certainly disheartening at the time, the decision to restrict trials to certain countries could actually help move drugs along more quickly, hopefully for the benefit of people with HD across the globe.

We recently heard positive Phase 1 trial news from Skyhawk Therapeutics, who is conducting their trial in Australia. Their decision to do this is likely a matter of cost. Healthcare costs in Australia are dwarfed in comparison to those in the US. So companies testing drugs there pay fewer fees to physicians and hospitals, making the trials a fraction of the cost. Although some drug companies are extremely wealthy organizations, smaller companies and start ups are often very cash-strapped. Spending less money to run a trial can improve their chances of survival, hopefully helping them advance their drug more quickly to convince more investors to pitch in and keep the program running.

In Europe, certain countries have faster or slower regulatory application review. Some countries, like Poland, Germany, or Hungary, have notoriously fast review processes. This allows them to attract different companies to their country for clinical trials. Other countries, like France, can be challenging to conduct clinical trials in for companies based in foreign countries, making it more common to see trials conducted there by French companies.

A company will consider trial costs and speed of regulatory approval when deciding where to conduct their trial. Ultimately though, these decisions should help a drug either fail more quickly or reach approval sooner. While we certainly don’t want drugs being tested for HD to fail, if they’re going to fail, we want that to happen as soon as possible. The sooner we know a drug won’t work, the sooner we can move on to something that will. And once we get to drugs that will work, we want those to move toward regulatory approval as quickly as possible.

On our way to triumphs

We would like to extend our heartfelt thanks to Cristina for sharing her expertise with us and talking through all of these complicated processes and considerations for drug approval so we could put this piece together. We are grateful to have experts like Cristina who dedicate their time and energy to helping the HD community. Overall, the process of

developing drugs isn't easy. Rightfully so! It's a risky business and we want to make sure drugs are effective, doing what is intended with little to no side effects, before they're dolled out to the masses.

Right now is an exciting time in HD research - there are countless companies working on drugs for HD, many companies are testing their HD drugs in clinical trials, and some are at the stage of applying for regulatory approval. As more drugs reach this stage, we at HDBuzz want to make sure HD families understand that process, what each of the phases and stages of approval mean, and where we could see setbacks and, hopefully soon, triumphs.

The future undoubtedly holds regulatory approval for HD-modifying drugs. While we take that journey, HDBuzz will be here to help you understand the steps along the way in getting those drugs from the lab bench to the pharmacy shelves.

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

Food and Drug Administration The government regulatory authority in the US responsible for approving new drugs

primary endpoint The main question asked in a clinical trial

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

therapeutics treatments

efficacy A measure of whether a treatment works or not
