RESEARCH NOTE

SAFE TO FOLLOW: FASTER ACCESS TO MEDICINES FOR KIWIS

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About the New Zealand Initiative

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When a car company develops a new model, Kiwis do not have to wait years while New Zealand authorities decide whether the car is fit for New Zealand's roads. Instead, New Zealand sensibly relies on certification provided by other reliable countries.

If Japan's authorities, Europe's, or America's, have already decided that a new model meets their standards, the imported car will be safe for New Zealand's roads.

Adding New Zealand specific standards would do more harm than good. In addition to the cost of running a local certification regime, access to new cars would be delayed while vehicle safety continues to improve. Process delays on new imports would mean older and less safe vehicles would stay on New Zealand roads for longer, adding to the road toll.

And some cars may never make it to New Zealand's market because it would not be worth the cost.

Safety differences between this year's and last year's car models can be small but add up over time.

New classes of pharmaceuticals, or vaccines against novel diseases, can have no good substitute. Access to the latest pharmaceuticals and vaccines is at least as important as access to the latest car model.

So why does the New Zealand government require Medsafe certification for pharmaceuticals already evaluated and approved by better-resourced overseas approval agencies?

While Medsafe provides expedited pathways for drugs already approved elsewhere, the process hurdle adds cost.

It seems unlikely that Medsafe's evaluation, however competently undertaken, would discover issues missed by approval agencies overseas.

America's Centre for Drug Evaluation and Research, the arm of the Food and Drug Administration responsible for drug approvals, had almost five thousand employees and an annual budget of over NZD $1.6 billion in 2021.[1] Pharmac's budget for *purchasing* pharmaceuticals in 2022/23 was about half a billion dollars smaller than America's budget for *evaluating* pharmaceuticals.

The European Medicines Agency has about nine hundred staff, while also drawing on over forty National Competent Authorities across EU Member states.

The UK's Medicines and Healthcare products Regulatory Agency has over a thousand staff.

Is it particularly likely that Medsafe's 60 staff would find something that has eluded two overseas agencies?

Delay is not costless and precautionary approaches cut both ways.

Economist Alex Tabarrok describes the American Food and Drug Administration's 'invisible graveyard'.[2] If an unsafe drug kills or harms someone, those tragic harms are very visible. Drug companies are sued, regulators questioned, and officials may be fired. But if extensive evaluation processes delay access to a safe and effective medication by months or years, people whose lives could have been saved by that medicine die instead. The place where people are buried who were killed by FDA delays is the FDA's 'invisible graveyard'.

Ideally, a drug certification process will balance the risks of harming people by delaying access to safe medicines against the risks of harming people by releasing drugs that are not safe. Work by Isakov et al in the Journal of Econometrics suggests that FDA processes are far too conservative, especially for severe diseases.[3] If FDA processes were faster and less costly, more people would be saved by faster access to safe medicine than would be harmed by medicines that failed to be stopped.

The same incentives face every drug approval agency. The political costs of erring by being too quick to release an unsafe drug are far higher than the political costs of the agency's invisible graveyard. So, agencies tend to err on the side of conservatism.

Adding further process costs to drugs already proven safe overseas is unlikely to provide net benefits.

For every Kiwi protected against a drug that made it through foreign approval systems that should not have, how many Kiwis are harmed by delayed or denied access to products that have already been proven safe elsewhere?

Should a precautionary approach assume that drugs proven safe elsewhere are unsafe here until proven otherwise – putting at risk all those who would have benefitted from the drug? Or should it assume that drugs proven safe elsewhere would also be safe here unless there is compelling reason to believe otherwise?

And how often does Medsafe's certification for new drugs protect Kiwis from drugs that should not have earned approval overseas, rather than just adding delay?

This research note suggests and provides some initial tests of an alternative approach: what we here call the Rule of Two.

It is highly unlikely that a medicine that has made it through one risk-averse foreign approval agency will be unsafe. It is even less likely to make it through two foreign approval agencies.

Under the Rule of Two, any pharmaceutical already approved by at least two trusted overseas approval agencies would automatically be approved in New Zealand – unless Medsafe had an extraordinary and compelling reason to believe that product to be unsafe for use here.

Medsafe decisions to block access to drugs approved by at least two foreign approval agencies could face ongoing evaluation. Did the decision protect New Zealanders from drugs that would here be unsafe, or only delay access to drugs that were safe all along?

The Rule of Two would not and could not replace Medsafe.

A pharmaceutical company may wish to develop a drug in New Zealand and pursue Medsafe certification rather than certification abroad. For example, QYNDR is an oral mucosal Covid vaccine currently under development in New Zealand that has reportedly shown promising Phase I results. They ran their trial through Medsafe and expect to continue further testing here and elsewhere.[4]

Medsafe also performs various other tasks that would not be replaced by the Rule of Two.

Under the Rule of Two, if a trusted overseas agency subsequently withdrew a drug's approval, Medsafe would assess whether continued approval were appropriate or whether it should follow suit.

Medsafe and access barriers

Medsafe approval is not the only barrier to access to new pharmaceuticals but can exacerbate other barriers.

New medicines are often costly.

Pharmac has a limited budget and prioritises cost-effective treatments. That budget means some drugs will not make the cut for public funding, regardless of certification.

In August, Pharmac published[5] a proposal to decline funding applications for 27 different medicines. In 24 of those 27 cases, Pharmac's stated reason for declining to progress funding applications was "We understand there is currently no Medsafe approved product available in New Zealand. We are not aware of any supplier willing to pursue Medsafe registration."

Whether any of those 24 medicines would have met Pharmac's cost-effectiveness hurdle had they been in Medsafe's approval process is impossible to determine. They were not evaluated.

But Tafamidis, an expensive treatment for cardiac amyloidosis, was among the drugs listed on 1 August to be declined for want of Medsafe approval. Three weeks later, the Australian Amyloidosis Network reported that Australia's Pharmaceutical Benefits Advisory Committee recommended Public Benefit Scheme listing of tafamidis.[6]

Australia is richer than New Zealand and can afford more expensive medicines than New Zealand can. Tafamidis may not have passed Pharmac cost-effectiveness assessment; it failed prior Australian assessments for public funding.

But Pharmac saw little chance Medsafe would evaluate the drug and proposed withdrawing it from funding consideration.

Why would pharmaceutical companies not put drugs up for Medsafe evaluation?

While Medsafe offers a simplified approvals process for drugs that have been approved overseas, New Zealand is a small country with limited willingness to pay for new medicines. Even simplified approvals processes require a pharmaceutical company's approvals team's time and attention. Companies will prioritise where to devote limited approval resources, and small countries with few expected customers will not be at the front of the queue.

Or, to put it more simply, the problem is not just that bespoke New Zealand approval processes mean added time while a drug goes through the local approval process. The problem is also that drugs with a limited potential market will not be put forward for evaluation at all. Unless the drug is likely to be Pharmac-funded, or prescribed widely despite not being publicly unfunded, New Zealand's small market is not worth the time and attention of a pharmaceutical company's approvals team.

It is akin to demanding that Lamborghini undergo destructive local crash testing to be able to sell its new Revuelto in New Zealand for a car that might sell a single unit. Relying on European certification makes more sense.

New Zealand's Medicines Act has provided an escape value. Section 29 of the Medicines Act allows doctors to prescribe medicines whose approval has not been sought in New Zealand, albeit with additional hurdles. But Section 29 did not hasten access to Covid vaccines; Medsafe approval took weeks to months after foreign countries had approved vaccines for different age groups.

The Therapeutic Products Act is replacing the Medicines Act and takes effect in 2026. While secondary legislation and regulation is still being developed, the Act appears to be more restrictive. Where the Medicines Act allowed import of unapproved medicines in anticipation of their being prescribed, the Therapeutic Products Act requires importation only on behalf of specific patients. Under the new Act, importation on demand for a named patient would delay access while increasing cost.

Assessing a Rule of Two: Does local certification add protection?

Wishing to better understand whether bespoke New Zealand authorisation provides value in addition to cost, we asked two teams of students at the University of Canterbury's Department of Economics and Finance to investigate.

The first team, Azlina Talhah, Cassidy Russell, and Henrietta Masson, supervised by health economist Associate Professor Andrea Menclova, were asked to check whether Medsafe has ever actively protected New Zealanders from drugs mistakenly approved overseas. If Medsafe had rejected a drug that was available overseas, and overseas regulators subsequently withdrew that drug from the market, Medsafe could be viewed as having provided protection from those unsafe drugs.

Their report is included as Appendix One.

They found that, from 2006 through 2022, Medsafe had refused twelve drugs. Nine of those twelve were subsequently approved by Medsafe and were currently active at the completion of the students' assessment.

Morphine immediate-release capsules were refused in 2014 and remain refused, though biosimilar products have been approved. The version refused by Medsafe is not found in other regulators' approvals databases, so it would not have been automatically approved by the Rule of Two. In any case, morphine prescription would be tightly restricted in New Zealand, even if approved.

Three formulations of local anaesthetic Lidocaine were refused in 2017 and remain refused. A high concentration version refused by Medsafe is not found on other agencies' databases and so would not have been automatically approved by the Rule of Two. A low-dose formulation has been approved by at least two other agencies, has not been subsequently withdrawn from those markets or demonstrated significant side effects seen in the high-dose formulation. The Rule of Two would have approved the low-dose formulation.

Finally, Arrow-Meloxicam 15 was rejected by Medsafe after having been previously discontinued by the FDA and remains unapproved. It would not have been approved by the Rule of Two.

It is difficult to make a case that Medsafe provided active protection against drugs that would have been approved here had Medsafe been required to follow a Rule of Two.

The students found that the Rule of Two would have seen Herceptin approved 9-10 years earlier, depending on the formulation, Methadone approved one year earlier, Panolimus approved twelve years earlier, and Plenvu approved one year earlier. Approval would hardly guarantee Pharmac funding, or private health insurance willingness to fund the drugs. But it would have opened options.

In other words, a Rule of Two would have hastened access in cases where Medsafe ultimately approved the drug, while providing little risk of approving drugs that went on to be withdrawn from foreign markets.

Assessing a Rule of Two: Does local certification mean faster withdrawal from market?

Under the Rule of Two, Medsafe would reassess a medicine if other agencies withdrew it from the market.

If it were the case that Medsafe is currently more proactive than others in withdrawing drugs, relying solely on a Rule of Two could mean that inappropriately approved medicines would stay on the market for longer, if Medsafe decided not to initiate its own withdrawal investigations.

The second team of students, Jamila Badis, Keruma Gibson, Emin Kaya and Matthew Lyons, supervised again by Associate Professor Menclova, built on the first team's work.

Their report is included as Appendix Two.

The students set a sample of drugs withdrawn by overseas approval agencies and checked whether Medsafe moved faster, in-step, or more slowly than others in withdrawing approval.

Generally, Medsafe moved in concert with other international agencies rather than leading.

For example, Dextropropoxyphene was withdrawn in New Zealand slightly ahead of the US and a year ahead of Australia, but slightly behind Europe, Canada and Singapore.

Sibutramine was withdrawn in New Zealand at the same time as the US, Australia, Canada, and Switzerland, but years after, it was withdrawn in Europe.

Vioxx was withdrawn at the same time as it was withdrawn in the US, Australia, and Canada.

Bextra was withdrawn here in parallel with the US, Europe, Canada, and Switzerland.

A Rule of Two that triggered drug re-evaluation if an overseas approval agency withdrew approval would not preclude Medsafe from initiating its own earlier review. But a preliminary review of a sample of drugs withdrawn from foreign markets does not suggest that Medsafe leads other agencies in removing risky drugs from the market.

Assessing a Rule of Two: Summing up

The two student projects are not determinative, but they do not provide cause for concern about automatically approving drugs already approved by at least two trusted foreign approval agencies. The work increases our confidence that a Rule of Two would hasten access to safe medicines while imposing little risk.

There remains a final way in which Medsafe might inadvertently protect New Zealanders from access to unsafe medicines, while also inadvertently barring access to safe drugs.

If seeking Medsafe approval is not worth the hassle for products expected to have a limited market, Medsafe might provide incidental protection against both good and bad drugs by discouraging applications.

Some drugs that were never assessed by Medsafe could well have been approved by at least two foreign approval agencies and subsequently withdrawn from foreign markets. Under the Rule of Two, those drugs would be authorised for the New Zealand market unless Medsafe had cause to pause their release.

The risk is low relative to the benefits.

For drugs released since 1960, the median interval between the first reported adverse reaction to a drug and its first withdrawal from a market was three years.[7] Medsafe has tended to move in parallel with other agencies in withdrawing drugs from the market; it could continue to do so under the Rule of Two. Access to a few unsafe drugs might increase for a limited period, while access to a broader range of safe and effective medicines would be improved for a longer period.

Research from the Leonard Davis Institute of Health Economics suggests that the FDA Accelerated Approval Program approved 48 drugs for 66 oncology-related indications from 2009 to 2022. Fifteen indications (23%) were later withdrawn, but not because of safety issues. Rather, the drugs showed a lack of benefit.[8] Had ineffective drugs been approved under the Rule of Two, it is unlikely that Pharmac would have funded them.

A Rule of Two would simplify and hasten access to safe pharmaceuticals while imposing little risk.

Drugs approved by Medsafe would have been approved between one and twelve years earlier under a Rule of Two. Medsafe would not need to put scarce resource into re-evaluating drugs already approved by two trusted overseas approval agencies. One barrier to timely access to new medicines would be eased.

The government should consider automatic approval of drugs already approved by at least two overseas approval agencies.

Appendix 1: NZ Drug Approval Process Report

NZ Drug Approval Process Report

Prepared for the New Zealand Initiative by

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Supervised by Andrea Menclova (University of Canterbury) & Eric Crampton (The New Zealand Initiative)

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1 Executive Summary

The research undertaken for this report was at the request of The New Zealand Initiative. It aims to determine the efficacy of having an independent drug approval agency, specifically Medsafe, in New Zealand. It also explores the implications of Medsafe relaxing their approval process, by relying on the application outcomes provided by two trusted agencies elsewhere. Our approach in undertaking this research was to extract and collate the approval processes of other countries' drug regulation authorities and compare them to Medsafe in New Zealand. Our research extended to the approval processes in USA, Switzerland, Europe, Canada, Australia, Japan and Singapore, and other less regulated markets.

Our report firstly provides a comparison of drug approval processes in New Zealand with the rest of the world. We then move to a more specific examination of Medsafe's role in the approval and distribution of COVID-19 vaccines and the issues around this.

To conclude our research, we focused on therapeutic drugs which have been rejected by Medsafe and whether this rejection was consistent with, or different from, overseas drug approval agencies. A case study was conducted to further explore the implications of adopting aspects of a regulatory reliance approach. Notwithstanding the limitations of this approach, results indicate that more timely approvals could be achieved if regulatory reliance was adopted.

A major limitation of our study was restricted access to data and lack of information available on world wide drug approval processes. The lack of published detail around the reason for Medsafe's rejection of certain drugs means that we have not been able to determine whether they were a result of safety issues or the inefficiency of the approval process. Nonetheless, our report identifies potential for further and more expansive and detailed analysis.

2 Introduction

The process for approval of distribution of therapeutic drugs in New Zealand has been questioned in recent years. The COVID-19 pandemic and its social and economic impact on New Zealand, and subsequent rollout of the vaccination programmes, has further highlighted the need to examine the efficiency and efficacy of the approval process.

Medsafe is New Zealand's independent drug regulatory authority with responsibility for approving and regulating drugs and other therapeutic products in New Zealand. Similar and differing approaches to drug approvals can be found around the world, all of which have the same aim – to ensure their citizens have access to safe, high quality therapeutic drugs and medicinal devices. Drug regulation is critical and cannot be taken lightly, but at the same time, an overly cautious approach can be costly, time-consuming and withhold the benefits of valuable products. An approval process that perfectly balances speed and circumspection will provide the most efficient outcome.

This report investigates the efficiency of NZ's independent drug regulatory strategy and questions the necessity of having our own regulator. We explored this in the context of COVID-19, by considering the need to conduct a NZ-specific assessment of the vaccine, when it had already been approved by multiple overseas regulators. We also examined regulatory processes around the world, compared the efficiency of each and considered the adoption of some of these strategies in NZ.

To further assess the necessity of an independent regulatory approach, we examined Medsafe's drug refusals over the past 16 years. Then, we compared how these drugs were handled by international regulators, specifically whether they were also refused and how they later performed, to gain insights into the justifiability of Medsafe's rejections.

Lastly, we conducted an analysis of a small hypothetical case-study, in which NZ adopted an algorithm that would allow automatic approval of a drug that had already been approved by two 'trusted' agencies. This again examined the role of an independent drug regulatory authority.

3 Medsafe

Medsafe is the New Zealand Medicines and Medical Devices Safety Authority. All drugs approved for use in New Zealand go through strict review by Medsafe. It is the medicinal product regulatory organisation run by the Ministry of Health. If a firm wishes to distribute and market a new drug in New Zealand, they must apply for consent from Medsafe in accordance with the Medicines Act 1981 and Medicines Regulations 1984.

Medsafe through this legislation manages the risk of avoidable harm associated with the use of therapeutic drugs. Consequently, the organisation ensures that all drugs available in NZ meet acceptable standards of safety, quality, and efficacy. All parties involved in the manufacturing, distribution and marketing of a particular drug must comply with Medsafe's requirements. This includes ensuring adequate and accurate information about the usage of the drug is presented to prescribers and consumers. Implementing this set of rules guarantees that medicinal goods accessible in New Zealand will provide more benefit than harm when used appropriately. Ultimately, Medsafe aims to enhance the health of New Zealanders by facilitating the access to pharmaceuticals in NZ, to maximise their safety and benefit.

Medsafe undertakes a variety of roles including:

- ascertain drugs meet the safety, quality, and performance standards;
- approving clinical trials of new drugs;
- surveilling reactions to drugs and medical devices;
- handling complaints, investigations, and recalls of medicines and medical devices; and
- auditing and licensing medicine manufacturers.

3.1 New Zealand Drug Approval Process

Medsafe's regulatory approval process ensures that both prescribers and patients have access to safe, high-quality medicines and medical devices. In New Zealand, therapeutic drugs are approved by the Ministry of Health, under advisement from Medsafe. The initial stage requires firms to attain pre-marketing approval by submitting a New Medicine Application (NMA) to Medsafe. This application must show that the medicine meets New Zealand and internationally approved standards for quality, safety and efficacy. If Medsafe considers the information submitted to be inadequate, it will request further information. Medsafe will evaluate the application and present it to the Ministry of Health to further assess whether to grant consent for the medicine to be marketed in New Zealand. If the medicine is approved, the New Zealand sponsor company then decides if the medicine will be supplied in this country.

In addition, firms need to submit a Changed Medicine Notification (CMN) application if changes are being made to an approved medicine. Medsafe will assess that the changes do not adversely modify the established quality, safety, and efficacy of the registered medicine before approval.

The criteria used in assessing drug applications in New Zealand are based on internationally established guidelines published by the EMA (European Union), the FDA (USA), Health Canada, the TGA (Australia) and the International Conference on Harmonisation (ICH). Not all medicines are required to be clinically

tested on patients in NZ before approval and assessments are based on all reports submitted to Medsafe. Manufacturers are subject to strict post-marketing surveillance by Medsafe or other international regulators, to ensure that they consistently produce medicines that meet the standard requirements. Furthermore, all medicines, regardless of the country of manufacture, are assessed to the same requirements.

The efficacy of a medicine is established through data collected from clinical trials carried out by the pharmaceutical companies. Depending on the type of drug and its stage of development, these studies might be undertaken with healthy volunteers or patients. Firms can also conduct bioequivalence studies with a reference medicine to compare the rate and extent of the active ingredients in terms of bioavailability, efficacy, and safety. Consequently, they do not need to repeat clinical studies if drugs are found to be similar. Finally, Medsafe evaluates the results from these clinical studies to determine if the safety profile is acceptable.

Medsafe aims to complete full evaluations within 200 days (Medsafe, 2013). However, the total time actually taken for a full evaluation varies depending on the sufficiency and complexity of information provided, the amount of additional information requested, and how long it takes the company to respond to Medsafe's request for more information. Medsafe reviews the risks and benefits of each specific medicine to ensure that the safety profile is acceptable (i.e., the benefits of the medicine outweigh its risks).

4 COVID – 19

COVID-19 has been a shining recent example as to why it is important to evaluate drug regulators like Medsafe and continue to improve them for society's needs. Medsafe gave the BNT162b2 [mRNA]/tozinameran (Pfizer Comirnaty) vaccine, the main one used in New Zealand, provisional approval on the 3rd of February 2021 (McGuinness Institute Te Hononga Waka, 2022) but it was not until August 2021 that the vaccine rollout truly began in New Zealand (Daalder, 2021). Most criticism of New Zealand's slow response to COVID-19 vaccines has been put on the government, due to the shortage of vaccine supply that stalled New Zealand's vaccine rollout. There has been little media coverage of Medsafe's part or of its approval processes for COVID-19 vaccines.

4.1 Medsafe's Response to COVID-19

Medsafe used their priority review to assess COVID-19 vaccines like the Pfizer vaccine, which has been the prominent vaccine used in New Zealand. The Pfizer vaccine has provisionally been approved until the 3rd of November 2023, where it will be reviewed again (Medsafe, 2022). In order to make Medsafe's approval process for COVID-19 vaccines easier, they used rolling applications so that pharmaceutical companies like Pfizer can submit documents gradually at different stages of their process, instead of all at once. Medsafe also have an 'abbreviated evaluation pathway', where they use drug reviews/evaluations from different countries' drug regulators when assessing own applications for COVID-19 vaccines. This alongside of their priority review of COVID-19 vaccines, sped the process up. The application for the Pfizer vaccines was received on the 13th of November 2020 and less than 3 months later on the 3rd of February 2021 it was approved by provisional consent (Medsafe, 2020a). This is roughly half of the time (of 200 days) that Medsafe typically aim to reach an approval of a new drug.

As a note, to ensure the safety of COVID-19 vaccines that Medsafe approves, they have a COVID-19 Vaccine Advisory group with experts that work parallel to Medsafe as well as a Medicines Assessment Advisory Group before a COVID-19 vaccine is finally approved or rejected for use in New Zealand (Medsafe, 2020b).

4.2 Other Countries' Reponse to COVID-19

One of the most mediatised responses and one that is often criticised is the European Union's response to COVID-19 vaccines. The EU decided to employ their vaccine strategy in buying and distributing vaccine to all EU member states (Deutsch & Wheaton, 2021). However, countries such as the UK and the US as a result procured earlier access to vaccines. The EU's response has been "accused by national leaders of being too bureaucratic, too limiting to its members, too slow" (Deutsch & Wheaton, 2021). By having solidarity across EU countries, it has been criticised for prolonging the spread of COVID-19 as people in the UK and US were receiving vaccine doses before those within the EU. Some EU states were frustrated with the bureaucracy and began to make their own deals with pharmaceutical companies. One example of this is the 'Inclusive Vaccine Alliance' between France, Germany, the Netherlands, and Italy who signed a contract for hundreds of millions of doses of the Oxford/AstraZeneca jab (Deutsch & Wheaton, 2021). EU Commission President Ursula von der Leyen stated that the fault of the EU and its poor response to COVID-19 was in part due to EMA being late to authorise many of the vaccines (BBC News, 2021). The UK, which was previously a part of the EU before Brexit, temporarily approved the Pfizer vaccine on the 2nd of December 2020, which was three weeks before the EU (Deutsch & Wheaton, 2021). The UK's health secretary at the time, Matt Hancock, stated that he believed the UK could only approve vaccines as fast

as they did because they were no longer apart of the EU and the EMA system (Morris, 2020). However, at the time the UK was still under the EU pharmaceutical law but used an emergency mechanism. Therefore, any EU state could have done what the UK did. The only difference with Brexit was that the UK had more ability to negotiate as many deals as they did without being politically held to account as other EU nations would have been. Indeed, the 'Inclusive Vaccine Alliance' faced backlash as many smaller countries argued the bigger ones were leaving them behind (BBC News, 2021). This serves as a warning that the more countries rely on a shared vaccine approver and supplier, the slower and more bureaucratic the approval process may become.

A second drug regulator of interest is the FDA in the US. It took the US three weeks to approve the Pfizer vaccine after it submitted application to the FDA on the 11th of December 2020 (Deutsch & Wheaton, 2021). The EMA, although criticised heavily in the media for its slow approval, took one less day than the FDA from when it received Pfizer's application, and the vaccine was conditionally approved in the EU on the 21st of December 2020 (Deutsch & Wheaton, 2021). In both cases (FDA and EMA), this is much quicker than the three months that it took Medsafe from receiving Pfizer's application to giving their provisional consent (Medsafe, 2020a). This brings up the question whether Medsafe is not as agile as these overseas regulators and if drug access in New Zealand could be improved if Medsafe's own process relied more heavily on outside approvals.

However, what must be taken into account is that Australia, unlike the US and UK, did not use emergency authorisation for COVID-19 vaccines. The TGA justified this by the fact that they had low COVID-19 numbers in Australia at the time (Australian Government Department of Health, 2021). Australia's COVID-19 experience was very similar to New Zealand's and may be a justification as to why Medsafe took longer to process COVID-19 vaccines. This is because both had relatively low numbers of cases in their community at the beginning of the pandemic. Both countries, therefore, were under less pressure to implement a COVID-19 vaccine quickly into their community compared to the EU, US or UK which were all experiencing high COVID-19 cases and their health systems were inundated. The TGA, much like Medsafe, accepted rolling data submissions to increase the speed of assessing possible COVID-19 vaccine applications that they would receive (Australian Government Department of Health, 2021). Australia approved the Pfizer application on the 25th of January 2021, which was over a week before Medsafe.

4.3 Molnupiravir Case Study

Molnupiravir is a drug which has garnered a lot of media attention. It is an antiviral treatment that is for people with COVID-19 who have a high risk of becoming hospitalised. Molunpiravir lessens the chances of hospitalisation by around 50% (Sowman-Lund, 2021) and works by increasing the mutations within COVID-19's genetic material or RNA which makes it harder for it to multiply (European Medicines Agency, 2021). Molnupiravir was approved by Medsafe in April 2022 for those with certain medical conditions, but it is still not widely available unless you have a prescription from a doctor (Ministry of Health NZ, 2022). Medsafe again was behind other major drug regulators in approving Molnupiravir, as Australia had approved it on the 20th of January 2022 (Australian Government Department of Health, 2022) and the FDA on the 23rd of December 2021 (U.S. Food and Drug Administration, 2021). Japan also approved Molnupiravir on the 24th of December 2021 with the condition that it needs special approval by doctors for emergencies in order for it to be used (Pharmaceuticals and Medical Devices Agency, 2022).

However, Molnupiravir has not been without its controversy. It is still under review in the EMA due to the EMA citing problematic data, but it can be used within EU countries if their governments individually allow it (European Medicines Agency, 2022). It is still under review in Canada (Public Services and Procurement Canada, 2022) and, in India, it has been extremely contested. Specifically, India's drug regulator, Central Drugs Standard Control Organisation, approved Molnupiravir on the 28th of December 2021. However, India's Council of Medical Research has said that it comes with too many risks as it "has major safety concerns [so] has not been included in their national protocol for the treatment of COVID-19" (Staff, 2022). This is because they believe not enough testing was done to ensure the safety of the drug as the FDA only approved Molnupiravir based on data from 1,433 patients (Staff, 2022). However, this is not the only risk that has been associated with Molnupiravir as Haseltine (2021b) believes that due to how Molnupiravir works by introducing mutations into the COVID-19 virus, there is a risk that these mutations could not be significant enough to stop it from replicating but instead just change how it functions. This is in part due to human error as it is more likely to occur if people are not taking sufficient doses at the proper times. As many as 40% of people do not complete their full antibiotic treatments, so treatment non-compliance is possible when taking Molunpriravir too (Haseltine, 2021b). Another risk with Molnupiravir is that there is no data on its long-term effects. Haseltine (2021a) believes that there is a possibility it could lead to cancerous tumours or birth defects. This is because when Molnupiravir creates errors within the COVID-19 genetic sequence, it could also mutate our own DNA. The trial that Merck, the producer of Molnupiravir, used was 1,500 people, who is insufficient to determine any rare mutagenic effects or long-term consequences of taking this drug (Haseltine, 2021a). Favipirvir is a similar drug to Molnupiravir as it is also antiviral and targets RNA but for influenzas. It had a trial of 5,000 people but was found to cause serious birth defects and has since been banned in many countries (Haseltine, 2021a). Therefore, the type of drug Molnupiravir is and the lack of data surrounding its long-term effect on people, creates doubts over the safety of this option to treat COVID-19.

5 Drug Approval Processes Around The World

5.1 Independent Regulatory Agencies

Independent drug approval agencies, like Medsafe, are present in many other countries around the world. However, some have arguably more efficient approval systems in place with the adoption of additional approval methods such as Mutual Recognition Agreements (MRAs), Regulatory Reliance strategies or simply a faster average approval turn-around. For example, the Health Products and Food Branch (HPFB), a division of Health Canada, is the national authority that regulates and is responsible for independent drug approvals in Canada. In addition to the independent approval process, Canada has MRAs with the European Union, Switzerland, the European Economic Area (including Iceland, Liechenstein and Norway), Australia and the United Kingdom. The HPFB under their MRAs recognise the equivalency of the drug and medicinal product compliance programs of these other regulatory authorities. They also offer an accelerated approval process via MRAs with a target of 7 months compared to the 1-year target for their standard approval process. The Food and Drug Administration, the independent drug evaluation body of the USA, follows a similar approach. They have MRAs with the EU and the UK and also offer a priority review scheme with a 6-month deadline. Their standard approval process takes around 10 months.

5.2 Regulatory Reliance

Where a country has no independent drug approval regulator, a range of different approval methods are used. Some countries have adopted a more algorithmic approach by determining a few trusted approval agencies and using a Regulatory Reliance strategy. Regulatory Reliance has become common practice in the Latin America and Caribbean (LAC) region. Thirteen out of 20 regulators in the region directly recognize or abbreviate the marketing authorization process in case of an earlier approval by a regulator from another jurisdiction. The regulators most relied upon are the EMA, FDA, and Health Canada.

5.3 Mixed Regulatory Strategies

Some regions have adopted a hybrid approach, utilizing a mix of an algorithmic approach and a more independent approval method. The EU models this, with two main authorization routes: centralized (the more algorithmic approach) and national (the more independent approach). The centralised route provides for the submission by pharmaceutical companies of a single marketing authorisation application to the EMA. After scientific assessment of the application and approval by the Committee for Medicinal Products for Human Use (CHMP) this process, if successful, leads to a recommendation by the EMA to the European Commission.

It is the European Commission which has legislative authority to permit marketing and distribution of a medicine throughout the EU member states and the European Economic Area. The centralised procedure is compulsory for some medicinal groups, including those which treat HIV, AIDS, cancer, autoimmune diseases, viral diseases and medicines derived from biotechnology processes. Each EU member state also has its own national authorisation procedures for medicines which are outside the scope of the centralised procedure. In cases where the centralized procedure is not appropriate but marketing authorisation for several EU member states is desired, then a company may apply either under:

- The Mutual-Recognition Agreement, whereby a marketing authorisation granted in one member state can be recognised in other EU countries. This evaluation process may take up to 210 days and ends with the granting of a marketing authorisation in that EU country. The concerned member states then have 90 days to recognise the decision of the reference member state. National marketing authorisations are granted within 30 days.
- Decentralised procedure, whereby a medicine that has not yet been authorised in the EU can be simultaneously authorised in several EU member states.

5.4 Efficiency of the Different Regulatory Approaches

It is hard to compare the efficiency of the different processes as there are many variables that need to be considered. There are advantages and disadvantages of all methods. Independent approval agencies may have the ability to consider the risks for a specific demographic group and provide more rigorous testing but is it a waste of time and money to assess a drug that has been proven safe elsewhere? An independent regulator also gives countries a chance to avoid mistakes made by others.

Regulatory reliance, on the other hand, may be less costly and time consuming, but is dependent on the extent to which the processes of the 'trusted agencies' are rigorous and not reliant on other agencies down the chain. Regulatory reliance also carries the inherent risk of compounding errors (an inappropriate or dangerous drug approval by one agency, e.g. the FDA, will flow through to others).

Appendix I provides more detailed information on regulatory processes around the world.

6 Medsafe Refused Drugs

Medsafe's drug approval database shows that between the years 2006-2022, only twelve drugs have been refused (some with applications for multiple doses). After analysing the data further, we found that nine of the twelve refused drugs have later been approved and are still currently active. The remaining three are still refused and not available in New Zealand. We then explored the individual drugs further to gain an understanding of why they were refused, whether they have been refused elsewhere, whether there have been any significant warnings issued and to investigate whether Medsafe's refusal was appropriate, or whether we could have received a better result by following a Regulatory Reliance approach. It is hard to compare the refusals exactly as different doses, different forms, and many other variables may change application outcomes but focusing on active ingredients and considering 'biosimilars' (a biosimilar is almost identical to the original product but is manufactured by a different company), we found the following:

6.1 MeNZB

MeNZB is a vaccine that was developed to protect against one particular strain of the meningococcal B bacterium. Its manufacturer, Novartis New Zealand Ltd, submitted an application to Medsafe in 2006, which was refused in 2008. However, it seems a change to shelf-life/storage conditions met Medsafe's requirements, and it was later approved in 2009. MeNZB is still available in NZ and no related warnings have been issued. This is an interesting case, as this particular strain of meningococcal B bacterium is only present in NZ, so the NZ market was the only necessary market to apply to. This means other regulators have not assessed this drug. This may be an example of the appropriateness of an independent regulatory authority and raises the question of whether the adoption of a complete Regulatory Reliance approach is suitable for a geographically isolated market such as that in NZ.

6.2 Herceptin

Herceptin is used to treat breast cancer and gastric cancer. Roche Products (NZ) Ltd applied for two different doses to be marketed in NZ in 2006 and both were refused in 2007. Roche Products (NZ) applied for these same two doses in 2009 and were granted approval in the same year. Herceptin and its biosimilar Ontruzant, have also been approved by the FDA, EMA, TGA and HSA. They are still active in all these countries including NZ and have not caused significant issues as of yet. This shows coherence between Medsafe and other drug regulators around the world and raises concerns about the necessity of Medsafe's initial refusal if overseas regulators had ruled this drug as safe.

6.3 Methadone

Methadone is a synthetic opioid agonist used for chronic pain and for opioid dependence. Methadone Hydrochloride (Methadone's active ingredient) was first introduced to Medsafe by AFT Pharmaceuticals Ltd who applied for three different doses of an oral solution in 2007 and were refused by Medsafe in 2009. Later in 2012, Boucher & Muir (New Zealand) Limited applied for the same three doses, with the same active ingredient but under the trade name Methadone Molteni. They were granted approval in 2013. Similar doses of Methadone Hydrochloride but in varying forms have been approved by the FDA and TGA. This does lead us to question whether Medsafe's initial refusal was necessary and also question why if Methadone and Methadone Molenti had the same active ingredient, same dosage, and same form, one was approved whilst the other was not?

6.4 Lostan

Medications with active ingredient Losartan Potassium, like Lostan, are used to treat high blood pressure and to help protect the kidneys from damage due to diabetes. Lostan of three different dosages, in film-coated tablet form, was refused by Medsafe in 2010. Later in 2010, Lostaar film-coated tablets of the same dosages were approved by Medsafe and are still active in NZ today. These tablets were also approved by the FDA, EMA, TGA, HPFB and HAS. This again, causes us to question the necessity of Medsafe's initial refusal.

6.5 Morphine Immediate Release Caps

Morphine immediate release capsules are used to provide relief from acute or severe pain. There were four different dosage amounts applied for in 2012 and all were refused in 2014. This product remains refused. The same drug has not been found on other countries' databases, but many had biosimilar products. Medsafe has also approved biosimilar products such as MST-Mono and MST-Continus. This may lead to a question as to why these drugs were approved and Morphine immediate release capsules were not. However, it is hard to evaluate the coherency of Medsafe with other countries' drug regulators for this drug as there are many different but biosimilar products that each country uses. It may also bring forth the question of why this drug has not been found on any other database and whether this shows Medsafe is consistent with other drug regulators in refusing this product.

6.6 Lidocaine

Lidocaine is a local anaesthetic used mainly for invasive procedures. It was submitted for approval to Medsafe in 2014 and was refused in 2017 and is currently still refused. The 1% dose of Lidocaine has been approved by the FDA, while the EMA has approved both the 1% and 2% doses. The PMDA and HSA have biosimilar drugs for both doses, while HPFB only has a biosimilar product for the 2% dosage. Medsafe has also approved other 1% and 2% lidocaine biosimilar products. Lidocaine has only faced negative reports on its 4% topical dose, that could supposedly cause patients to develop Lidocaine toxicity, which in extreme cases could lead to death (Crow, 2021). Where approved, the lower doses of Lidocaine have not demonstrated these significant side effects. However, with only the EMA approving both the 1% and 2% doses of this drug, it may suggest Medsafe was consistent with international drug regulators by rejecting it.

6.7 Plenvu

Plenvu is a powder for oral solution used to cleanse the bowl for operations that require empty bowls such as a colonoscopy. The manufacturer applied for approval from Medsafe in 2016 and was rejected in 2017. However, the drug was approved two years later, in 2019. Plenvu has been approved by the FDA, TGA, and Swissmedic. There have been no reports of significant issues or side effects of this drug within any of the approved countries. This shows consistency between Medsafe and other drug regulators around the world, but in doing so it raises questions as to whether Medsafe's initial decision was justified. One interesting thing to note is that Plenvu applied for Medsafe approval in 2016, but it was only in 2018 that Plenvu was put forth as an application for the FDA, TGA and Swissmedic. This could indicate that there were potential changes or further developments made to the Plenvu product over the two-year period, which may explain why Medsafe initially refused the product but then later approved it in 2019.

6.8 Hydroxychloroquine

Hydroxychloroquine tablets are used to treat acute and chronic rheumatoid arthritis, mild systemic and discoid lupus erythematosus, the suppression and treatment of malaria. Its manufacturer, LPCA Laboratories, submitted an application to Medsafe in 2007. Their application was declined in 2011 but was later approved in 2012 under a different trade name: Hydroxychloroquine Actavis. Hydroxychloroquine was approved faster by Medsafe as compared to TGA and PMDA which only approved it in 2015. However, the FDA, EMA and HSA had approved biosimilar drugs years prior. The drug remains active in all these countries including NZ and has not caused significant issues yet. There have been very few reported cases of sides effects in NZ. This shows consistency between Medsafe decision and other drug regulators around the world and raises concerns about the necessity of Medsafe's initial refusal if overseas regulators had ruled this drug as safe.

6.9 Arrow-Meloxicam 15

Arrow-Meloxicam 15 is a nonsteroidal anti-inflammatory drug. It works by reducing hormones that cause inflammation and pain in the body. It is used to treat osteoarthritis. As mentioned in the name, this drug's main active ingredient is meloxicam 15mg. In 2008, Suns Pharmaceuticals submitted an application and it was refused by Medsafe in 2010. Arrow- Meloxicam 15 remains refused until today. Internationally, the FDA discontinued the drug in 2006 and later only approved a drug with a similar active ingredient with a lower dosage of 7.5mg, under a different brand name. This raises issues about the quality and safety of this drug. However, the PMDA, TGA and HPFB had approved biosimilar drugs in years prior.

6.10 Revatio

Revatio is used to improve exercise ability and delay clinical worsening of pulmonary arterial hypertension (PAH; high pressure in the blood vessels leading to the lungs) in adult patients. Pfizer Ireland Pharmaceuticals submitted an application in 2008 and were rejected by Medsafe in the same year. However, Medsafe approved the application in the following year. The drug was approved by the FDA and EMA in 2005. In 2007 and 2008, the TFDA and PMDA respectively, approved drugs with similar dosage and active ingredient. This shows coherency between Medsafe and other drug regulators around the world and raises questions about the necessity of Medsafe's initial refusal if overseas regulators had ruled this drug as safe. The Agency's CHMP decided that Revatio's benefits are greater than its risks and recommended that it be approved for use in the EU and concluded that Revatio provides an alternative treatment option for PAH.

6.11 Sudafed Nasal Spray

Sudafed Nasal Spray is a decongestant that shrinks blood vessels in the nasal passages. Dilated blood vessels can cause nasal congestion (stuffy nose). Thus, it is used to temporarily relieve nasal congestion due to common cold and upper respiratory allergies. Side effects reported include dryness of the nasal mucosa, nausea, headache and uncommonly allergic reaction and blurred vision. Its active ingredient is 0.05% Oxymetazoline hydrochloride. Siegfried Ltd submitted an application in 2008 and it was refused the same year. The medicine was later approved for a different manufacturer in 2009. The same drug has not been found on other countries' databases. Nonetheless, medicine with the same active ingredients and dosage is available in the US as an over-the- counter (OTC) drug. Most OTC drugs are not reviewed and approved by FDA and may be marketed directly if they comply with applicable regulations and policies. Thus, the FDA has not evaluated this product. This demonstrates a specific situation in which

Medsafe is stricter in approving new drug access in the New Zealand market, but the approval is consistent with access to the drug overseas.

6.12 Panolimus

Panolimus is an immunosuppressant. It is a hard capsule medicine used to control the body's immune system response enabling the body to accept transplanted organs. Concord Biotech Limited submitted an application in 2009 for three different doses of its active ingredient; namely: Tacrolimus monohydrate 0.5mg, 1mg, 5mg. Medsafe rejected the applications in 2011 but the drug was subsequently approved under a new trade name Tacrolimus Mylan in 2020. Drugs with the same active ingredients and dosages were approved by the FDA, EMA and HPFB. The current access shows coherence between Medsafe and other drug regulators around the world and raises concerns about the necessity of Medsafe's initial refusal if overseas regulators had ruled this drug as safe.

Appendix II provides more information on Medsafe drug refusals from 2006 – 2022.

7 Case Study – A Potential Plan for NZ Drug Approvals

To consider the efficiency of the current drug approval system in NZ, we have created a small case study to further explore the advantages and disadvantages of implementing some aspects of a Regulatory Reliance approach.

In this hypothetical scenario, New Zealand will still have an independent drug regulatory authority, Medsafe, but with the addition of an algorithmic system. The algorithm will automatically approve a drug that has been approved by two 'trusted' overseas regulators. For this case, these 'trusted' agencies will include only those investigated within this report (FDA, EMA, TGA, HPFB, PMDA, Swissmedic and HSA). We have also assumed that the algorithm can only accept the exact same drug, therefore, biosimilar products are excluded. Considering the effect of this algorithm on a sample of Medsafe's refusals over the years gives the following results:

- **Herceptin 440mg:** If the above approach was followed, Medsafe would have approved Herceptin 440mg in August 1999. By this date, Herceptin 440mg was approved by both HSA and the HPFB, therefore meeting the requirements for automatic approval. In actuality, Medsafe approved this drug in August 2009. Therefore, if this hypothetical system had been implemented, Herceptin 440mg would have been approved 10 years earlier than under the current system.

- **Herceptin 150mg:** Under this programme, Medsafe would have approved Herceptin 150mg in August 2000. By this date, the FDA and the EMA had both approved Herceptin 150mg. This means Herceptin 150mg would have been approved 9 years earlier than its actual approval date in 2009.

- **Methadone 10mg:** The FDA was first to approve this drug in March 1973, followed by the HPFB in September 2012. Therefore, Methadone 10mg would have been approved in New Zealand 6 years earlier (2012 vs. 2018) if this algorithm had been implemented.

- **Panolimus 0.5mg:** The FDA were first to approve this drug in August 1994, followed by the PMDA in July 2008. Medsafe later approved this drug under a different trade name in March 2020. This shows how an algorithmic strategy could have sped up the approval process by 12 years.

- **Plenvu:** This was first approved in January 2018 by the TGA followed later by the FDA in May 2018. Medsafe however, did not approve Plenvu until May 2019. Therefore, under the hypothetical system, it would have been approved 1 year earlier than it was.

Drug:	Hypothetical Approval Date:	Actual Approval Date:	Difference in Approval Date:
Herceptin 440mg	August 1999	August 2009	Hypothetical approval is 10 years faster.
Herceptin 150mg	August 2000	March 2009	Hypothetical approval is 9 years faster.
Methadone 10mg	September 2012	October 2013	Hypothetical approval is 1 year faster.
Panolimus 0.5mg	July 2008	March 2020	Hypothetical approval is 12 years faster.
Plenvu	May 2018	May 2019	Hypothetical approval is 1 year faster.

Table 1 – Summary of Case Study Data

Analysing this small sample of data, it shows that Medsafe's current processes are slower than if NZ were to implement a strategy similar to the one outlined in this case study. However, there are also aspects not shown by this data set, that must be considered when evaluating which strategy is more effective.

If an algorithm were to completely replace Medsafe as NZ's regulatory authority, as mentioned earlier, New Zealand specific drugs, such as the MeNZB, may fall through the cracks of the other drug regulators. If there are situational determinants that require the release of a specific drug in only NZ, then inefficiencies may be created by the algorithm, as other countries may not prioritise its approval. However, if this system was to be implemented alongside Medsafe's current approval system, then it could potentially 'free up' Medsafe's limited resources, allowing more New Zealand-targeted drugs to be approved more quickly.

Another downside of the algorithm to consider is the risk of compounding errors. If two of the 'trusted agencies' make a mistake by approving a dangerous drug, New Zealand will also automatically fall into this trap. This situation raises the question of drug recalls, and how this would work under the algorithmic approach. Would NZ automatically recall their approval as well?

Another issue with the algorithmic approach is the ignorance of New Zealand-specific demographic profile. Racial and ethnic differences may cause variances in drug response and reaction to medication. Therefore, although 'trusted' overseas regulators may deem certain drugs as safe, this does not necessarily mean they are safe for New Zealanders.

8 Limitations and Recommendations

The most significant limitation of our research surfaced when Medsafe denied our request for more information about each individual drug refusal. Without knowing the details of why the drugs were denied, it is hard to conclude whether these rejections were necessary/justified. We also faced some restrictions when conducting the comparison of drug refusals with other countries around the world. This was due to the inability to access some information, in particular a language barrier when investigating Taiwan's refusals, but also arose from a lack of knowledge about the specific drugs. When comparing refusals, it is hard to know the equivalency between drugs with the same active ingredients but different forms or dosages and whether these variances would have had a significant impact on the outcome of their applications. However, we believe our report provides the foundations for a more in-depth analysis of the concept, one where there is time and capacity to work around these constraints.

While we addressed what we believed were the fundamentals of this topic, there are still some notable areas that could be expanded on. Some recommendations for future work are as follows:

- Medsafe allows applications of drugs that have been approved by their 'trusted agencies' to be put through a fast-track approval process. Investigating which agencies Medsafe includes in their 'trusted' category and whether there is coherency in application outcomes, would provide insight on whether a Regulatory Reliance strategy could be implemented in NZ.
- Exploring Medsafe's drug recalls, the speed of these in comparison to other agencies abroad, and the outcome, would provide insight into another dimension of Medsafe's role.
- Looking into the repercussions of Medsafe refusing drugs that were approved by overseas agencies, including the lives that were saved or the costs that were incurred by New Zealanders. This would again weigh in on the effects of NZ's drug approval process and the value of Medsafe.

9 Conclusion

Throughout this report, we have created an overview of Medsafe's drug approval processes compared to other independent drug approval agencies overseas. To compare differences across agencies, this report focused specifically on drugs rejected by Medsafe and on Medsafe's COVID-19 response.

Overall, Medsafe's decisions on drug applications are mostly consistent with the other independent drug approval agencies considered in our research. However, there is evidence of delay in Medsafe's verdicts. By analysing drug sample data in a hypothetical case study, we demonstrate how drugs initially refused and later approved by Medsafe would have been approved faster if there was an algorithm in place. The most notable example is Panolimus 0.5mg which could have been accessible to New Zealanders 12 years earlier under this hypothetical system. This points to delays in the current NZ drug approval system and shows how international regulators often move faster. Medsafe's response to the COVID-19 pandemic may be another such example, as their approval of the Pfizer Comirnaty vaccine was significantly slower than that of both the FDA and EMA. However, it must be mentioned that all countries were under varying degrees of pressure to approve a COVID-19 vaccines with both the US and EU facing greater COVID-19 threats to their citizens than Medsafe. Therefore, this could have been a factor into why Medsafe took longer to approve a COVID-19 vaccine as the New Zealand public was at a lower risk, justifying a slower response.

Nonetheless, our research regarding Medsafe's value as an independent drug approval agency in New Zealand is still preliminary, due to the plethora of missing aspects and limitations within our investigation. There is therefore potential to further refine and expand this study in the future.

10 Acknowledgements

We would like to thank The New Zealand Initiative for giving us the opportunity to explore an issue of such social, medical and economic significance. We would like to particularly thank The New Zealand Initiative's Chief Economist Dr. Eric Crampton for providing the University of Canterbury with this research recommendation. We have thoroughly enjoyed researching the New Zealand Drug Approval process and greatly appreciate your guidance.

We would like also to thank our supervisor Andrea Menclova from the University of Canterbury for the continued support, advice and instruction throughout our project. We have really enjoyed working with you and recognise the impact your guidance has had on our final report.

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12 Appendix I

Country	Approval process:	Average length of approval:	Cost of approval process:	Fast track process or MRAs:
USA	The USA has an independent drug evaluation company called the FDA (Food and Drug Administration).	Standard review approval – 10 month goal. Priority Review 6-month goal	Starting in 2022, it will cost $3.1 million to file a new drug application with clinical data.	They offer a priority review process. MRAs with the EU and UK.
Canada	Canada has an independent drug evaluation company called Health Products and Food Branch (HPFB).	Between 6 months to 2 years. Standard Review – target of 1 year. Accelerated Review – target of 7 months.	The fees as of April 1st, 2022, is $490,666. This is for a new active substance.	They offer an accelerated review process. MRAs with the EU, Switzerland, EEA (European Economic Area including Iceland, Liechtenstein and Norway), Australia and the UK.
African Union	There is currently no independent authority for approval of drugs prior to their introduction to the market. The African Medicines Agency (AMA) is in the process of being established with a goal of being fully			

	operation in 2022 and will be the central drug regulation agency for all African countries.			
South Africa	South Africa has an independent drug evaluation company called the South African Health Products Regulatory Authority.	Standard Review - Target of 350 days. However, median approval time is currently 792 days. Priority Review – Target of 250 days.		They offer a priority review scheme.
Nigeria	Nigeria has an independent drug evaluation company called The National Agency for Food and Drug Control (NAFDAC).	Standard Review – 12 months .		They do offer a fast-track scheme.
New Zealand	Has an independent drug approval agency (Medsafe).	Aims to complete full evaluation within 200 days but varies depending on how long firms take to provide further information required by Medsafe.	NZ$10,220 to NZ$102,210 Varies depend on type of application.	Consider the abbreviated evaluation route and priority assessment and applications for drugs with significant clinical advantage and cost saving. (120 day evaluation deadline).
Australia (TGA)	Has an independent	Aims 255 working days.		Allows fast track prescription medicines onto

	drug approval agency (TGA)	Mean 204 days.		the market-priority review (3 months earlier).
Singapore (HSA's)	Has an independent drug approval agency (HSA'S)	Aims 270 working days		Faster approval if approved by trusted agencies.
Taiwan (TFDA)	Has an independent drug approval agency (TFDA)			Faster approval if approved by trusted agencies US FDA, Health Canada, UK MHRA, Australian TGA and EMEA.
Japan (PMDA)	Has an independent drug approval agency (PMDA)			Offers priority reviews

13 Appendix II

Medsafe Drug Refusal Research link:

https://docs.google.com/spreadsheets/d/1wcPneNZhyjVrdLprjURjAgA7ljCieiCI/edit?usp=sharing&ouid=101041388182732506504&rtpof=true&sd=true

Appendix 2: NZ Drug Approval Process Report Part 2

NZ Drug Approval Process Report Part 2

Prepared for the New Zealand Initiative by

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Supervised by Andrea Menclova (University of Canterbury) & Eric Crampton (The New Zealand Initiative)

Table of Contents

1 Executive Summary

This research examined the feasibility of replacing the current approval process of Medsafe, the New Zealand medical regulatory body, with a regulatory reliance approach that utilises the decisions of other regulatory authorities around the world. The formula proposed by The New Zealand Initiative is that a therapeutic drug would be approved in New Zealand if it is approved by two trusted international regulators. Guided by prior work by Talhah et al. (2022), this set consists of six bodies: the EMA (EU and EEA), FDA (USA), HPFB (Canada), Swissmedic (Switzerland), the TGA (Australia), and HSA (Singapore).

This project built on the initial investigation by Talhah et al. (2022) into the efficacy and efficiency of an independent medical regulatory authority for New Zealand. Our research expanded on the prior work through comparisons of therapeutic drug withdrawals in New Zealand and in the six aforementioned areas of jurisdiction. This was to evaluate whether Medsafe's current approval process protects New Zealanders from substandard or potentially harmful drugs.

Our research found no instances of Medsafe providing active protection to the New Zealand market. That is to say, there were no cases in our dataset of therapeutic drugs that were withdrawn in New Zealand without also being withdrawn by other regulators. Thus, this finding supports the implementation of the framework proposed by The New Zealand Initiative; financial and time-savings are probable with this reliance approach and no costs of unaligned decisions are incurred.

Time was a limiting factor in this research. Withdrawn drugs were manually found for each regulator, which, coupled with our relatively brief timeframe and varied data accessibility, resulted in a non-comprehensive dataset. This may thus reduce the applicability of our findings to a broader scope. We were, however, aware of this limitation and hence chose to focus on more recent cases. Therefore, whilst there are more possible data points to include in future work, this research does provide a strong overview of data for the past two decades; the majority of Medsafe's existence.

In time, an investigation into the potential *passive* protection of Medsafe should be undertaken. This is where Medsafe might be protecting New Zealanders from harmful drugs simply by discouraging drug applications through the administrative burden. Whilst our research found no *active* protection, we were unable to rule out passive protection, which would diminish the viability of the proposed regulatory reliance approach that our research supports. Such work would be needed to make an informed evaluation of the use of the proposed formula.

2 Introduction

This report aims to examine the efficacy of Medsafe, the New Zealand Medicines and Medical Devices Safety Authority, and whether it could be replaced by considering the judgements of international regulatory bodies when deciding whether drugs should be allowed within Aotearoa New Zealand. In order to assess this, it needs to be considered whether Medsafe is protecting New Zealanders from harmful drugs. This could be occurring actively, by Medsafe refusing drugs that were approved elsewhere and then later withdrawn, or passively, by preventing pharmaceutical companies from applying, or preventing drugs entering in time for them to be recalled elsewhere.

Given the importance of drug safety and efficacy, it is essential that there is a robust and reliable system in place to monitor and regulate drugs in New Zealand, and therefore paramount that the necessity of Medsafe is considered thoroughly. Therefore, a formula was devised by Eric Crampton of The New Zealand Initiative that would be tested in order to see if Medsafe would still be necessary.

The proposed formula considered within this report is allowing drugs to enter the New Zealand market if at least two from a trusted list of international regulatory bodies deemed the drug in question to be safe and hence approved it for use - and, equally, withdrawing a drug from the New Zealand market if/once at least two ‘trusted’ regulators withdraw it. To examine the viability of this approach, this report looks at drugs recalled within New Zealand or internationally, and whether they were recalled by *both* Medsafe and international regulatory agencies, as well as the time frame with which these decisions were reached. This study was conducted between February and June 2023, and is a continuation of previous research examining the efficacy of Medsafe, which examined drugs that were refused entry into the New Zealand market (Talhah et al., 2022). No comprehensive lists of internationally recalled drugs were able to be found, therefore it was essential that research was undertaken to manually locate drugs that were approved and then recalled within the specific selected regulatory bodies. In the following sections of this report, we will outline our methodology and findings, as well as discuss the implications of our research for drug regulation in New Zealand.

3 Selection of Regulatory Bodies

The regulatory bodies initially considered in this project were the FDA (USA), EMA (EU and EEA), TGA (Australia), HPFB (Canada), Swissmedic (Switzerland), PMDA (Japan) and the HSA (Singapore). These agencies were chosen in order to build on the previous research conducted on Medsafe last year (Talhah et al., 2022). We began our research by investigating what drugs had been withdrawn by these agencies for various reasons. The results were mixed with some agencies such as the FDA and HPFB having a good amount of information online about drug withdrawals, but other agencies such as the HSA and PMDA having incomplete data. Finding drug withdrawal information from the HSA proved to be difficult as there was limited information published on the HSA website referring to drug withdrawals, which led to few drugs being found, and information on the PMDA website was not in English which led to translation errors. Due to the difficulties in finding drug withdrawals from the PMDA, we decided not to include the PMDA in our study. We further decided that other agencies would not be considered to replace the PMDA as to best align with the data and insights from the previous report. Consequently, our project focuses on a set of six ‘trusted’ international regulators.

4 Dataset of Drug Withdrawals

Our research expanded on Talhah et al. (2022) through comparisons of drug withdrawals in New Zealand and in the six previously mentioned overseas regulatory bodies. This was to evaluate whether Medsafe's current approval process protects New Zealanders from substandard or potentially harmful drugs.

SEE DATASET (Appendix I). 29 withdrawn drugs

Our research found no instances of Medsafe providing active protection to the New Zealand market. There were no cases in our dataset of therapeutic drugs that were withdrawn in New Zealand without also being withdrawn by other regulators. Thus, this finding supports the implementation of the framework proposed by The New Zealand Initiative; financial- and time-savings are probable with this reliance approach and no costs of unaligned decisions are incurred.

In time, an investigation into the potential passive protection of Medsafe should be undertaken. This is where Medsafe might be protecting New Zealanders from harmful drugs simply by discouraging drug applications through the administrative burden. Whilst our research found no active protection, we were unable to definitively conclude on the validity of passive protection existing, which would diminish the viability of the proposed regulatory reliance approach that our research supports. Such work would be needed to make an informed evaluation of the use of the proposed formula.

The next section will present two case studies of drugs that are well-known large-scale drug withdrawals that illustrate both a case that shows a lack of active protection by Medsafe and a case that hints a passive protection by Medsafe.

5 Case Studies

5.1 Vioxx

In the late 1990s, the U.S.-based multinational pharmaceutical company Merck & Co. created Vioxx, a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID). It became a widely prescribed medicine used to relieve symptoms and signs of osteoarthritis, painful menstrual cycles, and acute pain in adults. The main ingredient is Rofecoxib and it is related to the non-selective NSAIDs such as ibuprofen (FDA, 2004). It was first approved in the U.S. in 1999 and in Canada in the same year. It was approved in Europe shortly after and Australia also adopted the drug in 1999. Consistent with the delays discussed in Talhah et al. (2022), Vioxx did not make its way to New Zealand until Medsafe approved it in January 2000. Vioxx was a successful global drug that brought in about USD $2.55 billion of annual revenue on average during its sale (NBCnews, 2004). Merck reported an estimate of over 84 million people prescribed globally over the lifetime of the drug (Prakash & Valentine, 2007). On the 30th of September (1st of October in NZ) 2004, Merck & Co. announced their decision to recall Vioxx after concerns of an increase in the chance of cardiovascular issues. This was due to a 3-year study on Rofecoxib (25mg) against a placebo to see if it could prevent the recurrence of colorectal polyps (Compton, 2022). During the study, it was found that as a side effect, the risk of adverse cardiovascular events was doubled in the sample who used Vioxx for more than 18 months as opposed to the placebo. Patients' risk levels returned to normal after 1 month of discontinuation (Compton, 2022). Vioxx was used in over 80 countries at the time of the global withdrawal in 2004 (MedSafe, 2004).

Vioxx is considered to be one of the biggest drug recalls in history in terms of patient effects and fines to Merck & Co. On the morning of the announcement, the price of Merck & Co's shares plummeted by USD $12, or 26.78%. This led their market capitalization to decrease by around USD $25 million. The fact that the drug was so widely used caused extreme urgency to remedy its supply. Research published in 2004 in the medical journal *Lancet* estimated that 88,000 Americans had had heart attacks due to taking Vioxx and, of those, 38,000 had died (Prakash & Valentine, 2007). There are other studies that provide similar estimates worldwide (Lowe, 2012). This is an example of an extreme case of a drug recall that had a global effect. Vioxx was introduced in the early days of Medsafe and had no major complications in the pre-market clinical trials (MedSafe, 2004). As noted above, Medsafe evaluated it and approved it in 2000. In that sense, an independent regulator did not protect us from a harmful drug. On the other hand, under the proposed system of approving drugs after two trusted agencies have already approved them, Vioxx would have also made it through to New Zealand. It is important to remember that this is a single and extreme case and that there has not been a case of the same magnitude in recent years.

5.2 Belviq

The main ingredient of Belviq is Lorcaserin. It was designed by Japanese pharmaceutical company Eisai to be used with exercise and behaviour changes, as well as a reduced-calorie diet program, to help individuals lose weight. It was intended to be used by people who are obese or have weight-induced medical issues. The FDA approved Lorcaserin in 2012 (FDA, 2022) and, interestingly, it was rejected in Japan at the very late stages of the process, even though that is where the company's headquarters are based (the PMDA was not included in our analysis). Eisai also withdrew their applications for approval in countries around the world, including EU countries, Canada, Singapore, and Switzerland during the approval processes in 2012 and 2013. Neither event is a good sign for the drug. Following questions from the EMA at the final stage, Eisai stated that they would not be able to address all of the EMA's concerns within the timeframe for the application (EMA, 2018).

Upon approval, the FDA required Eisai to conduct a randomised, double-blind, placebo-controlled clinical trial to evaluate the risk of cardiovascular problems. The trial was conducted on 12,000 patients over 5 years and found that 462 or 7.7 percent of patients treated with Lorcaserin were diagnosed with cancer compared to the placebo group, in which 423 or 7.1 percent of patients were diagnosed with cancer. A range of cancer types were reported, with several different types of cancers occurring more frequently in the Lorcaserin group, including pancreatic, colorectal, and lung (Llamas, 2023). At this time, the authors did not have sufficient data to recommend withdrawal. In January 2020, the FDA announced that they were reviewing clinical trial data and alerted the public to a possible risk of cancer associated with Belviq (Lorcaserin) based on preliminary analysis. They said they were taking this action because they believed that the risks of Lorcaserin outweighed the benefits based on their completed review of results from a randomised clinical trial assessing safety. A month later, the FDA requested a withdrawal of Belviq from the U.S. market based on the side effect of increased cancer risk. Now, it is not available anywhere in the world (Llamas, 2023).

Eisai never attempted to introduce Belviq to the New Zealand market. The reason for this is not explicitly stated, however, it is likely that they believed the New Zealand market was too small to be worth the effort of going through Medsafe's approval process. Interestingly, they expanded their marketing contract in 2013 to include most countries worldwide but excluded New Zealand (Eisai, 2016). This case can be interpreted as Medsafe providing 'passive protection' from an unsafe drug. The mere existence of Medsafe possibly prevented a drug that was later proved unsafe from entering the country without having to investigate it. If the algorithm of automatically approving drugs that are recognised by two trusted regulators was in place, then Belviq might have entered New Zealand if it was able to get past the very last stage of multiple agencies like the EMA. However, it never has - so an algorithm would have led to the same outcome for New Zealanders as the presence of Medsafe.

The case of Vioxx demonstrated a lack of active protection on Medsafe's part, albeit an extreme case. The Belviq case demonstrates a potential passive protection of Medsafe existing,

however, in this example, the algorithm would have protected us anyway as the drug did not get approved by two trusted agencies.

We would have also liked to include a case of a drug that was: i) approved overseas and then withdrawn for safety reasons and ii) investigated by Medsafe and rejected. This would be an example of 'active protection'. We could not find any cases of this, as last year Talhah et al. (2022) found that Medsafe had only refused 12 drugs between 2006 and 2022 and only 3 of those are still refused today (Morphine Immediate Release Caps, Lidocaine, and Arrow-Meloxicam 15). These 3 drugs would not have made it through to New Zealand based on the proposed algorithm.

6 Simulation

To envision the effects of the proposed algorithm, we have produced a sample simulation to show what could have happened in New Zealand with some of the withdrawn drugs that we found in our research.

Following the approach in the previous year's report, our simulation holds that there is still an independent drug regulatory body in New Zealand but now with the algorithm of automatically approving a drug that has been approved by at least two trusted overseas regulatory bodies. The trusted regulators used are the ones we decided to include in our research: FDA, EMA, TGA, HPFB Swissmedic, and HSA. Biosimilar drugs are excluded; only the same drug that is approved by two overseas regulators is also approved here. Below is a random sample of overseas withdrawn drugs from our dataset and what would have happened in New Zealand if the algorithm was implemented in lieu of Medsafe's current regulatory procedures.

Sibutramine

The FDA, TGA, HPFB, and Swissmedic withdrew approval in October 2010 (FDA, 2010; TGA, 2010; CBC, 2010; Leybold-Johnson, 2015) after manufacturers voluntarily withdrew the drug from markets. EMA disapproved the drug slightly earlier, in January 2010 (EMA, 2010) before it was voluntarily withdrawn from markets. Therefore, if the formula was applied, the drug would likely have been withdrawn from the New Zealand market in October 2010, as this would be the point when at least two international agencies had disapproved it. Therefore, in this case, the formula would have had no impact on the timeframe in which approval for Sibutramine was withdrawn within New Zealand, as Medsafe also withdrew approval for the drug in October 2010 (Medsafe, 2010b).

Thelin (Sitaxentan)

Thelin (Sitaxentan) was voluntarily withdrawn worldwide by Pfizer on December 10th, 2010. Pfizer made this decision after new information was found about two fatal cases of liver failure that were causally related to Thelin (EMA, 2018). Thelin had initially been approved in 2006 by the EMU, TGA, and HPFB (Pfizer, 2010). It appears Pfizer never made an application to Medsafe for the distribution of Thelin in New Zealand. If the algorithm was applied in this case, Thelin would have been approved in New Zealand in 2006 before being withdrawn globally in 2010. This would mean that the potentially harmful drug would have been in New Zealand for four years. The possible harm of the drug (here, two fatalities in four years) would need to be considered as a trade off against expediting the approval of safe and effective drugs into New Zealand with this algorithm.

Dextropropoxyphene

Medsafe withdrew Dextropropoxyphene from the New Zealand market in August 2010 as a result of studies concluding that the risks from taking dextropropoxyphene exceeded the benefits (Medsafe, 2010a). Other agencies had already pulled Dextropropoxyphene from their markets as the HSA withdrew the drug in November 2009 (HSA, 2009) and the HPFB in January 2010 (BioSpace, 2010). Other agencies withdrew Dextropropoxyphene shortly after Medsafe: the FDA in November 2010 (FDA, 2010) and the TGA in March 2012 (TGA, 2011). Therefore, if the formula had been applied then Dextropropoxyphene would have been pulled seven months earlier from the market, as two international agencies, the HSA and HPFB, had already withdrawn the drug.

Lartruvo

Lartruvo (key ingredient and common name: Olaratumab) was aimed as a medicine for soft tissue-affecting cancers (European Medicines Agency, 2016). It was authorised in October 2016 by the FDA (U.S. Food & Drug Administration, 2016), in November 2016 by the EMA (European Medicines Agency, 2019), and in January 2019 by the HPFB (Stone & Fox, 2018). It was also authorised by Swissmedic in or before March 2017 (Lilly, 2017), though official approval records were not found. No application to Medsafe was found for Lartruvo. However, implementing the proposed formula would have resulted in approval of Lartruvo for New Zealand in November 2016 (assuming Swissmedic's approval was granted in 2017). Lartruvo was later found to lack the efficacy required to be a viable and worthwhile medicine, so it encountered a cascade of discontinuations, revocations, and approval withdrawals. This began in April 2019 by the EMA (European Medicines Agency, 2019), followed by Swissmedic on July 31st, 2019 (Swissmedic, 2019), then the FDA on February 25th, 2020 (Food and Drug Administration, 2020), and finally by HPFB on June 4th, 2020 (Drug Shortages Canada, 2020). Implementation of the formula would therefore have resulted in the approval for the New Zealand market of an unsuitable medicine that would not have been otherwise present. If withdrawals followed the same rule, Lartruvo would have been approved in New Zealand for nearly three years.

7 Limitations and Recommendations

In conducting research for this report, some limitations became apparent. One limitation was the lack of comprehensive and easily accessible data for some regulatory bodies. The absence of detailed and up-to-date information restricted the depth of analysis and hindered robust comparisons. Additionally, the time allocated for the research was limited, which, considering the potential scope of the project, constrained the breadth and depth of our analysis. This was amplified for the regulatory bodies for whom data was difficult to source.

Further research could build on our work and extend our database. A more comprehensive dataset may provide different insights, or greater strength to our findings. In addition, Medsafe is also responsible for the approval of medical devices in New Zealand. Therefore, future research could explore this aspect of regulation, and compare Medsafe with other agencies in this regard. By addressing these areas in future research, a more comprehensive understanding of the efficacy of Medsafe - and the potential implications of replacing it with the proposed formula - can be developed.

8 Conclusion

The proposed formula stipulates that in order for a drug/medicine to be approved for use in Aotearoa New Zealand, it must first be approved by two other regulators from a selection of trusted international authorities. Similarly, we stipulate that a drug would be withdrawn from the New Zealand market if/once it is withdrawn by at least two 'trusted' regulators. This research evaluated seven potential regulators that could form that list and compared their decisions on identified medicines to those of New Zealand's regulator, Medsafe. The seven assessed were the regulators for the USA, the EU, Australia, Canada, Switzerland, Japan, and Singapore. As mentioned above, the PMDA was removed from consideration for use in the formula following initial research that produced minimal results from that set. Thus, evaluation of the formula fell solely to the initial six bodies.

Our research found no cases of drugs/medicines that were kept in the market in New Zealand by Medsafe whilst having approvals withdrawn overseas. Medsafe hence acted in step with international regulators. Within the scope of this study, medicines approved in New Zealand were always approved by other regulatory bodies as well. Further, there were no instances found of medicines being withdrawn from the New Zealand market where they were not also withdrawn overseas. This finding thus supports the application of the proposed formula. Its use would lead to very similar results – the same products being withdrawn for safety and/or business reasons – as currently found through Medsafe's research, but potentially expedited and at lower costs given the removal of now-extraneous investigations by Medsafe.

However, it is feasible that the use of this formula would allow entry of unsafe medicines to the New Zealand market which would not have entered under the existing Medsafe structure. These are cases where Medsafe might be protecting us passively, through the administrative burden imposed on pharmaceutical companies. Whilst our research did not find evidence that Medsafe's approvals differed from those of international regulators, as per the formula, it did establish cases of medicines being approved internationally without ever appearing in the Medsafe register. That is to say, some medicines that are approved overseas and then later withdrawn are never even considered for the New Zealand market. In other words, manufacturers sometimes do not even approach Medsafe in the first place, presumably due to the extra costs and the relatively small market here. This passive protection thus gives rise to one potential drawback of the proposed formula: whether it inadvertently exposes Aotearoa New Zealand to dissatisfactory drugs that it would not have encountered if operating under its own regulatory body, Medsafe.

One potential solution to mitigate or minimise this could be through introducing a delay between international approvals and the subsequent approval for the Aotearoa New Zealand market. Excluding emergency situations, such as the approval process for COVID-19 vaccines, a four-month buffer could be introduced to allow observations of initial market reactions in other jurisdictions before automatic approval here. Determining the ideal length of such a gap is another potential extension to our research.

The potential cost and time savings of applying the proposed formula should be weighed against the loss of active and passive protection. Our research to date found little cause for concern, with the data primarily consisting of cases where this formula would be beneficial. However, that is evaluating purely the number of cases for each circumstance. It does not capture the potential gravity of an error - or the extent of financial and time savings.

9 Acknowledgements

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11 Appendix I.

Drug Research Link:

https://docs.google.com/spreadsheets/d/12aRQ82tHC0UdBb5o_NSNdIhaO7FCfON7SVXa6HsCgWo/edit#gid=1631006949

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