FDA Approval Delays for Drugs First Approved Abroad, and the RESULTS Act

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INTRODUCTION

This paper examines delays in FDA approvals of drugs that have been on the market abroad. As in-depth examples, we focus on domperidone (Part I) in treatment of gastroparesis and mifamurtide (Part II) for osteosarcoma. We discuss the RESULTS Act (Part III), a bill that would force the FDA to approve drugs that have been approved for marketing in countries with well-respected regulatory systems, as well as our recommendations (Part IV).

PART I – DOMPERIDONE (GASTROPARESIS)

Gastroparesis is a disorder in the gastric motility that delays gastric emptying. Normally, the stomach uses muscular contractions to grind and then push the chyme (liquefied food) to the intestine at the appropriate rate for continued digestion and absorption.¹

In the case of gastroparesis, these muscular contractions are impaired. As a result, the stomach empties its contents too slowly leading to the acute symptoms of gastroparesis – abdominal pain, fullness, nausea, and vomiting. The defective movements of the stomach can be because of many underlying health problems, including diabetes, infection, neurological disorders, side-effects of medication, or following gastric surgery. A large percentage of gastroparesis cases is idiopathic which means that there is no known cause.

Gastroparesis has a major impact on quality of life, and the maintenance of normal eating habits is difficult. In severe cases, some patients are hospitalized because of their inability to eat and digest food properly.

Symptoms

The common symptoms that associated with gastroparesis are:²

- Nausea
- Vomiting
- Bloating
- Abdominal pain
- Early sensation of satiety
- Changes in blood sugar levels
- Lack of appetite
- In severe cases: weight loss and malnutrition

¹ http://www.gastroparesisclinic.org/index.php?pageId=1149&moduleId=195a
² http://www.mayoclinic.org/diseases-conditions/gastroparesis/basics/symptoms/con-20023971
Also, gastroesophageal reflux disease (GERD) can be associated or even caused by gastroparesis.

The difficulty in treating these symptoms arises because they are similar to a number of other diseases. As a result, medical and physical testing should be considered to determine if gastroparesis is the cause of the patient’s symptoms.

**Types & Causes**

**Idiopathic gastroparesis** (36%): A large percentage of gastroparesis cases is idiopathic which means that there is no primary known cause for its symptoms, but sometimes the symptoms can begin following an infectious episode.

**Diabetic gastroparesis** (29%): Diabetes Mellitus is the most common disease associated with gastroparesis as almost 20-50% of longstanding diabetic patients experience gastroparesis.

**Post-surgical gastroparesis** (13%): The symptoms can begin after a surgery performed to the upper gastrointestinal tract.

**Statistics**

It is difficult to estimate the number of patients having gastroparesis because up to 4% of the population may experience gastroparesis-like symptoms. For example, the number of patients with gastroparesis caused by diabetes is estimated based on the number diabetic patients. So, statistics suggest that more than 1.5 million Americans suffer from severe gastroparesis. Unfortunately, standard medical therapies fail to relieve symptoms associated with gastroparesis in 30,000 of these patients.

The National Institutes of Health (NHI) in the United States estimated that five million Americans suffer from gastroparesis. Also, women are more commonly affected than men; indeed, 80% of all patients with gastroparesis are women.

**Treatment Options**

Gastroparesis cannot be cured, instead its symptoms are managed. Along with various treatments, health care professionals usually recommend patients to manage their dietary routine to increase the response rate to the treatment.

1. **Dietary therapy:**

Dietary therapy is considered to be the first line of management because it is important for gastroparesis patients to restore fluids and electrolytes levels through nutritional support. Also, it is important for patients with diabetes-induced gastroparesis to monitor and control their glucose levels.

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4 [http://digestive.templehealth.org/content/Gastroparesis.htm#Statistics about gastroparesis](http://digestive.templehealth.org/content/Gastroparesis.htm#Statistics about gastroparesis)
2. Prokinetic therapy:

Prokinetic therapy improves gastric emptying and the symptoms associated with gastroparesis. Of course, the benefits and risks of treatment must be taken into consideration. Figure 1 shows a treatment algorithm provided by the American Journal of Gastroenterology, Clinical Guideline: Management of Gastroparesis-2013. In addition to dietary modification, prokinetic therapy should be administered. Metoclopramide is the initial drug of choice; if patients do not respond to metoclopramide, domperidone and erythromycin should be employed.

![Figure 1. Algorithm for prokinetic therapy in gastroparesis.](image-url)

### Table 2: Treatment options for Gastroparesis

<table>
<thead>
<tr>
<th>Class</th>
<th>Metoclopramide</th>
<th>Domperidone</th>
<th>Erythromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Class</em></td>
<td>D2 (dopamine)-receptor antagonist. Also, acts as an agonist on serotonin 5-HT4 receptors and causes weak inhibition of 5-HT3 receptors, which is responsible for side effects seen in the peripheral and central nervous systems.</td>
<td>Peripherally selective dopamine D2-receptor antagonist. Domperidone is as effective as metoclopramide, but with fewer central side effects.</td>
<td>Macrolide antibiotic and a motilin receptor agonist. Erythromycin is the most potent prokinetic drug when administered intravenously. It is given intravenously in severe cases as initial management of hospitalized patients.</td>
</tr>
<tr>
<td><strong>FDA status</strong></td>
<td>The only FDA-approved drug for gastroparesis. It has a black box warning.</td>
<td>It is available only under an expanded access IND – an FDA program that allows prescribing by doctors who must participate as investigators under the expanded access IND (Investigational New Drug Application).</td>
<td>Approved as an antibiotic agent – used off-label (short course) in patients with persistent symptoms while taking metoclopramide.</td>
</tr>
<tr>
<td><strong>Formulations</strong></td>
<td>Oral dissolution tablet, oral tablet, liquid formulation, and parenteral formulation</td>
<td>Oral tablets, suspensions, suppositories</td>
<td>Oral, liquid, and parenteral formulations</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Tardive dyskinesia, acute dystonia (repetitive involuntary abnormal movements) and severe anxiety and depression due to its ability to easily cross the blood-brain barrier. Metoclopramide can be associated with QT interval prolongation.</td>
<td>Prolong corrected QT interval (treatment should be suspended if the corrected QT is &gt; 470 ms in male and over 450 ms in female patients). It may also cause increased prolactin levels.</td>
<td>Abdominal cramps, nausea, slow small intestinal transit, and increased risk of sudden cardiac arrest. Also, due to the risk of QT prolongation, the drug should not be administered if the QT is &gt; 450 ms in men and over 460 ms in women.</td>
</tr>
</tbody>
</table>

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3. Antiemetic agents:

Drugs such as phenothiazine (prochlorperazine and thiethylperazine) or antihistamine agents (promethazine) are the most common antiemetic agents for gastroparesis. Promethazine can cause sedation and possible cardiac toxicity (corrected QT prolongation).

4. Tricyclic antidepressants:

TCA can be considered for refractory nausea and vomiting in gastroparesis; however, this class of drugs does not address abdominal pain associated with the disease.

FDA AND DOMPERIDONE

Currently, domperidone is not approved for marketing and sales in the US. On June 7, 2004, the FDA published a warning that any kind of distribution, including compounding, for domperidone is considered illegal. FDA made this decision primarily because of the associated health risks of domperidone when used by nursing women to increase lactation, a known side effect of domperidone. Health risks include prolonged QT interval, cardiac arrhythmias, cardiac arrest, and sudden death. FDA allows the use of domperidone only through an expanded access investigational new drug application (IND) for patients who are older than 12 years old for specific conditions including gastroesophageal reflux disease, gastroparesis, and chronic constipation.

Physicians who intend to submit an IND for domperidone should download the Domperidone Packet from the FDA website. The IND packet which contains the required forms, instructions. They also can contact the Division of Drug Information (DDI) to discuss domperidone.

Domperidone IND Packet

There are two types according to the number of patients. If a physician is intended to treat one patient, he has to submit Single Patient IND (SPI) that should include all of the following:

- Cover letter
- Form 3926
- Clinical protocol
- Copy of the Informed Consent document that will be used, which will be reviewed by the institutional review board IRB

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6 https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm
If a physician is intending to treat multiple patients, he should submit Intermediate Size Patient Population (multi-patient) IND that should include all of the following:

- Cover letter
- Form 1571
- Form 1572
- Clinical protocol
- Copy of the Informed Consent document that will be used, which will be reviewed by IRB

While conceptually a good idea, the problem with the IND domperidone packet is that filing the appropriate paperwork and performing the required reporting is very tedious and time consuming for physicians whose primary job is treating patients, as opposed to performing clinical research. The latter often have multiple staff members that assist in managing clinical trials; the former do not have the infrastructure to comply with the requirements, therefore, they refrain from doing so. For example, the responsibilities as a Sponsor-Investigator of an IND listed in the IND domperidone packet include:

- Obtaining informed consent of patients to be treated under the IND
- Monitoring patients treated under the IND
- Maintaining control of and keeping records on the drug dispensed under the IND
- Notifying FDA of any changes made to the IND (e.g., changes to the protocol, a change in drug supplier)
- Reporting to FDA serious, fatal, and/or life-threatening adverse events that are associated with use of the drug
- Submitting an annual report to the IND within 60 days of the anniversary date that studies are initiated (i.e., begin administering the investigational drug) which is usually 30 days after FDA receives the application.
- Regularly visiting the FDA Website for important updates to the packet, e.g., regarding drug interactions or protocol changes.

**Prolonged QT Interval**

As shown in Figure 2, the QT interval is the time between the Q wave’s start and the T wave’s end in the heart electrical cycle.

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10 https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf
In simple words, it is a measure that represents the time that the heart’s ventricles take to contract and relax. The normal QT interval should be between 360 to 440 ms (milliseconds); however, it varies according to the age and gender.\textsuperscript{12}

The danger with prolonged QT interval is the development of Torsdaes de Pointes, a polymorphic ventricular tachycardia that may degenerate into ventricular fibrillation and cardiac arrest.\textsuperscript{13}

In a study of 44 patients, domperidone was shown to prolong QT interval minimally, transiently, and in a dose-limiting fashion.\textsuperscript{14} The double-blind, four-way crossover trial

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
 & Age 1 to 15 & Adult man & Adult woman \\
\hline
Normal & <440 ms & <430 ms & <450 ms \\
\hline
Borderline & 440 to 460 ms & 430 to 450 ms & 450 to 470 ms \\
\hline
Prolonged & >460 ms & >450 ms & >470 ms \\
\hline
\end{tabular}
\caption{QT interval averages}
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\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Illustration of ECG components}
\end{figure}


\begin{itemize}
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The double-blind, four-way crossover trial\(^\text{15}\) was performed in a single center. It assessed the oral 10 and 20 mg of domperidone effects on QT duration. A wash-out period of 4-9 days separated the treatment sequences. The authors concluded that domperidone in doses up to 80 mg per day did not cause clinically relevant increases in QT interval.

- No participant had a QTcP interval >450 milliseconds during treatment with domperidone 20 mg, moxifloxacin, or placebo.
- One participant (baseline value 443.1 milliseconds) had two QTcP intervals >450 milliseconds measured during domperidone 10 mg treatment—456.1 at 3 hours post-dose on Day 1 and 452.5 milliseconds at 5 hours post-dose on Day 4.
- No participant had a >30 milliseconds change from baseline in QTcP interval during treatment with domperidone 10 mg, domperidone 20 mg, or placebo.
- After a moxifloxacin dose, one participant had a >30 milliseconds increase from baseline QTcP value at 5 hours post-dose on Day 1 (412.6–443.5 milliseconds).
- Non-specific, flat T wave abnormalities were observed in one participant each in the placebo and domperidone 20 mg groups and two participants each in the domperidone 10 mg and moxifloxacin groups.
- There were no abnormalities in U-wave morphology or ECG morphology findings.

**Domperidone vs Metoclopramide:**

Metoclopramide is the only drug approved by the FDA to treat gastroparesis; it is effective in approximately 40% of patients.\(^\text{15}\)

Moreover, metoclopramide can cause serious central adverse effects because it can cross the blood brain barrier resulting in uncontrollable muscle movements in the limbs, face, arms, and legs (extrapyramidal effects). Additionally, it can worsen underlying anxiety and depression. Due to its serious side effects, metoclopramide has a black box warning from the FDA.

Alternatively, domperidone is a peripherally selective dopamine D2-receptor antagonist. As a result, it does not readily cross the blood-brain barrier, rarely causing extrapyramidal side effects. In fact, domperidone is considered the gold standard for treating gastrointestinal symptoms in patients with Parkinson’s disease (PD) because the risk of developing extrapyramidal adverse effects is considered minimal.\(^\text{16}\)

**Domperidone Status in Europe**

Domperidone was developed by Janssen Pharmaceutica in 1974 and was approved for use in Belgium in 1978.\(^\text{17}\)

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\(^\text{15}\) https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021793s008lbl.pdf
\(^\text{16}\) https://www.ncbi.nlm.nih.gov/pubmed/23656449

FDA Approval Delays for Drugs First Approved Abroad, and the RESULTS Act
On March 7th, 2014, the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) completed a review of domperidone and provided recommendations that incorporated “all of the available evidence on the effectiveness and safety of domperidone, including published studies and reviews, experimental data, reports of side effects, post-marketing studies and other external information and comments.”

The committee suggested the followings:

- Domperidone should only be used to relieve symptoms of nausea and vomiting
- Oral dose should be reduced to 10 mg up to three times daily for adults and adolescents weighing 35 kg or more.
- Patients may also be given the medicine as suppositories of 30 mg twice daily
- For children and adolescents weighing less than 35 kg, Domperidone should be given by mouth at a dose of 0.25 mg per kg bodyweight up to three times daily.
- It must not be given to patients with moderate or severe impairment of liver function, or in those who have existing abnormalities of electrical activity in the heart or heart rhythm.
- Products supplying a dose of 20 mg by mouth, and suppositories of 10 or 60 mg are no longer recommended for use and should be withdrawn.

PRAC considered that reducing the recommended dose and duration of treatment was a particular key to minimizing the risks with domperidone.

Domperidone worldwide

Domperidone was first developed and marketed in 1978 by Janssen Pharmaceuticals and since then it has been used regularly by millions of people in over 100 countries worldwide (e.g., throughout the European Union, Canada and Mexico and countries in the Middle East, for example, Egypt) for variety of gastric disorders.

In the United Kingdom, there are approximately two million prescriptions for domperidone written annually. Moreover, it is even available over the counter in some of these countries.

In Canada, domperidone, which has been on the market since 1985, two million prescriptions were written in 2013. At the time of their review of domperidone in 2015, Health Canada received just 18 reports of adverse heart effects from taking domperidone none, of which were death. Twelve of these cases were evaluated to determine whether the adverse effects were related to domperidone. As stated in the Summary Safety Review of Domperidone:

“It is difficult to determine to what extent domperidone contributes to heart events because other conditions known to cause electrical heart problems were also present in many cases.”

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In contrast, in the US, even though the FDA categorizes gastroparesis as a “serious life-threatening condition,” domperidone has never been approved by the FDA to treat any condition.

The FDA’s major concern with domperidone is QT prolongation; however, there are about 150 FDA-approved drugs that also are linked with QT prolongation.20 These drugs are being used for variety of medical conditions including cardiac problems. Surprisingly, one of these 150 drugs is even available over the counter - diphenhydramine (Benadryl), a very popular remedy for a variety of uses including allergic responses, cough, and insomnia.21 In 2014, just one preparation of diphenhydramine posted annual sales in excess of $120 million, which represents a 29.3% share of the $411 million sleep-aids market.22

There remain many open questions and conflicting studies regarding the dose of domperidone required to prolong the QT interval, and whether this is observed in otherwise healthy individuals or confined to patients with underlying heart disease.

**Practical Considerations**

Domperidone, like many drugs, may cause side effects and can be very dangerous in high doses. It is globally acknowledged, however, that the drug is effective in treating the symptoms of gastroparesis. The FDA is an outlier among its peers in developed countries in severely restricting the availability of domperidone. Practically, the expanded access IND is a huge hurdle that few practicing physicians are capable of clearing given the time constraints of their busy clinical schedules. Although the FDA has instituted programs to obtain the patient’s voice in drug development and approval, it seems not to be listening to patients with gastroparesis. We believe they deserve more consideration. The following issues are the most pressing:

1. **Eligibility in the domperidone expanded access IND program:**

   Some patients in desperate need of the drug are not even eligible for the domperidone IND program, for example, those younger than 12 years of age.

   Cassie Le’s daughter spent the first seven months of her life unable to eat without vomiting and her doctors tried everything and nothing worked; a feeding tube was placed.23 Her doctors tried domperidone, which was obtained via compounding. By age of four, the doctors removed the feeding tube and the girl started to eat normally again. Unfortunately, this came to an end in 2004 because of the new restrictions of the FDA that considered even the compounding of domperidone to be illegal. As a result, the only access for this little girl to domperidone is through the expanded access IND program, however, she is too young to qualify.

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22 http://adage.com/article/cmo-strategy/p-g-preparing-expansion-zzzquil/293998/  
2. Patient’s voice, FDA patient-risk assessment – let patients decide

Colleen Beener is 62 years old and she has taken domperidone for over 15 years without any heart problems. She is very cognizant of the side effects associated with it, yet she chooses to take it. She said that whatever it takes, she will get that drug.

“I am choosing quality of life over quantity of life, I don’t want to spend my days in bed. And if I get 10 years less because of that, so be it. I want to enjoy my grandkids. I want to enjoy my life, and domperidone helps me do that.”

The FDA developed a Benefit-Risk Assessment Framework to guide drug development and approval decisions. And the FDA is committed to meeting with patients to obtain their input as part of the Patient-Focused Drug Development effort.

The following is quoted from a meeting entitled, “The Voice of the Patient, Patient-Focused Drug Development Initiative - Functional Gastrointestinal Disorders.” The Public Meeting was on May 11, 2015.

Metoclopramide:

The most commonly discussed treatment was Reglan (metoclopramide). One participant with gastroparesis noted that after being put on Reglan, she was able to start eating regularly and “suffered less nausea and dizziness”; however, she continued to suffer from severe fatigue. Another participant commented that Reglan was a promising treatment for her when she first started the treatment, but she “quickly started developing some early tardive dyskinesia-type symptoms.” Other participants shared significant downsides to Reglan including more frequent vomiting, restless leg syndrome, and neurological side effects. A few participants also shared experiences where Reglan did not improve their symptoms at all.

Domperidone:

Several participants commented that domperidone was a part of their treatment regimen. One participant with gastroparesis commented that upon taking domperidone, she had “immediate, complete, reliable relief,” with no adverse effects. Some participants noted that higher dosages of domperidone resulted in higher hormone levels (such as prolactin); these participants shared that their physicians would make dosage adjustments accordingly. Finally, other participants commented that they were unable, unwilling, or afraid to take domperidone, since it is not an FDA-approved drug.
What practical steps has the FDA taken to respond to those perspectives? Unfortunately, none. We believe that patients should be empowered to decide in consultation with their doctors, and that domperidone should be readily available to them.

3. Monitoring and excluding criteria:

In its report in 2014, the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) stated that:28

The Committee’s recommendations follow a careful assessment of all the available evidence on the effectiveness and safety of domperidone, including published studies and reviews, experimental data, reports of side effects, post-marketing studies and other external information and comment. Domperidone was clearly associated with a small increased risk of potentially life-threatening effects on the heart. This was seen particularly in patients older than 60 years, those taking daily doses of more than 30 mg and those taking other medicines that have similar effects on the heart or reduce the breakdown of domperidone in the body.

Not surprisingly, domperidone side effects and the attendant risks increase with dose level. A simple solution would be to partner with Apple, for example, to develop an application that monitors EKG’s via iPhones and Apple Watches. The system could alert the patient and alert emergency services in the event of increased QT interval or Torsades de Pointes. For those patients with underlying heart problems, the use of this technology would be invaluable – they could even be tested in a tightly monitored setting to see the effects of several doses before they take the drug in an unsupervised fashion.

Canada and the European Union have limited the availability of domperidone to the 10-mg oral formulation in doses not exceeding 30 mg per day. And, use is further restricted in patients with underlying heart conditions or when risks increase.29

Risks increased in:

- Patients taking domperidone at doses greater than 30 mg a day
- Patients over 60 years of age
- Patients taking domperidone together with drugs that can lead to increased domperidone blood levels or with drugs that are known to affect the electrical activity of the heart.

4. By approving 10 mg Domperidone, the FDA will be protecting patients

FDA authorizes only one pharmacy in the U.S to supply domperidone through the IND program. Also, FDA is aware that many patients are attempting to procure the drug from other sources outside the US, and apart from IND program. For instance, some patients can buy domperidone over the counter in Mexico or many other countries. By doing so,

- Patients are not informed properly about appropriate use
- They are not aware of what to expect in terms of side effects
- Drug quality is questionable
- Their medical histories will not contain information on domperidone use
- They will not be monitored with the regular tests to ensure safety

5. Domperidone should be approved for patients with Parkinson’s Disease:

As mentioned above, domperidone is a peripherally selective dopamine D2-receptor antagonist. As a result, it does not readily cross the blood-brain barrier and it rarely causes extrapyramidal side effects. In fact, domperidone is considered the gold standard for treating gastrointestinal symptoms in patients with Parkinson’s disease (PD) because the risk of developing extrapyramidal adverse effects is considered minimal.

6. Limited course of therapy (6 months)

Domperidone is acknowledged worldwide to be an effective drug for nausea and vomiting. American patients should have a safer, more convenient way of obtaining a medication that could improve their quality of life, even if it is approved for use over a limited period (for example, 6 months). Doctors and patients can decide together, after an initial trial use of the drug, whether continued use is warranted and appropriate.

Personal Experience

One of the authors of this paper (Eman Makar) has taken domperidone – “From a very painful personal experience, domperidone was the only product that made the food stay in my stomach. I was treated with this drug for more than six months in Egypt at the 10-mg dose three times per day. I am lucky enough as I was not living in the U.S at this horrible time of my life.”

PART II – MIFAMURTIDE (OSTEOSARCOMA)

Osteosarcoma is the type of bone cancer that affects young people most frequently in the femur, tibia and humerus. It is the most common type of cancer that arises in bones and accounts for 3% of cancers in children; less than 1,000 patients develop osteosarcoma in the U.S annually.31 At diagnosis, osteosarcoma has spread in about 15 to 20% of patients, typically to the lungs and other bones.32 Unfortunately, clinical outcomes have stagnated over the past 20 years.

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\(^{31}\) http://sarcomaalliance.org/what-you-need-to-know/bone-sarcoma/
\(^{32}\) https://www.stjude.org/disease/osteosarcoma.html
Causes of Osteosarcoma

The precise etiology of osteosarcoma is not known; however, it can develop secondary to radiation. Mutations to the retinoblastoma gene (RB1) and p53 are associated with its development. It is often found in male teenagers who tend to be taller for their age.33

Osteosarcoma Signs and Symptoms

The most common symptoms of include:34

• Pain
• Swelling in the leg or arm
• Decreased joint motion
• Fracture (broken bone), less common

Treatment Options for patients with Osteosarcoma

Treatment of osteosarcoma is usually includes surgery, chemotherapy and radiation therapy.35

Before considering surgery, most patients with high grade tumors receive three months of chemotherapy. After completing the chemotherapy, surgeon will then remove the tumor to make the area free of the disease. Most tumors can be removed safely while sparing the involved limb - metal implants and allografts are used to replace diseased tissue.

After surgery, the necrosis rate of the tumor (the percentage of tumor cells that are dead) is evaluated to determine whether the tumor is responding to the chemotherapy. The decision to administer additional chemotherapy is subsequently made.

Radiation therapy is not commonly used in osteosarcoma treatment; however, it is recommended in when the tumor is difficult to remove surgically or when residual tumor cells remain after surgery.

Stages of Osteosarcoma

The MSTS (Musculoskeletal Tumor Society) system, also known as the Enneking system, is based on three key factors:

• The grade of the tumor (G)
• The extent of the main tumor (T)
• Metastasis to nearby lymph nodes (M)
Table 4: Illustration of osteosarcoma stages.\textsuperscript{36}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade of tumor</th>
<th>Extent of tumor</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>G1 Low grade</td>
<td>T1 intracompartmental</td>
<td>M0 (not spread)</td>
</tr>
<tr>
<td>IB</td>
<td>G1</td>
<td>T2 extracompartmental</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>G2 high grade</td>
<td>T1</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>G2</td>
<td>T2</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>G1 or G2</td>
<td>T1 or T2</td>
<td>M1 (spread)</td>
</tr>
</tbody>
</table>

Intracompartmental (T1) tumors are limited to the bone, while extracompartmental (T2) tumors extend beyond the bone into other nearby structures.

- Stage I: Low-grade, localized tumors.
- Stage II: High-grade, localized tumors.
- Stage III: Metastatic tumors (regardless of grade)

Survival of Patients with Osteosarcoma

As with virtually all cancers, survival rates are higher for patients with low grade disease, and lower when disease has spread:\textsuperscript{37}

- If the disease is localized (has not spread to other areas of the body), the long-term survival rate is 70 to 75%.
- If the disease has spread to the lungs or other bones at diagnosis, the long-term survival rate is about 30%.

Mifamurtide

Mifamurtide, liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE or MEPACT\textsuperscript{38}), is indicated (outside the US) in children and young adults for the treatment of high grade resectable non-metastatic osteosarcoma.\textsuperscript{39} It is used in combination with chemotherapy following complete surgical resection of the tumor.

Very few drugs to treat osteosarcoma have become available over the last two decades; two such drugs are levoleucovorin (Fusilev\textsuperscript{40}) and mifamurtide, the latter of which was granted orphan drug status by the FDA in 2001 and by the European Medicines Agency (EMA) in 2004.\textsuperscript{41}

\textsuperscript{36} https://www.cancer.org/cancer/osteosarcoma/detection-diagnosis-staging/staging.html
\textsuperscript{37} https://www.stjude.org/disease/osteosarcoma.html
\textsuperscript{38} http://www.takedaoncology.com/medicines/mepact
\textsuperscript{40} http://www.fusilev.com/downloads/m1-14-1-3-1125-000503-clean.pdf
\textsuperscript{41} http://monocl.com/consulting/2015/07/15/osteosarcoma-a-rare-disease-in-need-of-new-treatments/
The rationale for using mifamurtide in osteosarcoma is to imitate infection, thereby triggering an immune response that helps to eliminate micrometastases that were not eliminated by prior chemotherapy.\(^4^4\)

**Dose:**

Mifamurtide should be administered following surgical resection of osteosarcoma. The recommended dose is 2 mg/m\(^2\) body surface area. It should be administered twice weekly at least 3 days apart for 12 weeks, followed by once-weekly treatments for an additional 24 weeks for a total of 48 infusions in 36 weeks.\(^4^5\)

**Mifamurtide INT 0133 Study\(^4^6\)**

INT 0133 is the largest completed randomized trial in osteosarcoma. It was conducted from 1993 to 1997 on more than 700 patients with resectable non-metastatic osteosarcoma. Mifamurtide increased the overall survival (median follow-up of 6 years) from 70% to 78% (\(p = 0.03\)).

During the first administration of mifamurtide, almost all recruited patients and healthy volunteers experienced some adverse reactions including chills, fever, headache, myalgia, and fatigue. In subsequent dosing, the adverse reactions decreased in intensity and were often no longer observed.

Mifamurtide should be administered with caution with patients who have asthma, since mild to moderate respiratory distress is associated with treatment. Other reported toxicities included concerns include hearing loss and delayed fatigue.

**Mifamurtide status in Europe**

The EMA decision to approve mifamurtide in Europe was based on the assessment of more than 80 studies, the Committee for Medicinal Products for Human Use recommended that the benefits of MEPACT are greater than its risks when used in combination with chemotherapy for high-grade non-metastatic osteosarcoma after the complete surgical resection.\(^4^7\)

Clinical safety and efficacy quoted from the EMA summary document:

*The safety of liposomal mifamurtide has been assessed in more than 700 patients with various kinds and stages of cancer and in 21 healthy adult subjects. Mifamurtide significantly increased the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone. In a randomized phase III study of 678 patients (age range from 1.4 to 30.6 years) with newly-

\(^4^4\) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893760/
\(^4^6\) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893760/
\(^4^7\) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893760/
diagnosed resectable high-grade osteosarcoma, the addition of adjuvant mifamurtide to chemotherapy either doxorubicin cisplatin and methotrexate with or without ifosfamide, resulted in a relative reduction in the risk of death of 28%.

Also, the European public assessment report (EPAR) for Mepact states:

Mepact, used with other anticancer medicines, increased how long patients survived without their disease coming back: 68% of the patients receiving Mepact (231 out of 338) survived without the disease coming back, compared with 61% of the patients who did not receive it (207 out of 340). The risk of dying was also reduced by 28% in patients receiving Mepact.

Current Status of Mifamurtide in USA

Having been rejected in 2007 by the FDA, Mifamurtide is not available to US patients. Although INT-0133 demonstrated an increase in disease-free and overall survival, the FDA concluded that mifamurtide failed to demonstrate efficacy in treating patients with non-metastatic resectable osteosarcoma when administered in combination with chemotherapy. Also, FDA found that mifamurtide had no sufficient evidence of a survival advantage when administered with the standard chemotherapeutic regimen.

WHO's list of essential cancer drugs

The 2014 Review of Cancer Medicines on the WHO List of Essential Medicines includes information about the regulatory status of selected medicines in the USA by FDA and in the EU by the EMA. The review also specifies the licensed indications for each drug on the list.

Mifamurtide is considered an essential medicine. “Essential medicines are those that satisfy the priority health care needs of the population. Essential medicines are selected with due regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative costs and cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford”.

52 http://www.who.int/selection_medicines/committees/expert/20/applications/UICC_EMLreview-regulatory_info_patent_sStatus-2014.pdf?ua=1
53 http://www.who.int/medicines/services/essmedicines_def/en/
**Mifamurtide Testimonial - Diego Morris**

This is the written statement provided by Diego Morris to the Senate Committee on Homeland Security and Government Affairs - “Connecting Patients to New and Potential Life Saving Treatments” - February 25, 2016.

Good morning Mr. Chairman and members of the Committee. Senator Johnson, thank you for inviting me to testify. I am incredibly honored to be with you today. I am grateful to have the opportunity to explain my story and tell you why I am dedicated to the Right to Try movement.

Four years ago, I was a typical 11 year-old boy. I was playing two sports at the time, baseball and soccer. One morning I woke up with pain on the outside of my left knee. I thought it was just a typical sports injury. I continued to play in my games and did everything as usual for a few days. But the pain would not go away and it was causing me to limp. My mom took me to the pediatrician and thank goodness my doctor knew immediately that something was not right. She sent me to an orthopedic surgeon the following day for an X-ray. The doctor told my mom that he believed I had osteosarcoma, a rare type of bone tumor, just by looking at my X-ray.

The orthopedic surgeon sent us down to the lower floor for an MRI and my mom called my dad and asked him to come right over with my little brother, Mateo. My mom told me much later that she felt sick when she saw a technician running out the door. She knew he was running up to tell the surgeon of my results.

Everything happened quickly after that appointment. My parents consulted with many of their physician friends about what we should do next. My parents took the advice of our close family friends, he is a radiation oncologist and she is a pediatrician. They told my parents I needed to have a biopsy as soon as possible at a premier research institution.

Just three days after my trip to the pediatrician we were on our way to St. Jude Hospital in Memphis, Tennessee. We never stopped hoping I did not have cancer. After a long week of different types of tests and scans they performed a biopsy. We knew the surgeons would be looking at a quick type of analysis they perform in the operating room. They look at something called a frozen section during surgery to determine if a person’s tumor is cancerous. If the surgeons determine it is cancer at that point, they go ahead and place a port in the patient’s chest for treatment. When I had barely come out from anesthesia, I whispered to my parents - I asked them “do I have a port?” and they said “yes”. The three of us cried and my life was never the same again.

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After many conversations with physicians, we decided I should start chemotherapy treatment back home in Phoenix, Arizona. My parents came to the conclusion that if I would receive the exact same pre-surgery chemotherapy in Phoenix then I should be close to home, in my own bed as much as possible, surrounded by friends and family who love me. I received chemotherapy for ten weeks at Phoenix Children’s Hospital before returning to St. Jude for limb salvage surgery. I am so grateful the surgeons were able to save my leg and completely remove the tumor. They inserted a significant titanium device in my leg which partially replaced my femur and my knee.

After surgery, the analysis of the tumor indicated that the necrosis, or the amount of the tumor killed off by the initial chemo, unfortunately was only fifty percent. The doctors were hoping to see at least eighty percent necrosis. This meant that I would need to have a very aggressive plan of treatment. I needed a total of twenty-one rounds of chemotherapy, with some of the strongest chemo drugs.

Thank goodness my parent’s physician friends never stopped doing research on every available treatment for me. They told my parents about a drug called Mifamurtide, or MTP. MTP is an immune therapy drug that has improved survival rates for children with osteosarcoma. My parents were excited about the drug but quickly realized it had not been approved in the United States. MTP was available in so many countries all over the world, they were astonished it was not available in America. The trials for MTP had actually been started by physicians in the U.S.! My parents flew to Mexico City with our friend who is a pediatrician to see the results of MTP on their osteosarcoma patients. The doctors there showed them their findings and told my parents I was welcome in their hospital to obtain MTP.

The clock was ticking. In order to have MTP immune therapy I had to start it at the exact time I started my post-surgery chemotherapy - just ten weeks after undergoing significant surgery at St. Jude. My parents communicated with physicians in several countries and, after reviewing the facts of my case, every oncologist determined I fit the criteria and welcomed me at their hospital. My parents never gave up hope they could get MTP in America. They contacted our Congressman, the FDA, the drug manufacturer, and anyone they thought could help us find a way. They even spoke with the lead physicians for the US trials at MD Anderson and at Sloan Kettering. The doctor at Sloan Kettering explained MTP and answered all of my parents’ questions. He told them there are no guarantees with MTP. My parents told him they weren't looking for guarantees - just hope. My dad asked the doctor one last question. He asked whether if (God forbid) the doctor’s child or grandchild had osteosarcoma, would he take them out of the country in order to get MTP? He responded that he would indeed travel for MTP. Little did I know that we were about to make a very significant move in record time.

I will never forget my parents and their friends explaining to me and to my
brother that we were going to London so I could have MTP treatment along with my chemotherapy. We were so upset with my parents at first but ultimately accepted the fact that this treatment might help save my life. Our entire family left our home in Phoenix, Arizona and moved 5,000 miles away. My dad commuted between Phoenix and London for nine months and my mom, brother and I lived with family in England. Throughout my MTP treatment and chemotherapy my parents continued to look for ways to get this treatment at home but it was just not possible.

My chemotherapy treatment was brutal and I was in the hospital more often than not. My dad was always exhausted and hated not being with us when I had to be rushed to the hospital for emergencies. My mom was exhausted too, going back and forth between the hospital and home to take care of me and my little brother. We were blessed to have relatives in England who insisted we stay with them. Many relatives were amazing to us, and showed us so much love and kindness.

But there is no place like home. I felt so isolated. I missed my friends, my home, my puppy and my school.

My family and I were very fortunate to have the resources to relocate to another country to get this potentially life-saving treatment. Most people do not have that option. When my family and I returned to the United States we all agreed we would do anything to help other families not have to go through what we did to get treatment, or worse - not to have a promising treatment at all. So when the Goldwater Institute asked me to serve as the Honorary Chairman of the Right to Try campaign in Arizona I jumped at the opportunity. I am grateful to Darcy Olsen and the other people at Goldwater for giving me the chance to do something positive with my terrible experience. I am grateful to be alive and I am grateful to be here, with your esteemed Committee today.

Mr. Chairman, members of the Committee, thank you for giving me the opportunity to tell my story. I hope and pray we can make it possible for Americans to have easier, faster access to critical medical treatment. Please help us give Americans a better chance to save their own lives and those of their loved ones. No guarantees - just hope. Thank you very much.

As a result of his courageous fight, Diego became the honorary chair for Right to Try in his home state of Arizona.55 “Right to Try” is legislation that allows terminally ill patients to access investigational treatments that have passed basic safety testing (Phase I) with the FDA, but are not yet available on pharmacy shelves.56

“I am so fortunate to be cancer-free” says Diego. “I want to help children who need medical treatment get the medicine they need at home. I want to help others.”

56 http://righttotry.org/faq/
PART III - THE RESULT ACT

"Reciprocity Ensures Streamlined Use of Lifesaving Treatments" Act.\textsuperscript{57}

The FDA approval to market a new drug is a complicated process that can take more than 10 years and cost more than $1 billion. This makes the process of drug development in the U.S. harder not only for drug manufacturers, but also for some American patients with life threatening conditions who spend years struggling in getting new drug that might give them hope.

On December 2015, U.S. Sens. Ted Cruz (R-Texas) and Mike Lee (R-Utah) introduced the RESULT Act. This act would require the FDA to quickly review drugs and devices, and biologic applications from sponsors who have products approved and sold in developed and trustworthy countries. As a result, Americans will have access to drugs and devices that are being currently used and saving lives in other developed countries.

The full text of the RESULT Act can be found here.\textsuperscript{58}

Many cite the case of thalidomide during discussions regarding measures to increase the speed and efficiency of the FDA review and approval process. In 1957, the drug was approved in Germany and subsequently was marketed in 46 countries, with sales nearly matching those of aspirin.\textsuperscript{59}

In 1961, thalidomide was associated with severe birth defects in babies. The drug, when taken during pregnancy, caused babies to be born with phocomelia, resulting in flipper-like limbs. In Germany, 161 babies were adversely affected by thalidomide. In March 1962, the drug was banned in most countries. In July of 1962, President John F. Kennedy praised Frances Kelsey, the FDA inspector at this time, who prevented the drug’s approval in the U.S.

The thalidomide experience was responsible for amendments to the Food and Drug Act that included pregnancy testing warnings and precautions in order to prevent this tragedy from occurring again. So that the RESULT Act would not put Americans at risk, a provision that excludes drugs that have not undergone pregnancy testing would be appropriate.

A study was conducted to assess the potential clinical impact of reciprocal approval legislation.\textsuperscript{60} The analysis focused on the drugs that were first approved outside the USA; it examined a 10-year period of approvals from 2001 through 2010.

The conclusion of the study is that reciprocal approval legislation would most likely benefit only a small number of US patients receiving treatment for rare diseases, and the benefit may be somewhat mitigated by an increased exposure to harms.

\textsuperscript{57} https://www.cruz.senate.gov/?p=press_release&id=2554
\textsuperscript{58} https://www.cruz.senate.gov/files/documents/Bills/20151211_FDA.pdf
\textsuperscript{59} https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation
FDA Approval Delays for Drugs First Approved Abroad, and the RESULTS Act

Figure 3 contains a list of prescription drugs that were first approved outside the USA with novel mechanisms of action in a period of ten years from 2001 to 2010. The median delay between non-US approval and US approval was 415 days.

**Figure 3:** Prescription drugs first approved outside the USA with novel mechanisms, 2001–2010

<table>
<thead>
<tr>
<th>Prescription drug</th>
<th>First approval date (agency)</th>
<th>Log until FDA approval (days)</th>
<th>Mechanism</th>
<th>Main indication(s)</th>
<th>Ophthalmic use*</th>
<th>Alternative therapeutic class(s) as available in the USA?</th>
<th>Outcome of first FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitoxin (Armenian)</td>
<td>3/25/01 (FDA)</td>
<td>66</td>
<td>Agitoxin alpha replacement</td>
<td>Pain (pain)</td>
<td>Yes</td>
<td>Yes</td>
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https://doi.org/10.1136/bmjopen-2017-014582
However, the time gap between non-US approval and US approval was thousands of days in several cases, as indicated in Table 5. In fact, the time gap reached 7 to 10 years in some cases, including Artemether/lumefantrine (Coartem), Ivabradine (Corlentor), Trabectedin (Yondelis), and Vigabatrin (Sabril).

**Table 5:** List of some drugs that were firstly approved outside the U.S, then later they were approved by the FDA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>First Approval</th>
<th>FDA Approval</th>
<th>GAP</th>
<th>Alternative Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone (Esbrite)</td>
<td>Idiopathic pulmonary Fibrosis (IPF)</td>
<td>Japan - February 2008</td>
<td>October 2014.61</td>
<td>2,555 days</td>
<td>No</td>
</tr>
<tr>
<td>Artemether/lumefantrine</td>
<td>Malaria</td>
<td>EMA - November 2000</td>
<td>April 2009.62</td>
<td>2,920 days</td>
<td>Yes</td>
</tr>
<tr>
<td>(Coartem)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Anticoagulation</td>
<td>EMA - July 2008</td>
<td>July 2011.63</td>
<td>1,095 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Ivabradine (Corlentor)</td>
<td>Heart Failure</td>
<td>EMA - July 2005</td>
<td>April 2015.64</td>
<td>3,548 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Trabectedin (Yondelis)</td>
<td>Soft tissue sarcomas</td>
<td>EMA - July 2007</td>
<td>October 2015.65</td>
<td>3,018 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Sugammadex (Bridion)</td>
<td>Neuromuscular blockade reversal</td>
<td>EMA - May 2008</td>
<td>December 2015.66</td>
<td>2,755 days</td>
<td>No</td>
</tr>
<tr>
<td>Vigabatrin (Sabril)</td>
<td>Infantile spasms</td>
<td>Health Canada - January</td>
<td>August 2009.67</td>
<td>5,698 days</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Some of these drugs were developed for serious, life threatening conditions, for example, Ivabradine (Corlentor) is indicated for heart failure; it took 10 years to be approved by the FDA after EMA approval.

Moreover, for some of the drugs such as Pirfenidone (Esbrite) and Sugammadex (Bridion), there were no approved treatments with an alternative therapeutic class available to US patients. A more recent example, not contained in the study or the table, is Bexero, a vaccine for meningococcal group B. First approved by the EMA on January 2013, it was subsequently approved by the FDA on January 2015; that is a gap of 750 days. Before it was approved in the US, the mother of a woman who died from meningitis organized bus trips for dozens of children to Ontario, Canada to be vaccinated, and the mother of a UC Berkley sent her son to England to be vaccinated.

Another example is Galafold (migalastat) a drug used as long term treatment for Fabry’s disease, a genetic disorder, in patients older than 16 years of age. In May 2006, Galafold was designated as an orphan drug. In April 2016, Galafold was approved by the EMA and the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of marketing authorization. In November 2016, FDA rejected the accelerated approval for Galafold and asked its company to generate more clinical data that will not be ready till 2019, at the earliest.

Also, for the first time after 22 years, FDA approved (in May 2017) a treatment for amyotrophic lateral sclerosis (ALS), a debilitating condition in which patients lose the ability to move and eventually to breath. The drug is called Radicava (edaravone); it was firstly approved in 2015 in Japan and South Korea.

The question here is why should American patients suffer, or travel to other countries, to have access to drugs that are approved in Europe, Canada, Israel, and Japan. These countries have sophisticated and respected regulatory systems that are responsive to the health needs of their citizens. Americans deserve nothing less.

Note that Australia’s Therapeutic Goods Administration (TGA) is considering a proposal that would recognize the approval of devices from countries participating in the International Medical Device Regulators Forum (IMDRF).
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Note that Australia’s Therapeutic Goods Administration (TGA) is considering a proposal that would recognize the approval of devices from countries participating in the International Medical Device Regulators Forum (IMDRF).75

PART IV – RECOMMENDATIONS

We believe that the RESULTS Act should be approved and implemented because EU member countries, Israel, Australia, Canada and Japan have rigorous regulatory requirements and patients in these countries have not experienced greater harm from pharmaceu-
tical products than US patients. In order to protect against the possibility of untoward effects akin to those seen with thalidomide, drugs for which reproductive toxicity studies have not been performed should not be eligible for approval under the RESULT Act.

CONCLUSION

We believe that the RESULTS Act should be approved and implemented because EU member countries, Israel, Australia, Canada and Japan have rigorous regulatory requirements and patients in these countries have not experienced greater harm from pharmaceutical products than US patients. In order to protect against the possibility of untoward effects akin to those seen with thalidomide, drugs for which reproductive toxicity studies have not been performed should not be eligible for approval under the RESULT Act.

Innovation is fuel for more innovation. As a result, when FDA delays the approval of an innovative drug, it does not only affect the patients suffering from a disease treated by the drug, it affects ALL patients because this dissuades developers from pursuing truly novel therapeutics. Granting FDA approval to drugs that have been approved for us by rigorous regulatory bodies in other countries (for example, Europe, Israel, Canada, Australia, and Japan) can be done in a manner that does not expose Americans to greater risk. It will provide patients with innovative products, sooner, and encourage drug developers to continue to pursue the development of products that can materially impact the lives of patients afflicted with a myriad of diseases.