[April 27, 2022]

BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

CITIZEN PETITION

San Rocco Therapeutics LLC ("SRT"), (formerly Errant Gene Therapeutics, LLC ("EGT") submits this Citizen Petition pursuant to the Food and Drug Administration's ("FDA") regulations set forth at 21 C.F.R. § 10.30 and 21 C.F.R. § 14.1. For the reasons discussed herein, SRT respectfully requests that the FDA use the utmost scrutiny in reviewing any biologics license application ("BLA") submitted by Bluebird Bio, Inc. ("Bluebird") for Betibeglogene Autotemcel ("Beti-Cel"), also known as Zynteglo in Europe, for β-thalassemia. First, as explained below, there are serious safety concerns. Second, based on documents deposited in New York Supreme court case 150856/2017 (attached), there is ample reason to thoroughly scrutinize the accuracy of the information in Bluebird's BLA. Also, based on the cost of goods, Bluebird has announced an outrageous price for Beti-Cel, which will strain state budgets, bankrupt families, and exacerbate existing inequalities in the healthcare system. The truth behind the ridiculous price is extreme corporate greed. The CEO, Nick Leschly (from 2010-2021) was compensated well over $100,000,000, $24,000,000 alone, in 2018. Finally, after over a decade of deceit and treachery, proven by numerous court documents, Bluebird is also infringing U.S. Patent Nos. 7,541,179 ("the '179 Patent") and 8,058,061 ("the '061 Patent"), titled "Vector Encoding Human Globin Gene And Use Thereof In Treatment of Hemoglobinopathies," (hereafter collectively the "SRT Patents").[1] We urgently but humbly request that the FDA take this all into consideration when making any decision about the submitted Bluebird Bio BLA.

The FDA is the guardian of patients. In recent history we have seen the scandals of Vioxx, Paxil and Oxycontin. With this in mind and the lives which are guarded by your entity we humbly proceed.

I. ACTION REQUESTED

We respectfully request a careful investigation of the BLA from Bluebird seeking a license for Beti-Cel for the treatment of β-thalassemia.

II. STATEMENT OF GROUNDS

A. Factual Background

I am the father of a son with β-thalassemia. I am also the founder of Errant Gene Therapeutics ("EGT"), now known as San Rocco Therapeutics ("SRT"). SRT was founded in

[1] SRT has an exclusive (worldwide) commercial license to the '179 and '061 Patents.

1993, after my son Rocco's diagnosis. Rocco was treated with an experimental fetal hemoglobin enhancing drug Arginine Butyrate. The therapy was administered intravenously and as a consequence we lived in California hospitals. There are 25,000 Thalassemia patients in Italy and 2,500 in all of North America. To bring the medicine to where the patient population is, SRT opened Centro Medico San Rocco in Altamura, Italy in 1995 and provided healthcare free of charge for dozens of patients suffering from hemoglobinopathies.

In 2000, SRT-MSK researcher, Dr. Michel Sadelain published a paper demonstrating the potential of gene therapy in mice. In 2003, MSK informed SRT that MSK would no longer fund the gene therapy for Sickle Cell Disease and Thalassemia. SRT scoured the planet to find a company to sustain the MSK research. SRT was the only entity willing to step up and support this gene therapy project, which by many was considered scientific folly. In 2007, with the herculean support of researchers from Memorial Sloan Kettering ("MSK"), Weill Cornell and National Institutes of Health ("NIH"), SRT became the first team to pass the FDA Recombinant DNA Committee for gene therapy in Sickle Cell Disease and Beta Thalassemia (both SCD and Thalassemia are caused by defective Beta-globin genes and assumed to be cured by the same product). SRT was the first company to get Orphan Drug Designation for Thalassemia in the US and Europe and the first to produce a commercial batch (for 8-10 patients) of gene therapy for Sickle Cell Disease and Thalassemia. The SRT vector uses the natural wild-type beta globin gene.[2] Other companies, such as Bluebird Bio, use a mutant gene. To date, patients treated with the SRT vector have no incidence of clonal dominance, no Myelodysplastic Syndrome and no incidence of AML leukemia.

In January of 2022, Nature Medicine published an article based on the three patients treated on the protocol under Clinical Trial (NCT01639690) with the 2009 SRT-produced vector in the MSK Clinical Trial. The article reports that using reduced-intensity conditioning, that 2 out of 3 Thalassemia patients treated with SRT's vector, have sustained dramatic reduction (43%) in blood transfusions after eight and five years (today ten and seven years), respectively. The article does not report any serious side effects. These patients received a milder 8 mg/kg Busulfan preparation treatment. This is key for patients who have compromised organs, as Myeloablation can be harsh for these subjects. These 3 patients are the only patients treated with SRT's TNS9 in the US, for whom there is a 9-year follow-up.

SRT is the only company with experience using myelosuppression and more studies need to be done to verify the most safe preparation protocol for patients.

Up until 2010, the MSK/SRT relationship was stellar. SRT was set to start clinical trials with MSK and NIH, when the investment firm (Third Rock Ventures) met with MSK and "admitted" that the SRT vector was better than Bluebird's and that they wanted to purchase the SRT vector (attachments 001, 002).

Bluebird's product resulted in the halting of all gene therapy clinical trials by the FDA in June of 2009 (for clonal dominance). Bluebird Bio was essentially founded by bankers and as a father of a Thalassemic patient and as a "father" to innumerably more patients worldwide, I was

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[2] Boulad, F., Maggio, A., Wang, X., Moi, P., Acuto, S., Kogel, F., Takpradit, C., Prockop, S., Mansilla-Soto, J., Cabriolu, A., et al. (2022). Lentiviral globin Gene therapy with reduced intensity conditioning in adults with β-thalassemia: a phase 1 trial. Nature medicine 28

fearful that our superior product would be destroyed or minimally shelved for corporate greed. SRT met with Third Rock Ventures and the company which they owned, Bluebird Bio, on June 10, 2010. SRT refused to sell its gene therapy vector product to Bluebird unless Bluebird guaranteed that the SRT vector, which they also believed superior and safer for patients, would be used. No deal was consummated.

After being rebuffed, Bluebird was desperate. In the 2017 New York Times article "Gene Therapy Hits A Peculiar Road Block: A Virus Shortage," by Gina Kolata, the article states, "Then said Nick Leschly, the company's Chief Executive, he got bad news. Using Bluebird's recipe, the manufacturing company said it was going to cost Bluebird a million dollars to create enough viruses to treat one patient." CEO Leschly plainly stated and is quoted, "We got no virus, it was an Apollo 13 moment. We put everyone in a room, we have to figure this out. Everything at the company is now stopped. Nothing can be done without virus." [3]

Third Rock Ventures and Bluebird Bio executives' solution was to pillage and then sabotage the SRT vector. As a result, patients' lives have been lost and the gene therapy camp decimated. Proof (or evidence) is readily available in court documents. The bankers, however, were successful and over the past decade, Third Rock Ventures and Bluebird Bio executives have bilked billions of dollars from uninformed investors.

In the scheme, Third Rock Ventures and Bluebird Bio leaders made at least hundreds of millions of dollars in profit. In 2018 alone, Bluebird Bio sold over $1,100,000,000 (one billion-one-hundred-million-dollars) in Bluebird shares at $185 and $165 to intentionally misinformed investors. After their bank accounts were filled, they left the vessel. The ship quickly began sinking, costing the lives of patients and the resources of shocked, embittered investors who will not likely ever invest in gene therapy again. Today, the Bluebird CEO has become the Chief Kairos Officer of another ship and the Bluebird stock is trading at $4 a share. The company is warning of bankruptcy (I couldn't have made this up if I tried).

It is our firm belief that if this type of behavior is rewarded or condoned that the detriment to patients and the entire pharmaceutical industry will be colossal. With this shared conviction, illustrious academics, such as Eugene McCarthy have written widely published articles, such as "A Call To Prosecute Drug Company Fraud As Organized Crime." Highly respected physicians and researchers such as Dr. Amanda N. Fader and Dr. Lucio Luzzatto have written articles such as "The Orphan Drug Act: Restoring The Mission To Rare Diseases."

In Bluebird Bio/TRV PowerPoints, it was explained that the SRT vector was 3-5 times more effective and that the purchase of it would add $200,000,000 to the value of Bluebird Bio (attachments 001, 002).

SRT agreed that the IND would be filed by MSK and that MSK would lead the progression of the product.

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[3] https://www.nytimes.com/2017/11/27/health/gene-therapy-virus-shortage.html#:~:text=And%20the%20firms%20are%20itching,viruses%2C%20there%20is%20no%20treatment.

In a lawsuit filed in New York, SRT alleged that a scheme was masterminded to deliver SRT's gene therapy product to Bluebird so that Bluebird could exploit and then shelve SRT's intellectual property. Bluebird/Third Rock Ventures then attempted to implement their own inferior product and eliminated their only competition (attachments 001, 002).

In an email presented to the court, Nick Leschly, CEO of Bluebird, states:

> Pat Girondi—need to shut him down…curious what he called about…my emails were clear want to get him to buy into a CDA to review Michel's data. Be nice, suck up, etc… if you think (and I think) that Michel has valuable data.

It was readily displayed in countless court documents that Bluebird Bio ran a campaign of treachery and deceit to sideline and technically destroy their competitor, which by their own admission had a product which was 3-5 times more efficient and safer for patients (attachments 001, 002).

In June 2019, Bluebird, believing that they had eliminated their only competition, raised the estimated price of its therapy from what analysts assumed would be $750,000 to 1.8 million dollars per patient (Cowen analyst Yaron Werber said, "the list price was above the $750,000 price the investment bank had forecast."). The price is now being quoted at $2,100,000 per patient.

Treachery should not be rewarded.

The initial lawsuit against Bluebird was settled in November of 2020. SRT, after a decade of being blocked, can again begin to make progress for patients.

On October 21, 2021, a legal action was filed against Bluebird for infringement of the SRT Patents pursuant to the Patent Laws of the United States, 35 U.S.C. § 100, *et seq*., including §§ 271(a), 271(b), and/or 271(c), in the United States District Court for the District of Delaware. SRT brought this patent infringement action to protect its rights and investment in its innovations embodied in the '179 and '061 Patents infringed by Bluebird's Beti-Cel which is manufactured using (and containing) the BB305 lentiviral vector.

B. Legal Background

To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to Center for Biologics Evaluation and Research ("CBER") containing "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." 21 C.F.R. § 601.2. If FDA determines not to approve the BLA, the Agency will issue a complete response letter that "will describe all of the deficiencies that the agency has identified in a biologics license application or supplement." Id. § 601.3(a)(1). A BLA can be issued only if CBER determines that "the establishment(s) and the product meet the applicable requirements established" by regulation. Id. § 601.4(a).

C. FDA Should Carefully Consider a License Beti-Cel for the Treatment of β-thalassemia Because the Serious Risks of this Product Outweigh the Benefits.

1. Concerns with Bluebird Bio's Beti-Cel product

Bluebird has had issues in the past with their product, resulting in the halting of all gene therapy clinical trials by the FDA in June of 2009 (for clonal dominance), February of 2021 and again in August of 2021 (for cancer and leukemia).

Bluebird Bio has demonstrated repeated evidence of toxicity to date. The first safety alert came from European Medicines Agency (EMA) in May 2009 whereby on follow up on the first several patients, one patient exhibited a concerning clonal dominance that put a halt on the clinical trials. The EU press release stated, "This clonal dominance seems to result from the integration of the vector into a gene encoding the HMGA2 protein, associated with certain benign or malignant tumors." [4]

On Feb. 16, 2021, Bluebird placed its Phase 1/2 (HGB-206) and Phase 3 (HGB-210) studies of LentiGlobin gene therapy for Sickle Cell Disease (SCD) (bb1111) on a temporary suspension due to a reported Suspected Unexpected Serious Adverse Reaction (SUSAR) of acute myeloid leukemia (AML). [5]

In February 2021, the phase 1/2 SCD trial for LentiGlobin yielded two suspected blood cancer cases — one of Acute Myeloid Leukemia (AML) and one of Myelodysplastic Syndrome (MDS). Bluebird reported that it's "very unlikely" the AML diagnosis is linked to the BB305 lentiviral vector used to deliver the gene therapy, while the MDS diagnosis has been revised to transfusion-dependent anemia. Bluebird's two SCD clinical trials were put on pause because the drug is made using the same lentiviral vector as LentiGlobin. At the same time, Bluebird elected to stop selling Zynteglo in Europe.

On Dec. 20, 2021, Bluebird announced that the FDA has placed its clinical program for Lovotibeglogene Autotemcel (Lovo-Cel) gene therapy for Sickle Cell Disease (SCD) on partial clinical hold for patients under the age of 18.[6]

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[4] https://archiveansm.integra.fr/S-informer/Points-d-information-Points-d-information/Essai-clinique-de-therapie-genique-dans-les-hemoglobinopathies-Observation-biologique-chez-un-patient-traite-Point-d-information

[5] https://investor.Bluebirdbio.com/news-releases/news-release-details/Bluebird-bio-announces-temporary-suspension-phase-12-and-phase-3

[6] https://aldconnect.org/bluebird-bio-statement/

The partial, temporary suspension relates to an ongoing investigation by Bluebird Bio into an adolescent patient with persistent, non-transfusion-dependent anemia following treatment with Lovo-Cel, now 18 months post-treatment.[7]

On August 9, 2021 Bluebird Bio announced that the Elivaldogene Autotemcel (Eli-Cel, Lenti-D®), the company's gene therapy for Cerebral Adrenoleukodystrophy (CALD) in patients less than 18 years of age was placed on a clinical hold, following a Suspected Unexpected Serious Adverse Reaction (SUSAR) of Myelodysplastic Syndrome (MDS). Available evidence suggests that the event was likely mediated by Lenti-D lentiviral vector (LVV) insertion. Consistent with this known risk, two additional cases of MDS have subsequently been reported and details have been shared with the FDA and study investigators. The FDA clinical hold for Eli-Cel is ongoing and all patients who received Eli-Cel in the clinical program continue to be closely monitored, per study protocols. Given the devastating and fatal nature of CALD and lack of other treatment options, Bluebird Bio continues to assess the overall benefit/risk profile of the product as favorable for patients with CALD who do not have a matched sibling donor.

2. Concerns with the Bluebird BLA for Beti-Cel for the treatment of β-thalassemia without an insulator

We attach the recent Nature Medicine article of Dr. Sadelain and team using the SRT vector, produced in 2009 which demonstrates a safer product and the gene therapy lentiviral vector in Thalassemic patients for the longest period of time, in a product intended for the use in both Sickle Cell Disease and Thalassemia (attachment 003).

3. Benefit and Risk Profile

Dr. Sadelain uses reduced-intensity conditioning. Many patients, particularly those with compromised organs, may benefit from reduced-intensity conditioning versus myeloablation used in the Bluebird Bio product.[8]

Requisite for an Insulator to enhance safety:

Several clinical reports have established that globin vectors may be active in producing clones that lead to leukemias. The first was the occurrence of a major clonal expansion in a Thalassemia patient treated with the HPV569 vector (Bluebird Bio's vector subsequently named BB305 after removing the cHS4 insulator).[9]

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[7] https://investor.Bluebirdbio.com/news-releases/news-release-details/Bluebird-bio-announces-partial-clinical-hold-patients-under-18

[8] Boulad, F., Maggio, A., Wang, X., Moi, P., Acuto, S., Kogel, F., Takpradit, C., Prockop, S., Mansilla-Soto, J., Cabriolu, A., et al. (2022). Lentiviral globin Gene therapy with reduced intensity conditioning in adults with β-thalassemia: a phase 1 trial. Nature medicine 28

[9] Negre, O., Bartholomae, C., Beuzard, Y., Cavazzana, M., Christiansen, L., Courne, C., Deichmann, A., Denaro, M., Dreuzy, E., Finer, M., et al. (2015). Preclinical Evaluation of Efficacy and Safety of an Improved Lentiviral vector for the Treatment of β-Thalassemia and Sickle Cell Disease. Current Gene Therapy 15, 64–81).

Recent advances in vector design with the addition of a well characterized insulator to improve safety should be considered by the FDA. For background and in order to provide a stable and suitable vector for efficient globin gene therapy, it is known that certain enhancer elements are needed in an optimized fashion to construct a local control region (LCR).[10]

Specifically, certain elements of the LCR (HS1 and HS2) influence hematopoietic stem cells and myeloid progenitors. This influence is position-dependent and results in activation of promoter genes that could produce clones leading to proliferation and eventual leukemias.[11]

Sadelain and Stamatoyannopoulos (refs above) demonstrated that the addition of an A1 insulator overrides non-erythroid expression without reducing globin expression. In addition, at the 2021 annual American Society of Cell and Gene Therapy conference, a plenary lecture given by Dr. Sadelain[12] detailed the many decades of work to advance a safe gene transfer therapy utilizing lentiviral vectors and now with the addition of an insulator. This seminal work with now the addition of an insulator should be evaluated and considered prior to any drug approval.

The court case between SRT and Bluebird was settled 16 months ago. SRT is presently manufacturing its TNS9 vector with the A1 insulator used to achieve Dr. Sadelain's positive results published in March of 2022. SRT and its scientific team are convinced that with a more modern production and an insulator that SRT will be effective and in patients shortly with a safer product.

4. Public Policy

The first gene therapy product to be approved for a congenital disorder in the United States was Voretigene Neparvovec, for the treatment of vision loss due to inherited retinal dystrophy; this was launched in the market in 2017 at a cost of US $425,000 per eye for a single dose. More recently, Onasemnogene Abeparvovec, for the treatment of pediatric patients with spinal muscular dystrophy, became the most expensive drug on the market, costing the US $2.1 million per dose. With the handful of gene therapies already on the market costing on average 30 times the median household income in the United States per dose, there are growing concerns that not all patients will be able to afford these treatments, and this will exacerbate existing inequalities. Dr. Lucio Luzzatto, former Chair of the ASGCT's Ethics Committee recently commented on the barrier to access for most patients: "Nearly all recently introduced targeted

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[10] Sadelain et.a. Molecular Therapy, 28 February 2022) (ref, Li, Q., Peterson, Kenneth.R., Fang, X., and Stamatoyannopoulos, G. (2002). Locus control regions. Blood 100, 3077–3086)

[11] Maruggi, G., Porcellini, S., Facchini, G., Perna, S.K., Cattoglio, C., Sartori, D., Ambrosi, A., Schambach, A., Baum, C., Bonini, C., et al. (2009). Transcriptional enhancers induce insertional gene deregulation independently from the vector type and design. Molecular Therapy 17, 851–856).

[12] https://www.mskcc.org/videos/2021-asgct-george-stamatoyannopoulos-memorial-lecture

drugs are unavailable or unaffordable." [13] Newly appointed FDA Commissioner Dr. Robert Califf, and Andrew Slavitt, a former Acting Administrator of the Centers for Medicare and Medicaid Services voiced similar concerns in a 2019 editorial, writing:

US drug costs have reached unacceptable and unsustainable levels. Evidence shows that "financial toxicity" arising from drug costs and other medical expenses is reducing financial security for many families and prompting difficult choices, as patients defer or forgo therapies they cannot afford. Califf and Slavitt, 2019.

SRT aims for a one-time price of $700,000. The price will be lowered as more patients are treated. This is a third of the Bluebird's price of $2,100,000 and in line with EMEA and FDA wishes of Orphan Disease products which are affordable to patients.

Germans Rejected Bluebird's Exorbitant Price:

Zynteglo won conditional approval to treat TDT in Europe in mid-2019, but Bluebird pushed the launch into 2020 after it got word from regulators that it needed to "tighten up" manufacturing on the gene therapy. Zynteglo was launched in Germany in January 2021 and made available under value-based payment agreements with multiple statutory health insurers under which payers only pay if the therapy delivers on its promise. Subsequently, reimbursement negotiations with Bluebird in Germany broke down after German authorities stood up to Bluebird's demands for higher prices. In response, Bluebird withdrew from the German market and reduced its workforce, primarily in Europe. More recently, Bluebird has pulled Zynteglo from the European market entirely.

Legislative Attention on the Outrageous Cost of Gene Therapies:

In 2019, the House held hearings featuring two competing drug price "transparency" bills. One bill—Stopping the Pharmaceutical Industry from Keeping Drugs Expensive Act, aka the "SPIKE Act" (H.R. 2069)—has already passed the House Ways and Means Committee. The Energy and Commerce health subcommittee also considered the Fair Accountability and Innovative Research Drug Pricing Act or "FAIR Drug Pricing" Act (H.R. 2296). The two bills are similar, as both require companies to notify the Department of Health and Human Services (HHS) when the price of an existing drug increases by a certain percentage, or when a new drug is introduced whose price exceeds some threshold (SPIKE Act only). That notification must include certain information, including total expenditures on R&D, as well as revenue and profit for the applicable drug. Representative Mark Pocan (D-WI) has introduced a bill that would limit price increases. The Stop Price Gouging Act (H.R. 1093) imposes an excise tax on companies selling prescription drugs that are subject to price spikes and that exceed the annual percentage increase in the Chained CPI.

In 2020, Rep. Kurt Schrader (D-OR) introduced the bipartisan GENE Therapy Payment Act with Reps. Roger Marshall, M.D. (R-KS), Jason Crow (D-CO), Markwayne Mullin (R-OK), Ami Bera, M.D. (D-CA), Mike Kelly (R-PA), and David Schweikert (R-AZ). This legislation

[13] Lancet (Vol 8, April 2021)

recognized that gene-therapy treatments can be incredibly expensive, and allowed for a new value-based payment system so that Medicaid beneficiaries can receive these innovative treatments.

> "The GENE Therapy Payment Act will allow for value-based payments in Medicaid so that more Americans can benefit from potentially curative and groundbreaking gene therapies," said Rep. Schrader. This is common sense, bipartisan legislation that will help everyday Americans access the care that they need, without bankrupting state Medicaid programs, allowing for shared risk that will reward the companies working to advance these extremely expensive treatments, when and only when they obtain anticipated outcomes.[14]

Pursuant to 35 U.S.C. § 271(a) whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefore, infringes the patent. SRT's '179 Patent covers recombinant lentiviral vectors having a region encoding a functional beta-globin gene. SRT's '061 Patent covers isolated mammalian hematopoietic progenitor cells or isolated mammalian stem cells comprising recombinant lentiviral vectors having a region encoding a functional beta-globin gene. If the FDA approves the Beti-Cel gene therapy treatment then, consequently, the FDA will allow Bluebird to, without authority, make, use, offer to sell and sell Beti-Cell within the United States that infringes valid claims of U.S. patents during their patent exclusivity term — here, the SRT Patents.

For public policy reasons, the effect and status of SRT's Patents should be considered by the FDA in determining final approval of Bluebird's BLA application for Beti-Cel. In particular, given that Bluebird's Beti-Cel infringes the SRT's Patents, the FDA should withhold final approval of Beti-Cel until SRT's patent infringement case against Bluebird is resolved or until after expiration of the SRT Patents.

For public policy reasons, the timing of the FDA's final approval of Beti-Cel should be based on the SRT Patents, especially now that the FDA has been made aware that the Beti-Cel infringes one or more valid claims of the SRT Patents. Similar to 21 CFR 314.107 *et seq*, the date of a settlement order or consent decree signed and entered by the court stating that the SRT Patents are invalid, unenforceable or not infringed by Beti-Cel should govern when the FDA issues its final approval on Bluebird's Beti-Cel.

III. ENVIRONMENTAL IMPACT

The undersigned claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

[14] https://schrader.house.gov/newsroom/documentsingle.aspx?DocumentID=392761

IV. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

patrick girondi San Rocco Therapeutics Founder
(Dr. Michel Sadelain inventor)