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Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases; Public Hearing.

Thank you to the FDA for inviting the Caring for Carcinoid Foundation to come here today to speak on behalf of patients with neuroendocrine tumors. We are commenting in response to the FDA's question 1 from the Federal Register, specifically around the effectiveness of the review process for rare disease treatments.

Today, I will describe the specific needs of neuroendocrine tumor patients, our experience with some of the specific challenges in bringing drugs to market for these patients, and how these challenges necessitate novel approaches to the way potential treatments for rare diseases are approved and regulated. Patients with rare diseases deserve access to safe and effective treatments. As we are seeing, for many rare diseases, market forces and the FDA's Office of Orphan Products Development are insufficient to generate timely, new, effective treatments. We thank the FDA for its vision in convening today's hearing and willingness to re-evaluate the process for review and regulation of products for rare disease patients.

Slide 2: Caring for Carcinoid Foundation

The Caring for Carcinoid Foundation is dedicated to discovering a cure for neuroendocrine tumors. We fund research to bring novel treatments to patients; we work with pharmaceutical companies to advance patient care and we interact directly with patients.

Although neuroendocrine tumors were first discovered over 100 years ago, there is still no deep, scientific knowledge about them. There are no cell lines, no model systems, and only recently has there been an effort to create a standardized taxonomy for these cancers; this too is restricted by a fundamental lack of understanding.

The Caring for Carcinoid Foundation was founded by a metastatic carcinoid cancer patient in direct response to the lack of scientific understanding of these cancers. Nancy Lindholm started the Caring for Carcinoid Foundation when her doctor explained to her that no treatments existed, little was understood, and that there was no reason to hope that any of this would change in time to make a difference for her. It was and remains Nancy's vision that no other patient will hear this devastatingly bleak message.

In just 5 years, the Caring for Carcinoid Foundation has funded over $6 million in cutting edge research across basic science, genomics, proteomics and translational science. It is truly a hopeful time for patients. There is increased research and scientific interest at academic institutions. There is increased interest from the pharmaceutical industry manifesting in more clinical trials for patients. This is an

ideal time for the FDA to revisit its approach to reviewing Orphan Drug Marketing Applications.

Slide 3: Carcinoid cancer and neuroendocrine tumors

While progress is being made, diagnosis itself still presents an almost insurmountable challenge for many patients. Neuroendocrine tumors are a diverse and unique group of cancers. They can be benign or highly malignant, they can take indolent or highly aggressive clinical courses, they can be asymptomatic or cause debilitating syndromes, and they can originate almost anywhere in the body.

Neuroendocrine tumors that arise in the pancreas are called "pancreatic neuroendocrine" or "pancreatic islet cell tumors." When neuroendocrine tumors originate in other areas of the body, they are most commonly classified as carcinoid cancer.

In some cases, the tumors secrete biologically active hormones that can cause a wide variety of symptoms such as diabetes, flushing, heart valve problems, severe diarrhea and gastric ulcers. Symptoms can be so severe that they lead to the development of clinical syndromes such as Carcinoid Syndrome.

Currently, there are about 100,000 Americans diagnosed with neuroendocrine tumors and the incidence is rising for reasons not well-understood.

There is no FDA approved cure, few FDA-approved treatments exist and there are no uniform national standards of care. As a result, neuroendocrine tumor patients are increasingly desperate. They turn to clinical trials, radical surgery, and other experimental therapies. Those with the means travel abroad for treatments available only in Europe.

Every day, I see patients suffering under the current system in which treatments for neuroendocrine tumors are developed, approved and regulated. This system poses unnecessary hurdles for researchers, clinicians, pharmaceutical companies and patients. In the next few slides I will describe several barriers that prevent bringing safe, effective treatments to neuroendocrine tumor patients.

Slide 4: Barriers to development – (1) Bench

The first barriers to development arise in pre-clinical laboratory work.

There is limited scientific understanding of rare diseases like neuroendocrine tumors. The most fundamental scientific questions – What are the cells of origin? What molecular pathways are involved? What are the genomic causes? - Remain unsolved.

Necessary research tools, such as cell lines and animal models, do not exist. The natural history of these cancers is unknown. As a result, clinicians and researchers lack a baseline understanding of the clinical course these cancers can take; they don't understand why sometimes these cancers are indolent and at other times they progress rapidly.

Traditional endpoints commonly relied upon by clinicians in preparation for an FDA-reviewed clinical trial are either not applicable or require unfeasibly long and expensive studies. The lack of proven surrogate endpoints creates further barriers to treatment development.

The Caring for Carcinoid Foundation has invested millions of dollars to fund basic science, but many diseases do not have similar support. Until we gain a better understanding of these rare diseases, clinical trials will continue to involve guesswork.

To address these barriers we respectfully suggest the following to the FDA:

One – We suggest the FDA request increased appropriations for its Orphan Products Grant Program. Since the Orphan Products Grant Program was created in 1983, 44 products have been approved using data from these grants. Despite its critical role, since 1995 funding has decreased in inflation-adjusted dollars while clinical trial costs have increased faster than inflation. Last year, the program awarded 22 new grants and we have read that this year the program may only award three new grants.

Two - We also suggest that, if adequately funded, this program should expand to support natural history trials for rare diseases.

Three - We encourage the FDA Office of Orphan Products to collaborate with the NIH Office of Rare Disease Research. Both offices are concerned with rare disease issues, and together, could develop a joint plan to address the issues and scientific hurdles that exist in bringing treatments to patients with rare diseases. In particular, we suggest collaboration to systematically address barriers to development such as lack of model systems by centralizing these and other efforts for rare diseases in the NIH intramural research program or other programs.

Slide 5 – Barriers to development (2) Clinical trials

A low percentage of patients with more common forms of cancer enroll in clinical trials; for neuroendocrine tumor patients, the opposite is true. Neuroendocrine tumor patients seek out clinical trials because such trials are among their only options. Despite a high participation rate, patients with neuroendocrine tumors and the investigators running clinical trials for neuroendocrine tumors face unique challenges.

In our patient community, diagnosis and quality care are almost entirely dependent upon finding a physician well versed in treating these cancers. Patients cared for by an experienced and well-informed physician tend to have better access to relevant clinical trials and treatments. Patients treated in a less experienced setting are not afforded the same opportunities.

We encourage the FDA to help all patients get access to investigational treatments through clinical trials, both to benefit patients and to create diverse and robust data sets for analysis. In particular:

One - We encourage the FDA to focus on patient needs and be more flexible in review of clinical trials designed to meet the needs of the target population. We strongly encourage collaboration with outside experts, when necessary, so the FDA can obtain the expertise required to evaluate the idiosyncrasies associated with a product and trial design for a rare disease. We believe this approach will allow the review panel to better understand the disease they are evaluating and what may be innovative trial design, endpoints, or smaller sample size.

We hope to overcome what often seem like rigid statutory guidelines, which are geared towards more prevalent diseases and may inhibit drug development for diseases with small patient populations, lack of scientific understanding and unknown natural history. In the case of neuroendocrine tumors, their low incidence coupled with relatively long survival rates render classic clinical trial design and endpoints impractical.

In fact, rare diseases provide a key opportunity for developing a framework that can be used to review products for small patient populations laying the groundwork for a world in which medicine becomes increasingly personalized. As diseases are defined more precisely at the genetic level, it is conceivable that there will soon be many more rare diseases, hopefully accompanied by corresponding targeted therapies for review.

Two - We encourage the FDA to work with investigators in the early stages of trial design to discuss the specifics of the design and to help patients with rare diseases gain access to clinical trials.

The FDA should work to increase trial locations, which would help increase the size of trials and the geographical diversity of participating patients, allowing investigators to deliver stronger data. Most patients do not have access to trials, which operate only at a single geographic location.

We also suggest that the FDA work with industry to expand access to closed clinical trials for which there are no safety concerns in a way that keeps costs in check. If the FDA, industry and others can collaborate to create a process in which additional

patients can accrue then patients may gain access to trials, and the data collected & its diversity would increase.

Slide 6 Barriers to development (3) Investment risk-reward

For Venture Capital and Pharmaceutical companies, current incentives such as the Orphan Drug Act often do not compensate for the extra risk and disproportionately high costs of bringing drugs to market for rare diseases with small target populations.

Capital sources perceive that each Review Division in FDA responds differently to a product treating a rare disease. Drug companies cannot anticipate how flexible or stringent a Review Division will be. As a result, many sources of capital are reluctant to fund investigations into rare diseases.

For capital sources seeking defined returns, the lack of clarity and consistency in the process increases uncertainty and risks. Small start-up companies, in particular, cannot afford to take these "unquantifiable risks". Patients suffer as a result.

Ultimately, investors need more consistency from the FDA. The more investors know about the FDA approval process and how it will view their trials, the more they can define their risks and the more they will invest.

If the FDA provides this clarity, everyone will benefit. Investors will assume the risk that the product may be unsafe or ineffective, but will not have to assume the unnecessary risk of inconsistent FDA review.

To that end we encourage the FDA to be flexible, consistent and predictable in their reviews of products for rare diseases. In particular,

One - Communicate frameworks that provide consistency and transparency both in and among review divisions while allowing for interpretation relative to the specific application.

Two - we suggest the FDA advise investigators how they will view phase II studies and in what situations they will consider data from phase II for approval of marketing applications.

Slide 7 – Current Considerations for Patients

We applaud the FDA for their vigilance in ensuring that approved treatments are safe and effective for patients. Our concern, however, is that applying the same standards developed to evaluate safety and efficacy of treatments in diseases with higher prevalence and increased understanding puts rare disease patients at a significant disadvantage.

We are concerned that in the absence of FDA approved treatments patients are forced to make complicated risk benefit decisions. We want to emphasize to the FDA that risk exists in not acting quickly.

A few representative stories of neuroendocrine tumor patients illustrate what these patients must go through.

One Patient, who we will call Amy, was diagnosed and told she had inoperable liver metastases. Amy sought numerous second opinions, all of whom told her the same thing – there was nothing that could be done. That is, until she met a liver transplant surgeon who had recently read of a French transplant surgeon who had performed a radical two stage liver resection for carcinoid. With no other options and only hope, Amy approached the surgeon about her case. He was hesitant to do the procedure. Amy nonetheless insisted on the procedure, knowing she had no other treatment option.

Another patient, Beth, was diagnosed at 40 after 5 yrs of undiagnosed pain, flushing and other symptoms. Once correctly diagnosed, she was told there was nothing that could be done for her. Frustrated, but not willing to give up hope, she decided to learn everything she could about her disease. In order to do so, she had to travel across the country, seeking out the few experts. Her only options then were hepatic artery embolizations, phase I clinical trials, and now symptom-control treatments.

Charlie was first diagnosed with liver metastases but told that because the tumors were carcinoid and small, nothing needed to be done. At first, he listened to his physicians, undergoing scans and other testing. Over two years, he watched as his tumors slowly grew. Charlie continued to hear the same advice from his oncologist until he began to develop severe abdominal pain. Scans showed that his tumors were pressing on his hepatic portal vein and due to their location and size, inoperable. He sought numerous second opinions, all of whom told him there was nothing that could be done for him in the United States. Charlie decided to travel to Europe and undergo Peptide Receptor Radionuclide Therapy. PRRT is used widely to treat neuroendocrine tumors in Europe but currently is stalled in Phase II in the United States. Patients from the United States who undergo this therapy in Europe must pay for it out-of-pocket, in addition to travel costs. With no options here, Charlie left behind his family and friends in search of help that was only found in Europe.

There are many more examples, but I believe these few paint a picture of patient realities. Patients with advanced rare diseases are forced to make complicated risk benefit decisions. Those who do not have advanced disease are told to wait until their cancer becomes more serious – in some cases, too serious to treat. My experience is that only the most educated and financially secure individuals are able to pursue potential cures. Sadly, those who are not as educated and financially secure usually cannot and do not. Many of these individuals are no longer alive to tell their stories.

Slide 8 – Suggestions for the FDA

Neuroendocrine tumor patients suffer every day and take radical steps in the US and abroad in search of hope. We hope the FDA can help change this reality for neuroendocrine tumor patients and all rare disease patients by facilitating development of safe, effective treatments.

Those interested in investing in and treating rare diseases will continue to be thwarted if research efforts and funding proceed as they do now—that is, by majority rule; it is the unique role and responsibility of the FDA as a government agency to safeguard and further the interests of all patients, including those with rare diseases**.**

In conclusion we specifically recommend that:

1. The FDA should request increased appropriations for its Orphan Products Grants Program.

2. The FDA should create a rare disease review framework that allows them to react quickly and effectively to innovative treatments and trials supported by compelling scientific rationale. The framework should address considerations around product approval with phase II data in small patient populations.

3. The FDA should coordinate with the NIH Office of Rare Disease Research to strategically address scientific gaps. We also suggest the FDA consider collaborating with the NIH or other groups to develop robust natural history databases for rare diseases. The Caring for Carcinoid Foundation welcomes the opportunity to join these collaborations.

4. Finally, the FDA should move away from the rigid standards that apply to more prevalent diseases. For rare diseases, investigators may need to employ nontraditional endpoints, innovative trial design, or smaller trials. This approach may require collaboration with experts to develop new review approaches.

The 30 Million Patients with rare diseases and all of their loved ones need more choices and the FDA is uniquely positioned to provide them.

Thank you to the many people who spoke with me in preparation for today's presentation. First I thank the many patients willing to share their stories and make their voices heard. Thank you to the clinicians and researchers working on these issues. Thank you to the directors of clinical trials programs at academic medical institutions. Thank you to the pharmaceutical industry and others focused on drug development. Thank you to the Board of Directors of the Caring for Carcinoid Foundation and our founder, Nancy Lindholm, in particular for her dedication to improving the lives of those with neuroendocrine tumors. Thank you above all to Marlene Haffner for the guidance she has provided on orphan drug therapies to the pharmaceutical industry and patient groups for over two decades. Thank you to the FDA for your time here today and commitment to ensuring a better future for patients with rare diseases.