Interview
New US Orphan Drugs Director to Step up the Pace

The new director of the US Food and Drug Administration’s Office of Orphan Product Development, Tim Coté, talks to Neena Brizmohun about plans to boost the development of treatments for rare diseases.

Neena Brizmohun is deputy editor of The Regulatory Affairs Journals.

Early 2008 saw the 25th anniversary of the signing into US law of the Orphan Drug Act, a piece of legislation that regulates products designed to treat a rare disease affecting fewer than 200,000 Americans. The Act is intended to stimulate via special incentives to manufacturers the research, development and approval of products for rare diseases, which by definition does not offer companies a lot of financial incentive and/or much financial risk. Since it was passed in 1983, more than 300 designated orphan drugs have been approved.

In September 2007, Tim Coté became the new director of the Food and Drug Administration’s Office of Orphan Product Development (OOPD). He took over from Dr Marlene Haffner, who had held the position for 20 years. Dr Coté told RAJ Pharma about leadership changes in the organisational infrastructure supporting orphan drugs and of plans to clear various obstacles that currently hinder drug development for rare diseases.

NB: Please comment on the effectiveness of the Orphan Drug Act, which offers incentives such as seven years of marketing exclusivity, tax credit for clinical research and the provision of grants.

TC: The Orphan Drug Act has been one of the most successful legislations passed. Since its enactment, 309 designated orphan drugs have been approved, compared to fewer than 10 drugs approved for orphan indications in the decade prior to the Act’s passage. The Act has benefited over 12 million Americans with rare diseases. However, there remain over 7,000 rare diseases and conditions, most with poor or no therapy.

NB: What leadership changes in the organisational infrastructure supporting orphan drug development have occurred or are foreseeable and what will be the implications of these changes?

TC: Both Dr Haffner and Ms Abbey Meyers, who led the National Organization for Rare Disorders for 25 years, stepped down only recently. These two women were founders of a new movement in therapies for rare diseases and the wonderfully functional systems we’ve inherited are a direct testament to their vision, tenacity and hard work. The leadership changes that have occurred with my arrival and with the near-term arrival of a new leader at NORD represent a shift from foundling, revolutionary leaders who instituted new systems for drug development to a new crop of visionaries who seek to expand initial inroads into a much fuller and broader realisation of the spirit of the Orphan Drug Act. We are no longer scrambling for our first few orphan drug designations and approvals but are looking at the entirety of rare diseases and asking how can we serve them all.

NB: How do you intend to improve the path to more and better orphan designations?

TC: We’d like to be more proactive in the next few years in asking for applications rather than waiting for them. We plan to devise a simple, streamlined application that presents the fundamentals – ie prevalence and rationale – and nothing more. We also want to make sure that the OOPD review practices are transparent through revising regulations for clarity and the issuance of guidances – our office has not yet issued any guidance to industry seeking orphan
status designation. In addition, we want to support and educate FDA review divisions in the nuances of orphan products.

**NB:** How do you plan to go about asking for applications?

**TC:** We are doing that right now with the readers of this article: trying to reach out to industry, academics and patient groups and clearly solicit new therapeutic ideas. We’re going to make it easier and simpler to submit an application for orphan status designation. We’re pressing the flesh, going out on the road to industry and actively seeking applications while giving meaningful assurance that they will be received with hope and reviewed with expediency.

**NB:** What steps have you taken in your bid to devise the streamlined application and how will this application compare to that in current use and what advantages will it have?

**TC:** We have a “Tip Sheet” on our website; it specifies nine items that need to be included in an application for orphan status designation. We’re going to take a hard look at revising that because, while the sheet comprehensively itemises all the administrative data elements that are necessary for administrative processing, sponsors need to more clearly understand that an FDA application for orphan status designation really only needs to address two questions:

- Are the statutory prevalence requirements met? [and]
- Is there reason to believe this is a promising drug that can be expected to be effective against the proposed disease or condition?

An application that answers these two questions doesn’t need to weigh the multiple kilograms characteristic of most of the documents that now cross my desk. Frankly, I believe that this massive document-generation exercise is wasteful of sponsors’ resources, wasteful of FDA review resources and probably doesn’t serve the rare disease patient community very well. We have a long way to go if we’re really going to serve so many different rare diseases; it’s time to slim down for that long run.

**NB:** What steps are you taking to provide clearer guidance to industry seeking orphan status designation, and what particular areas will the guidance focus on?

**TC:** The 1992 regulations explicitly state that our office will, from time to time, issue guidance on matters related to orphan status designation. I intend to actively address this need. The inherent simplicity of an orphan status designation notwithstanding (ie prove you meet prevalence, and prove there’s a medical rationale for believing the drug will work), there are intricacies in how our office functions that would be much better to communicate through guidance than through the insular application of office policies that is revealed only through granting or denying of individual orphan status designations.

**NB:** Can you give me some examples of the nuances of orphan products that you plan to help FDA review divisions understand?

**TC:** Throughout the FDA review divisions there are many, many reviewers very sensitive to the needs of the rare disease community, people who clearly understand that if only 200 people in America have a particular condition then it doesn’t make sense to demand a clinical trial with 300 study participants in each, regardless of what power estimates might say. But it is true that there is currently no explicit policy for how the review of drugs for rare diseases should be different from the review for common diseases. This is partially intentional: it is true that persons with rare diseases are entitled to every bit of the evidentiary protection against ineffective or unsafe drugs as we provide to people with common diseases. However, I believe that in the end, not having special policies for rare diseases can be short sighted and may miss the opportunity to proactively address the issues in drug development that they engender: eg few available study participants requires careful conservation of this knowledge resource.
I also believe we could all benefit from a systematic review of recent innovations in study design for small clinical trials, an area of research that recently benefited when NASA commissioned the Institute of Medicine to look at the methodologies available to study biomedical data from astronauts (like people with rare diseases, there aren’t a lot of astronauts). Founded this critical process infrastructure, there is reason to believe FDA and industry can have much more success in this business of inventing miracles.

**NB:** You have said that one of your missions is to defend the integrity of the Orphan Drug Act. Can you give me an example of how this Act is “vulnerable to mischief” and comment on how you plan to prevent this from happening?

**TC:** The biggest potential for mischief that we regularly encounter is “salami slicing”; that practice of trying to identify smaller and smaller subsets of patients with a disease or condition when such sub setting has no justifiable medical rationale. While we have handled this pretty well on a case-by-case basis, we are working towards revision of our existing regulations to transparently explain what kinds of subsets are and are not acceptable.

**NB:** What other plans do you have to improve the efficiency of your programme?

**TC:** One of the first things I did after arrival was to compute the median time it requires OOPD to review an application for orphan status designation – it is currently 2.5 months. I think that’s quite good but that it can be even more rapid without sacrificing the integrity of an application for the aforementioned criteria.

**NB:** How important has the orphan products grants programme been as an incentive?

**TC:** Currently funded at $14 million per year, our grant programme has had an impressive history of generating a whopping 41 drugs that have gone on to approval. The grant is available to domestic or foreign, public or private, non-profit or for-profit entities, units of State government and non-HHS [Health and Human Services] federal agencies.

Nevertheless, for practical purposes a flat-lined budget for the past 15 years and the effects of inflation have considerably eroded the buying power of our grants programme. In these coming years, I would very much like to clearly communicate the impressive successes this programme has had so that policy-makers can make informed decisions about where they’d like the programme to go.

**NB:** Please comment on the recent adoption of a common application form in the US and the European Union for companies seeking orphan drug designation in both regions? And do you have plans for any similar initiatives?

**TC:** The common application form is a tangible testament to the fact that we recognise orphan diseases and the drugs to treat them are a global problem. Even if the processes by which those applications are considered are quite different on either side of the Atlantic, the symbolism of having one piece of paper either agency will accept is surely powerful. We will continue to work very, very closely with the European Medicines Agency. One of the most substantive ways we collaborate is by hosting each other in an “exchange student” kind of format – we regularly welcome European staff into our office and they likewise include us in their deliberative processes. Areas for future collaboration are many, and development initiatives in the tropical medicines – which are orphans for both the EU and the US – may be one of the first.

**NB:** Do you have any plans in the pipeline for any future incentives for industry to develop orphan drugs?

**TC:** The FDA Amendments Act 2007 also had provisions for incentivising the development of tropical medicine drugs with the issuance of priority review vouchers. We are deeply engaged in the implementation of that provision because they’re all orphans and because of our track record in incentive-based drug development programmes. We are also engaged in the new FDAAA
provisions requiring a meeting on the development of antibiotics for drug-resistant strains of bacteria.

NB: How many of those 7,000+ rare diseases that still need to be tackled do you think might be addressed in the next five years by the development of new orphan drugs?

TC: Goodness knows! But I suspect that the original drafters of the Orphan Drug Act would be surprised with the successes that we’ve made in the first 25 years. Having founded this critical process infrastructure, there is reason to believe FDA and industry can have much more success in this business of inventing miracles.