Tufts: Facing Many Challenges, Orphan Drugs Take 18% Longer to Develop

By Suz Redfearn

Orphan drug development takes 15.1 years to go from first patent filing to product launch, 18 percent longer than the average time required for all new drugs, according to the Tufts Center for the Study of Drug Development. And development time for drugs to treat ultra-orphan diseases—which affect only a few hundred patients in the U.S.—is even longer: 17.2 years.

The numbers are startling because they were measured differently, said Christopher-Paul Milne, research associate professor and director of research at Tufts CSDD who conducted the analysis, looking at 46 first-in-class orphan new molecular entities approved by the FDA between 1999 and 2012.

Others who have scrutinized orphan drug development timelines have focused on the period after new drug application (IND) to time to FDA approval. That, contends Milne, hasn’t provided the most accurate picture.

Tufts measured development time from first patent filing. Developers of orphan drugs “have a lot of problems before even getting the IND, like having to identify every patient who has the disease,” said Milne. “You have to understand a lot about the disease when you’re looking at first-in-class new molecular entities. These are the newest of the new.”

Other key findings from the report:

- From 1983 through 2017, nearly 4,000 drugs have received orphan drug

Experts Debate Methods to Overcome Clinical Trial Enrollment Barriers

By William Myers

A recent FDA guidance clarifying that sponsors may reimburse travel or daycare costs for patients in clinical trials removed a barrier to patient enrollment, but significant barriers remain.

The more than 30 experts and patients gathered at a roundtable discussion hosted by the Lazarex Cancer Foundation and Critical Mass: The Young Adult Cancer Alliance in Washington last week were divided over the solutions.

They met just a few months after the FDA changed language in one of its guidances that had previously considered reimbursements a form of inducement to enrolling in a clinical trial. All present agreed that the change was a great first step toward improving enrollment in cancer trials.

One potential model to improve enrollment comes from Massachusetts General Hospital’s Cancer Care Equity Program, co-sponsored by Lazarex. Program organizers regularly fan out into minority communities and record public service announcements for urban radio stations, said Jonathan Jackson, principal investigator at Mass General.

Since launching the program just a few years ago, researchers have been able to double minority enrollment and increase overall enrollment by 29 percent by focusing on helping patients improve their “basic literacy skills” in areas such as health, research

see Tufts on page 4 »

see Clinical Trial Enrollment on page 5 »
**HHS Announces Planned Rules Affecting IRBs and Clinical Trials**

HHS is planning to publish several new rules affecting IRBs and clinical trials over the next several months, according to the spring OMB Unified Agenda.

**Direct Final Rule: Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations** – Scheduled for this month, this final rule will permit an Institutional Review Board (IRB) to waive informed consent under certain conditions for minimal risk clinical investigations. According to the announcement, this will “facilitate certain minimal risk clinical investigations to support the development of new products to diagnose or treat disease and will harmonize with the HHS Common Rule waiver provision that has been adopted and successfully employed by other agencies.”

**Proposed Rule: Responsibilities for the Initiation and Conduct of Clinical Investigations** – Due in April 2019, the FDA will propose rule updates to investigational new drug application (IND) regulations to define and clarify the roles and responsibilities of persons engaged in the initiation, conduct and oversight of clinical investigations subject to IND requirements. “The proposed changes would better protect the rights, safety and welfare of subjects and help ensure the integrity of clinical trial data. The proposed rule should help reduce study misconduct and ensure the integrity of clinical trial data (benefits) while requiring additional documenting, reporting and recordkeeping for clinical investigators (costs),” according to the announcement.

**Proposed Rule: Institutional Review Boards; Cooperative Research** – Expected last year but now slated for December 2019, this proposed rule would replace current FDA requirements for cooperative research such that “any institution located in the U.S. participating in multisite cooperative research would need to rely on approval by a single IRB for that portion of the research that is conducted in the U.S., with some exceptions. This proposed rule also would also establish an IRB recordkeeping requirement for research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution.”

**FDA Advises on Clinical Trials for Uncomplicated UTI Treatments**

The FDA invited comments from stakeholders on a new draft guidance for clinical trial designs and drug development programs to support indications for uncomplicated urinary tract infection (uUTI) treatments. The draft guidance only discusses uUTI treatments and does not apply to treatments for complicated urinary tract infections. The FDA’s document provides guidance on the size of the clinical trial population, and advises that the size of the database should be discussed with the agency during clinical development. Patients showing signs of systemic illness, such as a fever greater than 100.4 Fahrenheit, shaking chills or other clinical manifestations suggestive of uUTI should be excluded, as well as patients being treated with other antibacterial drugs effective in treating uUTI. The document also provides guidance on trial design and other considerations for patient enrollment.

**Clinical Trial Studying Kidney Transplants Between HIV Patients Begins in U.S.**

The National Institutes of Health announced the launch of the first large-scale clinical trial to study kidney transplants between individuals with HIV. The HOPE in Action Multicenter Kidney Study will take place in multiple clinical centers across the U.S., to evaluate kidney recipients for potential transplant and HIV-related complications occurring post-surgery and determine the safety of the kidney transplantations. The study will track the clinical outcomes of 160 kidney transplants. Half will get kidneys from deceased donors with HIV, while the others will receive kidneys from HIV-free deceased donors that serve as the control group.

**Precision Medicines Get FDA Approval Based on Smaller, No-Frills Trials**

Precision medicines are approved faster than other drugs on the basis of smaller and less frequent clinical trials, according to new research published in the journal Health Affairs. Researchers led by Aaron Kesselheim, director of the Program on Regulation Therapeutics and Law (PORTAL) at Brigham and Woman’s Hospital, analyzed FDA reviews of precision medicines from 2013 to 2017 and found precision medicines go through the process nearly two years faster than similar drugs. While this was largely due to the regulatory fast tracks available to such drugs, including the “breakthrough” designation, researchers also found that the drugs are approved based on fewer pivotal trials involving fewer subjects and less likely to involve placebos, randomization or blinding, which limits the data that serve as the basis for FDA approvals.
MHRA Cites Data Management and Integrity Issues in GCP Inspection Report

Problems with inaccessible trial master files and confusing questionnaires are among the nonconforming practices cited in the latest GCP inspection report from the UK Medicines and Healthcare Products Regulatory Agency Annual Report and Accounts. From April 2016 to March 2017, the agency inspected 16 commercial and eight non-commercial organizations, recording 10 critical findings among seven businesses. Of the non-commercial organizations inspected, which comprised three universities, four National Health Service (NHS) trusts and a charity, only one critical finding was logged. One critical recordkeeping issue involved a firm retaining several essential documents in different electronic systems that were not defined as part of the trial master file (TMF) and were not accessible by inspectors. In addition, the TMF presented did not contain all the essential documents needed to reconstruct trial events and show compliance with regulations and the firm’s quality system. In addition, the report cited data management shortcomings such as incorrect eDiary data that was used in analysis, but could not be changed. eDiary devices used by subjects also had no audit trail to verify their authors or entry dates. The portal used to manage data clarification forms also had no audit trail. The inspections also revealed critical data integrity issues. For example, one site’s eligibility and primary endpoint data questionnaires contained confusing language and medical terms difficult for patients to understand. The forms were meant to be completed by a healthcare professional, the report stated, but investigators could not confirm that a healthcare professional had completed or overseen its completion, bringing into question the accuracy and quality of the data. During the site inspection, it also became evident that electronic health records (EHRs) and paper source data used in the trial had several notable deficiencies. For example, it wasn’t possible to verify who completed them, when they were completed, who made changes to them and why the changes were initiated. Read the full MHRA report here: www.fdanews.com/05-11-18-GCPInspections.pdf.

FDA Issues Advice to Sponsors of Pediatric HIV Drugs

Developers of pediatric HIV drugs should enroll clinical trial subjects in cohorts based on weight rather than age and base the selected weight-bands on World Health Organization (WHO) standards, according to the guidance. When sponsors are seeking approval for a new pediatric formulation, they should conduct bioavailability/bioequivalence studies in adults to demonstrate that the two formulations are comparable. If bioavailability is not comparable, they may need to instead support it through dose adjustments, an additional trial or scientific rationale to support the difference. The agency encourages sponsors to “have early discussions with the WHO, nongovernmental organizations, the FDA and others regarding pediatric plans to facilitate the development of drug products to meet the needs of pediatric patients (e.g., selection of formulation, strengths and dosage of a drug product).”

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Tufts (continued from page 1)

designations in the U.S., and more than 650 have been approved for marketing.

- In 2016, the FDA granted 333 (57%) of 582 orphan drug designation requests it received, or 10 times the number of designations granted in 1986 shortly after inception of the Orphan Drug Act (ODA).

- The number of approvals as a share of designations declined during the last few decades, to 12% in 2016, slightly lower than the 17% share for the entire 1986-2016 period.

While the number of orphan designations has grown dramatically over the past two decades, said the report, growth in the number of orphan approvals during the same years has been more modest.

Approvals as a share of designations for oncology orphan drugs outpaced all other therapeutic areas. Said the report, the emphasis on oncology orphan drug development reflects, in part, an increased understanding of biological pathways of cancer, as well as a favorable reimbursement environment.

But challenges to this burgeoning new area of drug development were numerous. They included variability in expression, severity, and/or course of the disease; geographically dispersed population; small population; selecting among multiple pathways; lack of endpoints and outcome measures; required flexibility in regulatory decision making; biology of disease not understood; natural history of disease not well known; and translating new knowledge into useful knowledge.

One-third of the developers responsible for the 46 first-in-class orphan NMEs approved during 1999-2012 said they encountered four of these challenges, 15 percent of them faced six challenges, and 11 percent faced two. None reported facing fewer than two.

“We were surprised that there are so many special challenges,” said Milne. “For instance, sometimes a disease was very different in men versus women. Sometimes it was very different in a child versus an adult. That explains why the FDA put a grant program for studying the natural histories of diseases in the latest version of 21st Century Cures Act.”

While Tufts measured the development of orphan drugs from first patent filing to product launch, others say the most accurate way to measure development timelines in orphan drugs is still an unsettled area.

“There are differing opinions on what qualifies as the start of drug development,” said Anne Pariser, director of the Office of Rare Diseases Research within the National Institutes of Health’s National Center for Advancing Translational Sciences (NCATS). “Some people consider using clinical development time, defined as investigational new drug application filing.”

Others, like Tufts, start before that, she said, and get a far different measurement, which can lead to greater confusion.

And Bernard Munoz, senior fellow at FasterCures, founder of InnoThink Center for Research in Biomedical Innovation and a former corporate strategy adviser at Eli Lilly, said Tufts’ focus on new molecular entities to the exclusion of other types of orphan drugs presented an incomplete picture.

Munos pointed out that the orphan drug universe is comprised of two subsets: new molecular entities, for which developers face the challenge of small patient populations; and the re-purposing of drugs already approved for non-orphan indications. The second subset, said Munoz, does not follow the same economics as the first.

He points out that an analysis by Kaiser Health News and National Public Radio last year found that one-third of orphan drugs approved since the program began in 1983 were either repurposed mass market drugs or drugs that received multiple orphan approvals. (The link to this analysis is found below.) The analysis showed this repurposing has been increasingly used in recent times to “evergreen” patents on major drugs.

Pariser also took issue with the fact that Tufts only included orphan drugs developed through 2012 in their study.

“It’s important to consider some of the very positive changes that have occurred in the orphan drug field since then,” said Pariser.

For example, she said, in 2012, the FDA’s Breakthrough Therapy Designation was implemented, granting priority review to drug candidates if preliminary clinical trials indicate that the therapy may offer substantial treatment advantages over existing options for patients with serious or life-threatening diseases. The majority of those have involved rare/orphan drugs, some of which have had very short timelines for development—in some cases, as quick as two and a half years, she said.

“Another important point to consider is the use of biologics, which was not included here,” said Pariser, explaining that many orphan drugs increasingly are biologics and the development time for biologics tends to be shorter than for drugs.

Said Milne, Tufts’ research helped to show that new approaches to study design—including use of patient advocacy groups and adaptive clinical trials—are helping to mitigate development problems.


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Note: CNS = Central Nervous System; CV = Cardiovascular; Other includes anti-microbial, metabolic, and genetic diseases

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and even insurance policy, Jackson said. “What we need to remember is that what we are doing, to the average American, is deeply weird,” Jackson said. “They don’t know what this work is.”

In a separate panel discussion, however, Kate Yglesias Houghton, Critical Mass’ president and CEO, said she wasn’t sure that knowledge was power. A survivor of leukemia, Houghton said that for young adults, raised in the post-Google era, education is less a problem than the steep economic and even social barriers to meaningful participation in clinical trials.

“You can’t get deferments on your student loans if you’re diagnosed with cancer,” Yglesias Houghton said, referring to one economic barrier.

As to social barriers, only five states have laws requiring care providers to warn their patients of the risk of infertility from cancer treatment and compounding a social anxiety with an economic anxiety in vitro fertilization isn’t usually covered by insurance plans.

In April, the American Cancer Society Cancer Action Network released results of a survey on barriers to enrollment in clinical trials:

- 56 percent of patients don’t have access to local trials
- 17 percent of patients will be ineligible for a trial due to exclusion criteria
- 27 percent of cancer patients will have the option of even enrolling in trials

The biggest barriers, Action Network Policy Principal Mark Fleury told the crowd, are patient awareness, but also patient fears, either of side effects or a loss of control of care, followed by practical concerns such as costs or logistics.

The Action Network’s report made 23 recommendations for improving enrollment in clinical trials, including:

- Modernizing “eligibility/inclusion/exclusion criteria to achieve the most relevant parameters that will ensure scientific integrity without unnecessarily excluding patients” and making sure that racial or demographic groups are not “preferentially excluded” from trials “unless specific rationale for exclusion exists.”
- Encouraging “broad-panel biomarker testing programs to help promote simultaneous pre-screening for multiple targeted therapy trials”
- Ensuring that research sites selected for multi-site trials have diverse patient populations that reflect the broader population with cancer
- Presenting cancer patients with specifically identified trial options as part of the physician-patient treatment decision discussion using evidence-based methods
- Providing cost transparency by providing full coverage analyses on all trials to clearly articulate responsibility for all anticipated trial costs
- Providing clinical trial navigation services for patients from medically underserved groups to connect with publicly available support resources and culturally sensitive education materials


You can learn more about the Massachusetts General Hospital’s Cancer Care Equity Program here: https://www.massgeneral.org/cancer/lazarex/default.aspx?display=events.

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### Drug & Device Pipeline News

**Company** | **Drug/Device** | **Medical Condition** | **Status** | **Sponsor Contact**
--- | --- | --- | --- | ---
Nektar Therapeutics | NKTR-358 | systemic lupus erythematosus (SLE) | Phase Ib trial initiated evaluating 50 subjects | nektar.com
Bonti, Inc. | EB-001T | elective abdominoplasty surgery | Phase II trial initiated | bonti.com
Amneal | IPX203 | advanced Parkinson’s disease | Phase III trial initiated to enroll 500 subjects | amneal.com
Prisyna, the oral care division of Synedgen | Moisyn product line | xerostomia | 510(k) clearance granted by the FDA | prisyna.com
C4 Imaging LLC | HDR MRI Marker | use prior to high dose rate (HDR) brachytherapy to accurately locate the position of the applicators that guide the placement of radioactive sources for the treatment of multiple cancers | 510(k) clearance granted by the FDA | C4imaging.com
Palladio Biosciences, Inc. | lixivaptan capsules | autosomal dominant polycystic kidney disease (ADPKD) | IND clearance granted by the FDA | palladiobio.com
Portola Pharmaceuticals | Andexxa | antidote for blood thinners rivaroxaban and apixaban | Approval granted by the FDA | portola.com
Janssen Pharmaceutical Companies of Johnson & Johnson | DARZALEX (daratumumab) in combination with VELCADE (bortezomib), a proteasome inhibitor (PI); melphalan, an alkylating agent; and prednisone - VMP | newly-diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) | Approval granted by the FDA | janssen.com
PaxVax, Inc. | Chikungunya vaccine | prevention of the chikungunya virus | Fast Track Designation granted by the FDA | paxvax.com
Debiopharm International SA | Debio 1347 (FGFR 1-3 Inhibitor) | unresectable or metastatic tumors with a specific FGFR gene alteration | Fast Track Designation granted by the FDA | debiopharm.com
Genentech | Tecentriq triple combination with Avastin (bevacizumab), paclitaxel and carboplatin (chemotherapy) | first-line treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC) | Priority Review granted by the FDA | gene.com

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**Alnylam Achieves Alignment with FDA on Accelerated Development Path for Lumasiran**

Alnylam Pharmaceuticals announced that the company has reached alignment with the U.S. Food and Drug Administration (FDA) on a pivotal study design for lumasiran, an investigational RNAi therapeutic for the treatment of primary hyperoxaluria type 1 (PH1). The company and the FDA have aligned on a primary endpoint for the pivotal study based on reduction of urinary oxalate at six months, a biomarker directly linked to the pathophysiology of PH1 and known to be well correlated with disease progression. In addition, Alnylam and the FDA have aligned on a study size of approximately 25 patients with PH1. The ongoing Phase I/II Part B study is designed as a randomized, single-blind, placebo-controlled trial. Lumasiran demonstrated a mean maximal reduction in urinary oxalate of 66 percent with monthly dosing at 1 mg/kg in the unblinded Cohort 1 of the study (N=4), with all patients achieving urinary oxalate levels at or near the normal range. Moreover, lumasiran lowered urinary oxalate excretion in all patients below a threshold well documented to be associated with reduced progression to end-stage renal disease. In all patients, lumasiran was generally well tolerated and the only drug-related adverse event (AE) reported was a mild and transient injection site reaction.

**Bonti Announces Start of Phase II Trial For Muscle Pain**

Bonti announced it has initiated dosing in its LANTERN-2 clinical trial, a Phase II clinical trial under Bonti’s LANTERN (Long-Acting NeuroToxin-E Relief, Non-opioid) clinical program aimed at treating focal muscle pain and reducing use of rescue medications, including opioids. LANTERN-2 is a randomized, placebo-controlled, ascending dose, double-blind clinical trial to evaluate the safety and efficacy of intramuscular (IM) injections of Bonti’s therapeutic product candidate, EB-001T, in subjects undergoing elective abdominoplasty (tummy tuck) surgery. The primary endpoint in this trial will be reduction of post-operative pain at rest as measured by the Numerical Pain Rating Scale (NPRS) over the first 96 hours. Secondary endpoints include NPRS during activity and patient use of rescue medications, including opioids, to address unrelied pain. LANTERN-2 trial was based on favorable safety results from the recently completed LANTERN-1 clinical trial, which was Bonti’s first trial in the LANTERN program. EB-001T showed favorable safety in a wide dose range and was well tolerated, and in which the maximum tolerated dose was not reached.

**Nektar Therapeutics Announces Initiation of a Phase Ib Clinical Study**

Nektar Therapeutics announced that it has commenced dosing patients with systemic lupus erythematosus (SLE) in a Phase Ib clinical study evaluating NKTR-358, a first-in-class regulatory T cell stimulator. NKTR-358 selectively stimulates the proliferation and activation of regulatory T cells (Tregs) in the body in order to restore the body’s self-tolerance mechanisms. The Phase Ib study is a double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics and immunological effects of multiple ascending doses of NKTR-358 in approximately 50 patients with systemic lupus erythematosus (SLE). The study will also evaluate the effects of NKTR-358 on disease activity in SLE patients. In preclinical studies, NKTR-358 has demonstrated that it could suppress antigen-driven inflammation in a model of cutaneous hypersensitivity. NKTR-358 has also shown that it reduces markers of progression in a mouse model of SLE. NKTR-358 is being developed as a once- or twice-monthly self-administered injection for a number of auto-immune diseases.

**vTv Announces Post-hoc Analysis for Experimental Alzheimer’s Drug**

vTv Therapeutics announced that based on post-hoc analyses of the data from Part A of the Company’s Phase II STEADFAST study of the investigational medication azeliragon in people with mild Alzheimer’s disease, despite not meeting co-primary endpoints, identified a subpopulation that showed statistically significant benefit (unadjusted for multiple, post hoc comparisons) from azeliragon relative to placebo on ADAS-cog. The patients in the identified subgroup (n=48) had a -1.9 point improvement in ADAS-cog relative to the placebo group (n=200) which was statistically significant (unadjusted for multiple, post hoc comparisons) (p = 0.02), and a 0.5 point improvement on CDR-sb relative to placebo (p = .06) despite the smaller sample size. This benefit was observed at 12 months. These findings are consistent with results from an earlier Phase Ib study of azeliragon, in which there was a dose response with improved results in patients who had lower concentrations of azeliragon. In contrast, participants in the Phase Ib and STEADFAST Part A study with high azeliragon concentrations performed worse on the ADAS-cog relative to placebo. The STEADFAST study, two independent and identical randomized, double-blind, placebo-controlled Phase III trials (Part A and Part B), was designed to investigate the safety and efficacy of azeliragon as a potential treatment for patients with mild Alzheimer’s disease. The 18-month study targeted enrollment of 800 patients (400 in each trial). Over the course of 18 months, patients with mild Alzheimer’s registered a 4.0 point improvement on the using the ADAS-Cog11 assessment scores. The first trial enrolled patients in the U.S. and Canada.
# Research Center Spotlight

Research Center Spotlight is a monthly selection of clinical research centers who have Research Center Profile pages posted on CenterWatch.com. Included in their annual subscriptions, company profiles are randomly selected to appear in this section, providing added exposure for their expertise and services in conducting and managing clinical studies.

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ActivMed Practices & Research is a registered woman-owned company with experience working in the field of clinical research. It offers a multi-specialty, freestanding research facility with experienced research physicians and psychiatrists.

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Infinity Clinical Research provides clinical trial-related services to pharmaceutical companies, CROs, biotechnology companies, medical device companies and clinical sites in need of partnering capabilities for ancillary services.

Lawrence OB/GYN Clinical Research is the research division of Lawrence OB/GYN Associates, which has been dedicated to serving women's health and social needs for over a quarter of a century. Lawrence OB/GYN Associates currently has 16 practitioners in three offices.

Metabolic Research Institute, Inc. is a dedicated research site with over 15 years of experience in clinical trials. The site is affiliated with eight board-certified endocrinologists with a patient base of over 16,000 patients. The research site has its own database of an additional 8,000 patients.

Midwest Chest Consultants, PC is a private, office-based medical practice specializing in pulmonary, critical care and sleep medicine. The facility specializes in pulmonary and sleep medicine-related clinical research activities and has conducted clinical research since 1990.

The Nicklaus is a full-service clinical research facility dedicated to clinical trials Phases I to IV in all therapeutic areas. The center offers the convenience of professional services for study sponsors seeking to conduct clinical trials in a university-affiliated institution, fully accredited by the AAHRPP.

Piedmont Ear, Nose and Throat Associates (PENTA Research) offers a full range of ear, nose and throat services. Our goal is to advance healthcare and provide novel therapies for our patients by conducting clinical trials.