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Perspectives

Clinical fellowship augmented by regulatory review experience: a perspective on the Children's National Hospital/FDA fellowship tracks

Jency Daniel, MD[a*], Nicholas Geagan, DO[b†], Nada Harik, MD[c], Debra Birnkrant, MD[d], Ramya Gopinath, MD[e], Prabha Viswanathan, MD[f], Sumathi Nambiar, MD, MPH[g‡], Mark Connelly, MD[h], Kirk Chan-Tack, MD[d], and Yodit Belew, MD[d]

[a]Division of Infectious Diseases, Department of Pediatrics, Bernard & Millie Duker Children's Hospital at Albany Med Health System, Albany, New York, USA; [b]Division of Clinical and Toxicology Review, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA; [c]Division of Infectious Diseases, Children's National Hospital, Washington, DC, USA; [d]Division of Antivirals, Office of Infectious Diseases, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA; [e]Division of Anti-Infectives, Office of Infectious Diseases, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA; [f]Office of Pediatric Therapeutics, Office of Clinical Policy and Programs, Office of the Commissioner, Food and Drug Administration, Silver Spring, Maryland, USA; [g]Johnson and Johnson, Washington, DC, USA; [h]Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA

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The collaboration between the Children's National Hospital (CNH) Pediatric Infectious Diseases division and the US Food and Drug Administration (FDA) offers a unique fellowship opportunity that combines rigorous clinical training with a public health–focused scholarly experience in the review of investigational drugs, biologics, and vaccines. This article describes the regulatory experiences of CNH fellows in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), highlights lessons learned, and discusses how these experiences help enrich fellows' training, diversify their skill sets, and strengthen their future career development prospects.

In addition to a traditional track, the pediatric infectious diseases fellowship at CNH has two FDA tracks: one in CDER and one in CBER.[1] Clinical training is comparable to other pediatric infectious diseases fellowships and is identical for all three tracks; the tracks differ in research training focus only *(Figure 1)*. Applicants can apply to and rank each of these tracks separately in the National Resident Matching Program depending on their interests and the nature of the scientific work in each center. Fellows in both FDA tracks serve as medical officers to fulfill their fellowship scholarly activity requirements. In these roles, fellows work in multidisciplinary teams that include pharmacologists, toxicologists, virologists, statisticians, microbiologists, chemists, and many other subject-matter experts. Medical officers are responsible for the clinical review aspects of various licensed or novel drugs and biologics with a specific focus on safety, efficacy, and overall benefit/risk assessments. This FDA regulatory review work occurs longitudinally over the 3-year fellowship period, during the blocks of time that fellows are not on clinical rotations at CNH,

Corresponding author: Yodit Belew, MD, Division of Antivirals, Office of Infectious Diseases, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993 (e-mail: Yodit.Belew@fda.hhs.gov)

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*Formerly at the Division of Anti-Infectives, Office of Infectious Diseases, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA

†Formerly at the Office of Infectious Diseases, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA and Division of Infectious Diseases, Children's National Hospital, Washington, DC, USA

‡Formerly at the Division of Infectious Diseases, Children's National Hospital, Washington DC, USA

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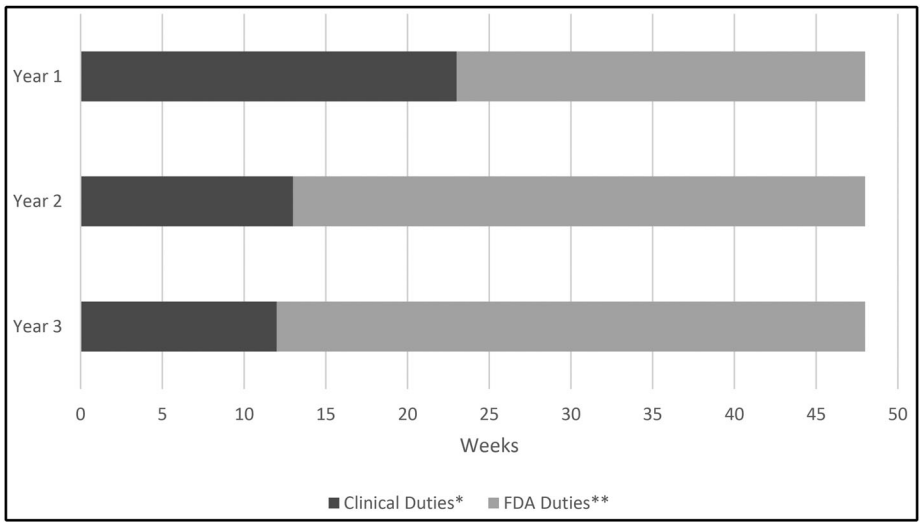

Figure 1. Children's National Hospital/Food and Drug Administration fellowship schedule. *clinical duties include inpatient infectious diseases consult service, immunocompromised/cystic fibrosis infectious diseases consult service, outpatient infectious diseases clinic, and in year 1 only a laboratory/antimicrobial stewardship/infection prevention rotation. Clinical duties are identical each year for traditional fellows. **traditional fellows have dedicated research time during these periods.

comparable to the traditional track fellows' dedicated research time to work on their scholarly activities *(Figure 1)*. Clinical work at the hospital and regulatory review work at the FDA enrich each other, as we will outline below.

DESCRIPTION OF FDA MEDICAL OFFICER DUTIES

Through their work as a medical officer, fellows learn about all stages of medical product development, ranging from Phase 1, first-in-human trials to Phase 4, postmarketing safety studies. As an example, a fellow may participate in the review process of an investigational new drug (IND) application. An IND application is submitted to the FDA by a pharmaceutical company or academic investigator (hereafter referred to as the sponsor) early in the development stages of designing a clinical program to study the pharmacokinetics, safety, and efficacy of a new product. The initial clinical study plan is reviewed by the multidisciplinary team within 30 days of submission to assess if the proposed clinical trial is safe to proceed. As the development program progresses, Phase 2 and 3 study protocols are subsequently submitted. The CNH/FDA fellow's responsibility, as a part of the larger review team, is to evaluate the proposed studies to ensure the key safety and efficacy elements are appropriately incorporated. Multidisciplinary internal meetings are held to discuss the preliminary results that support the proposed Phase 2 and 3 protocols and critically deliberate on the scientific and regulatory considerations for the proposed studies. The CNH/FDA fellows may take the lead in the clinical presentations.

The review team then provides feedback to the sponsor to optimize the study design, such that meaningful data collection is maximized while protecting study participants. Fellows also participate in meetings with sponsors to discuss and provide guidance on their product development programs. These opportunities for fellows to develop skills in high-level scientific communication are truly singular to this training program.

While reviews of submissions pertaining to early clinical product development provide valuable regulatory experience, reviews of marketing applications (new drug applications [NDA] and biologics licensing applications [BLA]) form the cornerstone of the CNH/FDA fellows' scholarly activity. To formally request a review and marketing approval or licensure of a new product, a manufacturer (referred to as the applicant) submits an NDA or BLA to the FDA. The application contains data gathered during the entirety of the product development program, including quality/chemistry data, nonclinical (animal) toxicology and proof-of-concept studies, clinical pharmacology studies, and Phase 1, 2, and 3 clinical trials. During the review period, the multidisciplinary team conducts background research, analyzes the raw data, and presents results during multidisciplinary team meetings to discuss the overall benefits and risks of the product for the intended use in the intended population. The primary focus for the fellows is to review the clinical data (safety, tolerability, and efficacy) in the application, but they also work extensively with members of the multidisciplinary team to review all aspects of the application, including statistical methodology, the spectrum of antiviral/antimicrobial activity and resistance evaluation, data supporting the optimal dose and duration, pragmatic aspects of the formulation such as the appropriateness for the proposed age group, and product labeling considerations.

The multidisciplinary team writes a review document to communicate the methodology used to conduct the review, summarize the data and their conclusions, and, most importantly, convey the overall risk/benefit assessment and their recommendation on whether the product should be approved for the proposed indication and population. For products that are approved, fellows also play an active role in

writing and revising the product labeling (also known as the package insert) to communicate the indications for use, the populations for whom the product is indicated, the recommended dose and duration, important safety information, and summaries of the safety and efficacy data that supported approval.

This level of scholarly and collaborative work is on par with de novo clinical or basic science research, both in the scope of work and in skills gained. On average, each FDA fellow completes approximately 1 to 2 NDA/BLA reviews and 5 to 7 IND reviews during their fellowship. Notably, many of the NDAs and BLAs that the fellows review are supplemental NDA/BLA submissions specifically for pediatric indications for products previously approved for use in the adult population.[2] This provides a unique opportunity for pediatric infectious diseases clinicians-in-training to gain an in-depth understanding of the benefits/risks of the various products prescribed to patients.

For example, one of the authors of this piece was the primary clinical reviewer of the supplemental NDA seeking to expand the use of dalbavancin, an antibacterial drug in pediatric populations for the treatment of acute bacterial skin and skin structure infections. After reviewing the pediatric clinical data, the fellow and the multidisciplinary team concluded that the overall benefit/risk assessment of dalbavancin was favorable to support its approval for the treatment of acute bacterial skin and skin structure infections in pediatric patients.[3] Dalbavancin is now a tool in the armamentarium of antibacterial drugs for pediatric patients for the treatment of acute bacterial skin and skin structure infections including but not limited to those due to methicillin-resistant *Staphylococcus aureus*.

CNH/FDA fellows also have the opportunity to learn more about how the FDA works with other federal agencies to accomplish the mission to protect public health—an incredible privilege as a physician trainee. Fellows are encouraged to take advantage of the experience and resources of this century-old federal agency through the pursuit of other scholarly activities in addition to their review work.

For instance, in pursuit of an interest in health policy, one of the authors of this piece was invited to participate in a virtual stakeholder discussion on clinical practice guidelines for antimicrobial-resistant infectious diseases.[4] This was a virtual gathering of 40 to 50 stakeholders from the FDA, the Centers for Disease Control and Prevention, the National Institutes of Health, the Infectious Diseases Society of America, and other leading groups to discuss how best to improve the development of clinical guidelines. Participants also strategized in large and small groups about how to improve dissemination and implementation of these guidelines in various care settings. It was certainly a highlight of the fellowship experience to gather with these thought leaders and feel empowered to be a valuable contributor to the discussion.

Additionally, one of the authors of this piece had the opportunity to participate in the Vaccines and Related Biological Products Advisory Committee meeting on respiratory syncytial virus vaccines. As the FDA clinical reviewer of one of these vaccine products, the author presented the efficacy and safety data to the advisory committee and responded to questions regarding the study data.[5] This experience was a unique and invaluable opportunity to demonstrate the knowledge obtained through this program while gaining insight into public health practices as they pertain to vaccines and their development.

PROFESSIONAL POSITIONS FELLOWS HAVE PURSUED AFTER FELLOWSHIP COMPLETION

The CNH/FDA experience expands and enriches fellows' training, diversifies their skill sets, informs their career decision-making considerations, and strengthens their future career development prospects. The CNH/FDA CDER track enrolled their first fellow in 1986, and the CNH/FDA CBER track followed suit in 2009. As of 2023, 32 fellows

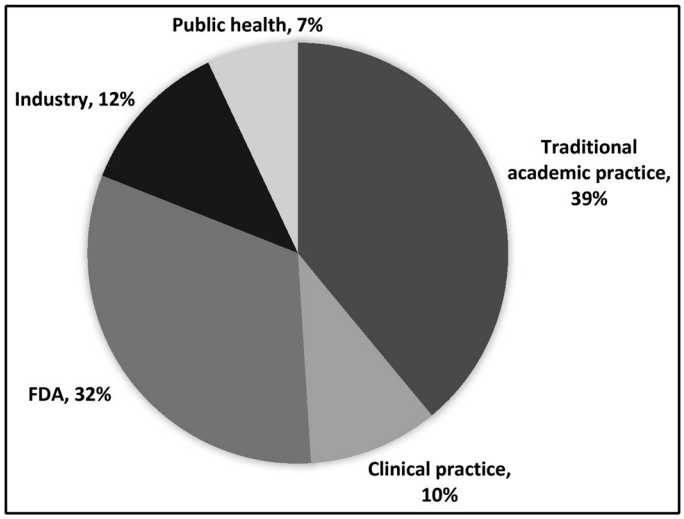

Figure 2. Career paths of Children's National Hospital/Food and Drug Administration track fellowship graduates (n = 43).

have completed fellowship in the CDER track and 11 in the CBER track. The graduates have pursued various careers in healthcare *(Figure 2)*. Currently, 39% work in a traditional academic practice (including several individuals who are division chiefs) and 10% work in primarily clinical practices; 32% work at the FDA (many in senior leadership positions); 12% work for industry (many in senior leadership positions); and 7% work in public health.

PERSONAL REFLECTIONS FROM THE FELLOWS

All medical trainees learn the principles of study analysis, safety monitoring, and efficacy assessments throughout their education and training. These are the foundational skills required to be a medical officer at the FDA. Yet, clinical review work at the FDA is unlike anything we have done in our training. It is a singular opportunity to learn on the job while also being supported through mentoring and oversight as a pediatric subspecialty trainee. It requires fellows to be detail oriented, diligent, and organized in reading, writing, and data analysis. This standard makes us better interpreters of primary literature, more succinct writers of clinical notes, and clearer communicators with clinical teams, patients, and families. For trainees interested in clinical research, the FDA experience also prepares fellows to write a protocol or research proposal.

Alongside the FDA work, having contemporaneous clinical duties and didactics in an academic medical center with thought leaders in pediatric infectious diseases has enriched our training experience. It allows us to stay abreast of the latest guidelines, expert opinions, and on-the-ground clinical experience, which we then contribute to team discussions at the FDA.

This fellowship program would be an excellent fit for those whose career goals align with any combination of pediatric infectious diseases specialty training, public health work, regulatory review, health policy, and advocacy work. Regardless of intended career path or stage of medical training, we each have a role in advancing public health. Seeking and seizing opportunities to do so in your medical school and residency programs are key: join a leadership committee, sign up for an American Academy of Pediatrics advocacy alert newsletter,[6] participate in local and national legislative sessions, gather with like-minded people to solve problems.

Bolstered by our experiences in medical school and residency, this fellowship program has allowed us to witness the passion, diligence, and camaraderie of CNH infectious diseases and FDA employees that we work alongside every day. It has been a profoundly fulfilling privilege to learn from these dedicated public servants and to train in this extraordinary dual CNH/FDA pediatric infectious diseases program.

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ORCID

Kirk Chan-Tack http://orcid.org/0000-0002-7477-9286

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