The Regulatory Pathway for Antifungal Drugs: A US Perspective

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Although there was a flurry of new antifungal drugs approved in the early part of the last decade, the growing need for newer agents to treat systemic fungal infections has escalated due to increasing resistance to the 2 main classes of drugs developed to date and shifts in the etiology of these diseases. In addition to this microbial shift, there are more at-risk patients who are being managed in increasingly heroic ways and are thus highly susceptible to these more common resistant fungi and yeasts. However, as we acknowledge the need for new drugs to treat these desperately ill patients, there is a basic problem facing the pharmaceutical industry as it tries to balance the conundrum of antifungal development. Globally there is a relatively low, but growing, number of systemic fungal infections, which creates significant hurdles in conducting clinical trials in a timely and economical manner. In the United States, there have been some significant moves to easing these hurdles and, potentially, to bringing new drugs to the clinic more quickly and efficiently. We will discuss the current unmet clinical need and the current US regulatory positions to encourage further investment in this critical field.

Keywords. antifungal resistance; FDA; orphan drug status; GAIN; QIDP.

As there is an increasing proportion of drug-resistant fungal infections in high-risk patient groups, it is critical that physicians appreciate the impact that this shifting situation has on a wide array of patients, such as posttransplant patients, oncology patients, those on biological therapies, and patients undergoing late- or end-stage hemodialysis. All of these, and other patients, are immunocompromised to some extent and thus at risk of a wide range of opportunistic and conventional pathogens including fungi. Many experts have recently highlighted the crisis we are facing with escalating bacterial resistance and how it is being disseminated globally with few therapy options, apart from some old drugs, which have a plethora of adverse effects and a rather bleak pipeline [1, 2]. The need for new antifungals is based on emerging azole resistance and the increased isolation of new opportunistic pathogens in patients who are increasingly immunocompromised.

Candida species are among the most common causes of bloodstream infections, and are associated with high morbidity and mortality. Data from the United States over the period 2010–2011 showed that although Candida albicans was still the most prevalent species, the non-albicans species were growing in incidence, and it is these species that are tending to be more resistant to both azoles and echinocandins. Pfaller et al [3] examined 7 antifungal agents against >3100 isolates that showed variable resistance to azoles; 8.8% of C. glabrata isolates were resistant, with 2.5% of other species being resistant. Candida albicans exhibited 0.4% fluconazole resistance. Both azoles and echinocandins were active against Aspergillus species, but the echinocandins were not active against other molds. This changing field is not confined to the United States, as shown by recent data from China by Xiao et al [4], who examined a range of non–C. albicans isolates from a 3-year period in 11 hospitals. Of 1072 isolates, 36.6% were Candida parapsilosis complex, 35.4% were Candida tropicalis, 24.3% were C. glabrata complex, and 3.7% were Candida krusei. Resistance was observed in C. tropicalis to voriconazole (11.6%) and fluconazole (9.5%). Interestingly, 7.1% of isolates were resistant to both azoles. Approximately 14.3% of C. glabrata isolates were
fluconazole resistant. All C. krusei isolates were fully susceptible to azole drugs. More than 97.7% of isolates were susceptible to echinocandins. The authors reported no azole–echinocandin cross-resistance.

Deorukhkar et al [5] highlighted data from India on non-
albicans and C. albicans infections, due to increasing numbers of immunocompromised patients. From almost 200 C albicans isolates, 10.4% were resistant to amphotericin and 33.8% and 41.7% were resistant to fluconazole and ketoconazole, respectively. Among the other more prevalent species isolated, C. tropicalis showed 7.7% resistance to amphotericin and 37.9% and 42.2% resistance to fluconazole and ketoconazole, respectively. Although only 9 strains of Candida dubliniensis were isolated, these strains exhibited low amphotericin resistance but up to 66.7% resistance to ketoconazole. These authors did not test echinocandins, but they focused on the fact that azole resistance was more widespread among non-albicans compared with C. albicans.

Currently, Aspergillus species infection occurs in 5%–13% of patients with bone marrow infections, 5%–25% of heart or lung transplant recipients, and 10%–20% of those who receive intensive leukemia therapy. Mortality associated with invasive aspergillosis (IA) ranges from 34% to 58%. The influence of acute renal failure on aspergillosis is marked, with 47% of solid organ transplant patients becoming infected [6].

In addition to Candida and Aspergillus infections, these high-risk patients are also at risk of contracting mucormycosis (zygomycosis), which is linked to certain emerging molds. Left untreated, mucormycosis is almost always fatal. This is another uncommon but critical unmet medical need.

Some less frequent Candida species are innately resistant to some drugs and are also increasing in incidence (C. glabrata, among others). It is the changing epidemiology and rising incidence of azole and echinocandin resistance that has prompted pharmaceutical companies to work with regulators at the US Food and Drug Administration (FDA) to find novel ways around the conventional prospective, randomized studies enrolling several hundred patients.

The US Centers for Disease Control and Prevention (CDC) recently published a list of problem pathogens, which were stratified into 3 main public health threat categories (urgent, serious, and concerning) [7]. Fluconazole-resistant Candida species are number 6 on the list overall. Additionally, Candida species are the fourth most common cause of bloodstream infections in the United States [8]. Moreover, some strains of Candida are resistant to first- and second-line antifungal drugs, with recent isolates being resistant to both azoles and echinocandins, thus leaving physicians with very few safe alternatives.

The CDC has estimated that there are 46 000 Candida infections annually in the United States, with around 7% being resistant (3400 being fluconazole-resistant strains), leading to 220 deaths. These drug-resistant bloodstream infections contribute to an extra 3–13 days in hospital, thus accounting for $6000–$29 000 in extra direct healthcare costs to health insurance companies and/or private parties [8]. However, what is most worrying in economic terms is the massive impact on the underlying condition, whether it be a transplant rejection or septicemia in a cancer patient, both of which will require significant expenditure.

Although the most antifungal resistance is reported among Candida species, this same issue occurs less commonly in Aspergillus species, with azole resistance occurring in 3%–6% of isolates [9].

Due to the advent of new and more complex management programs of these at-risk patients, there are standard protocols for hospitals and doctors to follow before and after surgery and treatment to minimize infection and resistance. However, a major obstacle in managing these patients is drug–drug interactions due to their polypharmacy management. Thus, it would be beneficial if future new antifungals were not only active against multidrug-resistant fungi and yeasts but also had fewer drug–drug interactions. Moreover, to highlight the dire unmet clinical need, >1.3 million patients will die from these fungal infections, as many as from tuberculosis.

CURRENT AND DEVELOPMENTAL ANTIFUNGAL AGENTS

Clinical practice has access to a limited range of drug classes used in fungal infections—namely, triazoles, echinocandins, amphotericin (in a variety of formulations), and 5-flucytosine. The azole group comprises itraconazole, fluconazole, voriconazole, posaconazole, and most recently, isavuconazole. The echinocandins, which were approved in the 1990s, include caspofungin, anidulafungin, and micafungin. Presently there are >1200 antifungal clinical trials listed at ClinicalTrials.gov, but the vast majority are focused on enhancing the use of existing agents; there are few new antifungal agents in development, although there are some novel biologicals being developed mainly for use in oncologic patients with fungal infections.

Table 1 shows the current status of early-stage antifungal agents in development and their designation with the FDA.

REGULATORY PROCESS: THE US APPROACH

As recently as September 2014, the US Presidential Council of Advisors on Science and Technology published a 78-page document detailing what needs to be completed over the next few years to gain a foothold in this burgeoning battle [10]. These efforts will reflect the CDC stratification of the public health threat status of the various pathogens. Interestingly, there was little mention of specific actions for the growing fungal issues, but it would appear that in the past 2–3 years, changes are being
made to the FDA approach to approving not only new antibiotics but also antifungal agents.

In July 2012, the US Senate passed a new bill as part of the FDA-ASIA regular reform process known as the GAIN Act (Generating Antibiotic Incentives Now). This new law seeks to encourage academic and pharmaceutical research of antibiotic resistance by giving companies manufacturing a “qualified infectious disease product” (QIPD) an additional 5 years of market exclusivity, with or without a patent. The GAIN Act is a relatively complex piece of legislation that requires detailed analysis; following are the key features.

**“NONINTELLECTUAL PROPERTY” MARKET EXCLUSIVITY**

Prior to the GAIN Act, several classes of new drug applications received statutory market exclusivity, regardless of whether the underlying drugs were protected by a patent. New drugs—that is, new active pharmaceutical ingredients—received 4–7.5 years of protection from the date of application. Old drugs with new uses received 3 years. Drugs for a “rare disease or condition,” as designated by the Secretary of the Department of Health and Human Services, received 7 years. These rare conditions occur in <200 000 patients in the United States. During these “exclusivity periods,” the FDA cannot approve another version of the same drug, even if those drugs were not protected by a patent.

**THE GAIN ACT**

The GAIN Act adds a class of applications to the list, QIPDs. (As with drugs for “rare diseases and conditions,” QIPDs are to be determined by the Secretary of DHHS.) If the QIPD fits any of the 3 categories above (ie, a new drug, an old drug with a new use, or a drug for a rare disease), then its market exclusivity is automatically extended by 5 years. This means that new drug QIPDs will have a statutory protection of 9 years; old drug/new use QIPDs will have a total of 8 years of protection; and rare disease (ie, “orphan” QIPDs) will have 12 years of “nonintellectual property” market exclusivity. It is unclear what happens to exclusivity when a sponsor achieves approval for another rare or QIPD indication or even a pathogen-specific infection: Does the drug receive an extra 5 years? This is a potential scenario for some drugs being developed by small, cash-strapped firms that can only afford to study either 1 pathogen or infection in a small clinical trial.

QIPD is assigned to a molecule that has the in vitro and in vivo characteristics that suggest it may fill an unmet clinical need. Currently, there is about 18 but this can change depending on epidemiological data. Interestingly, the GAIN Act provides that once an application has been classified as a QIPD, that designation—and its attendant exclusivity—cannot be taken away. Currently, there are about 63 QIPD designations approved that mainly apply to bacterial infections, but recently antifungals, isavuconazole, VL237, and SCY078 were granted QIPD status. Separately, but in parallel, the provision of Fast Track status has also assured sponsors that all reviews will be undertaken in specific time frames, the final review being typically 6 months from submission. In addition, orphan drug status was assigned to VT1129 for its program in cryptococcal meningitis. It is important to know that when applying for any of these designations, a submission must contain preclinical data demonstrating the various essential activities against resistant organisms; adequate pharmacokinetic data to establish infection site concentrations; an initial drug interaction profile; and, importantly, animal

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Drug Class</th>
<th>Indication</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPK843</td>
<td>Proaparts srl</td>
<td>Polyene</td>
<td>Invasive aspergillosis</td>
<td>Unknown: last updated in 2011 by Proaparts</td>
</tr>
<tr>
<td>VL-2397 (ASP-2397)</td>
<td>Vical Inc</td>
<td>Siderophore</td>
<td>Invasive aspergillosis</td>
<td>QIDP Fast Track</td>
</tr>
<tr>
<td>C001</td>
<td>Cidara</td>
<td>Echinocandin</td>
<td>Invasive aspergillosis</td>
<td>Preclinical</td>
</tr>
<tr>
<td>C101 IV</td>
<td>Cidara</td>
<td>Echinocandin</td>
<td>Intravenous—invasive candidemia</td>
<td>Phase 1 ongoing</td>
</tr>
<tr>
<td>C101 Topical</td>
<td>Cidara</td>
<td>Echinocandin</td>
<td>Topical—acute and recurrent vulvovaginal candidiasis</td>
<td>File IND and phase 1–2 trial in 2016</td>
</tr>
<tr>
<td>C016</td>
<td>Cidara</td>
<td>Echinocandin</td>
<td>Invasive aspergillosis</td>
<td>Preclinical</td>
</tr>
<tr>
<td>VT-1129</td>
<td>Viamet</td>
<td>Ergosterol inhibitor—oral</td>
<td>Cryptococcal meningitis</td>
<td>Orphan drug</td>
</tr>
<tr>
<td>VT-1161</td>
<td>Viamet</td>
<td>Ergosterol inhibitor—oral</td>
<td>Recurrent vulvovaginal candidiasis Onychomycosis, Tinea pedis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>SCY-078</td>
<td>SCYNEXIS</td>
<td>Glucan synthase inhibitor</td>
<td>Invasive aspergillosis Invasive candidemia</td>
<td>QIDP Fast Track</td>
</tr>
</tbody>
</table>

Abbreviations: IND, Investigational New Drug; QIDP, qualified infectious disease product.
will have an extended patent life, increased patent litigation, and licensing concerns. The current wisdom is that, on average, a pharmaceutical patent protection lasting after the FDA approval process—of about 14.5 years. The reality is probably much shorter due to recent backlogs at the patent office and the increasingly aggressive challenges from generic manufacturers. Regardless, the GAIN Act offers protection on par with patents, with the added advantages of being immune from challenges from competitors or “de-listing” by the Secretary. These seem like fairly significant protections and may even obviate the need for patents in some instances.

**GAIN VS PATENT TERMS**

There is concern that patents do not provide enough incentives to drug companies to develop new as opposed to follow-on drugs. There are a number of proposed reasons for this, including FDA approval uncertainty, the length of the approval process, increased patent litigation, and licensing concerns. The current wisdom is that, on average, a pharmaceutical patent will have an “effective patent-life”—the amount of patent protection lasting after the FDA approval process—of about 14.5 years. The reality is probably much shorter due to recent backlogs at the patent office and the increasingly aggressive challenges from generic manufacturers. Regardless, the GAIN Act offers protection on par with patents, with the added advantages of being immune from challenges from competitors or “de-listing” by the Secretary. These seem like fairly significant protections and may even obviate the need for patents in some instances.

**ORPHAN DRUG STATUS**

In addition to these GAIN-related benefits, there is now the added incentive of applying for “orphan drug” status. This status brings additional advantages to those provided by GAIN and can be viewed as even bigger incentives to industry to invest in these drugs. These incentives include regulatory fee reductions, tax breaks in the United States (typically applied to research costs), and market exclusivity for 7 years in the United States and 10 years in Europe. Orphan drug status was approved in 1983 to drugs that provided benefit to <200,000 patients in the United States. In Europe, the designation for orphan status refers to diseases that affect 5 in 10,000.

Currently, there are about 450 orphan drugs approved in the United States, mainly for rare genetic diseases that would otherwise go untreated. Indeed, the orphan disease area is very much in the spotlight, with both large and small pharmaceutical companies, including many specializing in these rare conditions. Moreover, there are approximately 7000 recognized orphan conditions.

The clinical development of orphan drugs is often more straightforward than conventional procedures, as there is frequently no current therapy; thus, placebo or self-controlled studies are acceptable.

**ADAPT ACT 2015/21ST CENTURY CURES ACT**

Finally, in this evolving sector, another bill is with the US legislators called Antibiotic Development to Advance Patient Treatment (ADAPT). This bipartisan bill acknowledges that using current clinical trial design is impractical as the studies would need large numbers in 2 randomized comparative trials. Thus, there has to be a new approach to this dilemma, which is largely based on statistical perspectives, not clinical views. The FDA agrees with the need to alter the feasibility of programs for new drugs in highly niched indications. Rex et al [11] proposed a 4-tier approach (tiers A–D), with tiers B and C being most applicable to the less common infections (ie, those which are drug resistant). These 2 tiers would enable a limited population to provide data for approval: Tier B is more conventional in design, whereas tier C is quite “revolutionary” and not too far removed from the orphan program designs. The ADAPT Act would provide for expedited or accelerated approval, but it does not guarantee a shorter review time by the FDA. The speedier process would be largely driven by the need for smaller studies.

**21ST CENTURY CURES ACT 2015**

In July 2015, Congress passed the ADAPT Act as the key piece of legislation that should help support more transparent development guidance for antibiotics. This enables the limited population pathway described by Rex et al [11] to be applied to antibacterials where there are small patient populations in which to study new agents. This streamlined process will enable adequate efficacy and safety data to be collected and support approval, but probably with some postapproval monitoring to continue the education of prescribers.

It is fair to note that bipartisan efforts in the US government have assisted the FDA in making progress in encouraging developers to design trials to support the approval of new antimicrobials.

**CURRENT PATHWAY FOR A NEW ANTIFUNGAL AGENT**

The overall process for a candidate molecule to be developed and approved for clinical use is complex and fraught with many challenges. The pathway has 5 distinct steps, from initial laboratory data through to postapproval requirements. There are various key decision points during the process that are influenced by several outcomes. An in-depth analysis of these steps by O’Neil et al [1] has estimated timelines, costs, and clinical success, as well as a brief description of the key activities at each phase; the baseline values are shown in Table 2. These steps apply to general antimicrobial agents; however, developmental antifungal agents require an alternative approach due to the paucity of infections, but the clinical imperative is clear.

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NEW REGULATORY PATHWAYS AND ANTIFUNGALS

To date, almost all of the drugs in the QIDP list are antibacterials. There are presently 3 antifungals granted QIDP status: isavuconazole (Astellas, Northbrook, Illinois; and Basilea, Basel, Switzerland); a novel enfumafungin, SCY-078 (SCYNEXIS, Durham, North Carolina, in partnership with Merck), which is in phase 1 trials for the treatment of Candida and Aspergillus infections; and, most recently, Vical’s VL-2397 (Vical Inc, San Diego, California) for invasive aspergillosis.

Isavuconazole has recently been approved for various indications in both the United States and Europe (Table 3). Isavuconazole is a once-daily intravenous or oral broad-spectrum agent shown to be active against a range of fungi including Candida, Aspergillus, Mucorales, and the true pathogenic fungi such as Histoplasma species and Blastomyces dermatitidis.

The isavuconazole phase 3 program (Table 3) comprised 3 pivotal studies, SECURE (for IA), VITAL (open label for aspergillosis or dimorphic fungi) and ACTIVE (invasive Candida). The first 2 studies were submitted as a New Drug Application to the FDA in July 2014 for IA and mucormycosis. The FDA approved isavuconazole in March 2015 for IA and invasive mucormycosis, marketed as Cresemba. The ACTIVE study in invasive candidiasis recently reported that this study failed to meet the primary endpoint. Thus, submission to the European Medicines Agency and FDA requires review and discussion [12–15].

Table 2. Development Pathway for Anti-infective Agents

<table>
<thead>
<tr>
<th>Stage/Key Activities</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Postapproval or Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose and main activities</td>
<td>Establish the antimicrobial activity, initial ADME, IND enabling studies</td>
<td>SAD, MAD, Special patient groups, eg, renal or hepatic dysfunction. Drug–drug interactions</td>
<td>Dose, frequency, or duration ascertainment</td>
<td>Comparison of test agent to current standard agent(s) in specified indications</td>
<td>Confirmatory safety data collection, life cycle management with new indications, formulations. Microbiological surveillance programs</td>
</tr>
<tr>
<td>No. of patients</td>
<td>Not applicable</td>
<td>50–90</td>
<td>100–200</td>
<td>&gt;700 for safety database</td>
<td>To be determined with regulators. Pediatric study plans</td>
</tr>
<tr>
<td>Time period</td>
<td>5 y</td>
<td>12 mo</td>
<td>18 mo</td>
<td>1 y 10 mo (add 9 mo for NDA review)</td>
<td>PSP ≥3 y</td>
</tr>
<tr>
<td>Estimated costs ($ millions)</td>
<td>10.7</td>
<td>10.0</td>
<td>26.3</td>
<td>96.3</td>
<td>146.3</td>
</tr>
<tr>
<td>Possibility of success</td>
<td>17.3</td>
<td>33.0</td>
<td>59.3</td>
<td>75.8</td>
<td>79.7</td>
</tr>
</tbody>
</table>

Overall timelines from discovery to approval: >10 years. Overall costs: >$300 million as a base case with $400 million for marketing activities over product lifetime. Modified from O’Neil [1].

Abbreviations: ADME, absorption, distribution, metabolism, excretion; IND, investigational new drug; MAD, multiple ascending dose; NDA, new drug application; PSP, pediatric study plan; SAD, single ascending dose.

* Marketing costs plus PSP.

Table 3. Summary of Regulatory Status of Isavuconazole

<table>
<thead>
<tr>
<th>Agency/Indication</th>
<th>US FDA</th>
<th>EMA</th>
<th>Study Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA and IM</td>
<td>Approved March 2015 with orphan status</td>
<td>Under review, expected 4th quarter 2015.</td>
<td>SECURE VITAL</td>
</tr>
<tr>
<td>IA in renal compromised patients and IFI caused by mucormycetes and other molds in patients with or without renal dysfunction</td>
<td>Study failed to meet primary endpoint</td>
<td>As per US</td>
<td>ACTIVE</td>
</tr>
<tr>
<td>Invasive candidiasis</td>
<td>Not submitted</td>
<td>Not submitted</td>
<td>ICAAC 2014</td>
</tr>
<tr>
<td>Invasive Scedosporium, fusariosis, and cryptococcal infections treated with isavuconazole</td>
<td>Not submitted</td>
<td>Not submitted</td>
<td></td>
</tr>
<tr>
<td>Disseminated mucormycosis due to Rhizomucor pusillus/Rhizomucor miehei</td>
<td>Not submitted</td>
<td>Not submitted</td>
<td>Case reports</td>
</tr>
</tbody>
</table>

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; IA, invasive aspergillosis; ICAAC, Interscience Conference on Antimicrobial Agents and Chemotherapy; IFI, invasive fungal infection; IM, invasive mucormycosis.
Utilization of the orphan disease process is being used in antifungal development and clearly is an easier future pathway, providing the incidence of said infection due to resistant species is identifiable. Interestingly, in Europe, the orphan review occurs during the marketing authorization approval process. Moreover, in Europe, if a drug is approved for both orphan and nonorphan indications, they must be named differently.

Presently, a key consequence of the GAIN Act and other regulatory processes, including regular trans-Atlantic communications, has been the encouragement of developers to seek FDA input into the program early and often. Although there are previous cases of inconsistent approvals for drugs between the United States and Europe, the 2 agencies are in constant communication and are endeavoring to better align the processes and assessments.

CONCLUSIONS

Clearly, the need for new, more active antifungal agents is vital, especially for those patients at high risk such as oncology and transplant cases, although other compromised patients such as those with rheumatoid arthritis, inflammatory bowel disease, chronic pulmonary diseases, and acute renal disease are also at growing exposure to these ubiquitous species. For those companies prepared to show a willingness and determination to invest resources and finances into this small but critical niche, the FDA is prepared to collaborate in designing feasible studies such that patients are not denied effective therapy against resistant Candida, Aspergillus, or other less frequent organisms. Recent evidence of the success of this approach is shown in the approval of isavuconazole in both the United States and Europe. The advent of orphan disease status for antimicrobials, the GAIN Act, and the 21st Century Cures Act will be the “tipping point” toward a renewed commitment by industry to reinvigorate innovation in fungal and bacterial infections.

Notes

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