New chemical entities of future for infectious diseases

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ABSTRACT

A number of infectious disease treatments are available today. However, infectious diseases still pose serious threats to patients because of the development of antibiotic resistance and the emergence of new infectious diseases. As of date, about 400 drugs, including New Chemical Entities (NCEs), biologics, vaccines, new dosage forms and drug combinations are at different phases of their development (pre-clinical, Phase I, Phase II, Phase III or pre-registration phase) against infectious diseases. This article provides preliminary information about New Chemical Entities (NCEs) for which New Drug Application (NDA) has been submitted by pharmaceutical companies to Food and Drug Administration (FDA) or which are in Phase III of their clinical trial. It would be interesting to see how many of New Chemical Entities (NCEs), among those discussed in this article, will see the face of the future.

Key words: New Chemical Entities (NCEs), Infectious Diseases, Clinical Trial, U.S. Food and Drug Administration (FDA) and New Drug Application (NDA).

INTRODUCTION

Infectious diseases have been problematic and devastating to human lives since centuries. A large number of vaccines and infectious disease treatments are available today. However, infectious diseases still pose serious threats to patients because of the development of antibiotic resistance and the emergence of new infectious diseases, for example, since 1970s about 40 new infectious diseases have been discovered including swine flu, avian flu, MERS, and SARS. According to the literature, antibiotic resistant infections affect more than 2 million American people annually, cause about 23000 deaths annually, and account for $20 billion in direct health care costs annually. Therefore, continuous efforts are required to develop new drugs for the treatment of infectious diseases[1]. However, for pharmaceutical research companies, bringing new treatments for infectious diseases to the market is a challenging process because of the development of antibiotic resistance. Once a treatment has developed resistance to an infectious disease, medical practitioners start prescribing new treatments available in the market. This leads to financial loss to pharmaceutical research companies. Accordingly, on July 9, 2012, the Generating Antibiotic Incentives Now Act (GAIN Act) was signed into law by the President of U.S.A. as part of the U.S. Food and Drug Administration Safety and Innovation Act. The GAIN Act grants five years of exclusivity for those new antibiotics designated under the law as a “Qualified Infectious Disease Product (QIDP). The QIDP has been defined as an antibacterial or antifungal drug for human use intended to treat serious or lifethreatening infections. During the exclusivity period antibiotics having QIDP designation can be sold without generic competition. This period of
exclusivity will increase the potential for profits from new antibiotics by giving pharmaceutical research companies more time to recoup their investment costs. Because of the implementation of GAIN Act, about 400 drugs including New Chemical Entities (NCEs), biologics, vaccines, new dosage forms and drug combinations, are in the development against, for example, bacterial infections, viral infections, fungal infections and parasitic infections. These drugs are in different phases of clinical trials (Phase I to Phase III) and for some of these drugs New Drug Application (NDA) has also been submitted by pharmaceutical companies to the U.S. Food and Drug Administration (FDA). The U.S. Food and Drug Administration (FDA) has also designated Fast Track status to many drugs which are in clinical trials. Fast Track designation is a process designed to expedite the development of new drugs and to get new drugs to the patient earlier. This article provides preliminary information about New Chemical Entities (NCEs) for which New Drug Application (NDA) has been submitted by pharmaceutical companies to U.S. Food and Drug Administration or which are in Phase III of their clinical trial.

A. Drugs for Which New Drug Application (NDA) Has BeenFiled / Anticipated to U.S. Food and Drug Administration (FDA)

1. Dalbavancin

Dalbavancin, 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O-[2-deoxy-2-[(10-methyl-1-oxoundecanoyl)amino]-β-D-glucopyranosyl]-38-[(3-(dimethylamino)propyl)amino]carbonyl]-42-O-α-D-mannopyranosyl-N13-N-methyl-ristomycin A aglycon, is a novel semisynthetic lipoglycopeptide that was designed to improve upon the natural glycopeptides currently available, for example, vancomycin and teicoplanin [2,3]. It has been developed by Durata Therapeutics (http://www.duratatherapeutics.com) for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Grampositive microorganisms, including MRSA (methicillin resistant Staphylococcus aureus). Dalbavancin is an intravenous antibiotic for once-weekly dosing, which may potentially reduce the length of a patient's hospital stay or avoid hospital admission altogether, with an impact on the overall cost of care for these patients. The New Drug Application (NDA) for dalbavancin was submitted to the U.S. Food and Drug Administration (FDA) on September 26, 2013. The U.S. Food and Drug Administration's (FDA) has accepted the NDA for priority review with an action date of May 26, 2014. If approved, dalbavancin will be the first drug for cSSTI with unique once-weekly dosing given in a short, 30-minute IV infusion time, which may help to reduce the overall burden of care without sacrificing patient outcome [4,5].

2. Tedizolid Phosphate

Tedizolid phosphate chemically is [(5R)-3-[[3-fluoro-4-[(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl]phenyl]-2-oxooxazolidin-5-yl]methyl hydrogen phosphate and has following structural formula[6].

Tedizolid phosphate (also known as TR-701) is a novel oxazolidinone antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety TR-700, which is a protein synthesis inhibitor and prevents the initiation of translation by inhibiting formation of the initiation complex. Tedizolid phosphate has been developed for both intravenous and oral administration in the potential treatment of acute bacterial skin and skin structure infections (ABSSSI). It is also being developed for potential use in nosocomial pneumonia. The sponsor for tedizolid phosphate, Cubist Pharmaceuticals (http://www.cubist.com), has submitted New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for the approval of tedizolid phosphate in October 2013. The FDA has accepted the company’s NDA with priority review and has assigned a Prescription Drug User Fee Act (PDUFA) action date of June 20, 2014. If approved, tedizolid phosphate may address the serious public health threat of MRSA and offer a new treatment option for patients [7,8].
3. Tavaborole
Tavaborole chemically is 5-fluoro-2,1-benzoxaborol-1(3H)-ol and has following structural formula[9].

![Tavaborole](image)

Tavaborole has been developed as topical antifungal product for the treatment of onychomycosis by Anacor (http://www.anacor.com). The company believes that tavaborole has a potential safety and efficacy profile that can make it a best-in-class therapy for the treatment of onychomycosis. Anacor’s New Drug Application (NDA) was accepted by the U.S. Food and Drug Administration for review in October 2013. The PDUFA date is July 29, 2014[10,11].

4. Miltefosine
The sponsor for Miltefosine (Hexadecylphosphocholine) is Paladin Labs (www.paladin-labs.com). It is already approved in Europe and marketed by Zentaris GmbH as Impavido. Miltefosine has been recognized by the World Health Organization (WHO) as being one of the only five therapeutic agents to be placed on their Essential Medicines List for the treatment of leishmaniasis. Miltefosine is an oral agent for the treatment of leishmaniasis and is currently the only oral treatment for leishmaniasis approved for sale in Europe, the Indian subcontinent, and Central and South America. Impavido has been granted orphan drug designation and fasttrack status by the U.S. Food and Drug Administration (FDA), and has also qualified for priority review. It was expected to be approved on December 19, 2013 by the U.S. Food and Drug Administration (FDA). However, FDA has extended the Prescription Drug User Fee Act (PDUFA) goal date for miltefosine, for the treatment of cutaneous, mucosal, and visceral leishmaniasis, to March 19, 2014[12-15].

5. Oritavancin
Oritavancin, a novel semisynthetic glycopeptide antibiotic, chemically is (4R)-22-O-(3-Amino-2,3,6-trideoxy-3-C-methyl-alpha-L-arabinohexopyranosyl)-N3-(p-(p-chlorophenyl)benzyl) vancomycin. The sponsor of oritavancin is The Medicines Company (www.themedicinescompany.com). It has been developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI). The Medicines Company anticipated submission of a New Drug Application (NDA) for Oritavancin in the fourth quarter of 2013[16,17].

6. Peramivir
Peramivir chemically is (1S,2S,3R,4R)-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-(carbamimidoylamo)-2-hydroxycyclopentanecarboxylic acid and has following structural formula[18].

![Peramivir](image)

The sponsor for Peramivir is BioCryst (www.biocryst.com). Peramivir has been developed as a potent, intravenously administered, anti-viral agent for the treatment of seasonal influenza. Peramivir is already approved in Japan and Korea. In December 2013, BioCryst submitted a New Drug Application (NDA) to the U.S. Food and
Drug Administration (FDA) seeking an indication as the first i.v. neuraminidase inhibitor approved in the U.S.A. According to the company, Peramivir may address unmet needs in the treatment of influenza. Since the drug has been given Fast Track Status, it is expected that it will be approved by the FDA by August 20, 2014[19,20].

B. New Chemical Entities in Phase III Having Fast Track Status by U.S. Food and Drug Administration (FDA)

1. Eritoran
Eritoran chemically is \([2R,3R,4R,5S,6R]-4-deoxy-5-hydroxy-6-\{[(2R,3R,4R,5S,6R)-4-\{(3R)-3-methoxydecoxy]-6-\{(methoxymethyl)\}-3-\{[(Z)-octatadec-11-enyl]amino\}-5-phosphonatoxoxyoxan-2-yl\}oxymethyl\}-3-\{(3-oxotetra decanoylamo\}nxan-2-yl\} phosphoric acid. The sponsor for Eritoran is Eisai (www.eisai.com). The sodium salt of Eritoran has been developed as intravenous injection for the treatment of severe sepsis, an excessive inflammatory response to an infection [21].

2. Surotomycin
Surotomycin chemically is \(N\{-[2E]-3-(4-pentylphenyl)but-2-enoyl\}-L-tryptophyl-D-asparaginyl-L-\alpha-aspartyl-L-threonylglycyl-L-\alpha-aspartyl-D-alanyl-L-\alpha-aspartylglycyl-D-seryl-(3R)-3-methyl-L-\alpha-glutamyl-(2S)-2-amino-4-(2-aminophenyl)-4-oxobutanoic acid (13→4)-lactone\[22\]. Surotomycin (CB-315), an oral antibiotic, has been developed by Cubist Pharmaceuticals (www.cubist.com) for the treatment of a severe and sometimes life-threatening diarrhea caused by the Gram-positive bacteria *Clostridium difficile*. This form of serious diarrhea is known as *C difficile* associated diarrhea or CDAD[23].

3. Isavuconazole
Isavuconazole chemically is 4-{2-\{(2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl}benzonitrile and has following structural formula[24].

![Isavuconazole](image)

Isavuconazole is being co-developed by Astellas Pharma (www.astellas.com) and Basilea Pharmaceutica (www.basilea.com). Isavuconazole, the possible to be marketed active pharmaceutical ingredient Isavuconazionum sulfate, is a once daily intravenous and oral broadspectrum antifungal agent for the potential treatment of severe invasive and life-threatening fungal infections. Isavuconazole has also received U.S. Orphan Drug Designation by U.S. Food and Drug administration (FDA) for invasive aspergillosis and zygomycosis [25].

4. Brincidofovir
Brincidofovir(CMX001 or hexadecyloxypropylecdofovir) chemically is 3-(hexadecyloxy)propyl hydrogen \(((1S)-1-\{(4-amino-2-oxopyrimdin-1(2H)-yl)methyl\}-2-hydroxyethoxy)methyl\)phosphonate and has following structural formula[26].
Brincidofovir is an oral nucleotide analog having broadspectrum antiviral activity against all five families of doublestranded DNA (dsDNA) viruses that affect humans, including cytomegalovirus (CMV), adenovirus (AdV), BK virus (BKV) and herpes simplex viruses. Brincidofovir has a favorable safety and tolerability profile. The sponsor, Chimerix (www.chimerix.com), believes that Brincidofovir has the potential to be the first broadspectrum antiviral for the prevention and treatment of clinically significant infections and diseases caused by dsDNA viruses [27,28].

5. Faldaprevir
Faldaprevir chemically is (1R,2S)-1-[(2S,4R)-4-[(8-bromo-7-methoxy-2-[2-(2-methylpropanamido)-1,3-thiazol-4-yl]quinolin-4-yl]oxy]-1-[(2S)-2-[(cyclopentyloxy) carbonyl] amino]-3,3-dimethyl butanoyl]pyrrolidine-2-carboxamido]-2-ethenylcyclopropane-1-carboxylic acid and has following structural formula[29].

Faldaprevir

Faldaprevir (formerly BI 201335), a hepatitis C virus protease inhibitor, has been developed by Boehringer Ingelheim (www.boehringer-ingelheim.com) for the treatment of hepatitis C. It is also being studied in combinations, both with and without interferon. Faldaprevir has already been granted accelerated assessment by the European Medicines Agency. If approved by the European Commission, faldaprevir could be available for marketing in the EU in the second half of 2014 as part of an interferon-based regimen [30].

6. Apricitabine
Apricitabine chemically is 4-amino-1-[(2R,4R)-2-(hydroxymethyl)-1,3-oxathiolan-4-yl]pyrimidin-2(1H)-one and has following structural formula.
Apricitabine is a novel deoxycytidine nucleoside reverse transcriptase inhibitor (NRTI) developed by Avexa (www.avexa.com.au) for the treatment of HIV infection. Apricitabine is reported to have good resistance profile that suggests that there is a low potential for cross-resistance with the currently available NRTIs and, thus, apricitabine may provide a treatment option for the treatment of experienced HIV-1-infected patients with resistance to other NRTIs [31,32].

C. New Chemical Entities in Phase III

1. Cadazolid

Cadazolid chemically is 1-cyclopropyl-6-fluoro-7-[4-([2-fluoro-4-[(5R)-5-(hydroxymethyl)-2-oxo-1,3-oxazolidin-3-yl]phenoxy]methyl)-4-hydroxypiperidin-1-yl]-4-oxo-1,4-dihydro quinolin-3-carboxylic acid and has following structural formula[33].

Cadazolid is a new oxazolidinone antibiotic that has been developed for the treatment of Clostridium difficile associated diarrhea (CDAD). Clostridium difficile is a leading cause of healthcare associated diarrhea with significant morbidity and mortality and new options for the treatment of CDAD are needed. Cadazolid has been developed by Actelion Pharmaceuticals (www.actelion.com) as oral treatment for CDAD. Cadazolid is also reported to have a low propensity for resistance development[34].

2. Delafloxacin

Delafloxacin chemically is 1-(6-amino-3,5-difluoro-2-pyridyl)-8-chloro-6-fluoro-7-(3-hydroxyazetidin-1-yl)-4-oxo-quinoline-3-carboxylic acid and has following structural formula[35].
Delafloxacin, a novel fluoroquinolone, has been developed by Melinta Therapeutics (www.melinta.com) as an intravenous formulation for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by Gram-positive (methicillin-resistant *Staphylococcus aureus*, or MRSA) and Gram-negative bacteria, an indication for which the U.S. Food and Drug Administration has designated delafloxacin a Qualified Infectious Disease Product (QIDP). In contrast to most approved fluoroquinolones, which are zwitterionic, delafloxacin has an anionic character, which results in a 10-fold increase in delafloxacin accumulation in both bacteria and cells at acidic pH. This property is believed to confer to delafloxacin an advantage for the eradication of *Staphylococcus aureus* in acidic environments, including intracellular infections. Melinta is also conducting clinical study of a single, oral dose of delafloxacin (900 mg) for the treatment of uncomplicated gonorrhea[36].

3. Delamanid

Delamanid chemically is (2R)-2-methyl-6-nitro-2-[4-({4-[(4-(trifluoromethoxy)phenoxy)piperidin-1-yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole and has following structural formula[37].

Otsuka Pharmaceutical (www.otsuka.com) has developed Delamanid (OPC-67683) for the treatment of multidrug-resistant tuberculosis. The European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) has already granted marketing authorisation for delamanid which is the second new TB drug to be developed in 50 years. It is hoped that the new drug, marketed by the Japanese company Otsuka, will be pivotal in improving treatment for drugresistant forms of tuberculosis, including multidrugresistant TB (MDR-TB) and extensively drugresistant TB (XDR-TB)[38].

4. Eravacycline

Eravacycline chemically is (4S,4aS,5aR,12aS)-4-(dimethylamino)-7-fluoro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[(pyrrolidin-1-ylacetamino)-1,4,4a,5,5a,6,11,12a-octahydropyrrolo[3,4-c]carbazole and has following structural formula[39].
Eravacycline

Tetraphase Pharmaceuticals (www.tphase.com) has developed Eravacycline, a novel, fully synthetic tetracycline antibiotic, as a broadspectrum intravenous and oral antibiotic for use as a firstline empiric monotherapy for the treatment of multidrug resistant (MDR) infections, including MDR Gramnegative bacteria[40].

5. Finafloxacin
Finafloxacin chemically is 7-[(4aS,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]-8-cyano-1-cyclopropyl-6-fluoro-4-oxoquinoline-3-carboxylic acidand has following structural formula.

Finafloxacin, a new generation of fluoroquinolone antibiotics, has an outstanding safety profile and exhibits an allinclusive spectrum of activity that covers Grampositive, Gramnegative, anaerobic and atypical pathogens. This novel member of the fluoroquinolone class of antibiotics has been developed by MerLion Pharmaceuticals (www.merlionpharma.com) for the treatment of Otitis Externa[41,42].

6. Nemonoxacin
Nemonoxacin chemically is 7-[(3S,5S)-3-amino-5-methyl-1-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acidand has following structural formula.

TaiGen Biotechnology Company (www.taigenbiotech.com.tw) has developed Nemonoxacin, a broad spectrum antibiotic, both for oral and intravenous administration. The U.S. Food and Drug Administration (FDA) has granted nemonoxacin Qualified Infectious Disease Product (QIDP) and Fast Track designations for community acquired bacterial pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI).TaiGen has also submitted New Drug Application (NDA) to regulatory authorities in China and Taiwan[43,44].
7. Ozenoxacin
Ozenoxacin chemically is 1-cyclopropyl-8-methyl-7-[5-methyl-6-(methylamino)pyridin-3-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and has following structural formula[45].

Ozenoxacin

Ozenoxacin belongs to a new generation of nonfluorinated quinolones and has been developed by Ferrer International (www.ferrergrupo.com). It has been formulated as topical cream for dermatological infections. According to the company, Ozenoxacin could represent a first-in-class nonfluorinated quinolone treatment option (best-in-class quinolone) for the topical treatment of a broad range of infectious dermatological conditions, including those due to *Staphylococcus aureus* and *Streptococcus pyogenes*, the most commonly encountered pathological causes of impetigo and other skin infections such as SITLs[46].

8. Solithromycin
Solithromycin chemically is (3aS,4R,7S,9R,10R,11R,13R,15R,15aR)-1-{4-[4-(3-aminophenyl)-1H-1,2,3-triazol-1-yl]butyl}-4-ethyl-7-fluoro-11-methoxy-3a,7,9,11,13,15-hexamethyl-10-{{3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy}octahydro-2H-oxacyclotetradecino[4,3-d]oxazole-2,6,8,14(1H,7H,9H)-tetrone[47]. It is a highly potent next-generation macrolide, the first fluoroketolide, which has potent activity against most macrolide-resistant strains. Cempra Pharmaceuticals (www.cempra.com) has developed this next-generation oral and intravenous fluoroketolide for the treatment of moderate to moderately severe community-acquired bacterial pneumonia [48].

9. Asunaprevir
Asunaprevir chemically is 1,1-dimethylethyl [[1S]-1-{[(2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-ethyl-7-fluoro-11-methoxy-3a,7,9,11,13,15-hexamethyl-10-{(3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy}octahydro-2H-oxacyclotetradecino[4,3-d]oxazole-2,6,8,14(1H,7H,9H)-tetrone[47]. Asunaprevir (BMS-650032) is an inhibitor of the hepatitis C virus enzyme serine protease NS3. It is developed by Bristol-Myers Squibb (www.bms.com) for the treatment of hepatitis C. It is also being tested in combination with pegylated interferon, ribavirin and in interferon-free regimens with other direct-acting antiviral agents including daclatasvir[50].

10. Daclatasvir
Daclatasvir chemically is Carbamic acid, N,N'-[(1S)-1-[(1S,2S)-2-ethyl-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl]carbamoyl]pyrrolidin-1-yl][carbonyl]-2,2-dimethylpropyl]carbamate[49]. Daclatasvir (BMS-790052) has been developed by Bristol-Myers Squibb (www.bms.com) for the treatment of hepatitis C. It acts by the inhibition of the HCV nonstructural protein NS5A. It is also being tested in combination regimens with pegylated interferon, ribavirin and with other direct-acting antiviral agents including asunaprevir and sofosbuvir[52].

11. Alisporivir
Alisporivir, [8-(N-methyl-D-alanine)-9-(N-ethyl-L-valine)]cyclosporine, has been developed by Novartis Pharmaceuticals (www.novartis.com). It is a cyclophilin inhibitor and inhibits cyclophilin A. It has been developed for the treatment of hepatitis C. Alisporivir is also being investigated for Duchenne muscular dystrophy[53,54].

12. Deleobuvir
Deleobuvir chemically is (2E)-3-[2-[[2-(5-bromopyrimidin-2-yl)-3-cyclopentyl-1-methyl-1H-indol-6-yl]carbonyl]amino)cyclobutyl]-1-methyl-1H-benzimidazol-6-yl]prop-2-enoic acid and has following structural formula[55].

Pelagia Research Library
Deleobuvir, a potent twicedaily non-nucleoside inhibitor of the HCV polymerase, has been developed by Boehringer Ingelheim Pharmaceuticals (www.boehringer-ingelheim.com) for the treatment of hepatitis C. It is also being tested with other drugs for same indication[56].

13. Vaniprevir
Vaniprevir, (5R,7S,10S)-N-(((1R,2R)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethyl cyclopropyl]- 10-(1,1-dimethyl ethyl)-15,15-dimethyl-3,9,12-trio xo-6,7,9,10,11,12,14,15,16,17,18,19-dodec ahydro-1H,3H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzox diazatricyclo[4,4,4,0,2,4]decane-7-carboxamide, is a macrocyclic Hepatitis C virus (HCV) NS3/4a protease inhibitor. It has been developed by Merck(www.merck.com) for the treatment of hepatitis C[57,58].

CONCLUSION
Infectious diseases cannot be eradicated completely. However, the efforts made by pharmaceutical research companies will help medical practitioners to combat infectious diseases. U.S. Food and Drug Administration (FDA) has also taken initiative to encourage pharmaceutical research companies to develop drugs for infectious diseases by providing Fast Track status and / or Qualified Infectious Disease Product (QIDP) status to the drugs which are under development. Therefore, it is expected that the process of development of drugs and / or New Chemical Entities (NCEs) for infectious diseases would be expedited. It would also be interesting to see how many of New Chemical Entities (NCEs), among those discussed in this article, will see the face of the future.

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