Aurobindo aims at cancer as it climbs the value chain

Developing and filing for both small-molecule and biological cancer therapies forms a key part of Aurobindo's strategy to target higher-value products. Aidan Fry examines the Indian group's plans.

By any measure, Aurobindo's 61 final approvals for abbreviated new drug applications (ANDAs), 31 ANDA filings and 35 product launches in the US during its financial year ended 31 March 2017 placed the Indian group in the highest echelons of industry. The US accounted for nearly three-fifths of the firm's Formulations sales, and approaching a half of its total turnover that increased by 8.1% to Rs151 billion (US$2.34 billion) during the 12-month period (see Figure 1).

The firm filed six ANDAs containing paragraph IV patent challenges on the first day possible, one year before the reference drug's new chemical entity (NCE) exclusivity expires. Additionally, chemical manufacturing processes were validated for two bulk drugs to ensure other paragraph IV challenges can also be submitted on the so-called NCE-1 date. "At the same time, 10 new molecules have been identified during the financial year and process development has been initiated for NCE-1 regulatory filing in subsequent financial years," the Indian group reveals in its recently published annual report.

But Aurobindo's achievements in its largest single market – where it claims to rank sixth by prescriptions dispensed – during its 2016-17 financial year were not limited merely to statistics.

In the 12-month period, the company obtained approval from the US Food and Drug Administration (FDA) for its first ANDA for an injectable penem antibiotic, meropenem 500mg and 1g vials that the firm launched in April this year (**Generics *bulletin***, 7 April 2017, page 13). Aurobindo also made its first four ANDA filings from its newly commissioned Unit X facility in Naidupet, India. Furthermore, the firm furthered its strategic goal of pushing into more complex formulations by submitting its first two oncology ANDAs through the joint venture, Eugia, that the firm formed with Hyderbad-based Celon Laboratories four years ago (**Generics *bulletin***, 6 September 2013, page 3).

In the US consumer health arena, the group's AuroHealth OTC business was by the end of the financial year shipping a basket of 56 products to 24 customers. And the Natrol dietary supplements business acquired in 2014 saw its existing products gain market share as it continued to expand its portfolio.

A total of 16 drug master files (DMFs) submitted for active pharmaceutical ingredients (APIs) in the US were complemented by seven certificates of suitability (CEPs) in Europe and three similar filings in Japan. "During the year," Aurobindo added, "manufacturing processes of three APIs were validated to bring down the raw material cost. Additionally, processes of six APIs have been modified to significantly lower the raw material cost, which will be validated in 2017-18."

And Aurobindo's current financial year has seen the company even pick up the pace in the US. In the first quarter of its financial year running until March 2018, the firm launched 15 products - including three injectables - in the US, as it filed nine ANDAs for oral

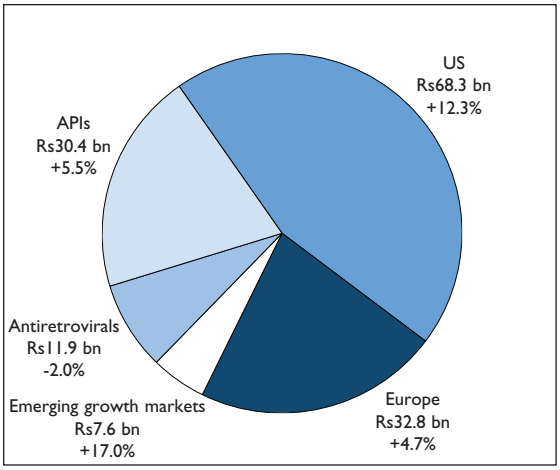

Figure 1: Breakdown of Aurobindo Pharma's turnover that increased by 8.1% to Rs151 billion in its financial year ended 31 March 2017 (Source – Aurobindo)

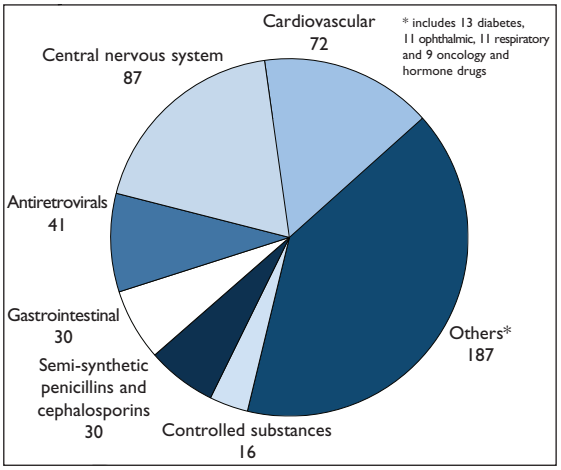

Figure 2: Breakdown by therapeutic category of the 463 abbreviated new drug applications (ANDAs) that Aurobindo had approved or pending as of 30 September 2017 (Source – Aurobindo)

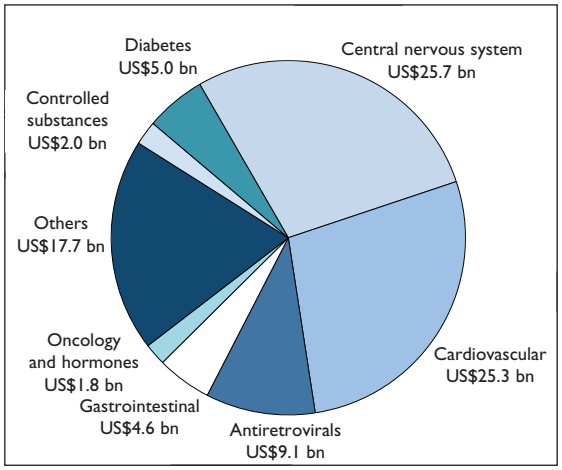

Figure 3: Breakdown by therapeutic category of the US$91.2 billion addressable market value of Aurobindo's 463 approved and pending abbreviated new drug applications (ANDAs) as of 30 September 2017 (Source – Aurobindo)

drugs and four for injectables. One injectable was among the 17 ANDA approvals that the company secured during the three-month period.

Another eight launches, including two injectables, followed in its second quarter ended 30 September 2017 as the firm achieved 21.0% sales growth in the US (**Generics *bulletin***, 17 November 2017, page 7).

Having filed 21 ANDAs during the quarter – 11 for oral dosage forms, and 10 for injectables – Aurobindo had by 30 September submitted a cumulative total of 463 generic applications to the FDA, as shown by Figure 2.

Nearly a fifth of those 463 ANDAs fall into the central nervous system therapeutic category, while another 15.6%, or 72 ANDAs, are in the cardiovascular space. More than 40 of the approved or pending ANDAs are for antiretroviral HIV treatments, while 30 each are for gastrointestinal drugs and for semi-synthetic penicillin and cephalosporin antibiotics.

Viewed by the addressable market potential of the 463 ANDAs (see Figure 3), central nervous system and cardiovascular medicines account for just over half of the value. Another tenth of the value comes from antiretrovirals, and around 5% each from diabetes and gastrointestinal drugs.

A relatively small, but growing, proportion of the value of Aurobindo's US portfolio and pipeline derives from the nine oncology and hormone ANDAs that the company had filed as of 30 September this year.

Through a new research and development centre in Hyderabad, India, Aurobindo is developing an array of generic oncology and hormone drugs in dosage forms that include wet and dry vials, pre-filled syringes, soft-gel and hard capsules, and tablets. These are intended for use in hospitals as well as in oncology and renal clinics.

"Infrastructure for an oncology API facility has been created," Aurobindo states in its annual report. "Formulations manufacturing facilities for oral solid-dosage and injectable forms have been commissioned," the firm said, adding that its oncology injectable line had also been equipped to handle lyophilised products.

To fill those facilities, the Indian company has lined up a considerable pipeline. "We have identified more than 58 oncology and eight hormonal products for development and commercialisation in regulated and emerging markets," Aurobindo revealed. "The portfolio comprises several products with potential first-to-file opportunities and 180-day market exclusivities."

With at least 16 different cancer indications targeted – along with hormone products for treating conditions such as pre-term birth, birth control, amenorrhea and hypogonadism – the Indian group says the global market size for products in its oncology and hormone pipeline was more than US$40 billion in 2016, encompassing more than 10 blockbusters with annual sales of over US$1 billion.

"Exhibit batches of 10 products have been completed during 2016-17, and regulatory filings initiated in the fourth quarter of the [financial] year," Aurobindo states in its annual report. "Regulatory inspections are scheduled in 2017-18."

Over 50 oncology drugs identified

"The facility is preparing to take exhibit batches for 20 to 22 products during 2017-18, as well as in each of the two subsequent years, and file the dossiers in regulated and emerging markets. Out of these 66 products that have been short-listed, two products were filed in the US in 2016-17," Aurobindo continues. "The plans are to file at least 15 products in 2017-18." Manufacturing operations for the 66 products – 58 oncology drugs, and eight hormones – are scheduled to start in the group's 2018-2019 financial year.

"Process development of six oncology APIs is underway," the firm states, adding that it will "commercially validate" these bulk drugs during its current financial year.

Aurobindo's push into cancer treatments is not limited to small-molecule formulations. Through its acquisition in February this year of five biosimilar candidates from Switzerland's TL Biopharmaceutical (**Generics *bulletin***, 17 February 2017, page 1), the Indian group gained development rights to four monoclonal antibodies in oncology indications.

Clinical trials for the lead molecule covered by the TL deal, bevacizumab for treating several oncology indications such as metastatic colon and rectal cancer, are scheduled to take place next year.

"Building on these products licensed from TL, Aurobindo is expanding its portfolio by eight more next-wave biosimilars, ensuring a strong and diverse pipeline of 13 products," the annual report comments. Beyond oncology, this biosimilar pipeline also covers rheumatology, ophthalmology and autoimmune diseases.

A team of around 80 scientists are working on early-stage cell-line development through to process development and product characterisation at a dedicated research and development centre. Drug-substance and drug-product production is being handled through a mammalian and microbial facility in Hyderabad that has an independent fill-and-finish section.

The company's Unit III and Unit VII oral formulations facilities in India each accounted for a little over a third of the 294 final ANDA approvals that Aurobindo held as of 30 September this year, with more than 100 approvals each. The firm also submitted another 16 approved

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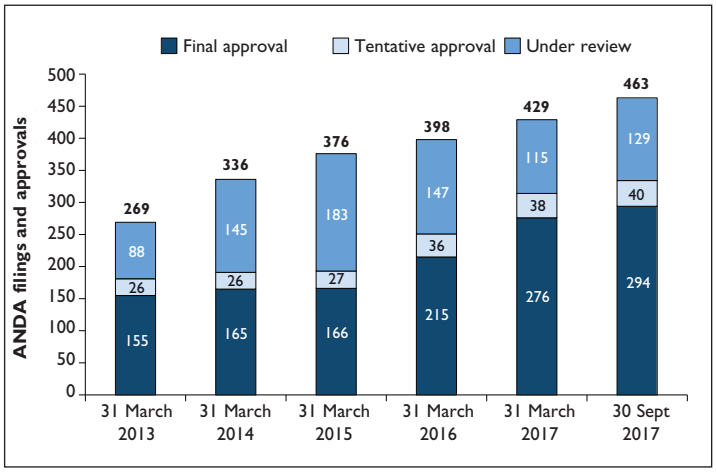

Figure 4: The number of abbreviated new drug applications (ANDAs) for which Aurobindo held final or tentative approval, or had pending review, in the US on 31 March 2013-17, as well as on 30 September 2017 (Source – Aurobindo)

ANDAs from its AuroLife plant in Dayton, US.

From the group's more specialised facilities have come 42 US approvals from its Unit IV injectables and ophthalmics plant in Pashamylaram, India. The Unit XII site dedicated to oral and injectable penicillin antibiotics has got 19 approvals, while another 11 have come from the Unit VIB oral cephalosporins site. As of 30 September, the group's AuroNext plant in Bhiwadi, India, had made a single successful filing for an injectable penem antibiotic.

The vast majority of the 40 ANDAs for which Aurobindo had received tentative FDA approval as of 30 September this year – including 11 through the US President's Emergency Plan For AIDS Relief (PEPFAR) – were filed out of either the Unit III or Unit VII oral formulations factories, with the Unit IV injectables and ophthalmics site contributing just two tentative approvals.

By contrast, the sources of the 129 ANDAs that Aurobindo had under review pending approval at the end of September (see Figure 4) were far more varied. The largest contributor with 45 pending filings was the Unit IV site, a testament to the Indian group's increasing move into harder-to-make delivery formats such as injectables and ophthalmics.

While the recently established, large-scale Unit X oral formulations facility has already submitted 17 ANDAs that are under review, and the US AuroLife site another 11, the AuroNext penem injectables plant has made three filings that have yet to be approved. And all nine of the ANDAs filed out of the group's majority-owned Eugia venture with Celon are still pending review by the FDA.

"In the short term, Aurobindo proposes to increase its controlled substance filings to at least seven products per year"

Address market of over US$90 billion

Citing Iqvia data for the year ended September 2017, Aurobindo said its cumulative 463 ANDA filings targeted a combined addressable market of US$91.2 billion. Within that total, a value of US$63.2 billion for the 169 ANDAs that were under review or tentatively approved did not include the addressable market of products approved under PEPFAR.

And that pipeline continues to be restocked with complex products such as injectables, dermatology drugs, inhalers and peptides, as well as pneumococcal conjugate vaccines. "In the short term, Aurobindo proposes to increase its controlled substance filings to at least seven products per year," the firm stated.

Along with the oncology exhibit batches and the planned bevacizumab clinical trial, the next 12 months or so should also see exhibit batches produced early next year for four depot injectables based on microsphere technology. These niche formulations will be made using dedicated machinery that is being installed at an injectables facility in Hyderabad.

At the end of the group's financial second quarter on 30 September 2017 – during which its AuroMedics US injectables business grew by 21% to US$46 million – the firm held final or tentative approval for 51 of the 90 injectable ANDAs it had filed. Managing director Narayanan Govindarajan told investors on a second-quarter results call that the company expected to achieve US injectables sales growth of 40%-50% in its current financial year, helping to offset low double-digit price erosion in the oral solids sector.

Having recently opened a US development and production centre for speciality generics in Durham, North Carolina – supported by complementary inhalation and topical laboratories in Hyderabad – Aurobindo has started "prototype development work" for seven nasal sprays and six pressurised metered-dose inhalers (pMDI), as well as for 18 topical products that include six solutions, four creams, three ointments and two gels.

Pharmacokinetic and pharmacodynamic bioequivalence studies for the pMDIs are set to be conducted early next year, while clinical trials for topical drugs are scheduled to start towards the end of 2018.

While it strives to bring complex formulations to the US market, Aurobindo believes it enjoys a significant competitive advantage in its base portfolio through the firm's extensive in-house API capabilities. The group says it makes almost 70% of the raw materials for its global generics offering.

"Pricing pressures in US markets are expected to stay and there is a risk to the ability to maintain current margins," the Indian company acknowledges in its annual report. "Price sensitivities will test all the players in a crowded market where price tends to sag as volume business gets done."

However, Aurobindo does not perceive such price erosion as a significant threat due to its burgeoning US portfolio, largely supported by the group's own bulk drugs. "The company is a dominant player in the active ingredients business and has been able to control its quality, improve on timelines, be competitive on costs, and deliver at short notice," the firm insisted. "This is a unique advantage that Aurobindo enjoys over competing manufacturers across the world."