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Oncology, CNS lead therapeutic areas of opportunity

By Suz Redfearn

The drug pipeline is robust. Fat, some might even say.

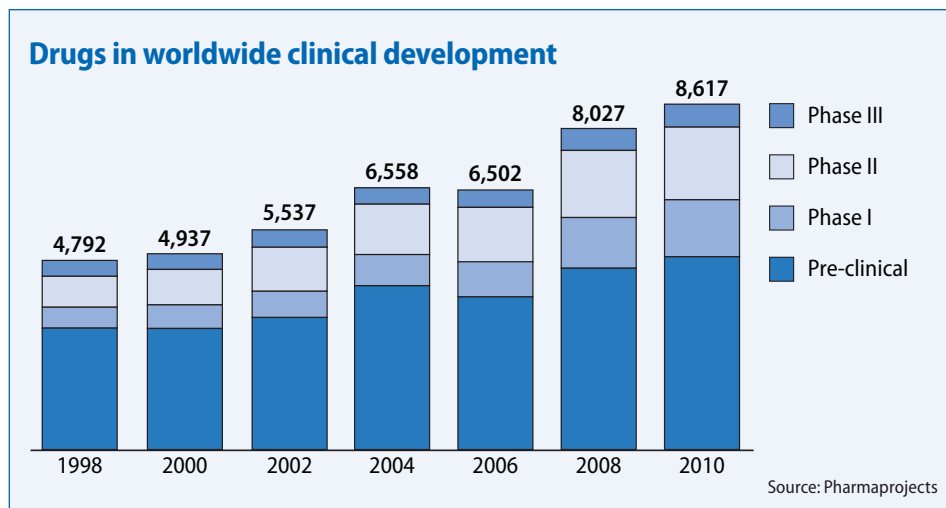
According to numbers from Pharmaprojects, which observes and analyzes drug research and development, 8,617 drugs were in development (from pre-clinical to phase III) in 2010. That number has risen steadily since 1998, when 4,792 drugs were in various stages of development—with the biggest spike seen between 2006 and 2008, when the number of drugs in development shot up from 6,502 to 8,027.

A large portion of those R&D efforts has fallen consistently into four distinct categories: oncology, central nervous system (CNS), infectious diseases and cardiovascular. In addition, more recently a new focus has emerged in biosimilars, the development of generic copies of expensive biotech drugs. The industry is also expecting an uptick in medical device trials.

Following is a review of each of these therapeutic areas, highlighting the areas of opportunity for both site professionals to target grants and service providers to pursue partnerships.

Oncology

Oncology leads the pack among therapeutic areas. According to *EvaluatePharma*, in 2010, a full 31% of all compounds in clinical testing were oncology drugs



and immunomodulators. The next closest therapeutic area was CNS, which represented 18% of drugs in clinical trials. And according to Citeline, a research company focused on pharmaceutical clinical trials and intelligence, from October 2009 to September 2010 more than 400 late-stage trials were initiated in the oncology sector, more than any other therapeutic area.

Non-small cell lung cancer was the leading disease type, followed closely by breast cancer, then multiple hematological cancers. Twenty companies sponsored more than half of all new trials during the year. Roche and Novartis initiated nearly twice as many oncology trials as any other company, with Celgene, Lilly and Pfizer rounding out the top five, said Citeline.

One big oncology breakthrough—as well as a breakthrough in the vaccine area—was

the FDA's approval last year of Dendreon Corp.'s Provenge, a "vaccine" that uses a patient's own immune system to fight advanced prostate cancer that's no longer responding to hormone therapy. This is likely to spur development of similar drugs.

The dominance of oncology as a therapeutic area is driving acquisitions, too. Christopher Crucitti, senior vice president of business development for inVentiv Clinical, said expertise in oncology was one of the major reasons inVentiv recently acquired CRO PharmaNet. "We recognized the need to build up expertise in this core area," said Crucitti. "We hadn't had real strong depth in oncology, and PharmaNet did."

Central Nervous System

The therapeutic area of CNS, which includes Alzheimer's disease, dementia, depression, bipolar disorder and anxiety, was seeing rapid growth. But more recently activity has slowed, much of it due to confusion about exactly how these conditions work in the body.

"Do we understand enough about the pathophysiology of these diseases to even

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target them? The answer is no,” said Amir Kalali, a psychiatrist and vice president of medical and scientific services and CNS global therapeutic team leader for CRO Quintiles. “It’s very different from, say, infectious diseases, where the target is clear. We have been stalled on targets.”

For this reason, CNS trials have come to be seen as high risk. “In many indications in CNS, the literature will say there’s a 50% failure rate,” Kalali said.

“The ability to show efficacy is getting more and more difficult,” added Inventiv’s Crucitti. “Unless there’s a very strong signal very early on, a company may pull out, and the placebo effect is really high.”

Sponsors have, in fact, been leaving the area. GlaxoSmithKline pulled out of CNS entirely in 2009. At the time, GSK CEO Andrew Witty said pain, depression and anxiety were areas in which “we believe the probability of success is relatively low, [and] we think the cost of attaining success is disproportionately high.” A few

weeks later, AstraZeneca said it was ceasing drug discovery work in schizophrenia, bipolar, depression and anxiety. Recently, Pfizer and Johnson & Johnson have limited their CNS work to niche areas, said Kalali, who is editor of the journal *Innovations in Clinical Neuroscience*.

“We shouldn’t look at each other as competitors, but rather as peers with the same problems. In the old days, you might have been happy if your competitor made a mistake, but now we’re realizing that to be ethical, we must collaborate.”

—Amir Kalali, CNS global therapeutic team leader, Quintiles

Many of the big dogs may be pulling out, but interest is still high among medium and small pharma and biotech that understand the need is huge and any breakthrough drugs in this area will end up very profitable, said Kalali. Last year, he launched an annual meeting focused on drug discovery in CNS, and it sold out quickly.

At PPD, CNS work shows no signs of slowing. Said Christine Dingivan, executive vice president and chief medical officer, “In aggregate, we’re seeing a lot more requests for work in that field.”

The key to success now, Kalali says, lies in collecting larger data sets and collaborating, which he acknowledges is unusual among drug sponsors, but even more unusual among drug sponsors working in CNS.

“People within CNS do not go to the same conferences,” he said. “Psychiatrists and neurologists don’t tend to end up in the same room at all. In academia, you have to be expert on your particular area, maybe bipolar, and you probably

don’t even talk to the schizophrenia expert next door, but there’s so much we can learn from each other.”

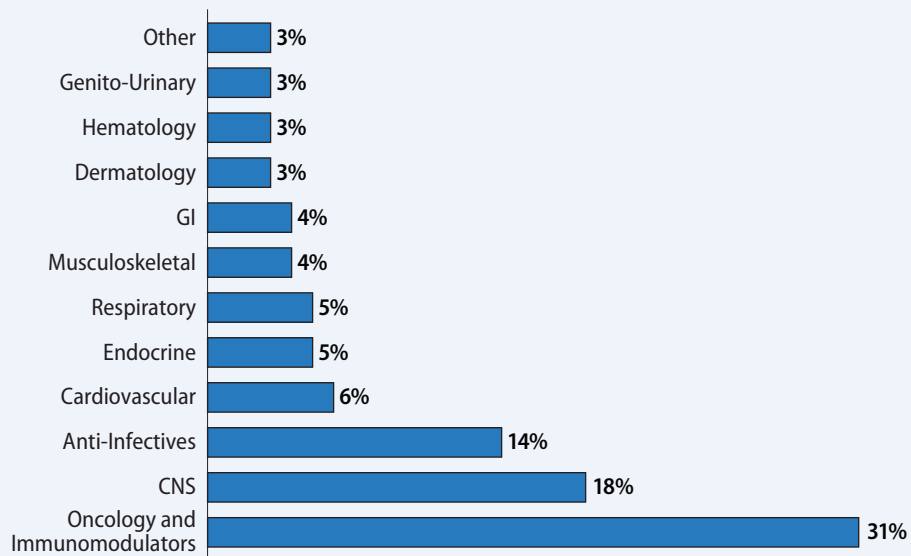
Collaboration may not be natural for those involved, but it will keep the therapeutic area alive and ultimately bring breakthroughs, said Kalali, who has set up a speed dating-like structure for people in CNS to meet during his annual CNS Summit.

“We shouldn’t look at each other as competitors, but rather as peers with the same problems,” he said. “In the old days, you might have been happy if your competitor made a mistake, but now we’re realizing that to be ethical, we must collaborate. We are the largest company in the space,” he said of Quintiles. “If we can act this way, anyone can.”

The good news for CNS is that a few large trials focusing on promising, novel agents for depression and schizophrenia are ongoing. “If those are successful, it will open the flood gates for companies wanting to be involved,” said Kalali.

Dingivan agrees. “It’s like cancer—there are a lot of failures, but if you achieve a breakthrough, the potential is enormous.”

Distribution of active global R&D projects by therapeutic area



Source: EvaluatePharma 2010

Infectious diseases/vaccines

The therapeutic area of infectious diseases saw an explosion after the H1NI virus sent drug makers scrambling to come up with a vaccine quickly in 2009. That level of frenzy has died down since, but not by too much; the area of infectious diseases/vaccine remains really active, said John Lewis, vice president of CRO trade group the Association of Clinical Research Organizations (ACRO).

“Vaccines are definitely a hot area,” he said. “Everyone’s looking at it.”

John Rubino, medical director for investigative site group PMG Research’s Raleigh, N.C. site, agrees. “Immunizations have been really big in the last couple years,” he said. “Two years ago, we were working on more than ever before.”

According to *EvaluatePharma*, in 2010 14% of all drugs in clinical trials were anti-infectives.

Dingivan of PPD, which is heavily invested in vaccine-trial infrastructure and bought a large vaccine lab from Merck in 2009, said work is underway to develop vaccines for more strains of the flu virus, as well as flu-vaccine adjuvants, and to “put more punch in the vaccine.” Other active areas have been dengue fever, shingles, meningitis, hepatitis C and HIV.

Most active therapeutic areas

	Active compounds found in development	5-year CAGR
Cancer	717	5.3%
CNS	323	5.0%
Infectious diseases	233	5.6%
Cardiovascular disease	182	2.9%
Endocrine disorders	152	7.2%
Respiratory illnesses	140	6.9%
Pain/Inflammation	137	4.8%

Source: R&D Directions, 2009

One of the more novel vaccines to come along in the last decade, she said, was Gardasil, a vaccine for human papillomavirus which, if left untreated, can advance to cervical cancer. Gardasil quickly became a household name and opened the door for other drug developers to consider less standard types of vaccines, said Dingivan.

Also invigorating the area of vaccines is last year’s approval of Provenge, a vaccine for advanced prostate cancer. “It’s the first cancer vaccine, and it has re-energized research,” she said.

Working on vaccines doesn’t tend to produce blockbuster drugs, but produces steady income. “It’s a robust area and safe for pharma companies, relatively speaking,” said Dingivan. “There’s not quite as much return, but a likely return; not huge money, but sure money.”

It’s also one of the reasons Pfizer bought vaccine-centric Wyeth in 2009, she added.

Vaccine trials are huge, which is good for CROs. Explained Dingivan, infectious disease vaccine trials require a very large safety database before regulatory bodies will approve one, so it’s not uncommon to see 60,000 to 100,000 patients in a trial. “That’s where CROs come in—where there’s a need for a global footprint,” she said.

Also a boon to CROs that have gotten deeply involved with vaccine work: The trials require concurrent-use testing, which means one must prove to regulatory bodies that the new vaccine under consideration doesn’t interfere with the effect of other

standard vaccines in the body. This means a great amount of testing, said Dingivan.

Cardiovascular/lipids

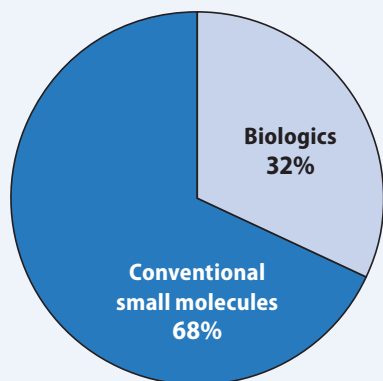
Statins, which lower cholesterol, have been wildly popular, and are credited with having reduced the incidence of cardiac mortality, heart attack and stroke by about 50%. But only half of patients who have high cholesterol can take them. For the last several years, drug makers have set their sights on tweaking the statin concept to serve the other half, said PMG’s Rubino.

But that endeavor hit a bump in the road in 2006, when excess mortality necessitated that Pfizer pull the plug on torcetrapib, its HDL-boosting agent. The compound was in phase III trials and had much promise of becoming the next blockbuster drug in the space. This caused a collective gasp among pharmaceutical companies working on HDL drugs. The result was increased caution about similar drugs in their pipelines, and consequently they pulled back on trials.

“Pfizer’s disaster with torcetrapib froze things,” said Michael Koren, a cardiologist and CEO of the Jacksonville Center for Clinical Research and the Encore site group.

According to *EvaluatePharma*, in 2010 just 6% of drugs in clinical trials fell into the cardiovascular category. Even so, cardiovascular was the fourth most active therapeutic area after oncology, CNS and anti-infectives.

Distribution of global R&D projects by molecule type



Source: EvaluatePharma 2010

But, said Koren, action—as well as morale—has been picking up in cardiovascular lately. Last year, Merck won approval for the CEPT inhibitor AnacEtrapib and is soon to launch a large outcome study on the drug. This is a thumbs up for the entire therapeutic area.

“That’s a signal that this area is growing,” said Koren.

Also, a new primary target was recently identified: PCFK9, a receptor that modulates the effect of HDL on the liver. A number of companies are working it, which bodes well for the space.

“As these guys get more and more positive reports on what they’re doing so far, other people start looking at similar agents,” said Rubino.

A new game in town: biosimilars

A discussion of what lies ahead among therapeutic areas would be incomplete without mentioning biosimilars. Biosimilars are essentially the generic versions of pricey biotech drugs. And instead of merely falling to the realm of generic drug makers as patents expire on several successful biotech drugs, drug developers are getting involved in this hot new area.

According to a recent report from market analysis firm Datamonitor, the worldwide market for copies of biotech medicines will grow to \$3.7 billion by 2015 from just \$243 million in 2010.

“You can create the same basic structure, but the protein may look different. The whole issue around biosimilars, then, is in knowing that you can never show that something is fully the same, but rather that you can show that the differences are non-important.”

—Dirk Reitsma, vice president of global product development, PPD

And the deals and restructuring are there to prove it. For example, drug maker Merck formed a strategic partnership with CRO Parexel in January with the express purpose of developing biosimilars. Merck told investors it plans to have five biosimilar medicines in late-stage testing by 2012, including versions of Amgen drugs that boost white blood cells.

“This is potentially a very big area,” said ACRO’s Lewis. “These are expensive drugs. If you can develop them at a reduced rate,

the possibilities are endless. A lot of companies are looking at biosimilars.”

Biosimilars range from simple molecules such as insulin to complex monoclonal antibodies, which involve the engineering and use of molecules that will attach to specific defects in cells, mimicking the antibodies naturally produced by the body to fight germs and other invaders. The point is to stimulate the immune system to attack defective cells.

“Monoclonal antibodies are hot,” said Dirk Reitsma, vice president of global product development at PPD.

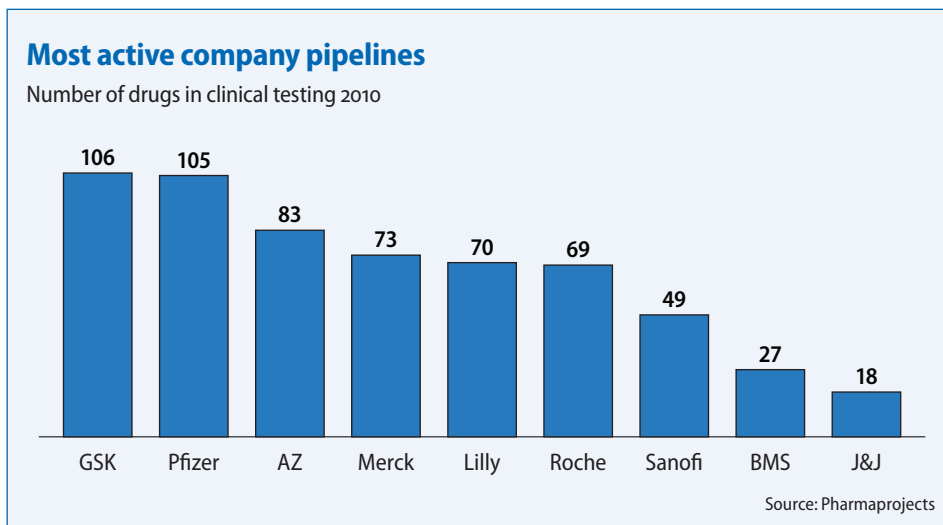
Disease areas that are seeing the most movement are rheumatoid arthritis, multiple sclerosis and various cancers.

The EMA has published regulations on this burgeoning new area, but the FDA has not. Currently under scrutiny is the concept of comparability of the original molecule to the molecule that has been created, as the two can never be completely identical, said Reitsma.

“These cells are sensitive to the circumstances they grow in,” he explained. “You can create the same basic structure, but the protein may look different. The whole issue around biosimilars, then, is in knowing that you can never show that something is fully the same, but rather that you can show that the differences are non-important.”

The FDA is still sorting it out, but has said it will publish guidelines this year. Meanwhile, drug companies and CROs are moving ahead in developing biosimilars and knowing that, as a result, their schedules for phase IV trials could soon become packed.

Said Reitsma, “Biosimilars will probably be approved on relatively small data sets, so there will be less extensive safety data. So once a biosimilar gets approved, there



will likely be a post-approval commitment to watch it closely.”

Medical devices to surge

Medical device trials are not something that pharmaceutical companies and traditional CROs have typically been involved in, but that's likely to change.


The Government Accountability Office (GAO) recently criticized how the FDA oversees device trials, saying that the FDA needs to require device makers to do far more extensive testing on their wares before approval is considered. Naturally, the result has been an uptick in the number of device trials.

“Because of this, we're hearing in the

market that there's a nice growing demand for device work,” said Neal McCarthy, managing director of investment firm Fairmount Partners, which focuses on the CRO space. And companies are getting ready. For example, CRO Medpace recently acquired medical device company Symbios.

Another reason the popularity of device trials is likely to grow: venture capital firms have been investing in them.

“They have a quicker time to market, so the VCs recently shifted their attentions to medical device companies,” said Jeff Williams, CEO of CRO Clinipace, which began focusing on the device-trial space two years ago. He added that the hottest area in devices is cardiovascular, followed by orthopedic.

ACRO's Lewis added that part of the impetus is the recent development of medical devices that deliver pharmaceuticals, creating a marriage of the two formerly disparate parts of the industry. 

Suz Redfearn is an award-winning journalist and former senior staff writer for ClinPage.com. Her articles have appeared in numerous publications, including the Washington Post, Slate, Salon, Politico, Men's Health, Physicians Practice, and the Baltimore City Paper. Suz holds a degree in print journalism from Loyola University in New Orleans and has been a medical writer since 1990, focusing on clinical research since 2007. She can be reached at suz.redfearn@centerwatch.com.

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