The Changing R&D Landscape

Emerging Technology Needs and Value Proposition for Strategic Partnerships with Contract Development and Manufacturing Organizations (CDMOs)

The pharmaceutical product landscape is rapidly and fundamentally changing with profound impact on research and development strategy and technology needs. After a precipitous fall in new drug approvals during the last two decade of the 20th century, there has been a gradual recovery going into the second decade of the 21st century.Figures 1 and 2 map drug approvals by molecule type and route, excerpted from the publication by Ouyang et al1 based on 34,673 drug products approved by the FDA over a 37-year period from 1980 through 2017. The number of biopharmaceutical products show a considerable growth accounting for nearly a quarter of the new molecular entities approved in 2017. While oral delivery route (62%) is still the most prevalent amongst marketed drug products, alternative adminstrations such as injection (22%), cutaneous, mucosal, inhalation, and others are making up a greater percentage as the industry works to improve bioavailability and subsequent efficacy.

Figure 1: FDA Drug Approvals

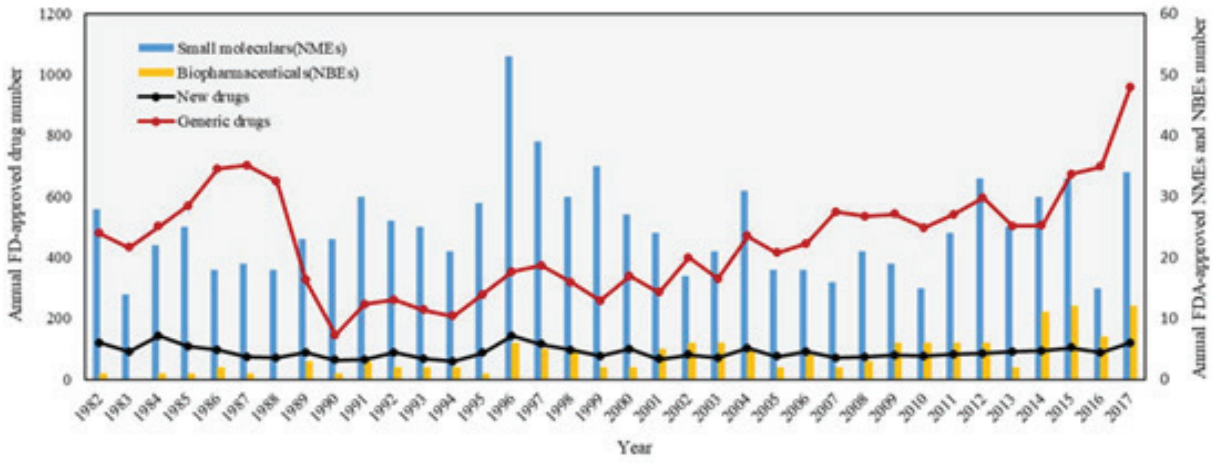
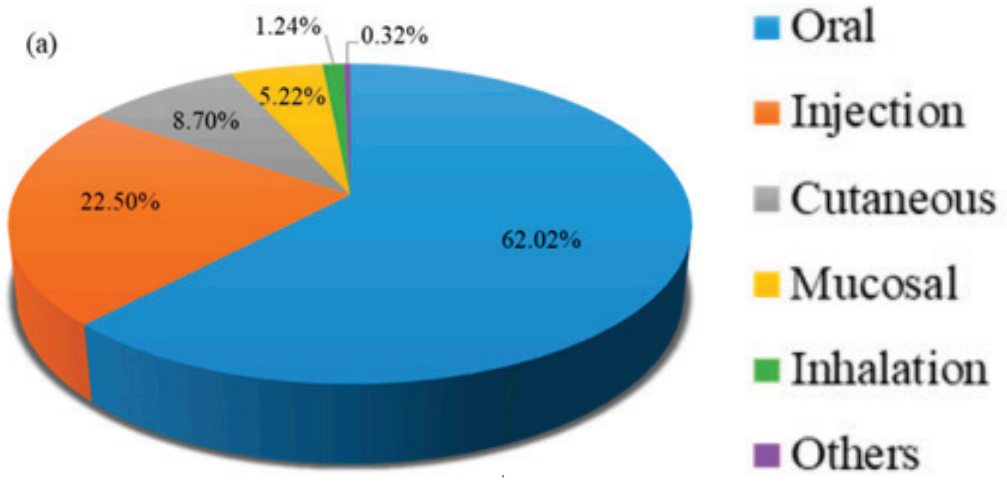


Figure 2: Administration Routes of FDA Approved Marketed Products



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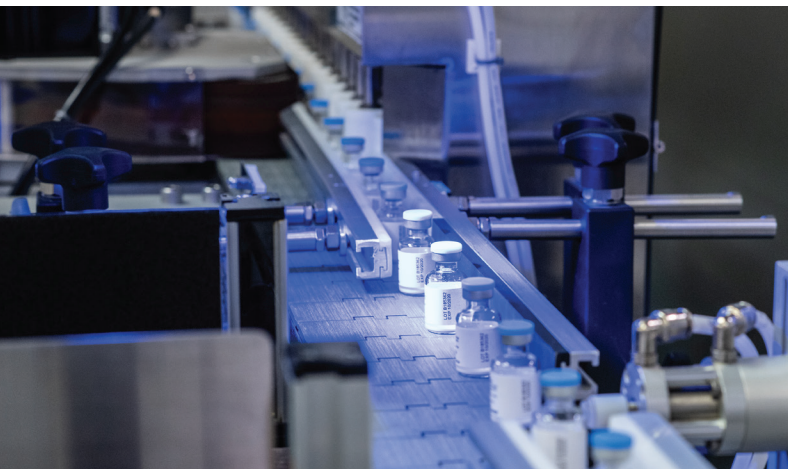


Drug Development Challenges

Despite a myriad of technology advances, drug discovery and development by-and-large remains a risk-laden, costly, and inefficient endeavor. Overall, the success rate of a drug candidate making it from the bench to market is estimated at a meager 8% (2). The failure rate of a drug candidate at each stage of clinical trials is reported to be 46% (Phase I), 66% (Phase II), and 30% (Phase III) (3). The average time required from drug discovery to product launch is 12-15 years (4). The total cost of bringing a new drug to market is estimated at $2.87 billion (5). Despite the purported high cost of drugs, only 3-in-10 approved drugs generate sufficient revenues to offset the associated R&D cost (6). Moreover, most drugs are 50-75% effective as determined by patient response (7). Transformative changes in scientific mindset, pharmaceutical technology, and business strategy are needed for sustainability in R&D.

Emerging Technology Needs

New pharmaceutical products are increasingly complex requiring nonstandard manufacturing technologies and subjected to higher standards of regulatory scrutiny and market expectations. Notably, with the emphasis on precision medicine- an emerging approach of disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyles for each person- there will be a greater number of biologics drugs, multidrug combination products, drug device combinations, and targeted drug delivery systems introduced to the market. Parenteral manufacturing of these complex drug products will require special equipment, technologies, and control strategies. It will also require highly skilled process engineers, manufacturing operators, and quality assurance personnel. Furthermore, a greater number of new molecules will be highly potent requiring special containment facilities, environmental controls, and operator training that is not commonly available in many of today's manufacturing facilities. These new parenteral products will bring with them the challenges of new packaging technologies far removed from standard stoppers and vials. Process Analytical Technology (PAT) will need to evolve to keep up with the control strategies employed with more complex treatments. It is possible, with the appropriate use of PAT, solid understanding of critical process parameters, and a robust control strategy, that drug products could be released parametrically (not only terminally sterilized products) which would greatly reduce the time to patient. (CPG Sec. 490.200 Parametric Release of Parenteral Drug Products Terminally Sterilized by Moist Heat)

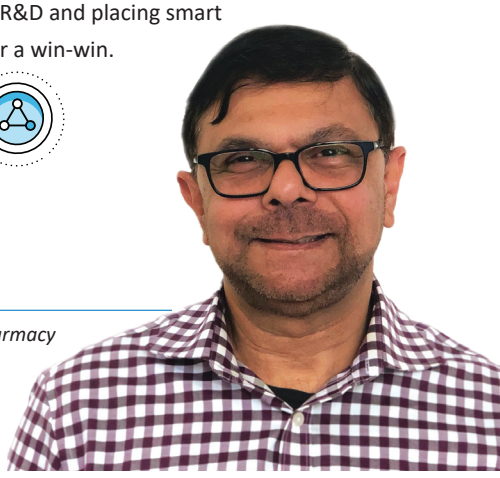
With the advent of precision medicine, certain types of finished dosage forms are gaining importance – such as self-administered drugs and combination products. The therapeutic landscape is rapidly shifting away from a "one size fits all" to a "personalized and precision medicine" paradigm that will integrate basic science, diagnostic testing, and clinical management of complex health conditions with the primary focus on prevention. The resulting impact on drug

products of the future will be an increasing need for patient-tailored flexible dosing; fixed dose and free combination multidrug treatments; kits containing diagnostic testing and correlary drug products; “smart” drug delivery systems comprising drug-device combinations; specialty “convenience” packaging for an increasing geriatric population; high potency compounds; and a shift to large molecule therapeutics including proteins, Mabs, Fabs, and scFvs. In addition, there will be a greater need for targeted drug delivery systems such as liposomes, multiparticulates, controlled and sustained release, trigger and activated drug delivery systems, and ancillary routes of parenteral administration more amenable to self-administration.

Value Proposition for Strategic Partnership with CDMOs

As a consequence of precision medicine there is an increasing emphasis on open innovation. With the spiraling cost of drug discovery and high attritions in early development, it is expected that a greater proportion of cutting-edge research will be conducted by small biotech and inventors often referred to as “two people and a patent.” The goal will be to rapidly advance promising candidates to first-in-human, proof-of-concept studies to create attractive licensing opportunities. Research and development sponsors operating in increasingly virtual states are seeking more strategic partnerships with CDMOs with the capability and skillsets to provide full scope, end-to-end CMC services to support early phase clinical studies all the way through market launch. Large pharmaceutical companies deploy sophisticated due diligence assessments that require innovators and inventors to demonstrate high probability of technical success and developability of their asset. Many of these inventors are academics, investors, and basic scientists with scant CMC background. Hence, these customers are likely to partner with CDMOs with a high degree of CMC expertise manifest by successful regulatory applications (INDs, CTA, CTX) while being capable of de-risking critical technical issues that could delay scale-up and downstream development (i.e. time to market). It is no longer a transactional technology transfer model, but rather a technology creation partnership.

We expect the importance and value proposition of manufacturing to exponentially increase in the next decade and the foreseeable future. Most importantly, parenteral manufacturers need to move away from a myopic “fill-finish” mentality to a fully integrated development mindset that is in line with client expectations, patient needs, and regulatory requirements. It will require “out of the box” thinking and strategic, at-risk investments to remain ahead of the curve. This will take innovation, courage, and collaboration across R&D and placing smart bets for a win-win.



ABOUT THE AUTHOR

Dr. Imran Ahmed is Senior Director and Head of Formulation Development at Alcami. He has a Bachelor of Science in Pharmacy from the University of Michigan and his M.S. and Ph.D. in Pharmaceutical Chemistry from the University of Kansas. Dr. Ahmed has 30+ years of experience in pharmaceutical product development for small and large molecules with subject matter expertise in sterile injectables, ophthalmics, and oral controlled release dosage forms. He has over 30 scientific publications in peer reviewed journals, authored 3 book chapters, and has 6 granted patents.