A Review on Importance of CRO in the management of Bioavailability and Bioequivalence study

Shilpa Chapekar[1], Poonam Pardhi[2], Vishakha Oimbe[3], Shubhangi Raut[4], Darshana Shende[5]
Shree Sainath College of Pharmacy, Dawlameti, Nagpur,440023

Abstract- In pharmaceutical industry, outsourcing is becoming more commonplace. The practice of contracting out corporate operations and procedures to outside parties, known as outsourcing. There are numerous reasons why a company would decide to outsource specific operation, ranging from cost savings and efficiency advantages to a stronger competitive advantage. Enhanced concentration on business operations, heightened productivity, cost management, improved quality, and a stronger competitive edge are just a few of the acknowledged advantages of outsourcing. Pharmaceutical research services are rendered by contract research organizations (CROs) to biotechnology and pharmaceutical industries. CROs serve as connection between the clinical trial's sponsor, the party hiring the services, and other participants. Ensuring therapeutic equivalency between pharmaceutically equivalent test medications, generic or reference drugs is the goal of bioequivalence-bioavailability investigations. Bioanalytical studies, clinical study design, clinical protocol development, clinical site selection, clinical monitoring, data management, project management, FDA/regulatory consultation are representative services that outsourced for Bioequivalence-Bioavailability studies.

Keywords: Outsourcing, CRO, Bioavailability, Bioequivalence.

INTRODUCTION

An extensive history of outsourcing exists in the pharmaceutical sector. Formulation, clinical trials, and registration began to use the outsourcing approach around thirty yearsago. The previous ten years have demonstrated the increasing outsourcing of most development and registration procedures. Companies have turned to outsourcing whenthey require capacity and specialized knowledge and procedures. The previous ten years have demonstrated the increasing outsourcing of most development and registration procedures. Companies have turned to outsourcing when they require capacity and specialized knowledge and procedures. This analysis discovered that between 2010 and 2012, the top 50 pharmaceutical firmshad an average of 27% growth in their regulatory affairs spending. One of two basic concepts can guide the outsourcing of pharmaceutical procedures. Pharmaceutical businesses may concentrate on their core competencies and long-term objectives through strategic outsourcing. According to Clemens, a lot of pharmaceutical companies currently focus on only a few full-service CROs within a strategic partner-based relationship. The company's workload is hereby optimized, and the internal resources can focus on ensuring the overall performance of the CRO.

Previous studies have demonstrated how extensively the pharmaceutical business has examined both back-sourced and outsourced tasks. Studies on outsourcing in thepharmaceutical sector have mostly concentrated on the practice's financial advantages [1].

The Rise of the CRO Industry

The thalidomide tragedy led to numerous birth abnormalities, prompting the inclusion of the Kefauver-Harris Act in the US legal system in 1962. Supporting an NDA requireda significant increase in work [3].

Today, the global CRO market comprises approximately 1300 companies. Based on this, it seems that CROs are now an essentialcomponent of the drug development process since the biotechnology, pharmaceutical, and device industries use contract resources to enhance their resources [2].

Bioavailability and Bioequivalence

Bioavailability refers to the proportionate amount of a drug that enters the systemic circulation from an administered dose, as well as the rate at which the drug becomes detectable in the systemic circulation. Following drug administration, bioavailability studies are conducted by measuring the concentration of the drug in the plasma or blood following a systemic protocol of studies, which are documented over time.

Bioequivalence The purpose of conducting bioequivalence studies was to differentiate between two pharmaceutical products that shared a common active ingredient. A single substance may be formulated into two distinct formulations, provided that they demonstrate therapeutic equivalency, thereby qualifying as interchangeable.

Examination of bioavailability/bioequivalence (BA/BE) in adult volunteers in good health. The timely completion of the study and quality report made possible by a well-selected CRO will ensure that the regulatory agency's dossier is accepted without any problems.

OUTSOURCING

Contract research organizations' (CROs') services are very beneficial to the pharmaceutical sector. Complete assistance Greater capabilities are provided by CROs, although smaller, "niche" CROs can concentrate only on particular areas like clinical or analytical.[1]

The CRO and client must realize the importance of close collaboration and seamless communication between their organizations. This collaboration is necessary to achievestudy success on time.

The following are among the essential components required for success:

- Sensitivity to deadlines and project-specific needs;
- Communication between the pharmaceutical company and the CRO at all levels.
- The ability to adapt to unforeseen circumstances as they arise within the project'stimetable [3].

Table 1: lists of a selection of CRO services.

Check Sheet Providing Typical Outsourced Services for BA/BE Studies		
	Sponsor (✔)	CRO (✔)
Bioanalytical Analysis		
Bioanalytical site selection and qualification		
Clinical study design		
Clinical protocol development Clinical site selection and qualificationClinical conduct		
Clinical monitoring		
Data management		
Pharmacokinetic analyses		
Statical Analysis		
Project management FD/Regulatory		

Reasons for outsourcing

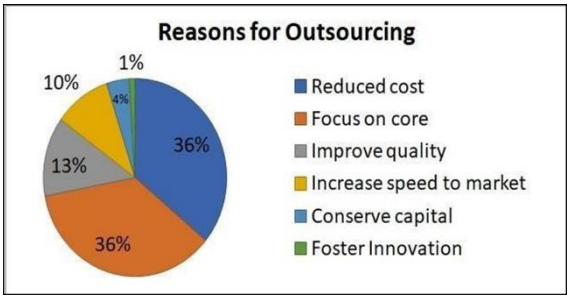

Figure 1: Reasons for outsourcing

Advantage:

a) Improved customer service.
b) Increase productivity and efficiency.
c) Better people management.
d) Focus on core competencies.
e) Access to world-class solutions

Figure 2: Advantages of outsourcing

CONTRACT RESEARCH ORGANIZATION

A contract research organization (CRO) is a business that offers contract-based research services to the biotechnology, pharmaceutical, and medical device sectors in the life sciences. The following services are possible from a CRO: pharmacovigilance, real- world evidence, biological assay development, marketing, clinical development, clinical trials management, and biopharmaceutical development [4]

Several CROs specialize in supporting clinical trials and/or studies for medications and/or medical devices.

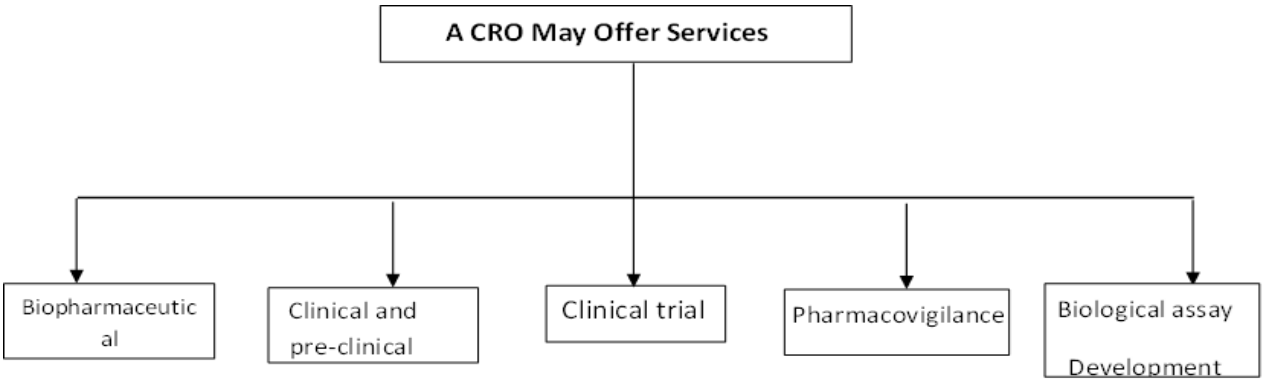

Figure 3: Services offered by CRO

SELECTION CRITERIA FOR CRO'S

Pharmaceutical enterprises, resource-constrained, require CROs, while smaller businesses rely on the CRO's comprehensive knowledge, which can provide more general assistance in addition to the acquired specialized service. The CRO's experience, expertise, size, cost-effectiveness, location, level of recognition, recommendations, e-submission tools, and collaboration network were taken into consideration when defining the requirements [6]

Your CRO is required to approve corporate processes for every aspect of clinical research. These procedures ensure the adherence to good clinical practices (GCP), goodlaboratory practices (GLP), and other pertinent regulatory practices and guidelines in all study aspects, such as clinical conduct, laboratory analysis, data management, biostatistics, pharmacokinetics, and medical writing. In summary, these protocols safeguard the veracity of the information and uphold the autonomy and honesty of the individuals participating in the research [5].

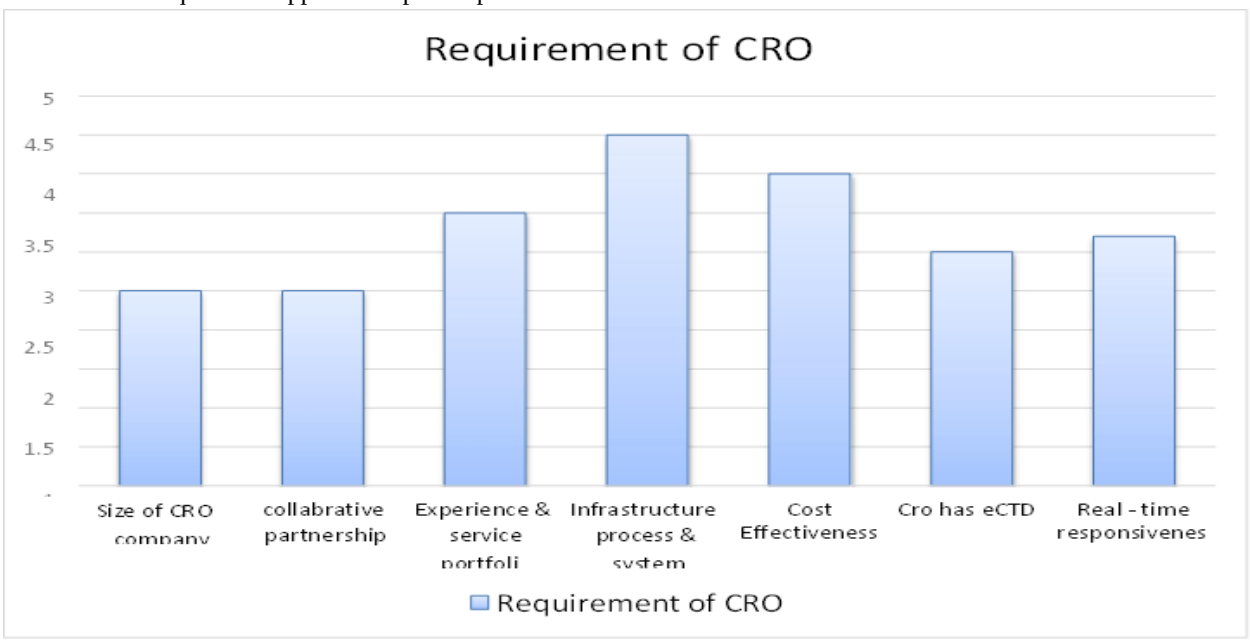

Figure 4: Requirement of CRO

CRO QUALIFICATION

1) Due Diligence:

If the pharmaceutical company has previously worked with the CRO, they ought to assess their experience with the CRO impartially. If the experience was positive, the company ought to determine the elements that worked well and make sure they apply them to their upcoming research project. The CRO should include performance metrics. The company ought to ask for "references"; these should be businesses that

contracted out research that was approved as an ANDA or NDA [7], [8].

2) Clinical Site-Qualification

There should be a site qualification visit by the sponsor.

3) Bioanalytical Site Qualification

It's also important to evaluate potential CROs for bioanalytical laboratory work. The company audit should include an evaluation of the laboratory's inspection as well as cGLP compliance. Finally, to support the BA/BE study, the CRO must provide written documentation outlining the contents of the final analytical report. The FDA mandates comprehensive validation to support BA and BE studies in NDAs and ANDAs [9].

4) Pharmacokinetic Site Qualification

Additionally, the pharmaceutical company needs to certify the CRO location (or division) in charge of pharmacokinetic and statistical analysis as well as finishing the final integrated report. Every program should be completely validated by the group incompliance with FDA programming criteria.

The CRO Industry's Trends in Therapeutic Areas:

1. Oncology: In pharmaceutical contract research, oncology remains a prominent therapeutic area. According to a 2023 study, the oncology category held more than53.9% of the Asia Pacific market share in 2021 due to the increasing number of cancer cases.
2. Respiratory: Clinical CROs that work on respiratory disease clinical trials and offer services like bronchoscopies respiratoryfunction testing, and specialized assessments linked to clinical endpoints for evaluating treatment effectiveness will have an edge over traditional CROs.
3. Rare diseases: Rare diseases, also known as orphan diseases, only affect a small portion of the population and present formidable obstacles to detection and treatment. To satisfy this demand, numerous CROs are enhancing their capacities and knowledge in carrying out rare illness trials.
4. Infectious Diseases: The recent COVID-19 epidemic has made infectious diseases more prominent. The main factor driving this increase in demand is the availability of SARS-CoV-2 vaccinations and other treatments for infectious disorders.
5. Cardiovascular Diseases: Cardiovascular research is conducted by CROs, who offer services such as patient recruiting, electrocardiography, cardiovascular imaging, and monitoring of cardiovascular outcomes in clinical trials.
6. Central Nervous System (CNS) Disorders: In CNS-focused clinical trials, CROs provide services such as biomarker analysis, neuroimaging, cognitive evaluations, and patient recruiting. Many pharmaceutical companies continue to prioritize the development of innovative medicines for CNS illnesses. [11]

THE FUNDAMENTAL REGULATORY FACTORS AND OPPORTUNITIES FOR CARRYING OUT STUDIES ON BIOAVAILABILITY AND BIOEQUIVALENCE (BA/BE)

Over the past three decades, innovative medicine discoveries (brand-name drugs) and generic drug production have boosted patient life expectancy internationally.

A significant tactic to reduce prescription costs and, consequently, their share of overall healthcare expenses is the launch of genericversions of name-brand medications (also known as innovator pharmaceuticals) [18]. Given the significance of generics in healthcare. The generic formulation is (among other things) bioequivalent to the innovator formulation, according to the FDA, which also designated it as "therapeutic equivalence," [19]. The pertinent situations in which bioequivalence studies are required include: - I) when the proposed marketed dosage form is different from that used in pivotal clinical trials; ii) when significant changes are made in the manufactureof the marketed formulation; iii) when a new generic product tested against theinnovator's marketed product. Based on this background, bioavailability (BA) and bioequivalence (BE) information has been determined to have practical and public health value for pharmaceutical industries, regulatory agencies, patients, andpractitioners. [14]

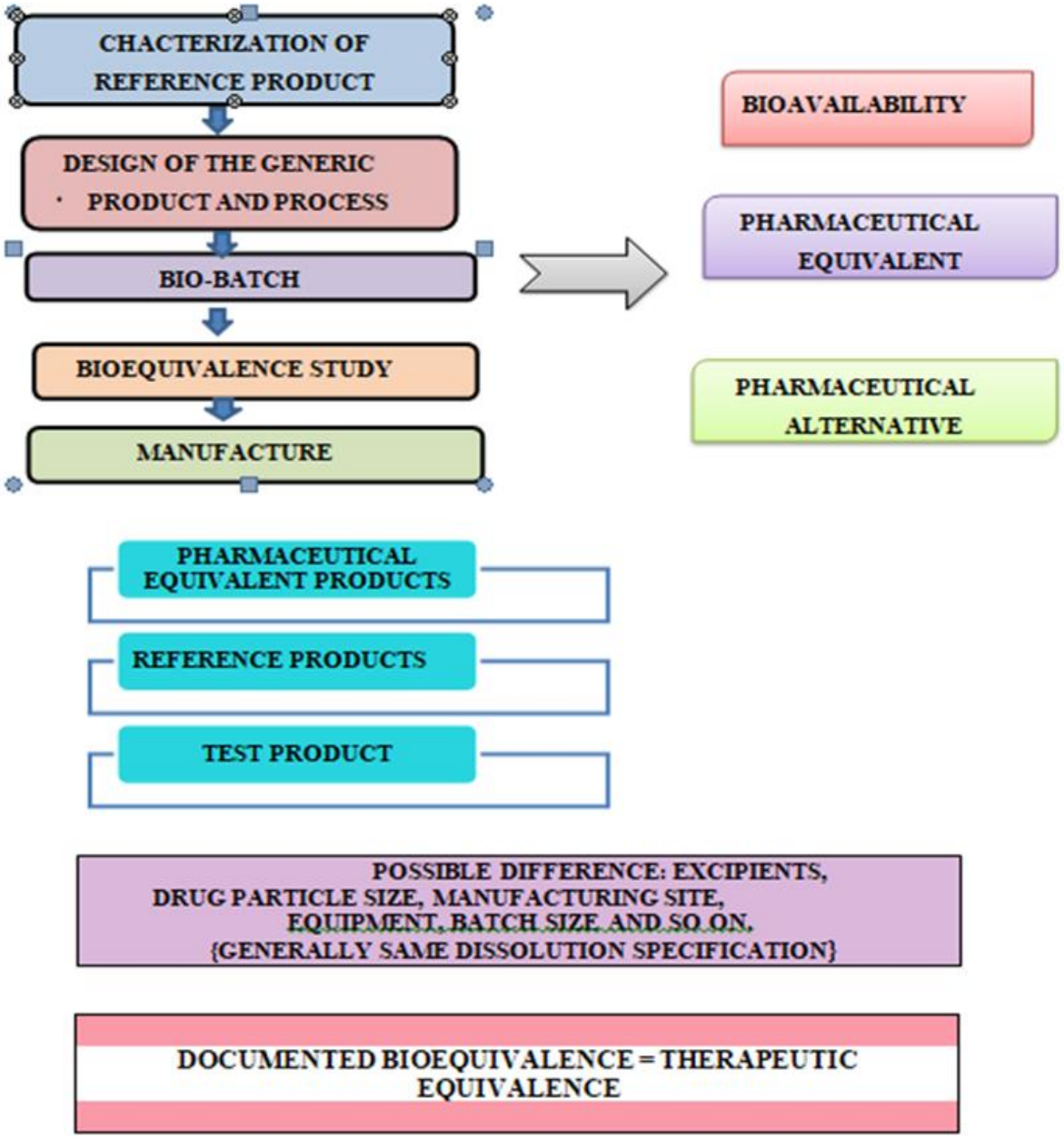

Figure 6: Important route for the creation of a generic medication

SIGNIFICANCE OF RESEARCH ON BIOAVAILABILITY AND BIOEQUIVALENCE

1. Global perspective on relative bioavailability

The majority of bioavailability studies are conducted for a common theme, whether they are for a novel or generic product. The assessment of the pharmacokinetic parameters of an oral formulation in comparison to an intravenous dose or the performance of a modified-lease formulation in contrast to a traditional capsule is done using the absolute bioavailability of a new drug. Comparative bioavailability studies share commonalities that point to a shared experimental methodology [9], [17].

2. Research comparing the bioavailability of novel medications

To ascertain the bioavailability and bioequivalence of the formulation in humans for safety and efficacy, comparative bioavailability studies are utilized for

novel drugs. Researchers gather data on the bioavailability of the novel medication formulation. by contrasting the pharmacokinetic characteristics of new medication formulations administered orally with those administered intravenously at the same dose [18].

3. Comparative generic drug bioavailability (ANDA)

When a producer wants to achieve therapeutic equivalency to launch a rival generic medication into the market, it does not need to carry out the entire set of clinical trials required for the initial product. Once therapeutic equivalency has been established, thestudy must be conducted following the guidelines, and the product must be comparableto or better than the prior or innovative one. [14].

CRO SERVICES FOR BIOEQUIVALENCE AND BIOAVAILABILITY

In India for bioequivalence investigations many CROs keep up-to-date with multi-bed clinical facilities and well-equipped bioanalytical laboratories. The CRO's clients use these healthy volunteers to test their generic medications, and the attached bioanalytical laboratories, equipped with top-of-the-lineequipment like LCMS and HPLC, examine their biological samples for pharmacokinetic parameters. The bioequivalence information supplied by these CROsis a crucial component of the shortened new drug application that pharmaceutical companies submit to the US FDA to obtain clearance for generic goods [26]. Outsourcing bioanalysis frequently provides sponsors with increased flexibility, a global reach, and a reduction in capital infrastructure and staff costs. It is crucial to fully understand your current and future needs to select a suitable partner for the outsourcing of bioanalytical services. The study involves the investigation of bioavailability/bio equivalency (BA/BE) in volunteers who are healthy adults. The CRO's clients test the generic drugs on thesehealthy volunteers, and the adjacent bioanalytical laboratories, equipped with state-of-the-art machinery like LCMS and HPLC, analyze their biological samples for pharmacokinetic parameters. [27].

CONCLUSION

Outsourcing bioequivalence and bioavailability studies to contract research organizations (CROs) offers several advantages to pharmaceutical companies. By leveraging the expertise, infrastructure, and resources of CROs, companies can ensure the efficient and cost-effective conduct of these critical studies. [28]. Additionally, outsourcing allows companies to focus on their core competencies while benefiting from faster turnaround times and cost savings. Overall, partnering with CROs for bioequivalence and bioavailability studies is a strategic approach that enhances the drug development process and facilitates regulatory approval of generic products [30]. It represents a strategic and efficient approach for pharmaceutical companies seeking to demonstrate the equivalence and efficacy of generic drugs. By entrusting these studies to specialized CROs. In the end, using CROs helps pharmaceutical companies confidently handle the complicated processes of bioequivalence and bioavailability testing. This makes it possible for patients all over the world to get safe, effective, and affordable generic medicines on time.

CONFLICT OF INTEREST

No conflict of interest

REFERENCE

[1] A. Gummerus, M. Airaksinen, M. Bengtström, and A. Juppo, “Outsourcing of Regulatory Affairs Tasks in Pharmaceutical Companies—Why and What?” *J Pharm Innov*, vol. 11, no. 1, pp. 46–52, Mar. 2016, doi: 10.1007/s12247-015-9235-4.

[2] “Indian Contract Research Industry Set for Rapid Growth.” [Online]. Available: https://pharmaboardroom.com/articles/indian-contract-research-industry-set-for-rapid-growth/

[3] L. Miller, “COMMENTARY: OUTSOURCING OF REGULATORY ACTIVITIES: HOW A POLICY CAN DRIVE GOOD DECISIONS.”

[4] C. Dhanunjaya Reddy and N. Vishal Gupta, “OVERVIEW ON CONTRACT RESEARCH AND MANUFACTURING SERVICES (CRAMs) AND ITS PRESENT STATUS IN INDIA.”

[5] S. Drabu, A. Gupta, and A. Bhadauria, “Emerging trends in contract research industry in India,” *Contemporary Clinical Trials*, vol. 31, no. 5. pp. 419–422, Sep. 2010. doi: 10.1016/j.cct.2010.06.008.

[6] “Research and Markets_ Regulatory Affairs_ Safeguarding Submission Success and Product

Development Strategy _ Business Wire".
[7] "Investigation for a New Chemical Entity (NCE) using a BA or BE."
[8] B. S. Piachaud, "Outsourcing in the pharmaceutical manufacturing process: an examination of the CRO experience," 2002. [Online]. Available: www.elsevier.com/locate/technovation
[9] D. Hema Nagadurga, "Bioavailability and Bioequivalence Studies," in *Pharmaceutical Formulation Design - Recent Practices*, IntechOpen, 2020. doi: 10.5772/intechopen.85145.
[10] H. Adobor, "Ethical Issues in Outsourcing: The Case of Contract Medical Research and the Global Pharmaceutical Industry," *Journal of Business Ethics*, vol. 105, no. 2, pp. 239–255, Jan. 2012, doi: 10.1007/s10551-011- 0964-0.
[11] M. Lowman, P. Trott, A. Hoecht, and Z. Sellam, "Innovation risks of outsourcing in pharmaceutical new product development," *Technovation*, vol. 32, no. 2, pp. 99–109, Feb. 2012, doi: 10.1016/j.technovation.2011.11.004
[12] M. S. Shih, "Roles of contract research organizations in translational medicine," *J Orthop Translat*, vol. 3, no. 2, pp. 85–88, Apr. 2015, doi: 10.1016/j.jot.2015.01.001.
[13] D. Hema Nagadurga, "Bioavailability and Bioequivalence Studies." [Online]. Available: www.intechopen.com
[14] S. C. Chow, "Bioavailability and bioequivalence in drug development," *Wiley Interdiscip Rev Comput Stat*, vol. 6, no. 4, pp. 304–312, 2014, doi: 10.1002/wics.1310.
[15] H. Pander Maat and L. Lentz, "Improving the usability of patient information leaflets," *Patient Educ Couns*, vol. 80, no. 1, pp. 113–119, Jul. 2010, doi: 10.1016/j.pec.2009.09.030.
[16] R. Hayes, "Bioanalytical outsourcing: Transitioning from Pharma to CRO," *Bioanalysis*, vol. 9, no. 15. Future Medicine Ltd., pp. 1149–1152, Aug. 01, 2017. doi: 10.4155/bio-2017-4996.
[17] S. A. Kumar and D. Sanjita, "A Review Article on Bioavailability and Bioequivalence Studies."
[18] P. K. Noonan, "2 Outsourcing Bioavailability and Bioequivalence Studies to Contract Research Organizations."
[19] S. H. Haidar, H. Kwon, R. Lionberger, and L. X. Yu, "8 Bioavailability and Bioequivalence."
[20] "Editorial Guidelines _ Contract Pharma".
[21] E. F. Ferrer Romero, "Gestión estratégica de proyectos: una metodología para una ventaja competitiva sostenible," *Revista Escuela de Administración de Negocios*, pp. 15–31, Oct. 2018, doi: 10.21158/01208160.n0.2018.2016.
[22] S. Sariola, D. Ravindran, A. Kumar, and R. Jeffery, "Big- pharmaceuticalisation: Clinical trials and Contract Research Organisations in India," *Soc Sci Med*, vol. 131, pp. 239–246, 2015, doi: 10.1016/j.socscimed.2014.11.052.
[23] "Drug Discovery Informatics Market Drug Discovery Informatics Market Outlook 2031." [Online]. Available: https://www.transparencymarketresearch.com/drug-discovery-informatics- market.html
[24] R. Vinoth, P. Pandian, and K. Kathiresan, "CONTRACT RESEARCH ORGANISATIONS IN INDIA-A REVIEW," *IJBPAS*, vol. 11, no. 8, p. 11, 2022, doi: 10.31032/IJBPAS/2021/11.8.6314.
[25] "Crossley R". "STUDY ON CRO SECTOR IN INDIA CONDUCTED BY DEPARTMENT OF PHARMACEUTICALS MINISTRY OF CHEMICALS & FERTILIZERS GOVERNMENT OF INDIA AUGUST, 2023."
[26] Fda, Cder, and Purdief, "Guidance for Industry Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs-General Considerations DRAFT GUIDANCE," 2014. [Online]. Available: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Gui dances/default.htm
[27] "Review on bioavailability and bioequivalence studies." [Online]. Available: https://www.researchgate.net/publication/288464660
[28] "India Cro Market Information Bwc2070 INQUIRE BEFORE BUYING REQUEST FOR SAMPLE." [Online]. Available: https://www.blueweaveconsulting.com/report/india-cro-market-information-bwc20702/7
[29] S. S. Mathew, G. N. K. Ganesh, and P. Patel, "An over view of contractresearch organization and analysis on aro-cro model."