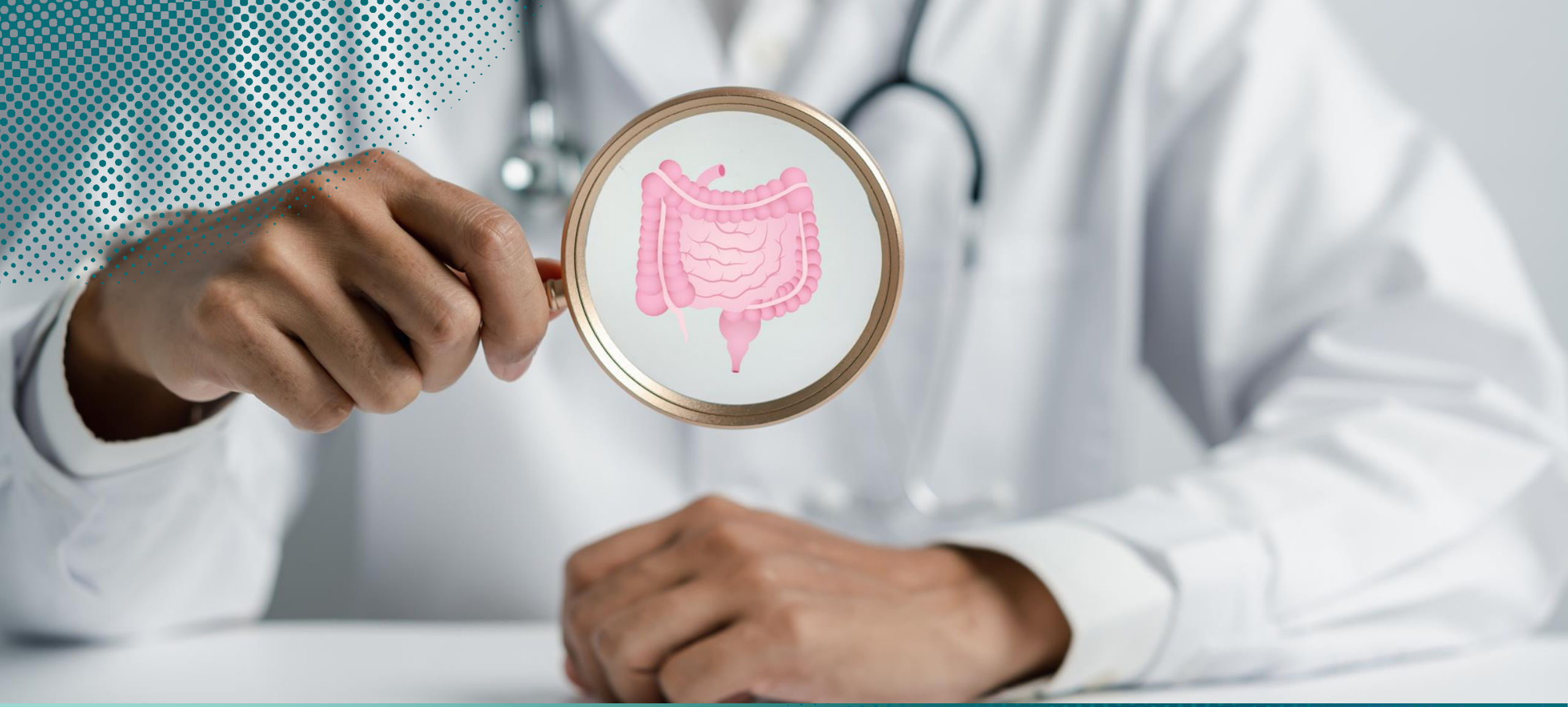

Inflammatory Bowel Disease (IBD):

Treatment Drugs Approved, Failed, and Lessons Learned

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Introduction

In the highly competitive world of drug development, the journey from the laboratory bench to the pharmacy shelf is fraught with challenges.

Drug Development in the inflammatory bowel disease field is challenging.

From the outset the economic argument for a novel investigational product has to contend with the near-absolute market domination of already approved monoclonal antibodies such as adalimumab, a therapeutic with a revenue in excess of USD 20 Billion, 2.5-fold greater than the next highest selling mAb[1].

The challenges don't end with issues around preclinical viability. Globally, and across the therapeutic gamut, pharmaceutical clinical development is growing harder with around 50% of patient clinical trials failing to meet patient recruitment timelines and the premature termination of 1 in 5 clinical development programs[2].

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Challenges

Specific to the Inflammatory Bowel Diseases, the biggest challenge to clinical development programs is the oversaturation of the trials landscape with Phase 2/3 development programs competing for the same patient population.

A study that sought to define the difficulties around patient recruitment revealed an increase in the number of moderate-to-severe IBD trials of 140 trials (1998 – 7 trials; 2018 - 147 trials) in the 20 years to 2018[3].

While diagnosis and recruitment activities have shown considerable improvement over this time - the more diagnosed patients the more potential participants - the fact is any new development program in the Phase 2/3 space is in competition for participants. Interestingly, there is a preponderance of trials targeted to ulcerative colitis rather than Crohn's disease, likely due to the comparatively easier ability to monitor endoscopic and mucosal response in the distal colon amongst other reasons.

Capturing and retaining participants in this landscape is critical to the overall success of a clinical development program with strategies to achieve this ranging from changes to clinical trial design to adopting novel marketing strategies. Regarding trial design, reducing unnecessary exclusion criteria and employing adaptive or other novel trial designs as well as reducing participant treatment burdens can improve participant retention and most efficiently utilise a valuable participant.

FDA-Approved IBD Therapeutics and Associated Pivotal Endpoints

Drug Name	Year of Approval	Disease Indication	Endpoints Used in Pivotal Studies
Upadacitinib (Rinvoq)	2023	Crohn's, UC	Clinical remission, Endoscopic response
Ozanimod (Zeposia)	2021	UC	Clinical remission, mucosal response
Ustekinumab (Stelara)	2019 (UC), 2016 (Crohn's)	Crohn's, UC	Clinical remission, Endoscopic response
Tofacitinib (Xeljanz)	2018	UC	Clinical remission, Mucosal response
Vedolizumab (Entyvio)	2014	Crohn's, UC	Clinical response, Clinical remission, and Mucosal response
Golimumab (Simponi)	2009	UC	Clinical response, Clinical remission, and Mucosal response
Natalizumab (Tysabri)	2008	Crohn's	Clinical response, Clinical remission
Certolizumab (Cimzia)	2008	Crohn's	Clinical response, Clinical remission
Adalimumab (Humira)	2012 (UC), 2007 (Crohn's)	Crohn's, UC	Clinical remission
Infliximab (Remicade)	2005 (UC), 1998 (Crohn's)	Crohn's, UC	Clinical remission, Mucosal response
Balsalazide (Colazal)	2000	UC	Clinical Response, Sigmoidoscopic appearance
Mesalamine (Lialda)	1987	UC	Clinical Response, Sigmoidoscopic appearance

Examples of Drugs That Have Failed Clinical Trials for IBD

Drug Name	Sponsor	Reason for Failure	Lessons Learned
Tofacitinib (Xeljanz)	Pfizer	Failed to demonstrate statistically significant treatment effect/clinically efficacy in phase 2 trial	Importance of selecting appropriate patient populations (high proportion of concomitant corticosteroids) and endpoints for clinical trials.
Etrolizumab	Roche	Failed to meet primary efficacy endpoints over a suite of Phase 3 trials	Important to consider timing and collection of early efficacy data when embarking on big development programs
Mongersen (GED-0301)	Celgene (Now Part of Bristol-Myers Squibb)	Failed to demonstrate efficacy in Phase 3 interim futility analysis	Difficulty of extrapolating early phase/proof-of-concept data to likelihood of success in later phase trials. Reliance on data from improperly designed early phase trials.
Etrasimod	Arena Pharmaceuticals	Did not achieve primary endpoint in Phase 2 trial for ulcerative colitis but has gone on to demonstrate success in Phase 3	Further evaluation of drug's efficacy and safety in IBD.
Mirikizumab	Eli Lilly	Rejected by the FDA on manufacturing grounds rather than safety or clinical efficacy grounds.	Understand that clinical development does not occur in a vacuum, with multiple other factors to consider.

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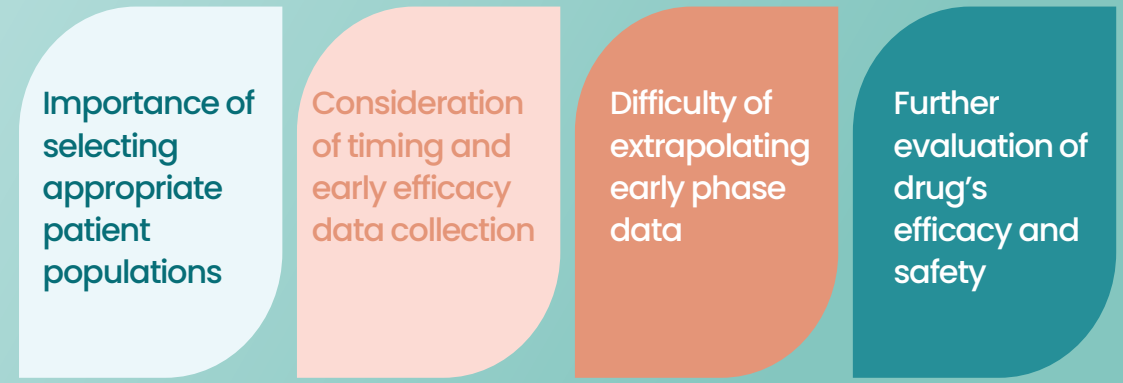
Conclusion

These examples illustrate the complexity of developing effective treatments for IBD. Failures in clinical trials often underscore the importance of patient selection, appropriate endpoints, and the need for a deep understanding of the disease's underlying mechanisms. The IBD field continues to evolve, with ongoing research and development efforts aimed at improving the lives of individuals living with these chronic conditions.

Some key lessons learned:



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1. Lu RM, Hwang YC, Liu IJ, Lee CC, Tsai HZ, Li HJ, et al. Development of therapeutic antibodies for the treatment of diseases. J Biomed Sci. 2020 Dec;27(1):1.
2. Uzzan M, Bouhnik Y, Abreu M, Ahmad HA, Adsul S, Carlier H, et al. Declining Enrolment and Other Challenges in IBD Clinical Trials: Causes and Potential Solutions. J Crohns Colitis. 2023 Jul 1;17(7):1066–78.
3. Harris MS, Wichary J, Zadnik M, Reinisch W. Competition for Clinical Trials in Inflammatory Bowel Diseases. Gastroenterology. 2019 Dec 1;157(6):1457-1461.e2.
Please consult updated sources for the current status of IBD drug development.

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

Dr Sud Agarwal
Chief Executive Officer
BSc (Hons), MB ChB FANZCA DDU
dr.sudhanshu@ingenucro.com

Adam Moodie
Director, Scientific Engagement
BSc
adam.moodie@ingenucro.com

Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com