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Review Article

Comparison of the FDA and EMA guidance on drug development in ulcerative colitis: an expert panel review

Sophie Vieujean,[1,2] Bruce E. Sands,[3] Remo Panaccione,[4] David T. Rubin,[5] Vipul Jairath,[6] Silvio Danese,[7] Laurent Peyrin-Biroulet,[2] Stefan Schreiber,[8] Séverine Vermeire,[9] Geert D'Haens,[10] Axel Dignass,[11] Parambir S. Dulai,[12] Neeraj Narula,[13] Walter Reinisch[14]

[1]Hepato-Gastroenterology and Digestive Oncology, University Hospital CHU of Liège, Liège, Belgium
[2]Department of Gastroenterology, INFINY Institute, CHRU Nancy, Vandœuvre-lès-Nancy, France
[3]Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[4]Inflammatory Bowel Disease Unit, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[5]University of Chicago Medicine Inflammatory Bowel Disease Center, Chicago, IL, United States
[6]Division of Gastroenterology, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada
[7]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milano, Italy
[8]Department of Internal Medicine I, University Hospital Schleswig-Holstein, Kiel University, Kiel, Germany
[9]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium
[10]Department of Gastroenterology, Amsterdam University Medical Centers, Amsterdam, The Netherlands
[11]Department of Medicine I, Agaplesion Markus Hospital, Frankfurt/Main, Germany
[12]Division of Gastroenterology, Northwestern University, Chicago, IL, United States
[13]Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada
[14]Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

*Corresponding author: Walter Reinisch, Department of Internal Medicine III, Division Gastroenterology & Hepatology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria (walter.reinisch@meduniwien.ac.at).

Abstract

Background and Aims: The Food and Drug Administration (FDA) and European Medicines Agency (EMA) ensure the safety, efficacy, and security of treatments, including therapies for immune-mediated disorders such as inflammatory bowel disease (IBD). Their clinical trial guidelines aid sponsors in designing robust studies. While the EMA updated its guidelines for ulcerative colitis (UC) in 2018, the FDA issued new recommendations in April 2022. This paper compares these guidelines, assesses their implications for IBD clinical trials, and proposes strategies to improve alignment and trial efficiency.

Methods: A comparative analysis of the FDA's 2022 guidelines and the EMA's 2018 guidelines for UC clinical trials was conducted. Key elements reviewed include trial population criteria, study design, assessment tools, endpoints, and safety considerations. Recommendations for optimization were developed in consultation with an expert panel.

Results: The FDA's 2022 updates emphasize balanced participant representation, the use of full colonoscopy for endoscopic severity assessment, and introduce "maintenance of remission" as a new concept. Other novelties include updated statistical guidance and stricter safety requirements. While these updates enhance trial robustness, they also pose challenges for implementation.

Conclusions: Harmonizing FDA and EMA guidelines is essential to streamline global IBD clinical trials, reduce redundancies, and improve patient outcomes. Recommendations include adopting less invasive assessments, standardizing remission definitions, and prioritizing patient-centered endpoints. These measures could reduce trial complexity, increase inclusivity, and accelerate the development of effective therapies for UC.

Key words: ulcerative colitis; Food and Drug Administration; European Medicines Agency

1. Introduction

The primary contemporary role of agencies, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) is to assess and ensure the safety and efficacy (and subsequent approval for marketing) of all drugs used in the "cure, mitigation, treatment, and prevention of disease". This is based on preclinical and clinical trial data as well as post-marketing reviews provided by sponsors.[1,2] To conduct these clinical trials, the agencies have drafted guidance documents to assist sponsors in the clinical development of these candidate drugs, including those for inflammatory bowel diseases (IBDs). These guidelines reflect the agencies' current thinking regarding the essential elements of clinical trials for drugs being developed (and should only be considered as recommendations), covering considerations on trial populations, trial designs, assessment tools, endpoints, statistical considerations, and safety assessments.[3,4]

In 2016, the FDA developed draft guidance reflecting its current perspective on efficacy endpoints for ulcerative colitis (UC) clinical trials. While the EMA guidelines on UC have not been revised since June 2018,[5] the FDA outlined new

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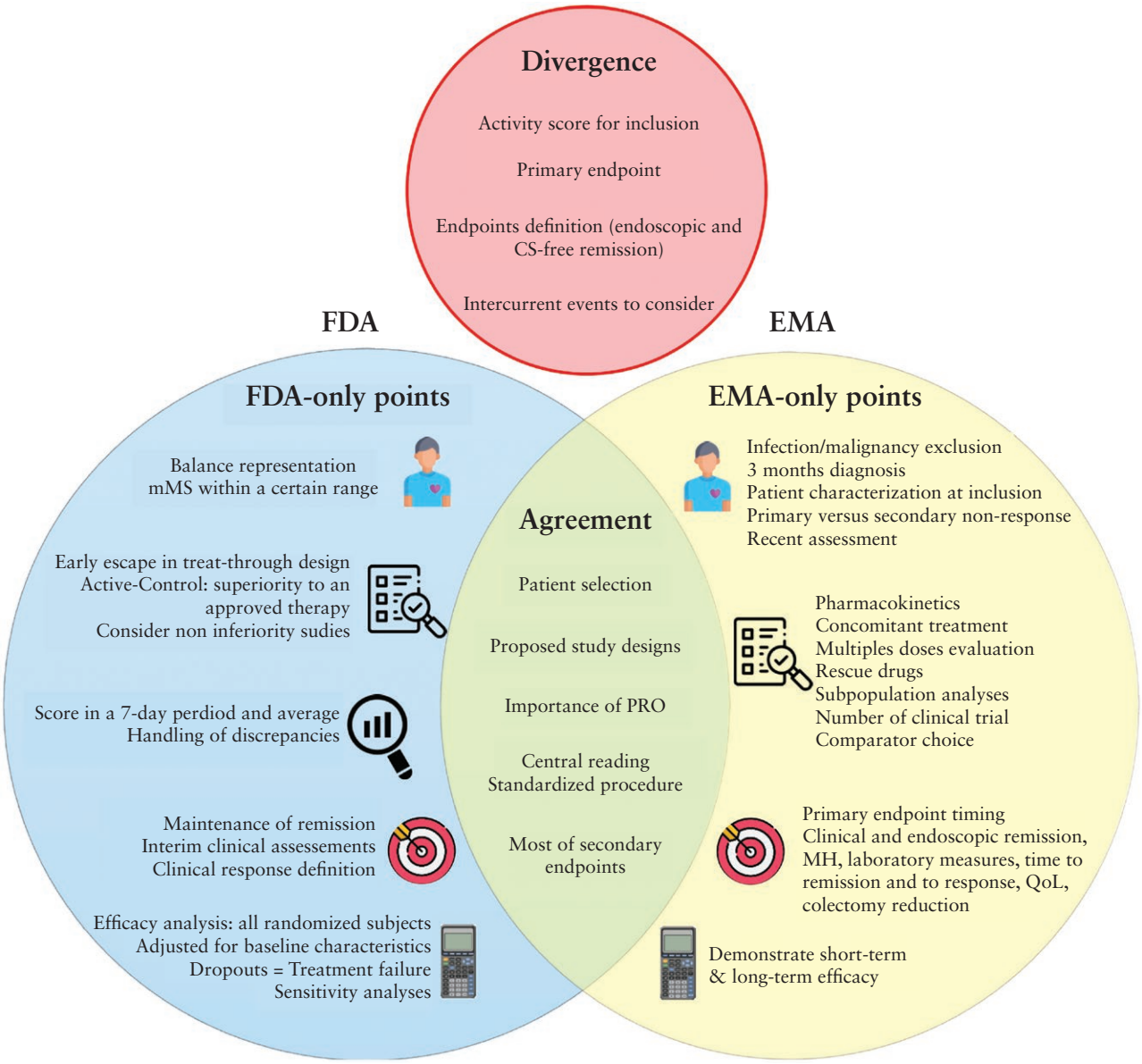

Figure 1. Points of agreement, divergence, and those addressed exclusively by either the FDA or EMA. Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.

recommendations on UC clinical trial design in April 2022.[3,6] In this paper, we aim to summarize the FDA's updates and compare them to the EMA guideline, in line with our previous work.[7] Additionally, we reflect on how these changes should be contextualized within today's IBD clinical trials landscape, discuss the importance of a guidance alignment between these agencies, and provide potential revisions for future guidance involving global IBD clinical trials.

2. Methods

This article is based on a detailed review and comparison of the FDA and EMA guidance documents on clinical trial design in UC, including the FDA's 2016 draft guidance and its updated version from 2022, as well as the most recent EMA guideline from 2018. These documents were carefully analyzed to identify key areas of alignment and divergence. A panel of experts in clinical trial design in IBD was consulted. Panel members were selected based on their academic and clinical expertise, as well as prior involvement in IBD drug development and regulatory discussions. The initial comparative analysis was circulated among the authors, who provided structured feedback. While no formal consensus methodology was applied, all authors actively contributed to shaping the interpretation of the findings and refining the key messages.

3. FDA guideline updates in comparison with EMA

3.1 Updated recommendations for the development program

Points of agreement, divergence, and those addressed exclusively by either the FDA or EMA are presented in Figure 1. The FDA and EMA are aligned with the concept that the treatment effect of a study drug should be documented both

through symptomatic relief, as measured by patient-reported outcomes (PROs), and by control of the inflammatory process, as directly evaluated by endoscopy. Both agencies have rejected the need for the physician global assessment, which is part of the full Mayo score. Instead, they favor the 3-item version known as modified Mayo score (mMS), which includes stool frequency, rectal bleeding, and endoscopic severity. According to the EMA, this score "… may be used until fully validated scores are available."

In terms of *trial population*, the revised FDA guidance document specifies that participants must have a confirmed diagnosis of UC based on endoscopy and histopathology, which aligns with EMA's position. However, only EMA recommends a minimum symptom duration of 3 months at inclusion. The FDA's 2022 update states that trials for moderately to severely active UC should enroll participants with an mMS of 5 to 9, while the 2018 EMA guidance refers to a full Mayo score of 9 to 12. Both agencies require a minimum endoscopic subscore of ≥2 with central reading. FDA emphasizes a balanced representation of participants across the spectrum of disease severity, including those naïve to and those who have failed prior biologic or advanced therapies. EMA focuses more on thorough characterization of participants at inclusion. For trials in mildly to moderately active UC, FDA recommends enrolling participants with an mMS ≥4, including an endoscopy subscore ≥2 and a rectal bleeding subscore ≥ 1. FDA advises that study populations should reflect clinically relevant diversity, including race and ethnicity.[3]

Guidance on *trial design*, not addressed in the 2016 FDA document, was introduced in the 2022 update. FDA recommends randomized, double-blind, placebo-controlled trials that demonstrate sustained therapeutic benefit during a maintenance phase to support chronic drug use. Both *induction followed by randomized withdrawal* and *treat-through* designs are acceptable, with a recommended treatment duration of at least 1 year. In *treat-through* designs, the FDA advises periodic early assessments to capture time to clinical improvement, along with predefined escape criteria to allow access to active treatment. This aligns with EMA guidance, which also recommends predefining rescue drug use. The FDA further encourages active comparator trials to demonstrate superiority over approved therapies, though noninferiority designs may also be acceptable.

Therefore, the FDA and EMA both support double-blind trial designs with parallel arms, including active comparator and/or placebo, and require demonstration of both short- and long-term efficacy over at least 12 months. According to EMA, claims may target either "induction of remission" or "maintenance of remission." While their positions on trial design are generally aligned, EMA provides additional guidance not covered by the FDA. This includes recommendations on pharmacokinetics, interactions with commonly co-administered treatments (eg, corticosteroids, immunosuppressants), and dose-finding studies. EMA also emphasizes the need to predefine relevant subpopulations and stratify based on prior or background treatments. Moreover, EMA expects at least 2 confirmatory trials to support a treatment claim, potentially in different disease stages such as early UC or in patients refractory to multiple therapies. For first-line indications, EMA requires direct comparison with the current standard of care and advises limiting placebo use to a maximum of 6 months.

In terms of *assessment tools*, the FDA maintains its 2016 recommendation to score endoscopic severity using high-definition video recordings reviewed by blinded central readers. Assessments by both the site endoscopist and central readers should be documented, and protocols should specify how discrepancies will be resolved (eg, adjudication by a third reader). Thus, both agencies support standardized central reading. However, the 2022 FDA guidance explicitly recommends full colonoscopy to assess all colonic segments, whereas EMA does not specify whether sigmoidoscopy or colonoscopy should be used. While the 2016 guidance aimed to standardize stool and rectal bleeding reporting over 24 hours, the 2022 update provides more specific instructions for calculating the mMS stool frequency and rectal bleeding subscores. A 7-day assessment period is recommended, excluding days of bowel prep and endoscopy, with averages calculated from at least 3 consecutive or 4 nonconsecutive diary days.

The endpoints recommended by the FDA in 2016 and 2022, along with their definitions, are summarized in Table 1. The FDA's *primary endpoint* remains unchanged: the proportion of participants achieving clinical remission, defined as an mMS of 0–2. *This composite endpoint requires meeting predefined thresholds*, including a stool frequency subscore of 0 or 1 (and no higher than baseline), a rectal bleeding subscore of 0, and a centrally read endoscopy subscore of 0 or 1 (excluding friability). The definition of a Mayo endoscopic subscore of 0 has evolved since 2016. The earlier guidance allowed signs of inactive disease (eg, pseudopolyps, scarring, atrophy). While EMA accepts the same endoscopic and rectal bleeding targets, it defines symptomatic remission as a clinical Mayo score of 0 or 1, and expects significant effects on both PROs and endoscopy as co-primary endpoints at the population level.

For *secondary endpoints*, the 2022 FDA guidance provides more detailed criteria. Clinical response is defined as a decrease in mMS of ≥2 points and at least a 30% reduction from baseline, along with a rectal bleeding subscore decrease of ≥1 or an absolute score of 0 or 1. The FDA provides a more specific definition of clinical response, whereas the EMA leaves its interpretation to the particular tools used to assess symptoms and endoscopic findings. Overall, EMA proposes a broader vision on secondary assessment criteria, while FDA is more specific on definitions to be used (see Table 2). EMA also considers the timing of the primary endpoint in relation to treatment objectives and pharmacodynamics and recognizes time to remission and time to response as secondary endpoints. For corticosteroid-free remission, the FDA requires a steroid-free period of 8–12 weeks at trial completion, whereas EMA provides no specific timeframe. The FDA introduces maintenance of remission as a new concept to assess the durability of therapeutic benefit from the end of induction through to the conclusion of the maintenance phase. This requires patients to achieve remission at the induction endpoint and sustain it through the end of maintenance.

In the FDA's 2022 document, the terms endoscopic improvement and endoscopic remission were introduced to replace mucosal healing, which is considered to be a more holistic concept extending beyond the visual assessment of the mucosae. Due to the lack of scientific consensus on defining or scoring histologic resolution of mucosal inflammation, the term mucosal healing is currently not accepted. Histologic endpoints, for which sponsors must provide adequate justification, are considered exploratory. As such, the FDA also considers interim symptom assessments based on noninvasive measures (eg, noninvasive components of the mMS like stool

Table 1. Comparison of the FDA 2016 and 2022 guidance for UC clinical trials.

	2016	2022
Primary endpoint	*Clinical remission* - Stool frequency subscore = 0 - Rectal bleeding subscore = 0 - Endoscopy subscore = 0 or 1 (modified) on Mayo score; or 0 on UCDAI An alternative to a stool frequency subscore of 0 is at least 1-point decrease in stool frequency subscore from baseline (start of trial) to achieve a stool frequency subscore = 0 or 1	*Clinical remission* *mMS score of 0 to 2*, including the following 3 components: - Stool frequency subscore = 0 or 1 - Rectal bleeding subscore = 0 - Centrally read endoscopy subscore = 0 or 1 (score of 1 modified to exclude friability)
Secondary endpoints	Change in treatment arms of each of the subscores (stool frequency, rectal bleeding, and endoscopy) and/or total score (ie, sum of the stool frequency, rectal bleeding, and endoscopy subscores).	*Clinical response* Decrease from baseline in the mMS of greater than or equal to 2 points and at least a 30 percent reduction from baseline, and a decrease in rectal bleeding subscore of greater than or equal to 1 or an absolute rectal bleeding subscore of 0 or 1.
	Corticosteroid-free remission Clinical remission without concomitant corticosteroids *at a particular time point* in patients *who were using corticosteroids at baseline* * To ensure clinical meaningful of this endpoint, its definition should be based on a minimum duration of time over which a patient is considered to be both corticosteroid-free and in clinical remission	*Corticosteroid-free remission* Participants who are in clinical remission *at the conclusion of the controlled trial* (eg, 52 weeks) and having *no corticosteroid exposure during a prespecified period* (eg, at least 8 to 12 weeks) before that assessment. * The proportion of participants achieving corticosteroid-free remission, of those who were using corticosteroids at enrollment, is of interest and should be reported.
	Assessment of mucosal healing vs. endoscopic appearance of the mucosa *Mucosal healing* Mayo endoscopic subscore of less than or equal to 1 point. However, a claim of mucosal healing would not be supported through endoscopy that provides only an assessment of the visual appearance of the mucosa. Any claim related to findings on endoscopy, in the absence of validated histological assessment of the mucosae, would be limited to the endoscopic appearance of the mucosa.	*Endoscopic improvement* Centrally read endoscopy subscore of 0 or 1 (score of modified to exclude friability). *Endoscopic remission* Centrally read endoscopy subscore of 0. * Recommendation to not use *mucosal healing* at this time, as there is no consensus as to how best define this concept.
		Maintenance of remission • For trial designs in which participants who achieve clinical response at the end of the induction phase are rerandomized in the maintenance phase: sponsors are recommended to assess remission within the subset of participants who enter the maintenance phase in remission to support the ability of the therapy to maintain a durable state of remission. • For trial design in which participants are treated continuously without rerandomization (treat-through design), sponsors should assess the proportion of participants who individually achieve clinical remission at both early (eg, 8 weeks) and late (eg, 52 weeks) time points to demonstrate that a clinical benefit was attained and was durable.
Exploratory endpoints	In view of the limitations of histologic scoring systems and of community standards for definitions of histologic improvement, there are no criteria for histological assessment of mucosal healing.	*Histological response/remission* No scientific consensus on a definition of, or scoring system for, histologic remission in UC.
		Interim clinical assessments based on noninvasive measures (noninvasive components of the mMS such as stool frequency and rectal bleeding subscores) at prespecified time points during the trial, up until and including the last visit (eg, 52 weeks), to support maintenance of remission.
		Additional endpoints Sponsors are encouraged to explore the effect of an investigational drug on additional symptoms of UC identified by participants as important but that are not captured within the mMS (eg, abdominal pain, urgency) using fit-for-purpose PRO instruments.

Abbreviations: FDA, Food and Drug Administration; mMS, modified Mayo score; PRO, patient-reported outcome; UC, ulcerative colitis; UCDAI, Ulcerative colitis Disease Activity Index.

frequency and rectal bleeding subscores), at prespecified trial time points up to and including the final visit (eg, 52 weeks), as *exploratory endpoints* to support maintenance of remission.

In the 2022 FDA draft guidance, for the first time, an entire section is dedicated to how sponsors may develop *future PRO instruments* not captured within the mMS or adapt

Table 2. Comparison of the 2022 FDA and 2018 EMA guidelines for clinical trials in ulcerative colitis.

	Points of agreement between the EMA and FDA	Points of divergence between the FDA and EMA		Points addressed only by FDA	Points addressed only by EMA
		FDA	EMA		
Patient selection	* A confirmed diagnosis based on endoscopy and histology * Have an active disease * Study population should match the proposed target population * Patients included must have a minimal level of mucosal inflammation	* Inclusion criteria: a score of 5 to 9 on the mMS including an endoscopy subscore of at least 2	* Patients included must have a score of 9-12 on the Mayo score with a certain minimal level of mucosal inflammation (such as a score ≥ 2 when using the endoscopic part of the Mayo score)	* Balanced representation of participants bio-naïve and bio-experienced and also the enrollment of participants across the whole range of both moderately and severely active disease categories * Sponsors should enroll patients with an mMS within a certain range in trials evaluating compounds for mild-to-moderate disease activity	* Infectious colitis and malignancy must be ruled out * The minimum time from onset of symptoms and inclusion (3 months) * A particular attention must be paid to the characterization of patients at inclusion in terms of disease extend, disease duration, disease activity, smoking status, previous treatment experience (refractory UC, intolerance to treatment dependence on treatment, secondary nonresponse to treatment, and UC in remission) * Difference between patients who had primary nonresponse and secondary nonresponse to treatment * Recent (1 month) evaluation of degree and extend of mucosal inflammation
Study design	* Randomized, with parallel, active comparator and/or placebo treatment and double-blinded * Both short- and long-term efficacy should be demonstrated * 2 study designs for maintenance trials: treat-through design or induction followed by randomized withdrawal maintenance * Total duration for maintenance study should be of at least 12 months * Wash-out period should be defined			* Incorporation of early escape criteria in the treat-through design * Active controlled trials design to demonstrate superiority to an approved therapy encouraged * Sponsors can consider noninferiority studies (but an acceptable noninferiority margin with the appropriate review division before initiating clinical trials)	* Pharmacokinetics properties assessment * Efficacy and safety of concomitant treatments known to be co-administered (CS, IS) * Evaluation of multiple doses recommended * The number of clinical trial provided to fulfill a claim for the treatment * Predefinition of criteria for use of rescue drugs and standardization of these * Assessment of relevant subpopulation or subgroup analyses should be prospectively planned * Patients stratification according to previous treatment and/or background treatment * Specificity for studies intended to claim of either "induction of remission" or "maintenance of remission" * Indications regarding the choice of comparator * Duration and dose of concomitant treatment prior to inclusion, especially for corticosteroids
Assessment tools: clinical assessment	* Use PRO and a score including stool frequency and rectal bleeding, without PGA * The importance to develop new PRO as tool			* Calculation of score in a 7-day period before visit (excluding day of bowel preparation and day of endoscopy) and do an average Min 3 consecutive or 4 nonconsecutive days of completed diary are necessary	

Table 2. Continued

	Points of agreement between the EMA and FDA	Points of divergence between the FDA and EMA		Points addressed only by FDA	Points addressed only by EMA
		FDA	EMA		
Assessment tools: endoscopic assessment	* Central reading of the examinations * Standardized procedure			* Endoscopist and central reader blinded to treatment assignment + document endoscopic findings * Specify how discrepancies will be handled	
Primary endpoints UC		Primary endpoint: proportion of patients achieving clinical remission	Co-primary endpoint: the proportion of patients with symptomatic remission (Mayo score of 0 or 1 and cessation of rectal bleeding) and endoscopic remission (Mayo endoscopic of 0 or 1)		* The timing to measure primary endpoint (depends on the aim of the treatment and the pharmacodynamic properties of the test drug)
Secondary endpoints UC	* Clinical response * Endoscopic response * CS-free clinical remission * Histologic response/ remission (rather as exploratory endpoint for FDA) * Additional secondary endpoints can be added	* Endoscopic remission (considered as primary by the EMA)	* MH and symptomatic remission	* Maintenance of remission * Interim clinical assessments based on noninvasive measures	* Clinical remission using a more stringent definition * Endoscopic remission without CS * Numerical, separate evaluations of the individual components of the symptoms and of the MH score * MH (judged endoscopically), as well as combined symptomatic biomarker (normaliwzation of FC) and histological normalization * Laboratory measures of inflammation * Time to remission * Time to response * QoL * Reduction in number of colectomies
Endpoint definition		* Endoscopic healing: score of 0 or 1 (more stringent definition preferred, less stringent definition acceptable)	* Endoscopic remission: endoscopy subscore of 0	* Clinical response definition to use	
		* CS-free remission: clinical remission at conclusion of the trial and having no CS exposure during a prespecified period before that assessment	* CS-free remission: proportion of patients in whom either or both symptomatic and endoscopic remission are achieved without concomitant CS treatment/ at particular dose of concomitant CS treatment		

Table 2. Continued

	Points of agreement between the EMA and FDA	Points of divergence between the FDA and EMA		Points addressed only by FDA	Points addressed only by EMA
		FDA	EMA		
Statistical considerations	* Target of estimation (estimand) * Differentiation between intercurrents events and missing data * Specify method to handle missing data * Patient follow-up after intercurrent event, treatment discontinuation, use of rescue therapies * Treatment discontinuation, use of rescue medication as intercurrent events * Potential strategies for defining and handling intercurrent events	* Other intercurrent event to consider: UC-related surgery	* Other intercurrent event to consider: change in background therapy, failing to taper CS according to the protocol-planned fixed schedule, use of prohibited medication	* Efficacy analyses in all randomized participants * Statistical analyses adjust for participant characteristics at baseline that may affect efficacy outcome * Drop out before the end of treatment = treatment failures * Sensitivity analyses	* Short-term and long-term efficacies should be demonstrated
Safety consideration	* Sufficient number of exposed participants * Immunogenicity assessment; evaluation of neutralizing capabilities of antidrug antibodies and their impact on clinical efficacy and safety * Safety analyses should be prospectively planned to compare treatment groups with respect to risk			* Wash out period of 5 half-lives for prior therapies or undetectable serum levels * Sponsors should stratify by study any analyses of integrated data from multiple studies	* To characterize adverse events in relation to the duration of treatment, dosage, age, and other relevant variables * Register the concomitant use or not of IS * Register re-treatment outcomes
Others					* Recommendation for studies in special population (pediatric and elderly patients, patients with EIM) as well as for acute severe ulcerative colitis and pouchitis

Abbreviations: CS, corticosteroids; EIM, extraintestinal manifestation; EMA, European Medicines Agency; FC, fecal calprotectin; FDA, Food and Drug Administration; IS, immunosuppressant; MH, mucosal healing; mMS, modified Mayo score; PGA, physician global assessment; PRO, patient-reported outcome; UC, ulcerative colitis.

existing ones for FDA review. To guarantee that new PRO concepts might achieve labeling claims, sponsors must collect supportive attributes. Selected symptoms should provide relevant qualitative information from the patient perspective. Sponsors must show that patients understand and can use the item instruments. Further development and validation of PRO instruments align with EMA's position.

In terms of *statistical considerations*, the FDA's 2022 guidance builds on its previous recommendations by advising adjustment for potentially outcome-predictive baseline characteristics, such as disease duration, severity, corticosteroid use, or prior biologic therapy, when evaluating overall treatment effects. In line with the EMA, efficacy analyses should be conducted in all randomized participants with treatment discontinuation being considered as failure to study drug. For both agencies, sponsors should prespecify a primary meaningful estimand of interest for each endpoint. Additionally, the FDA requires analyses to assess the robustness of primary and secondary analysis results, particularly regarding assumptions about missing data. When defining the estimand, both agencies emphasize the need to account for intercurrent events (events occurring after treatment initiation that could affect outcome interpretation) such as treatment discontinuation due to lack of efficacy or adverse events, use of rescue medication (eg, corticosteroids), and UC-related surgery. Participants should continue to be followed after any such events.

In the "safety considerations" section, the FDA concurs with the EMA that a sufficient number of participants should receive the intended marketed dose for at least 52 weeks in long-term treatment settings, though the minimum acceptable sample size for safety analyses may vary based on drug-specific considerations. Safety analyses should be planned prospectively to enable comparison of treatment-related risks. The EMA offers further guidance on immunogenicity assessments for therapeutic protein products, including evaluation of neutralizing antibodies and their impact on efficacy and safety.

The FDA recommends a washout period of at least 5 half-lives or undetectable serum levels of prior therapies.

Table 3. Why it matters—implications for clinicians and patients.

Topic	Regulatory change or gap	Why it matters for clinicians	Why it matters for patients
Trial population criteria	Requirement for balanced inclusion of moderate/severe UC and biologic-naïve/experienced	Difficult to implement; risks selection bias and limits generalizability of results	May exclude certain patient profiles from trials, reducing access to novel therapies for diverse populations
Diversity and inclusion	Agencies recommend but don't require diversity plans	Lack of structured guidance limits representative recruitment and limits applicability of trial results to real-world population	Underrepresented populations may not benefit equally from innovations
Placebo vs. active comparator	Placebo still often required, though many effective treatments exist	Raises ethical and practical concerns; may limit trial feasibility	Patients may avoid trials due to fear of receiving placebo; this could result in a treatment not being approved for marketing if its difference from an active comparator appears modest, even though it may demonstrate a clinically meaningful benefit over placebo
Endpoints	FDA retains clinical remission as primary endpoint (but including endoscopic remission); EMA promotes co-primary (symptoms + endoscopy)	Affects definition of trial success, sample size calculation, and interpretation of comparability of study results across studies	May lead to difficulties to communicate trial results to patients
PRO	New focus on developing validated, disease-specific PROs	Better tools to assess treatment impact from the patient's perspective	Ensures what matters to patients (eg, fatigue, QoL) is captured and valued
Use of colonoscopy	FDA recommends full colonoscopy; EMA is nonspecific	Increases trial burden and procedural risks	May lead to unnecessary invasive procedures and reduce trial participation
Dose adjustment guidance	No clear recommendations post-52 weeks	Uncertainty on flexible dosing for long-term management	Patients risk overtreatment or unnecessary exposure to side effects
Pediatric and special populations	Pediatric guidance is outdated or missing; little on pouchitis, EIMs	Limits ability to make evidence-based decisions in niche populations	Slower access to new therapies and lack of tailored guidance
Lack of FDA–EMA harmonization		Risk of delay of regulatory approval, risk of lack of generalizability beyond jurisdictional boundaries	Differences in indications, restrictions of use, risk of incremental trial burden, regulatory delays, and increased drug development costs passed on to patients

Abbreviations: EIM, extraintestinal manifestation; EMA, European Medicines Agency; FDA, Food and Drug Administration; PRO, patient-reported outcome; UC, ulcerative colitis.

Proposals for shorter washout periods, intended to avoid corticosteroid escalation as a bridging therapy, must be justified with appropriate monitoring and risk mitigation strategies, particularly early in the trial. The EMA guidance bases adequate washout periods on the pharmacokinetics of the agent and further specifies the required duration and dose of concomitant treatments, including corticosteroids, prior to randomization. It also recommends characterizing adverse events by treatment duration, dosage, age, immunosuppressant use, and outcomes after re-treatment following an extended drug-free interval.

While the FDA's 2016 guidance included a dedicated section on *pediatric drug development*, addressing Pediatric Research Equity Act requirements related to extrapolation, data collection, and other pediatric considerations, this section is absent from the 2022 update. In contrast, the EMA addresses studies in special populations, including pediatric and elderly patients, those with extraintestinal manifestations, acute severe colitis, and pouchitis. The 2016 FDA document also briefly mentioned biomarkers ("Sponsors are encouraged to prospectively collect data for nonendoscopic markers of inflammation, such as C-reactive protein, fecal calprotectin, lactoferrin, or other putative biomarkers, throughout the trial"), a topic no longer included in the 2022 version.

4. Implications of these changes in today's IBD clinical trials landscape

The FDA's 2022 guidelines introduce several significant updates that, while aligning with the EMA recommendations in many aspects, can also pose new obstacles for clinical practice and trial recruitment, in particular through recommendations for *study population*. Achieving balanced representation of participants across moderate and severe disease categories, including those naïve to or previously treated with biologics or other advanced therapies, is challenging in practice. To date, no study protocol outlines a clear strategy for ensuring this balance, such as predefined targets for enrolling moderate versus severe cases. Compounding the issue, there is no universally accepted definition distinguishing moderate from severe disease, nor a clear threshold separating moderate from mild forms.[8–12] Most trials rely on the baseline mMS, which combines PRO and endoscopic findings, 2 elements that carry different weights in assessing disease severity. Similar median mMS values across trials may mask underlying differences in patient populations due to variability in score components. This lack of standardized severity definitions and the composite nature of the mMS result in blurred category boundaries, leading to heterogeneous, poorly replicable findings and complicating the real-world implementation of FDA recommendations.

The FDA's new guidelines encourage the development of novel *assessment tools*, particularly new or adapted PRO instruments not included in the mMS. This initiative is highly welcome, as the current PROs in the mMS are neither the most relevant from the patient's perspective (as shown in the CONFIDE study, for example) nor prognostically significant for outcomes.[13] In addition to aligning with FDA recommendations, new PROs should be more disease-specific (capturing symptoms, signs, or functional aspects directly related to disease status) and more sensitive to change, with low placebo effects and better predictive value for clinical outcomes.[14] Another major update concerns the recommendation to use full colonoscopy to document endoscopic severity across all colonic segments, whereas the EMA does not specify whether colonoscopy or sigmoidoscopy should be used. While full colonoscopy may support the development of innovative scoring techniques (eg, via AI or machine learning),[15] evidence supporting its superiority over sigmoidoscopy remains limited. Recent studies have not demonstrated a clear superiority of colonoscopy over sigmoidoscopy in clinical trials or routine care settings. The discordance rates between these 2 methods range from 0.7% to 5.8%, suggesting that both are largely comparable.[16] Historically, the development of IBD drugs has relied on findings from sigmoidoscopy, which is both less costly and significantly less burdensome for trial participants.[16,17] Colonoscopy, by contrast, is more invasive, costlier, and carries a higher risk of procedure-related adverse events.[16] Using colonoscopy exclusively could also limit comparability with past trials, where sigmoidoscopy was predominantly used.[16] Additionally, isolated right-sided inflammation or cecal patches are rare in UC, and their impact on prognosis remains unclear, raising further doubts about the necessity of full colonoscopy in every instance.[16,18] While these guidelines are only recommendations, they have not yet been widely adopted into new clinical trial protocols. The development of refined scoring systems should be encouraged, but may only require full colonoscopy in a subgroup of participants, rather than universally.

While the EMA recommends co-primary endpoints of symptomatic and endoscopic remission, the FDA retains the proportion of patients in clinical remission as the primary endpoint. However, it is important to note that the FDA's definition of clinical remission incorporates endoscopic remission, specifically a centrally read endoscopy subscore of 0 or 1. In addition, the secondary endpoints used by the FDA to approve UC drugs have evolved. The FDA's definition of clinical response has evolved and now includes a ≥2 point and ≥30% reduction in mMS from baseline, plus specific rectal bleeding criteria. Since PROs account for 2 of the 3 mMS components, this may overemphasize subjective measures at the expense of objective ones like endoscopy. This imbalance is problematic, as PROs have limited predictive value for (long-term) outcomes and are susceptible to manipulation, particularly in *treat-through or rerandomization trials*, where lack of response may grant access to open-label extensions, raising concerns about their reliability and validity. The FDA also introduced the concept of "maintenance of remission" to assess the durability of treatment benefits from the end of induction through maintenance. However, the term may be misleading, as patients could lose and later regain response before the maintenance endpoint. Referring to this instead as "durable remission" across all timepoints might improve clarity, though this concept is neither defined nor formally adopted.

In terms of *statistical considerations*, the FDA's updated guidance expands on previous recommendations by emphasizing the importance of adjusting analyses for baseline participant characteristics associated with outcomes. Accounting for these variables can improve the precision of treatment effect estimates by controlling for potential confounding and may enable stratified analyses to explore subgroup responses. However, adjusting for multiple baseline variables increases trial design and analytical complexity, and often requires larger sample sizes, leading to longer recruitment periods and higher costs. It should also be pointed out that it is not perfectly clear which characteristics are predictive of the outcomes. For example, disease duration appears to be less relevant in UC than in Crohn's disease. Exploring the association of such variables with outcomes, rather than adjusting for all of them, may be more practical given the wide range of potentially influential factors.

The FDA's proposal to allow a shortened *washout period* is a welcome advancement, further supported by emerging evidence.[19,20] First, specifying an exact number of half-lives lacks a strong rationale, as drug clearance can vary with disease activity—patients may eliminate drugs more rapidly under certain conditions.[19] Second, emerging combination therapy trials have not revealed major safety concerns.[19] Third, washout periods are rarely applied in real-world practice when switching between advanced therapies.

Several aspects of the updated FDA guidance could further *hinder clinical trial recruitment*, which has already been declining.[21] The requirement for a certain threshold of disease severity and a balanced mix of biologic-naïve and biologic-experienced participants can limit eligibility. Insufficient disease activity frequently leads to screen failures, while the increasing availability of approved treatments, including biosimilars, makes it increasingly difficult to enroll biologic-naïve patients in placebo-controlled trials.[22,23] This may result in a trial population that is not representative of the actual patient population that will use the drug. Moreover, with more treatment options available, patient willingness to participate in placebo-controlled trials is decreasing.

The current PROs included in the mMS are often not meaningful from the patient perspective and have limited predictive value for long-term outcomes. In contrast, endpoints such as mucosal healing and histological remission—which are more strongly associated with sustained outcomes—are less emphasized in the updated FDA guidance.[7,24–30] Finally, while we are trying to move towards less invasive assessments for our patients, the new recommendations seem to give less importance to biomarkers and impose colonoscopies rather than sigmoidoscopies, while the latter could allow less invasive management. Table 3 summarizes the key reasons why understanding and improving regulatory guidance for clinical trials in UC has direct implications for clinical practice and patient care. It highlights why this topic is relevant not only to researchers and trial designers, but also to all clinicians involved in the care of UC patients.

5. Where do we go?

This lack of harmonization between the US and European draft guidance may lead to the duplication of clinical trials to confirm the same concept, resulting in unnecessary burden for patients, that should be avoided.[31] As different procedures are carried out, or a single procedure is submitted as separate

applications for different markets, pharmaceutical companies may face divergent regulatory outcomes, as agencies can interpret data differently and reach varying conclusions.[31–39] This could result in increased development costs for drug manufacturers, which may be passed down to consumers as higher drug prices.[31] This can have a huge impact on clinical practices by including or excluding certain patients populations, leading to discrepancies in clinical guidelines, public funding, pricing policies, and drug use.[33] There is a need to assess how such regulatory misalignments affect the safety, quality, and efficacy of approved products. Greater alignment in draft guidance for IBD therapy evaluation between regulatory agencies would prevent redundant trials, reduce time and resource wastage, and ultimately lower development costs. This, in turn, would support faster drug approvals, improve affordability and access globally, and accelerate the dissemination of pharmaceutical innovation.[31,33,40]

In addition to harmonization, a series of suggestions could be made by regulatory agencies to improve and optimize IBD clinical trials guidance. As trial populations should reflect those who will ultimately use the product, agencies should develop a formal diversity plan to improve the inclusion of underrepresented groups in IBD studies.[41] They should also more actively promote the use of active comparator trials or suggest more approaches to reduce the need for concurrent placebo control in upcoming phase 3 registrational studies.[26] With the increasing availability of effective treatments for IBD, assigning patients to placebo may be considered unethical, particularly in early disease, and guidance regarding trials of active comparators and preference for those when clinical equipoise is at risk should be provided. However, placebo-controlled trials offer a clear benchmark for evaluating the absolute efficacy of new treatments, help reduce bias, and enable the detection of modest yet clinically meaningful effects. They also enhance assay sensitivity and are particularly valuable in early-phase trials or when existing therapies have limited efficacy or present safety concerns.

It is important for regulatory agencies to establish common evaluation indices and unified definitions of remission levels, as these directly influence clinical trial sample sizes and can significantly affect trial outcomes.[42–44] There is also a growing rationale to shift from endoscopic remission as the primary endpoint toward mucosal healing (which would similarly require a harmonized definition between agencies), given increasing evidence that more stringent disease control leads to better patient outcomes, including reduced risks of relapse, hospitalization, surgery, and colorectal cancer.[7,24,25] As accumulating evidence suggests that histological remission yields better long-term outcomes for UC patients than endoscopic improvement alone, a plan is needed to incorporate histology as an endpoint to assess treatment performance in UC.[26–30]

Recently, the management of chronic disease has shifted from a purely disease-focused approach toward patient-centered care, leading to increased interest in the integration of PROs in both clinical trials and routine practice.[26] However, no IBD-specific PRO instrument has yet been formally developed and validated according to regulatory agency standards.[14,45] Aligning agency recommendations with what is practically feasible could help support the incorporation of PROs as primary or co-primary endpoints.[14,45] In the same patient-centered perspective, there is also a need to move toward less invasive assessments, complementing PROs with biomarkers as secondary endpoints. Osterman et al. offered a proof of concept that fecal calprotectin (but it could be other biomarkers) can be used effectively in clinical trials.[46,47] However, limitations such as variability in measurement and sensitivity to disease location must be acknowledged. Using specific thresholds, rather than median decline alone, may provide a more consistent and clinically relevant measure of treatment response. As discussed above, colonoscopy should be used at baseline in UC trials, but the choice of subsequent endoscopic procedures should be left to the endoscopist's clinical judgment, based on the patient's disease history.

Furthermore, artificial intelligence for central reading of endoscopies in IBD trials shows promise in improving accuracy, efficiency, and standardization of assessments (by reducing human error, increasing objectivity, and applying uniform criteria).[15] However, its implementation requires careful planning to address development, validation, and integration challenges. Therefore, the creation of guidelines for the use of AI in clinical trials would be a valuable step forward. It would also be helpful if agencies provided guidance to sponsors on dose adjustments, particularly regarding optimization or de-escalation in patients who are doing well and in remission after the 52-week period. This would be especially relevant during open-label extension phases and post-marketing safety studies. While agencies require long-term exposure (≥52 weeks) to the intended market dose, IBD is a lifelong condition, and treatment regimens are often adjusted based on clinical response or blood drug levels.[48] Additionally, neither agency currently defines acceptable escape criteria, leading to inconsistencies in their application by both sponsors and regulators.

In addition, draft guidance for clinical trials in pediatric IBD or recommendations on the possibility of extrapolating adult clinical trial data to children need to be developed. Crowley et al. highlighted that new medications for pediatric IBD are often approved with substantial delays following adult approval, with a median lag of 7.5 years at the FDA and 6.8 years at the EMA.[49] Several other important areas remain unaddressed, including guidance on extraintestinal manifestations of IBD and drug development for chronic inflammatory pouchitis (a rare condition for which current recommendations are limited). Finally, growing evidence suggests that combination therapies may offer added benefits to IBD patients.[50] In this context, clinical trial recommendations for combination strategies should be considered. Similarly, as interest in precision medicine grows in IBD,[51] guidance is needed for trials incorporating biomarkers that support personalized treatment approaches.

One of the most critical and complex challenges moving forward is not only to identify areas of divergence between regulatory agencies, but also to establish a practical and sustainable path toward harmonization. As a next step, a globally active organization such as the International Organization for the Study of Inflammatory Bowel Disease could play a pivotal role in formalizing recommendations, unifying the voices of clinicians, and providing a structured platform for dialogue with regulatory authorities. Several mechanisms could help foster regulatory convergence, including joint workshops or roundtable discussions focused specifically on IBD clinical trials. These would promote ongoing communication between agencies such as the FDA and EMA, enabling the identification of shared challenges and the gradual alignment of regulatory approaches. Multi-stakeholder consensus meetings, bringing together academic experts, industry sponsors,

and regulators, would also be essential to define common endpoints, assessment tools, inclusion criteria, and acceptable trial designs. Patient organizations should be central to this process—not only to promote equity and ensure that measured outcomes reflect what matters most to patients, but also to improve trial feasibility and advocate for greater transparency and accountability in regulatory decision-making. This effort must extend beyond North America and Europe, as true global harmonization of clinical trial guidance requires the active involvement of actors from all regions, including Asia, Australia, Africa, and other parts of the world. Pilot programs modeled on successful cross-agency initiatives like Project Orbis in oncology could also serve as valuable models. Project Orbis allows for the concurrent review of applications by multiple regulatory agencies.[52] While each agency retains its decision-making authority, the shared review process promotes efficiency and accelerates access to innovation. This demonstrates how international collaboration can preserve regulatory independence while improving outcomes for patients. Finally, international bodies such as the International Council for Harmonisation could provide the structural framework and governance needed to support unified technical standards across jurisdictions. Similarly, Parallel Scientific Advice meetings between regulators and sponsors offer a pragmatic avenue for early alignment. While complete harmonization may not always be achievable, such platforms help reduce duplication, clarify differing expectations, and foster mutual understanding, ultimately benefiting both scientific advancement and patient care.

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The data underlying this article are available in the article.

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