NDA Whitepaper

Single-Arm Trials in Oncology: Key Insights from the Latest EMA and FDA Guidance

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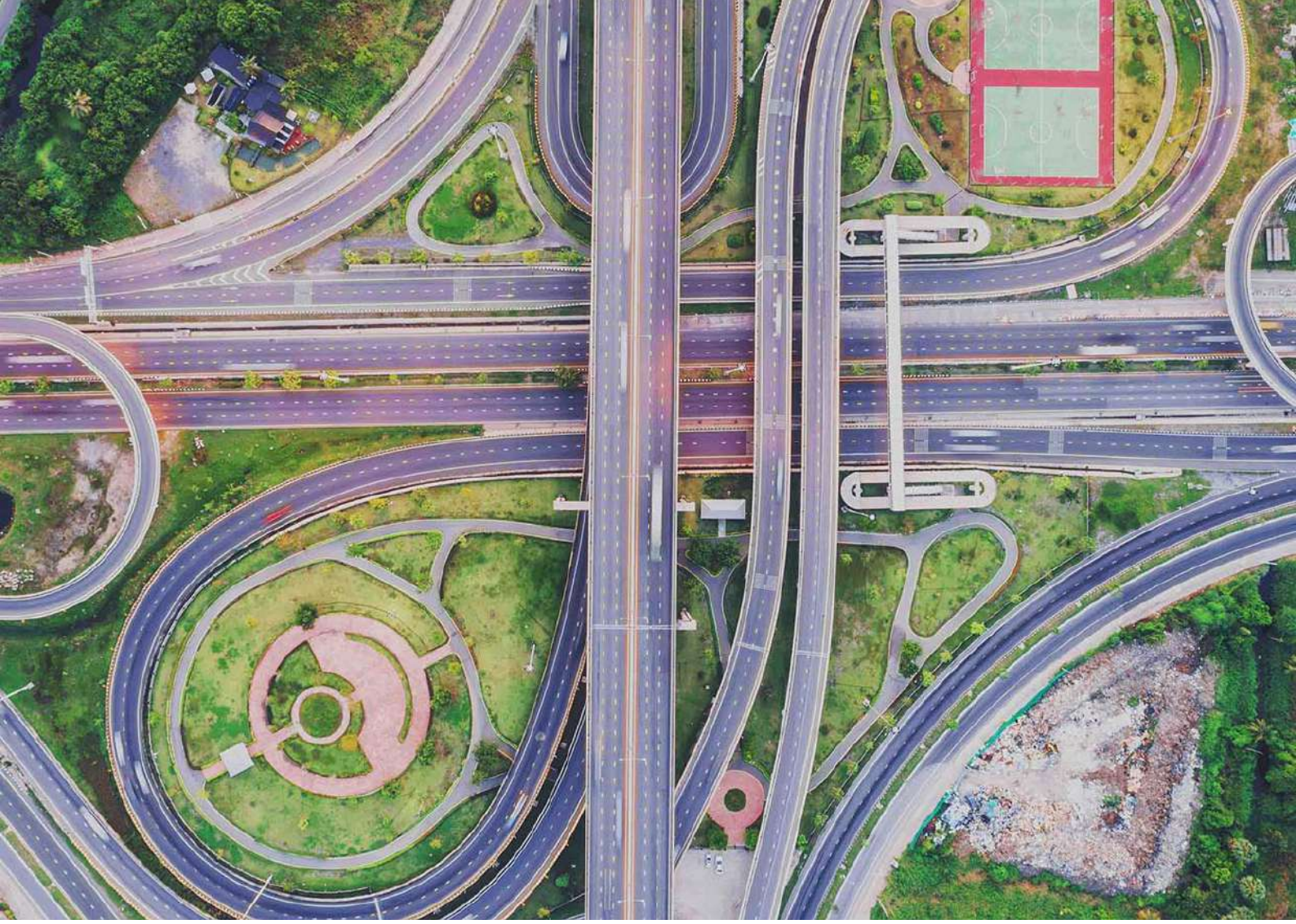
Adriana is an MD and MPH with 12 years of regulatory experience and broad knowledge of the EU scientific and regulatory requirements for clinical drug development. Before joining NDA in 2022, Adriana worked for the Croatian Medicines Agency (HALMED) and served as a delegate at EMA's COMP from 2013 to 2016, PDCO from 2016 to 2019 and SAWP from 2018 to 2022.

As an EMA delegate, Adriana was involved in the assessment of orphan drug designation requests, paediatric investigation plans and scientific advice requests for various types of products. At the COMP and PDCO, Adriana acted as Rapporteur across different therapeutic areas, while at the SAWP she mostly focused on pivotal clinical trials in oncology and haemato-oncology. Adriana was involved in the assessment of over 120 scientific advice requests and is experienced in SAWP discussions on key design elements of registrational studies and their respective regulatory strategies. Adriana was the inaugural head of HALMED's Scientific Advice Office and was responsible for establishing and supporting HALMED's participation at the SAWP. She was leading a multidisciplinary team of assessors which focused mostly on scientific advice requests, but were also involved across various other procedures, such as centralised marketing authorisation and pharmacovigilance referrals.

Adriana's role at NDA involves supporting clients with various regulatory procedures, applying her knowledge to successfully support companies on the clinical and regulatory aspects of drug development.



Expedited approval pathways have gained significant traction in recent years for authorizing oncology medicines. Notably, accelerated approval in the United States (US) and conditional approval in the European Union (EU) have emerged as prominent pathways. These streamlined processes are often utilized for drug developments based on single pivotal trials, including those employing a single-arm trial (SAT) design. However, the release of highly anticipated draft guidance documents by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) occurred only in 2023. This article provides insights into the regulatory guidance offered by the EMA and FDA, assisting sponsors in navigating the rapidly evolving landscape of expedited approvals in oncology.

The Broader Context

Oncology represents 85% of all accelerated approvals granted in the US over the past 10 years, while a recent study of the EU conditional approvals indicated that more than half were granted for haemato-oncology or oncology indications[1,2].

The regulatory practices around expedited pathways and/or oncology approvals have been subject to scrutiny from both broader scientific community and regulator themselves alike [3-11].

An analysis of the decisions on new drug marketing applications submitted to the FDA and EMA in the period 2014 – 2016 indicated that sponsors tend to make marketing submissions for oncology and haematology products to EMA later than to the FDA, often including additional clinical trials or more mature data from the same clinical trial than were submitted to the FDA[12]. This analysis showed that, in oncology and haematology, the FDA more commonly granted accelerated approval than the EMA granted conditional marketing authorisation or authorisation under exceptional circumstances. However, the accelerated approval in the US has been scrutinized over the recent years, primarily due to a number of approvals that were withdrawn by the FDA because the confirmatory studies failed to verify clinical benefit. According to the data on withdrawn approvals published through FDA's Project Confirm, since the beginning of 2021 the FDA has withdrawn accelerated approvals of 17 cancer drug indications[13].

In another review, that compared cancer treatment approvals in the US and Europe between 2010 and 2019, the lower number of new oncology therapies receiving conditional marketing authorisation and higher median review times was suggested as indicative of EMA's more cautious approach to cancer therapy approvals[14]. The uncertainties relating to EU conditional approvals of anticancer medicines that required post-authorisation measures were mostly related to efficacy and the pivotal trial design, and sample size[1].

Expedited approvals are often granted for the developments based on single pivotal trials, many of which deploy the SAT design. The advantages, namely facilitating patient access to novel therapies, as well as limitations of the SAT approach, have also been a matter of scientific and regulatory debate over the past years. However, it was not until 2023, that the EMA and the FDA have issued their respective, much-anticipated draft guidance documents on these complex topics. These guidance documents, once finalised, are expected to better inform the planning of the expedited approval pathways for oncology medicines, and of the oncology medicines development in general.

New Guidance Documents

In April 2023, the EMA has opened a public consultation on "Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation"[15]. According to the announcement[16], the reflection paper is intended to reflect the current EMA's thinking on the topic and "aims to stimulate the scientific discussion around key concepts and challenges associated with single-arm trials and to improve their design and conduct". The EMA further notes that the randomised controlled trials (RCT)s are "widely considered as the gold standard for generating evidence needed by regulatory authorities to assess the efficacy and safety of a new medicine", but that in certain areas such as rare diseases, a proportion of marketing authorisation applications are submitted to EMA with clinical data from SATs as pivotal evidence.

The reflection paper discusses considerations in relation to the design, planning, conduct, analysis, and interpretation of results derived from SATs, and is applicable across different therapeutic areas, including rare diseases, i.e., it is not specifically intended only for oncology products. Importantly however, defining general conditions under which SATs may be considered acceptable as pivotal evidence for marketing authorisation is outside of the scope of the

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document. Although the focus of the paper is on establishing efficacy via SATs, "also establishing safety via SATs is fraught with substantial shortcomings and many of the critical considerations discussed equally apply to the assessment of safety".

FDA's draft guidance for industry "Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics"[7], issued in March 2023, describes considerations for designing, conducting, and analysing data for trials intended to support accelerated approvals in oncology. According to the announcement[18], the increased use of accelerated approval pathways in oncology is partly due to the serious and life-threatening nature of cancer, and partly because the surrogate or intermediate clinical endpoints that are available in the oncology field are considered reasonably likely to predict clinical benefit for patients. However, in this draft guidance, the FDA is articulating a clear preference for RCTs, as opposed to SATs, to support accelerated approval of oncology therapies. Specifically, the draft guidance provides recommendations addressing the design, conduct, and analyses of data for either two

separate RCTs or for using a single RCT in the so-called 'one-trial' approach to support accelerated approval.

The draft guidance provides only high-level recommendations for designing, conducting, and analysing data from a SAT intended to support accelerated approval. However, in February 2023, the FDA issued another draft guidance, "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products"[19]. This draft guidance, issued as part of the FDA's mandate to issue guidance about the use of Real-World Evidence in regulatory decision-making, provides more detailed considerations on the use of externally controlled trials to provide evidence of the effectiveness and safety of a medicinal product. The draft guidance discusses various challenges due to absence of randomisation, use of external controls and various biases that are inherent to externally controlled trials.

Key Takeaways for Industry

Draft guidance documents from EMA and FDA extensively cover the various design elements that sponsors must address in order to sufficiently justify to regulators the pivotal evidence of efficacy provided by a SAT. Importantly however, both regulators clearly express their definite preference for RCTs, strongly recommending that sponsors seek early interaction/advice to discuss their planned approach and stating that the acceptability of SATs as pivotal evidence will be assessed on a case-by-case basis.

EMA's draft reflection paper pinpoints that it is the randomisation that provides the basis for statistical inference, i.e. the causal interpretation of the effect of the treatment, whereas in case of SATs, "due to the lack of randomisation, the design does not support a causal interpretation […] and must rely on knowledge external to the SAT" to estimate the treatment effect of interest, i.e., whether there is an effect attributable to treatment. EMA's draft reflection paper further elaborates that the external information may take the form of (i) external knowledge about the natural course of the disease, or (ii) external clinical data. The use of external information is considered a crucial design element and should be pre-specified in the study protocol. According to EMA's draft reflection paper, key features "that are instrumental to avoid bias" and are lacking in SATs, other than the randomised allocation to treatment, are a concurrent control arm, enrolment of patients without knowledge of their subsequent assignment, and blinding of participants, investigators, and outcome assessors to treatment assignment. EMA's draft reflection paper features a tabulated list of various types of bias and measures aiming to reduce them but cautions that "demonstration that the mitigation strategies were applied may not be sufficient to alleviate concerns about biased results derived from a SAT, as formal proof that treatment effect estimates are unbiased is impossible".

FDA's draft guidance on accelerated approvals also lists some of the key limitations of the SAT approach, including: uninterpretable common time-to-event efficacy endpoints, low magnitude response rates (that may not be reasonably likely to predict clinical benefit), challenges in establishing the contribution of individual components to the claimed effects of combination treatments, reliance on cross-trial comparisons to historical trials to assess whether the observed treatment effect represents an improvement over available therapy (with the risk of erroneously attributing differences in response rate to the investigational product), and small safety datasets which limit the assessment of rare events, and of their attribution, in absence of a comparator.

Importantly, both regulators seem to take a firm stance on external controls, with EMA's draft reflection paper asserting that an external control that would be taken into the analysis to inform efficacy assessment is envisaged only in exceptional cases. The FDA's draft guidance on externally controlled trials, which presents a tabular summary of considerations for assessing comparability of data, states that "the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low, and sponsors should choose a more suitable design, regardless of the prevalence of disease". The latter appears to be of particular relevance in the context of the requirement of the

accelerated approval in the US that the drug must provide a meaningful advantage over available therapy.

The main difference between the draft guidance documents released by the EMA and the FDA seems to be in whether they discuss the broader policy implications for oncology developments. Importantly, EMA's draft reflection paper does not provide considerations on how the notions expressed in the document would translate into practice, in terms of utilising the existing marketing authorisation routes in the EU, i.e., full, conditional or approval under exceptional circumstances, nor does it discuss the implications for specific obligations to provide comprehensive data post-authorisation for conditional approvals based on SATs. In contrast, FDAs draft guidance on accelerated approval of oncology products seems to be explicit policy-wise, not only in recommending that "confirmatory trials are underway when the marketing application is submitted, and are well underway, if not fully enrolled, at the time of marketing authorisation action", but also, and more importantly, by renewing the emphasis on the use of RCTs in lieu of SATs.

In particular, FDA's draft guidance on accelerated approvals in oncology lays out that, to support the accelerated approval, sponsors can conduct two separate RCTs – one with an early response endpoint, and the second one powered for a time-to-event endpoint to verify clinical benefit. For the second RCT, it may be acceptable to evaluate

the product in the same cancer type but in another line of therapy. Alternatively, sponsors could design a single RCT to support accelerated approval based on an early response endpoint; the trial should also be powered for the time-to event endpoint to verify clinical benefit (i.e., 'one-trial' approach).

According to the draft guidance, the "one-trial" approach "maintains efficiency in drug development and can provide early access to a drug using the accelerated approval pathway, while ensuring that a post-marketing trial is fully accrued and well underway to verify longer term benefit in a timely fashion". The FDA officials outlined the concepts included and expanded upon in this draft guidance in an earlier 2022 commentary in the New England Journal of Medicine[2]. The apparent lack of correlation between early efficacy endpoints, namely objective response rate and progression-free survival, and the overall survival is discussed, among other topics, by FDA officials in another recent paper[20]. The authors of that paper conclude that "In 2023, the FDA's OCE plans a series of workshops to examine the role of early endpoints, their relationship to OS, and considerations around obtaining the information necessary to make informed decisions on the risks and benefits of a novel cancer therapy".

Conclusions

Apart from noting that SATs could be acceptable in small populations/where RCTs are not feasible, the EMA and the FDA do not provide detailed scenarios or examples when, in fact, a SAT can be accepted to support oncology approval. Nevertheless, as first guidance documents from major regulators on the topic, the draft guidance documents do provide a comprehensive discussion on various methodological and statistical considerations in relation to SATs, their limitations, and potential sources of bias, thus bringing some much welcome clarity on the topic.

Both regulators do clearly articulate their preference for RCTs, and strongly recommend the sponsors to seek early interaction/advice to discuss their planned approach. Although the tone of the EMA's draft reflection paper is ostensibly more open to SAT approach, in the context of previous EMA's and FDA's practices, and of the renewed emphasis on the use of RCTs within the current draft guidance documents, seeking early discussion with both regulators when the SAT design is considered for a pivotal study seems to be of even greater importance than it was in the past.

References

1. Bloem LT, Schelhaas J, Lopez-Anglada L, Herberts C, van Hennik PB, Tenhunen O. European Conditional Marketing Authorization in a Rapidly Evolving Treatment Landscape: A Comprehensive Study of Anticancer Medicinal Products in 2006-2020. Clin Pharmacol Ther. May 2 2023;doi:10.1002/cpt.2906

2. Fashoyin-Aje LA, Mehta GU, Beaver JA, Pazdur R. The On- and Off-Ramps of Oncology Accelerated Approval. N Engl J Med. Oct 20 2022;387(16):1439-1442. doi:10.1056/NEJMp2208954

3. Agrawal S AS, Amiri-Kordestani L, de Claro RA, Fashoyin-Aje L, Gormley N, Kim T, Lemery S, Mehta GU, Scott EC, Singh H, Tang S, Theoret MR, Pazdur R, Kluetz PG, Beaver JA. . Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021. JAMA Oncology. 2023;9(2):266-272.

4. Beaver JA, Pazdur R. "Dangling" Accelerated Approvals in Oncology. N Engl J Med. May 6 2021;384(18):e68. doi:10.1056/NEJMp2104846

5. da Costa Goncalves F, Demirci E, Zwiers A. A detailed analysis of expedited regulatory review time of marketing authorization applications for new anticancer drugs in the US and EU. Clin Transl Sci. Aug 2022;15(8):1959-1967. doi:10.1111/cts.13308

6. Johnston JL RJ, Ramachandran R. US Food and Drug Administration Approval of Drugs Not Meeting Pivotal Trial Primary End Points, 2018-2021. . JAMA Intern Med 2023;1(183(4)):376-380.

7. Mahase E. FDA allows drugs without proven clinical benefit to languish for years on accelerated pathway. BMJ. Jul 29 2021;374:n1898. doi:10.1136/bmj.n1898

8. Mehta GU, de Claro RA, Pazdur R. Accelerated Approval Is Not Conditional Approval: Insights From International Expedited Approval Programs. JAMA Oncol. Mar 1 2022;8(3):335-336. doi:10.1001/jamaoncol.2021.6854

9. Salcher-Konrad M, Naci H, Davis C. Approval of Cancer Drugs With Uncertain Therapeutic Value: A Comparison of Regulatory Decisions in Europe and the United States. Milbank Q. Dec 2020;98(4):1219-1256. doi:10.1111/1468-0009.12476

10. Tenhunen O, Lasch F, Schiel A, Turpeinen M. Single-Arm Clinical Trials as Pivotal Evidence for Cancer Drug Approval: A Retrospective Cohort Study of Centralized European Marketing Authorizations Between 2010 and 2019. Clin Pharmacol Ther. Sep 2020;108(3):653-660. doi:10.1002/cpt.1965

11. Vokinger KN, Kesselheim AS, Glaus CEG, Hwang TJ. Therapeutic Value of Drugs Granted Accelerated Approval or Conditional Marketing Authorization in the US and Europe From 2007 to 2021. JAMA Health Forum. Aug 5 2022;3(8):e222685. doi:10.1001/jamahealthforum.2022.2685

12. Kashoki M, Hanaizi Z, Yordanova S, et al. A Comparison of EMA and FDA Decisions for New Drug Marketing Applications 2014-2016: Concordance, Discordance, and Why. Clin Pharmacol Ther. Jan 2020;107(1):195-202. doi:10.1002/cpt.1565

13. FDA. Project Confirm. https://www.fda.gov/about-fda/oncology-center-excellence/project-confirm

14. Lythgoe MP, Desai A, Gyawali B, et al. Cancer Therapy Approval Timings, Review Speed, and Publication of Pivotal Registration Trials in the US and Europe, 2010-2019. JAMA Netw Open. Jun 1 2022;5(6):e2216183. doi:10.1001/jamanetworkopen.2022.16183

15. EMA. Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing_en.pdf

16. EMA. Single-arm trials as pivotal evidence for the authorisation of medicines in the EU. https://www.ema.europa.eu/en/news/single-arm-trials-pivotal-evidence-authorisation-medicines-eu

17. FDA. Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics. Draft guidance for industry. https://www.fda.gov/media/166431/download

18. FDA. Notice of availability of a draft guidance for industry "Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics". https://www.regulations.gov/document/FDA-2023-D-0110-0002

19. FDA. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. Draft guidance for industry. https://www.fda.gov/media/164960/download

20. Merino M, Kasamon Y, Theoret M, Pazdur R, Kluetz P, Gormley N. Irreconcilable Differences: The Divorce Between Response Rates, Progression-Free Survival, and Overall Survival. J Clin Oncol. May 20 2023;41(15):2706-2712. doi:10.1200/JCO.23.00225

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