
Clarivate
Mastering regulatory complexity
Strategies for a shifting landscape

The pharmaceutical R&D landscape has undergone a dramatic transformation toward greater complexity over the past four decades as companies pursue innovative, yet technically challenging, therapeutic modalities that promise to address hard-to-treat diseases. The success of pharma and biotech companies in this quest is reflected in the growing number of regulatory approvals for first-in-class drugs and drugs for orphan or rare diseases (Figure 1).

Major innovations over the last couple of decades include antibody drug conjugates (ADCs), bispecific antibodies (BsAbs), radioligand therapies (RLTs), gene therapies and more. Although they are successfully addressing unmet patient needs, these treatments often require additional R&D, safety monitoring, manufacturing and distribution considerations. For example, the potential for side effects with ADCs prompts close regulatory scrutiny for safety; gene therapies have limited long-term clinical monitoring data, necessitating a closer review of the risk-benefit trade-off; and gene editing raises ethical questions, requiring enhanced transparency and compliance with ethical guidelines by companies developing these therapies.

These factors, coupled with the global nature of drug commercialization and stricter regulatory oversight, mean that pharma and biotech companies face considerable challenges when navigating drug development and approval.

Here, we present some of the tougher obstacles to regulatory approval of innovative treatments and strategies to overcome them.

Figure 1: Trends in drug approvals by the U.S. FDA in 2024

48%

of FDA approvals in 2024 were for first-in-class treatments

52%

of FDA approvals in 2024 carried an Orphan Drug Designation

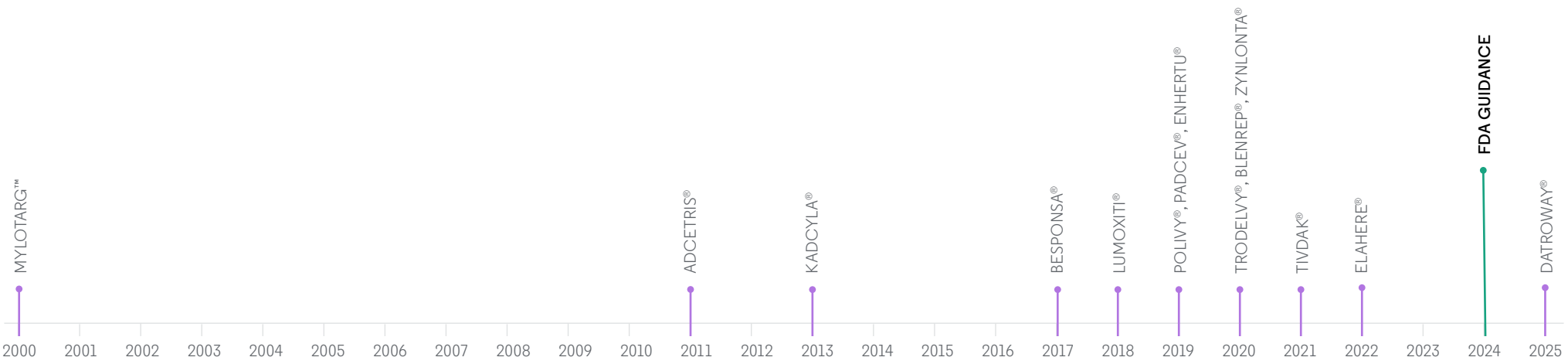
Source: Food & Drug Administration Center for Drug Evaluation and Research

Challenge: A lack of established regulatory frameworks for groundbreaking modalities creates unique hurdles

Regulatory agencies learn and adapt as new modalities are introduced. For early entrants, a lack of precedent and long-term real-world safety data create uncertainties for companies and regulators alike. This means the first compounds to submission or approval are often contributing to the regulators' learning curve and lack clearcut guidance. As more assets enter the regulatory approval process and the market, regulators gain the experience to begin developing guidelines and recommendations from which later entrants benefit.

For example, antibody-drug conjugate (ADC) submissions and approvals in the United States preceded the Food & Drug Administration (FDA) guidance on clinical pharmacology considerations for ADCs with a small molecule payload, which was established in March 2024 (Food and Drug Administration, 2024). For more information, read the ADC Companies to Watch Report 2024.

Figure 2: U.S. FDA guidance for ADCs, released in March 2024, followed multiple ADC approvals



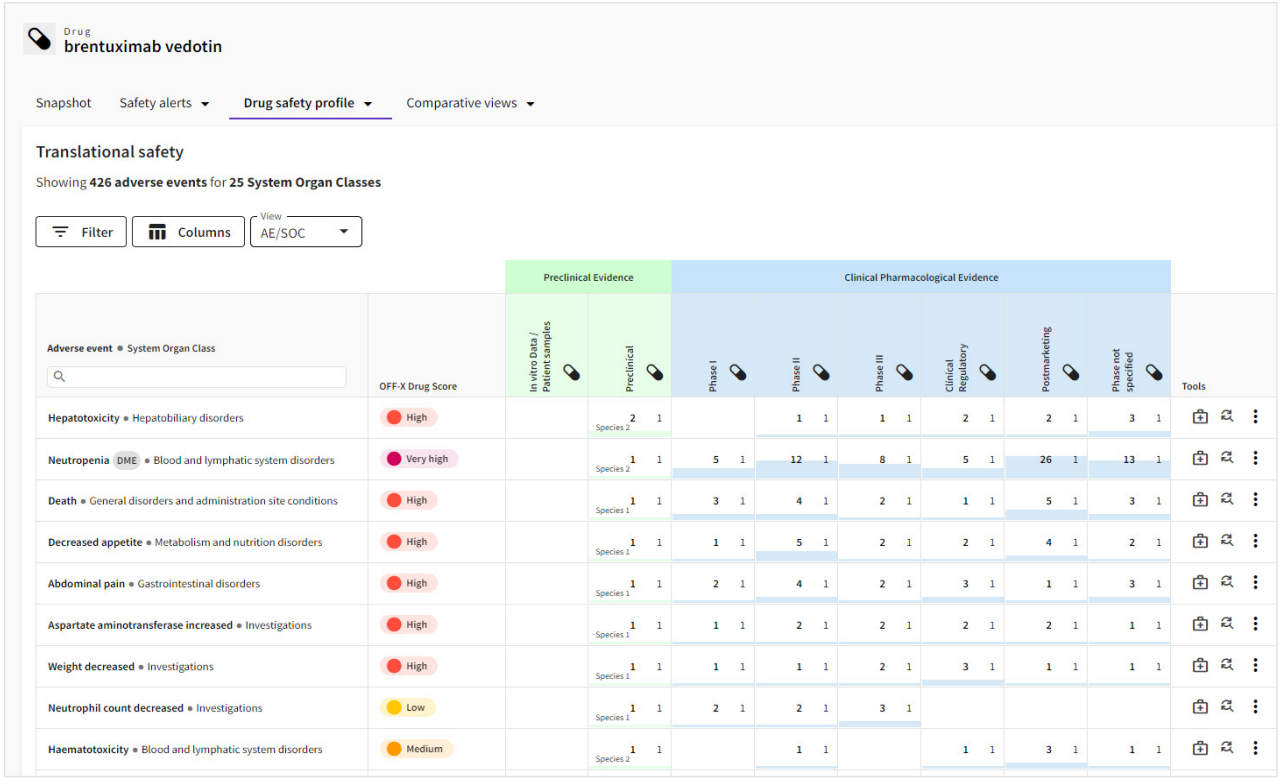
Source: Cortellis Regulatory Intelligence

Challenge: Uncertainty surrounding specific requirements for investigational new drug (IND) applications persists

Small molecules form the foundation of the therapeutic pathways for numerous conditions and remain the major component of emerging innovative products. One key drawback of small molecules, however, is their lack of specificity and potential for off-target effects. Although some of these effects can have minimal impact, they frequently lead to adverse events that compromise a drug's safety profile and patient outcomes.

However, regulatory guidelines often lack clear recommendations about which off-target effects to monitor in vitro during preclinical drug development. The same is true for many new modalities and technologies, for which limited if any regulatory guidance exists. This can result in a submission package that omits the safety data necessary to proceed to human testing, prolonging timelines. Other uncertainties include pursuing candidates whose risk-benefit ratios lean too heavily toward risk (Figure 3).

Figure 3: Evaluating the safety profile of a candidate ADC



Source: OFF-X

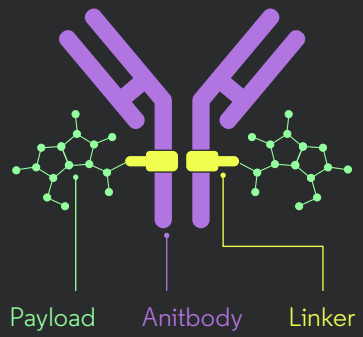
Challenge: Integrating cutting-edge technologies within existing regulatory concepts is not straightforward

New modalities comprise multiple constituent parts that independently impact the compound's safety and efficacy. This could require compliance with more than one guidance or separate evaluations for each constituent part, complicating regulatory submission preparation and review.

The FDA's guidance on clinical pharmacology considerations for ADCs emphasizes the importance of considering the independent impact of an ADC's constituent parts on safety and efficacy (Food and Drug Administration, 2024), with a particular focus on:

- dosing strategies,
- dose- and exposure-response analyses,
- intrinsic factors,
- QTc assessments,
- immunogenicity and
- drug-drug interactions

ADC: payload + antibody

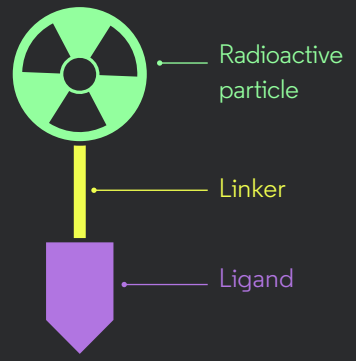


Radioligand therapy (RLT) approvals require data collection beyond just clinical outcomes—chemical, radiochemical and pharmaceutical parameters must be established and verified (European Medicines Agency, 2008; European Medicines Agency,2018; Food and Drug Administration, 2018; Food and Drug Administration, 2019; Korde, 2022). As a result, studies might be required to investigate:

- non-clinical pharmacology,
- radiation exposure and effects,
- toxicology,
- pharmacokinetics and
- the contribution of imaging

Multiple government agencies can be involved in regulating the source material, development, distribution and use of RLTs. In the U.S., for example, these could include the Nuclear Regulatory Commission (NRC), the FDA and individual states.

RLT: radioisotope + vector/binder/ligand (eg, small molecule, peptide, antibody, particle)



In addition, a greater focus on personalized medicine relies on biomarker stratification, which is not always clearly defined within existing guidelines. For example, the regulatory submissions of one of the **Drugs to Watch in 2024**, DATROWAY (datopotamab deruxtecan, from AstraZeneca/Daiichi Sankyo), have not been straightforward, delaying its expansion to treat non-small cell lung cancer (NSCLC) by approximately a year.

DATROWAY approval timeline

February 2024: U.S. FDA accepts the BLA for previously treated, locally advanced or metastatic non-squamous NSCLC based on data from the phase 3 TROPION-Lung01 trial. The PDUFA date is set for Q4 2024.

March 2024: European Medicines Agency (EMA) validates the marketing authorisation application (MAA) to treat locally advanced or metastatic non-squamous NSCLC who require systemic therapy following prior treatment based on data from the TROPION-Lung01 trial.

May 2024: Additional findings are released showing a numerically favorable but not statistically significant improvement in overall survival (OS) vs chemotherapy in TROPION-Lung01 trial.

November 2024: The companies voluntarily withdraw the BLA from the U.S. FDA based on FDA feedback. A new BLA is submitted for accelerated approval for the subset of patients with epidermal growth factor receptor-mutated (EGFR) NSCLC based on results from the phase 2 TROPION-Lung05 trial, supported by data from the TROPION-Lung01 and phase 1 TROPION-PanTumor01 trials.

December 2024: The companies voluntarily withdraw the MAA in the E.U. to treat locally advanced or metastatic non-squamous NSCLC based on the TROPION-Lung01 trial based on EMA Committee for Medicinal Products for Human Use (CHMP) feedback.

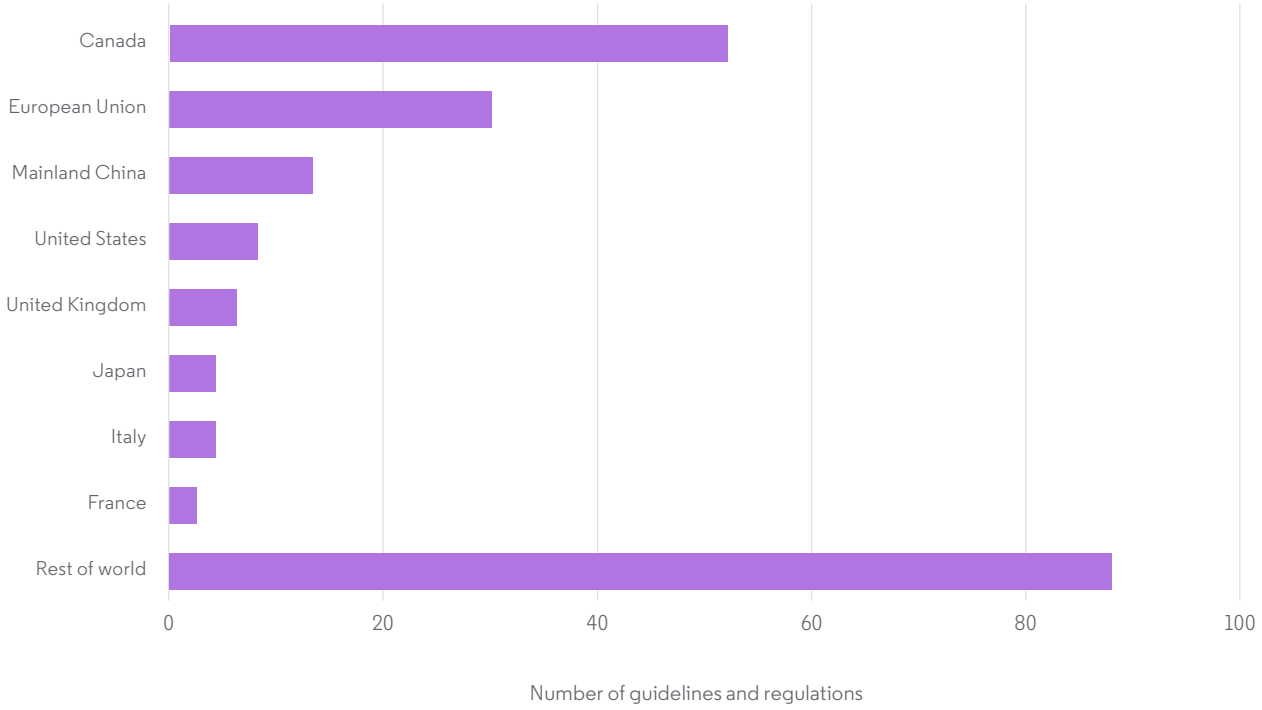
January 2025: The BLA for EGFR NSCLC is accepted by the FDA and granted Priority Review, with a PDUFA date in Q3 2025.

Challenge: Staying abreast of regulatory requirements across countries is time-consuming

With more regulators requiring localization of data collection, the lack of harmonization across regulators creates challenges for companies aiming to commercialize globally or at least in more than one country or region. Between 2015 and 2021, there was a 39% increase in multinational studies as companies comply with these requirements (Tufts Center for the Study of Drug Development, 2023), a trend that is likely to continue as companies seek revenue opportunities.

For RLTs, numerous regulatory documents apply by region and even within countries, pertaining to development, the safety of constituent parts, manufacturing, handling and post-marketing surveillance (Figure 4).

Figure 4: Guidelines and regulations from health authorities in the G7 countries, overall European Union, Mainland China and other countries or territories with their own guidelines (note: nuclear agency guidelines not included)



Source: Cortellis Regulatory Intelligence

Strategy: Establish regular and meaningful engagement with regulatory authorities to foster productive dialogues

Because regulatory processes and guidance are continuously evolving for innovative products, approval processes can be lengthy. Getting ahead of the process can minimize unexpected concerns or comments and potentially shorten timelines. Therefore, it is not surprising that regulatory agencies recommend communicating early and often, even after approval to stay on top of post-marketing concerns.

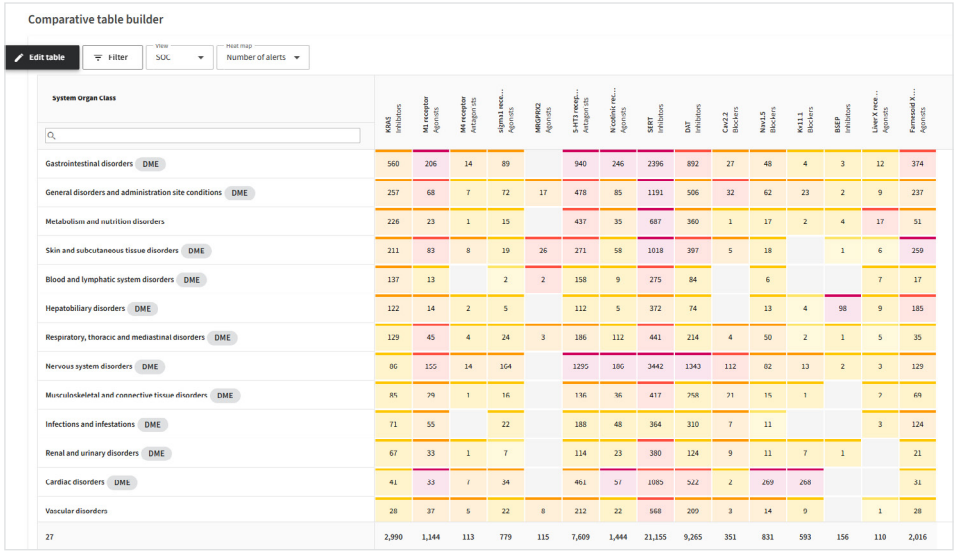
Early communication with the FDA, before IND submission, can be conducted via meetings such as pre-IND meetings and Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) meetings to discuss product-specific considerations for transitioning to clinical trials. The latter can be particularly helpful to obtain preliminary informal feedback, earlier in development than the pre-IND stage, on issues related to chemistry, manufacturing and controls (CMC) and both non-clinical and clinical development of innovative investigational products. According to the FDA, INTERACT discussions should be conducted after collecting proof-of-concept data demonstrating preliminary evidence of safety and efficacy from in vitro and in vivo non-clinical studies but prior to pivotal non-clinical studies.

For investigational products lacking robust regulatory guidance in Europe, sponsors are encouraged to seek tailored support from the EMA, such as via innovation task force meetings and the PRIME (priority medicines) scheme and designation and to solicit scientific advice directly from the EMA.

Preliminary evidence of safety and efficacy increasingly includes proactive use of in vitro pharmacological profiling. This approach enables researchers to identify and mitigate potential off-target effects, thus preventing costly development delays or post-market issues (Bowes et al., 2012). Specifically, in vitro profiling serves as a safety screen, testing against a wide array of targets beyond the intended therapeutic target(s) to pinpoint specific molecular interactions that might cause unwanted side effects.

However, current regulatory guidelines lack specificity regarding the composition of in vitro pharmacological profiling panels and the optimal timing of their use within the drug discovery process, although the FDA suggests that secondary pharmacology data be available with the initial submission to support first-in-human (phase 1) trials (Papoian et al, 2015). Intelligence regarding the safety liabilities associated with each potential off-target effect can help anticipate the potential toxicities and the questions or requests to expect from regulators, especially if regulators are using the same intelligence (Figure 5).

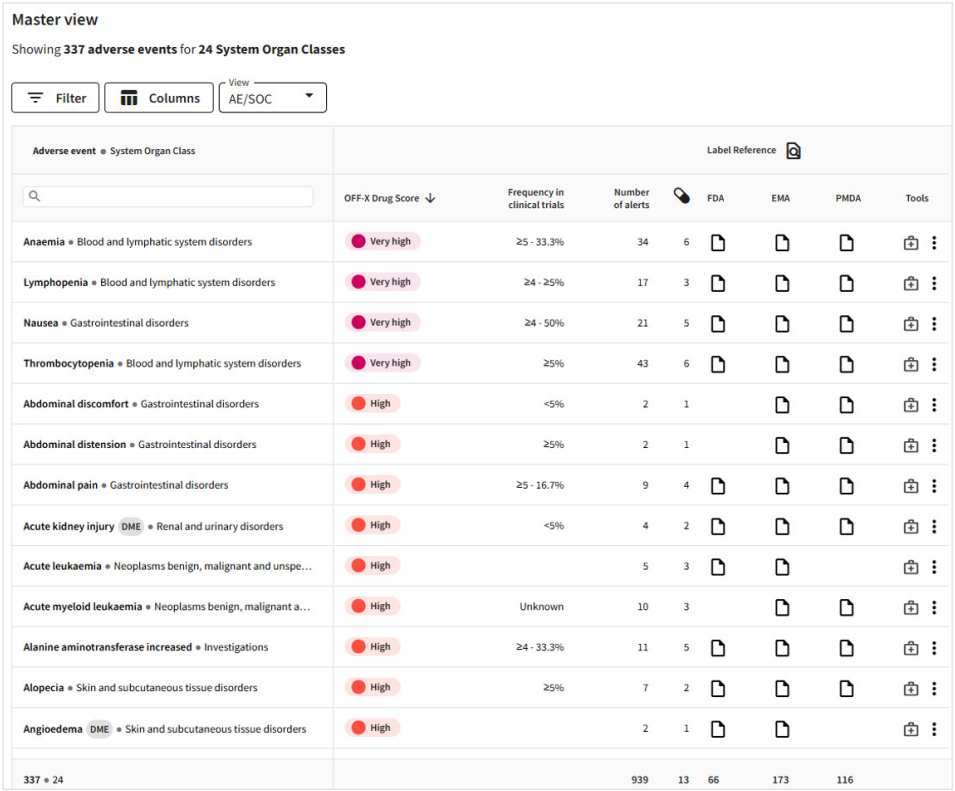
Figure 5: Safety profile of all targets hit by a hypothetical new small molecule designed to inhibit KRAS (on-target) and including all the additional secondary targets (off-targets) found during in vitro screening



Source: OFF-X

Gathering data about similar products, both successful and failed, before these meetings can also be used to anticipate questions and compare the safety concerns of the new product to those of similar products for the same therapeutic area or within the same class. For example, accessing information about the established safety findings of existing drugs like LUTATHERA® based on regulatory agency documentation (Figure 6) helps establish a baseline by which similar investigational drugs can be compared.

Figure 6: Information about the established safety findings in regulatory agency drug approval packages for LUTATHERA



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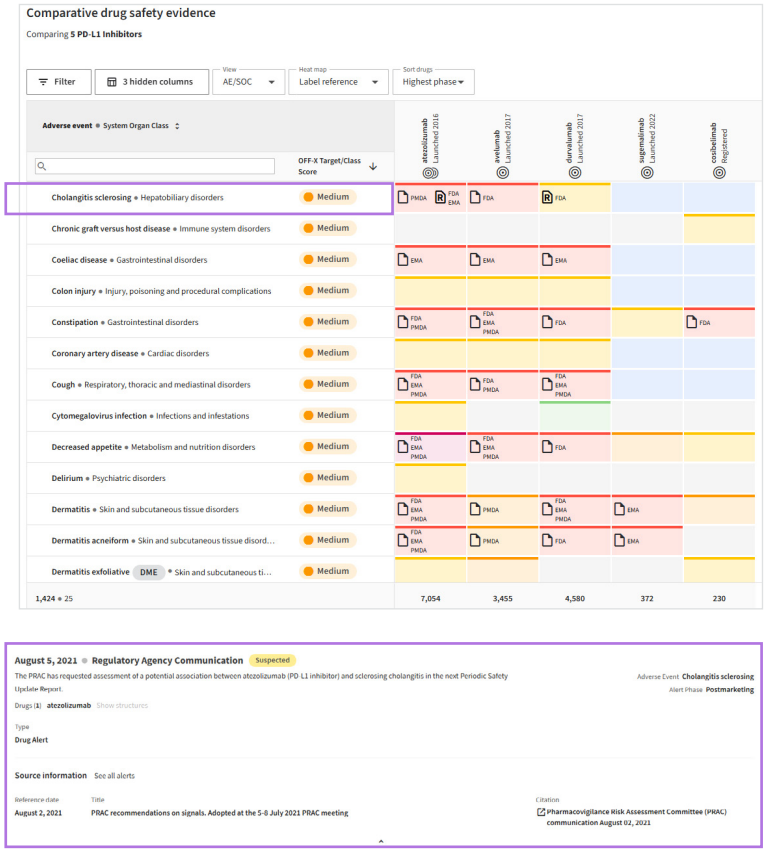
Similarly, regulatory requests can be anticipated based on intelligence regarding competitors' drug label changes, regulatory findings or requests in different regions and clinical holds of drugs under development, which are typically only published in company communications (Figure 7).

Figure 7: Safety details included in EMA, FDA and PMDA drug labels of approved PD-L1 inhibitors, including potential signals that are or have been under discussion by any of these agencies



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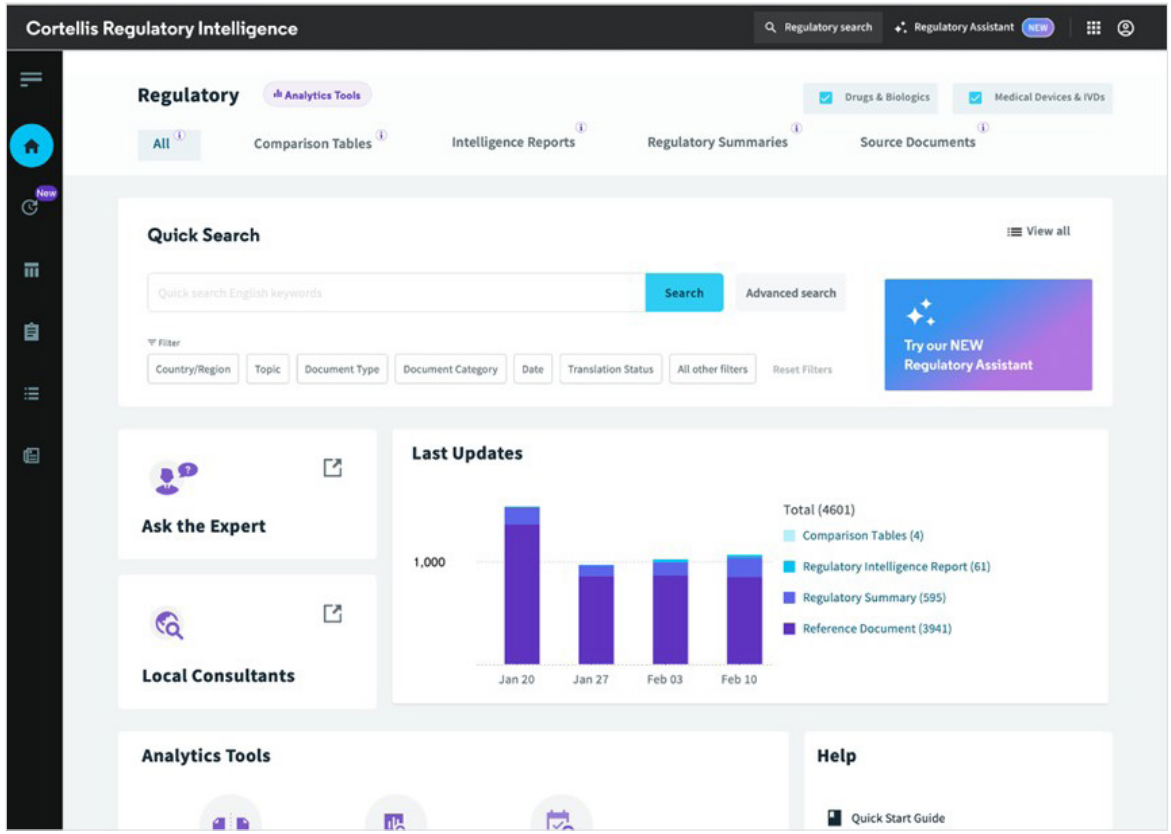
Strategy: Create a comprehensive global regulatory strategy to ensure a proactive approach to compliance

To create a robust regulatory strategy that covers clinical development through post-marketing surveillance, pharma teams need to thoroughly evaluate and interpret the applicable regulatory landscape and conduct a proactive assessment of potential risks and hurdles across all markets of interest. This requires an understanding of the nuances between countries and regions, such as which have established recommendations, the markets in which similar products are already available and previous decisions by regulatory agencies. An ideal strategy responds to regulatory changes, adapts to evolving internal and external circumstances and is tailored to the company's specific needs and objectives.

Staying up-to-date with the information needed to achieve this is challenging enough but is further complicated by the lack of archiving of some previous documents and decisions on agency sites. A searchable repository of historical and current global regulations, press briefings, regulatory summaries, intelligence reports, comparison tables and more provides a single source of information to create a robust regulatory strategy (Figure 8).

Figure 8: Single-source repository of key regulatory documents needed to create a robust regulatory strategy



Source: Cortellis Regulatory Intelligence

Strategy: Invest in regulatory intelligence tools to empower teams to stay informed of the latest developments

Given the lack of precedent and established guidelines for many innovative products, staying on top of evolving regulatory guidance and historical decisions becomes even more imperative but is time-consuming. Intelligence tools that synthesize global regulatory guidance reduce this burden and provide actionable insights based on existing recommendations and as they change.

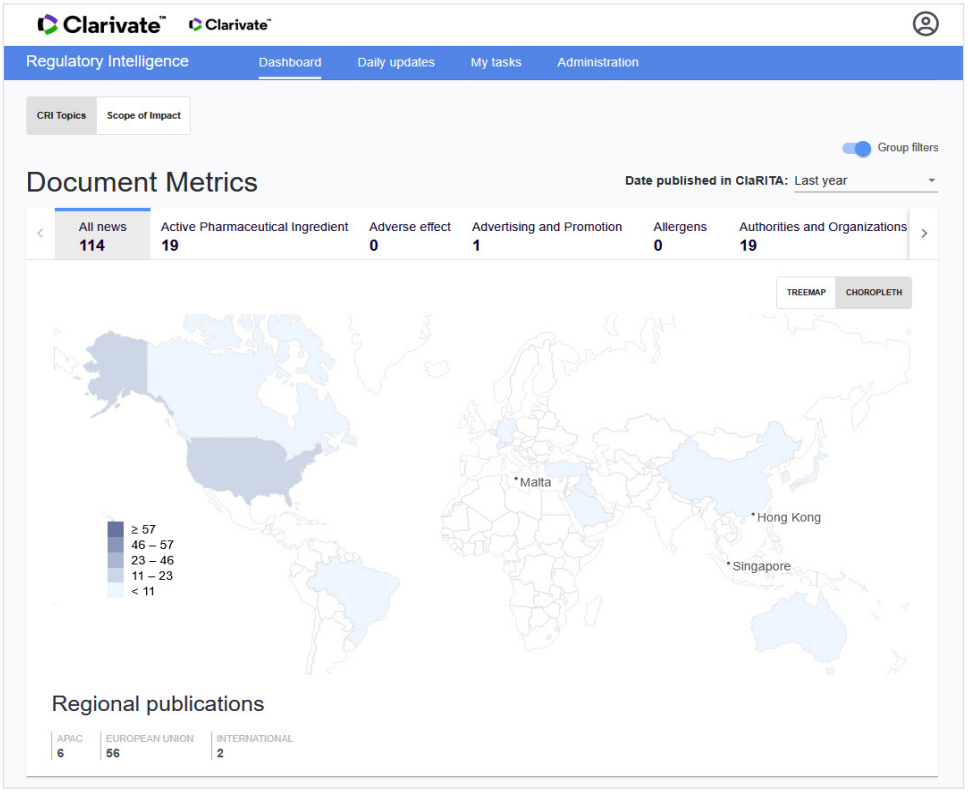
For example, in the absence of formal guidance for gene editing, representatives from the EMA published an article summarizing insights from 16 scientific advice procedures conducted between 2019 and 2022 for gene editing medicinal products (Tavridou et al, 2024). This provided a baseline against which to evaluate gene editing development. However, since then, the EMA published its 'Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials' in January 2025, which is scheduled to go into effect on July 1, 2025 (European Medicines Agency, 2025). The guidance covers development, manufacturing and quality control as well as non-clinical and some clinical aspects for gene therapy medicinal products, somatic cell therapy medicinal products, tissue engineered products and combined advanced therapy medicinal products.

Understanding the impact of this formal guidance on ongoing development activities requires robust impact assessments, including understanding how new rules may affect existing processes and the changes required to ensure compliance—within and between regulatory functions. Manual tracking through spreadsheets consumes large amounts of time to scour individual sites and repositories for new or changed information, and document sharing via email lacks version control, search functions, collaborative abilities and audit trails.

A customizable system that integrates data from multiple systems, allows collaboration between teams and propagates the information to relevant recipients provides the following advantages (Figure 9; Clarivate, 2024):

- A single, searchable source of regulatory updates by region and topic of interest
- Ability for all teams to complete and view impact assessments
- Automated notifications and alerts on the latest regulatory requirements globally
- If AI-capable, daily processing of new regulations and legislation, for faster triaging

Figure 9: Dashboard showing relevant regulatory information by region



Source: Clarivate Regulatory Intelligence Tracking Application (ClaRITA)

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