



RWE ready for reimbursement? A round-up of developments in real-world evidence relating to health technology assessment: part 27

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In this update, we review the US FDA's updated compendium of real-world evidence (RWE) use in medical device regulatory decisions, a comprehensive scan of RWE utilization in Canadian drug reimbursement submissions, and Institute for Clinical and Economic Review's use of RWE to inform US Medicare drug price negotiations under the Inflation Reduction Act.

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The US FDA's Center for Devices and Radiological Health published an updated compendium in April 2026, documenting 73 examples of market authorizations between 2020 and 2025 that incorporated real-world evidence (RWE) [1]. This builds on the 2021 report covering 90 examples from 2012 to 2019, and together the two publications now document 163 examples spanning over a decade of regulatory practice. To contextualize the findings, it is helpful to understand the FDA's tiered regulatory framework for medical devices. The premarket notification, or 510(k), is the most common and least burdensome pathway, used for moderate-risk devices that can demonstrate substantial equivalence to an already legally marketed device. *De novo* classification requests provide a pathway for novel, lower-risk devices that lack an existing equivalent on the market. The humanitarian device exemption (HDE) is a specialized pathway for devices intended to treat or diagnose conditions affecting fewer than 8000 individuals per year in the US, requiring demonstration of probable benefit rather than the full effectiveness standard. The premarket approval application (PMA) is the most stringent pathway, required for high-risk devices (Class III) and demanding valid scientific evidence of both safety and effectiveness, typically from clinical studies. PMA supplements are submitted for modifications to already-approved PMA devices, such as indication expansions, design changes, or labeling modifications, and the level of evidence required depends on the nature of the change.

The 2021 report covered 90 examples comprising 18 510(k) submissions, 14 *de novo* requests, two HDEs, 20 new PMA applications and 37 PMA supplements. The 2026 report covers 73 examples comprising 44 510(k) submissions, seven *de novo* requests, one HDE, nine new PMA applications and 12 PMA supplements. The most notable shift in the distribution of submission types is the substantially increased proportion of 510(k) clearances – from 20% of examples in the 2021 report to 60% in the 2026 report. The 2021 report was dominated by registry-based examples, which accounted for the largest share of real-world data (RWD) sources. In the 2026 report, medical records have become the most frequently used RWD source (43 examples), followed by registries (33 examples). Five examples in the 2026 report employed linkage of multiple RWD sources. While the 2021 report documented early examples of propensity score-matched analyses (for example, a pediatric ventricular assist device using propensity-matched historical controls from the ELSO Registry), the 2026 report shows these methods becoming more routine and sophisticated. The 2026 report also highlights the emergence of hybrid study designs

– 14 studies were single-arm studies using concurrent real-world controls and three single-arm studies used external control arms derived from RWD. Additionally, 21 examples involved validation studies for digital health or AI/ML-based software devices – a category that has expanded substantially from the three digital health examples in the 2021 report, reflecting the rapid growth of AI/ML-enabled devices entering the regulatory pathway. Regarding data quality and bias, neither the 2021 nor the 2026 report includes formal bias assessments or quality scoring of the RWE submitted. Both reports frame the RWE examples as illustrations of accepted practice rather than as critically appraised evidence. However, several patterns emerge from comparing the two reports. RWE appears most readily accepted – and most likely to serve as the primary source of clinical evidence – in contexts where the RWD source has established data governance and completeness, the outcome of interest is objectively measurable in routine care, and the regulatory question is well-suited to the available data. Professional society registries with defined data collection protocols (such as the STS/ACC TVT Registry, VQI and ELSO Registry) feature prominently in both reports' strongest examples. These registries typically address many of the data quality and content concerns that plague other more administrative RWD sources.

The evolution between the two reports, taken together, offers several implications for device manufacturers. First, the trajectory is clearly toward broader and more routine acceptance of RWE across all submission pathways. Second, while neither the 2021 nor 2026 report applies formal bias assessment tools, the increasing use of propensity score methods and other advanced statistical techniques suggest growing regulatory expectation for methodological sophistication in addressing confounding. For the health technology assessment (HTA) community specifically, these regulatory packages will increasingly serve as the evidentiary foundation upon which coverage and reimbursement decisions are made. As medical devices progress from regulatory approval to HTA evaluation, the RWE generated for the FDA will likely form the starting evidence base presented to HTA agencies. The critical lesson from the FDA compendium is that methodological rigor – appropriate study design, use of validated data sources and application of advanced statistical techniques to address confounding – is what will enable RWE to be accepted across both regulatory and HTA decision-making contexts.

While the FDA compendium documents growing regulatory acceptance of RWE for devices, the question of how RWE is received when submitted to HTA agencies for pharmaceutical reimbursement decisions provides a complementary and instructive perspective. Janoudi and colleagues examined the associated reports for 274 reimbursement submissions to Canada's Drug Agency (CDA-AMC) between January 2020 and June 2024, characterizing RWE utilization patterns, study designs, geographic data origins and reviewer feedback [2]. The researchers found that RWE has become a routine component of Canadian HTA submissions, with 70 submissions (25.5%) incorporating RWE and a median of 17 RWE-inclusive submissions annually. Of the 113 distinct RWD/RWE sources cited across these submissions, retrospective cohort studies were the dominant methodology (57.5%), particularly in oncology submissions reviewed by the pan-Canadian Oncology Drug Review Expert Review Committee (pERC), where this figure reached 70.5%. The Canadian Drug Expert Committee (CDEC), covering non-oncology submissions, saw prospective cohorts being used more frequently (30.4 vs 4.5% for pERC). RWE most commonly informed comparative clinical effectiveness (54.0%) and addressed evidence gaps identified in systematic reviews of pivotal trial data (52.2%). It was also frequently cited in pharmacoeconomic evaluations (54.9%), and in oncology submissions, RWE was particularly prominent within indirect treatment comparisons (ITC; 85.2% of pERC submissions with an ITC utilized RWE). Perhaps the most striking finding relates to the geographic origin of RWE sources. US data were the most common (38.9%), followed by European sources (38.1%), with only 10.6% of RWE studies originating from Canada. This geographic imbalance was reflected in reviewer critiques: the lack of Canadian data was specifically noted in 50% of submissions. More broadly, reviewer concerns focused on data quality issues (70.0%), generalizability (61.4%), short follow-up duration (52.9%) and potential bias or confounding (50.0%). Within the small subset of submissions that included Canadian-sourced RWE ($n = 10$), generalizability concerns decreased (40% vs 61.4% overall), although data quality issues persisted at the same rate (70.0%). This analysis was conducted during a period of evolving national RWE frameworks. Health Canada and CDA-AMC jointly endorsed national Guidance for Reporting RWE in 2023 [3]. As the study period largely precedes the implementation of this guidance the findings offer a valuable baseline against which future trends can be measured. The consistent HTA critiques around data quality and bias are similar to what we have previously discussed, for example coming from reviewing submissions to NICE in England [4] and HAS in France [5]. One of the key differences in the CDA-AMC review of RWE was a remarkable absence of submissions including Canadian data. Sponsors should therefore potentially invest in domestic data generation or, employ formal transportability analyses to bridge evidence from non-Canadian cohorts [6]. With the wealth of RWE guidance now available, the implications for manufacturers are

clear, and all efforts should be made to select the most appropriate data source and rigorously generate RWE for HTA purposes. As noted with the FDA device compendium discussed above, the use cases where RWE has been most successfully accepted are those employing rigorous methods on high-quality data. The CDA-AMC findings reinforce this: data quality and bias concerns were the primary barriers to acceptance.

RWE can be decisive when it addresses questions randomized controlled trials (RCTs) cannot. Richardson and colleagues present a detailed case study of how observational evidence informed the Institute for Clinical and Economic Review's (ICER) assessment of fluticasone furoate/vilanterol (Breo Ellipta) and fluticasone furoate/vilanterol/umeclidinium (Trelegy Ellipta), both manufactured by GSK for chronic obstructive pulmonary disease, conducted for the second cycle of Medicare drug price negotiations under the Inflation Reduction Act (IRA) [7]. The IRA, enacted in 2022, authorized the Centers for Medicare and Medicaid Services (CMS) to negotiate prices for selected high-expenditure branded drugs that have been on the market for a minimum of 9 years (small molecules) or 13 years (biologics) [8]. This case is particularly instructive for understanding RWE's role in price negotiations because RCTs demonstrated comparable efficacy between the single-inhaler products and their multi-inhaler alternatives. Systematic reviews and network meta-analyses showed no significant differences in moderate-to-severe exacerbations between Trelegy Ellipta and other triple therapies, or between Breo Ellipta and other dual therapies. However, both Trelegy and Breo Ellipta are single-inhaler, once-daily products compared with their multiple-inhaler or multiple-daily-dosing (typically twice-daily) comparators. RCTs are not designed to detect adherence differences between these regimens, as clinical trials typically use matching placebo inhalers to equalize the number of devices and inhalations per day, patients in trials tend to be more adherent than those in clinical practice, and study staff actively work to promote adherence. Thus, any real-world advantage from the convenience of a simpler regimen would be invisible in the RCT evidence base. ICER conducted a systematic literature review identifying both RCT and observational evidence across multiple outcome domains, as well as a targeted literature review specifically for cost-effectiveness model inputs. For clinical effectiveness, RWE was the sole source of evidence for three domains (adherence, persistence and healthcare resource utilization) and provided supplementary validation evidence for two additional domains (moderate-to-severe exacerbations and mortality). For adherence, six studies (n = 48,861) examining Trelegy Ellipta and one study (n = 9026) examining Breo Ellipta provided the evidence base. Adherence was measured as the proportion of days covered, derived from claims or electronic health record data. Both products demonstrated higher adherence compared with their multi-inhaler alternatives, though absolute adherence remained low across all groups. Risk of bias was assessed using the ROBINS-I tool, with most studies rated at moderate risk, primarily due to potential channeling bias – the possibility that physicians anticipated low adherence and preferentially prescribed the simpler single-inhaler product. In the cost-effectiveness analysis, RWE played a decisive role, illustrated by the model's results: over a lifetime horizon, patients receiving Trelegy Ellipta spent 37% of their time on triple therapy compared with 33% for patients on multi-inhaler triple therapy, with corresponding differences in time spent on subsequent lines of therapy and off all therapy (50% vs 56% on no therapy). For Breo Ellipta, patients spent 26% of their time on dual therapy compared with 24% for multi-inhaler dual therapy, with 58% versus 61% of time on no therapy. These seemingly modest differences in percentage of time on active therapy, when applied across a lifetime horizon and combined with the differential efficacy of each treatment line, generated incremental health benefits that translated into differentiated value-based pricing recommendations. Without these RWE-derived persistence differences, the products would have been considered therapeutically equivalent to their generic alternatives and would not have warranted differential pricing.

For manufacturers of drugs subject to future CMS negotiations, this case study offers several important lessons. First, it demonstrates that RWE can provide differentiation evidence between treatments and directly drive value-based pricing recommendations – a role for RWE that may be more important in re-assessments versus an initial product assessment. Second, it highlights the critical importance of prospective planning for post-launch evidence generation. The IRA requires that drugs have been on the market for at least 9 years before selection for negotiation, providing a substantial window during which manufacturers can generate the observational evidence needed to support their products' value. All aspects of potential value differentiation should be considered, as in the example here the differentiating outcome was persistence. Third, CMS has not yet provided specific guidance on how it will incorporate RWE or what quality standards it will apply; however, guidance from other HTA/regulatory bodies as noted above can be used as they all largely align on what 'good' RWE looks like.

Taken together, these three developments illustrate a consistent theme: the expanding role of RWE across the full spectrum of health system decision-making is accompanied by rising expectations for methodological rigor. For manufacturers, the strategic implication is clear: RWE generation should be planned prospectively, beginning before

product launch, with specific attention to the evidentiary needs of multiple decision-makers – regulators, HTA agencies and payers. Rigorous study design, appropriate data source selection, and advanced analytical methods to address confounding are the common denominators of successful RWE across all three contexts examined here.

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