The Role of Real-world Evidence in Supplemental or Conditional Approvals

Over the past few years, the FDA and biopharma companies have prioritized the generation of **real world evidence (RWE)** as a method to **better understand clinical outcomes** and **support supplemental drug approvals**. The field is gaining considerable traction and with the RWE-driven approval of Pfizer's Ibrance (pablociclib) in early April, we expect interest to continue to rise.

Three years ago, the 21st Century Cures Act was passed, requiring the FDA to release a plan for advancing RWE efforts. In Dec. 2018, the FDA announced a **new strategic framework to encourage the use of RWE** in new supplemental applications:

Notable Components of the Framework for the FDA'S Real World Evidence Program	
1	• Real world data may be **derived from a variety of sources** (e.g., electronic health records, medical claims, disease registries, laboratory test results, etc.), with guidance on quality control
2	• The FDA will consider use of real world data to support **randomized controlled trials in integrated health systems** and **across established registries**
3	• The FDA will **increasingly examine non-randomized, single arm trials with external RWD controls** (e.g., historical controls), particularly where randomization may not be feasible or ethical

Several products have achieved **supplemental or conditional approvals** based heavily in the generation of real world evidence:

	Product	*Approval*	*Indication*	*Description*
Innovative Use of RWE for Approval	**Ibrance** (Pfizer)	April 2019 (FDA)	Male HR+, HER2- Metastatic Breast Cancer	• The expanded indication was awarded primarily based on post-marketing reports and electronic health records showing a safety profile consistent with females
	Lutathera (Novartis)	January 2018 (FDA)	Gastroentero-pancreatic Neuroendocrine tumors (GEP-NETs)	• Lutathera was studied in both an RCT as well as an expanded access program (EAP) and leveraged real world evidence from the EAP to support approval in a rare group of cancers
RWE as a Historical Control	**Bavencio** (Merck/Pfizer)	April 2017 (FDA)	Merkel Cell Carcinoma (MCC)	• Since an RCT for Bavencio wasn't feasible, Merck/Pfizer were able to create a comparator arm to their Phase II study through the retrospective analysis of EHRs of patients treated with chemotherapy
	Blincyto (Amgen)	April 2014 (FDA)	Ph(-) B-cell precursor Acute Lymphoblastic Leukemia	• Blincyto gained approval in Ph(-) B-cell precursor ALL based on a single-arm trial as response rates were compared to data from 694 patients extracted from over 2,000 patient records in the U.S. and EU

It's important to note that supplemental approvals based on RWE are likely to be **more common in rare disease** where a **large randomized clinical trial may not be feasible** and physician-initiated prescribing can drive the development of evidence. While supplemental approval in these rare indications may not drive sales volume, particularly for drugs like Ibrance, generation of RWE may serve to **increase access to populations with an otherwise high level of unmet need.**

Additionally, the **use of RWE may ultimately reduce costs by eliminating the need for expensive post-market monitoring studies**, and already has for five products according to the FDA. Ultimately, **planning for the generation of real world data** should be considered by manufacturers as an alternative to traditional clinical trials and post-marketing studies.

Contributors: Rishi Dalsania, Managing Director (rishi.dalsania@clearviewhcp.com)**; Julia Lord, Senior Analyst; Sonya Li, Senior Consultant**

Source: Framework for the FDA's Real World Evidence Program (Dec. 2018); ClearView Analysis.