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EXPANDING DRUG INDICATIONS: STRATEGIC LIFECYCLE MANAGEMENT VS. EVERGREENING IN SGLT2 INHIBITORS

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ABSTRACT

In the rapidly evolving pharmaceutical industry, Lifecycle Management (LCM) strategies are critical for maximizing the profitability and extending the market life of drugs. This study investigates the strategic importance of expanding indications for sodium-glucose cotransporter 2 (SGLT2) inhibitors before the expiration of their foundational patents. By analyzing these pre-expiration strategies, the balance between genuine innovation and strategic evergreening is addressed. The analysis covers the legal, regulatory, and clinical dimensions of indication expansions across the US, EU, and Japan, contrasting with the traditional focus on LCM strategies post-patent expiration.

Keywords: Lifecycle Management (LCM) strategies, SGLT2 inhibitors, patent protection, chronic kidney disease (CKD), pharmaceutical regulatory frameworks, drug indication expansion, healthcare innovation, international patent law

INTRODUCTION

In the rapidly evolving pharmaceutical industry, Lifecycle Management (LCM) strategies are crucial for maximising the profitability and extending the market life of both novel and established drugs. Howard (2007) describes LCM as a strategy to enhance returns from pharmaceutical development, while Eelco Kappe (2013) outlines its application across marketing, research, development, and legal aspects. Amidst rising development costs and declining approval rates for new molecular entities (NMEs), Yamanaka and Kano (2016) emphasise the importance of identifying novel therapeutic applications for existing medications to rejuvenate their market value.

The impetus for adopting LCM strategies is closely linked to the diminishing patent protections, which lead to the introduction of generic pharmaceuticals and reduced profits for originator companies (Kakkar, 2015). This competitive pressure helps control public health expenditures and improves consumer welfare, while

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also driving innovation in novel drugs (Song and Han, 2016). The practice of evergreening, however, is often criticised for extending patent protection through minor modifications rather than genuine innovation (Feldman, 2018). Kapczynski et al. (2012) indicate that generic market entry is delayed by an average of 7.2 years following the expiration of statutory exclusivity periods for small molecules.

Within this context, the practice of adding new indications can be seen as a form of drug repurposing. This study assesses whether these additions constitute minor modifications or offer significant therapeutic benefits, focusing on SGLT2 inhibitors. The evaluation aims to determine whether expanding indications for SGLT2 inhibitors before patent expiration represents genuine innovation or strategic evergreening.

DISCUSSION

ANALYSIS OF LEGAL AND CLINICAL DIMENSIONS

LEGAL EFFECTIVENESS OF ADDITIONAL INDICATIONS IN THE US, EU, AND JAPAN

The effectiveness of patent rights for additional indications varies significantly across the US, EU, and Japan, influencing Lifecycle Management (LCM) strategies for pharmaceutical companies.

In the United States, second medical uses can be patented as treatment method inventions (United States Patent and Trademark Office, 2019). However, the off-label use of generics by physicians can circumvent these patents (Rai and Rice, 2014). In Europe, Supplementary Protection Certificates (SPCs) for second medical use inventions are not allowed (Santen SAS v. CJEU, 2020). In Japan, new medical uses of known active ingredients are treated as "inventions of substance." A 2009 notification from the Ministry of Health, Labour and Welfare allowed the sale of generics excluding the efficacies covered by remaining use patents, reducing motivation to apply for use patents (Ishino and Shimura et al., 2017).

These regional legal disparities complicate LCM strategies for extending product market life through new indications.

CLINICAL IMPACT OF INDICATION EXPANSION PRIOR TO GENERIC ENTRY

Sodium-glucose cotransporter 2 (SGLT2) inhibitors illustrate the impact of expanding indications before generic entry. Initially approved for managing type 2 diabetes, these inhibitors have demonstrated benefits for chronic kidney disease (CKD) and heart failure (Davies and Aroda, 2022; Neuen and Young, 2019; Nuffield Department of Population Health Renal Studies Group & SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium, 2022). Despite

projections that CKD will become a leading global cause of death by 2030, the clinical adoption of SGLT2 inhibitors remains low. Only about 10% of diabetes patients with CKD in the UK and US are prescribed these inhibitors (Lamprea-Montealegre, 2024), and Australian research suggests that prescribing SGLT2 inhibitors to eligible patients could prevent significant cardiorenal events (Neuen et al., 2023).

While various SGLT2 inhibitors are available, few have renal protection indications. This renal protective effect is consistent across the SGLT2 class (Suzuki and Kaneko et al., 2022). Previous studies often neglected the clinical significance of expanded indications in favour of market impact analysis. Evaluating prescription trends for CKD indications before generic entry offered valuable insights into the strategic challenges posed by these expanded indications.

RESEARCH FINDINGS, ANALYSIS, AND INSIGHTS

PREVALENCE AND ANALYTICAL DESIGN OF SGLT2 INHIBITORS IN CKD

Lamprea-Montealegre (2024) reported a notably low prescription rate of SGLT2 inhibitors for patients with CKD in primary care hospitals across Australia. Following this observation, this study conducted an analysis of the usage patterns of different types of SGLT2 inhibitors in Japan. The focus on the diversity of SGLT2 inhibitors in Japan stems from the availability of six different SGLT2 inhibitors for the treatment of type 2 diabetes (see Table 1). Among them, dapagliflozin (Forxiga 10 mg) was the first to be granted an additional indication for CKD, regardless of diabetes status, in August 2021. Approximately two years later, empagliflozin

Table 1. Approval status of SGLT2 inhibitors in Japan

Drug name	General name	Status of chronic kidney disease indication expansion in Japan
Suglat	ipragliflozin	-
Forxiga	dapagliflozin	August 2021: Addition of indication for chronic kidney disease without diabetes
Lusefi	luseogliflozin	-
Apleway, DEBERZA	tofogliflozin	June 2022: Addition of indication for chronic kidney disease with type 2 diabetes as a condition
CANAGLU	canagliflozin	-
Jardiance	empagliflozin	February 2024: Addition of indication for chronic kidney disease without diabetes

Source: Created by the author.

(Jardiance 10 mg) also received a similar CKD indication, marking a distinctive phase where only dapagliflozin had this additional CKD indication. This unique situation facilitated a targeted analysis of the implications of dapagliflozin's CKD indication. Patent rights of dapagliflozin (Forxiga 10 mg), as listed in the Orange Book, which organises patent rights associated with FDA-approved drugs, were analysed. Additionally, the prevalence of SGLT2 inhibitors was assessed using anonymised patient data from the EUCALIA Inc. database, illuminating the prescription patterns of SGLT2 inhibitors among patients.

INTELLECTUAL PROPERTY PROTECTION STATUS

A review of the FDA's Orange Book for dapagliflozin (Forxiga 10 mg), which is indicated for CKD, revealed 17 patents. The foundational patent for type 2 diabetes (US6515117B2) is valid until 4 October 2025, and the heart failure-related patent extends until 2040. However, there are currently no specific patents for CKD. A Google Patents search identified PCT/EP2021/058727, filed by AstraZeneca on 1 April 2021, as a potentially significant application for an additional CKD indication. However, no patent rights based on this application have yet been realised in any jurisdiction, including Japan, the US, and Europe.

THE REALITY IN A MEDIUM-SIZED HOSPITAL IN JAPAN

This study extracted patient data from a 200-bed medical facility primarily focused on primary care services. The analysis centred on patients diagnosed with type 2 diabetes, excluding those receiving insulin therapy, from 1 September 2020 to 31 August 2022. This period was chosen to encompass one year before and one year after the approval of dapagliflozin for CKD in late August 2021.

The examination specifically focused on patients with type 2 diabetes because only three individuals with reduced renal function without a diabetes diagnosis received SGLT2 inhibitors during this interval. This observation aligns with the reported low utilisation rate of SGLT2 inhibitors for CKD treatment by Neuen and Jun et al. (2023). The demographic details of the patients included in the study are depicted in Table 2.

Prescription trends for dapagliflozin and other sodium-glucose cotransporter 2 (SGLT2) inhibitors are depicted in Figures 1 and 2. The categorisation of estimated glomerular filtration rate (eGFR) (<60 and ≥60 mL/min/1.73 m²) was based on the test date closest to 1 September 2020. To explore variations in prescription patterns for dapagliflozin and other SGLT2 inhibitors according to these eGFR categories, a time series analysis employing the AR(1) model was conducted. The analysis for dapagliflozin showed an autoregressive coefficient (ar.L1) of 0.9477, with a 95% confidence interval (CI) of 0.8282 to 1.0672, indicating slight fluctuations in prescription rates without significant

Table 2. Patient background

Number of patients	**2214**
Gender (Male)	1046 (47.2%)
Age	67.30 ± 16.56 years
eGFR (initial measurement)	64.69 ± 21.00 mL/min/1.73 m²

Source: Compiled by the author.

Note: Age and eGFR (estimated Glomerular Filtration Rate) values are presented as mean ± standard deviation. The gender distribution is indicated by the number of male patients, with their percentage of the total cohort in parentheses.

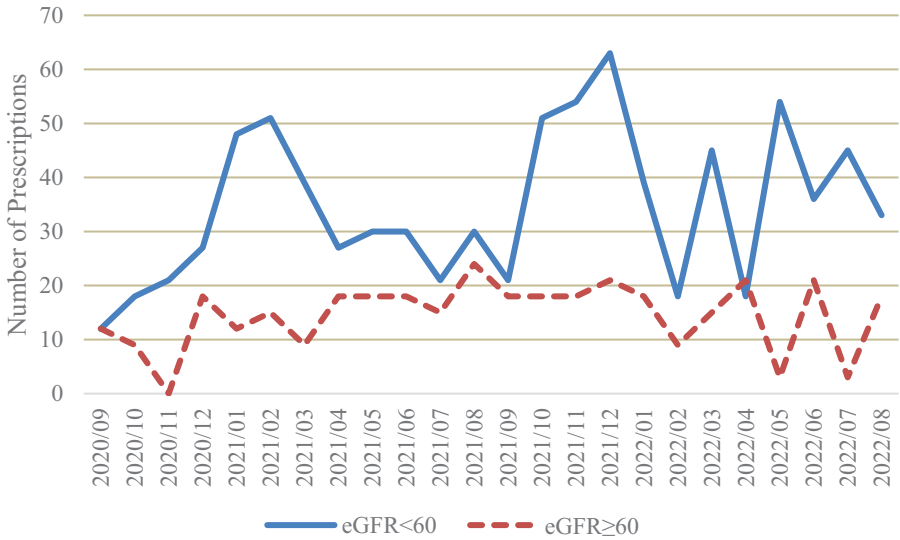

Figure 1. Trends in dapagliflozin prescription counts among patients with type 2 diabetes

Note: eGFR < 60: Prescriptions for patients with eGFR less than 60 mL/min/1.73 m². eGFR ≥ 60: Prescriptions for patients with eGFR 60 mL/min/1.73 m² or greater.

statistical evidence of a trend over time. The model's noise variance (sigma^2) was 0.0438, with a 95% CI of 0.0180 to 0.0695, indicating some variability, yet suggesting that prescription patterns remained relatively stable.

In contrast, the analysis for other SGLT2 inhibitors revealed a higher autoregressive coefficient (ar.L1) of 0.9921, with a 95% CI of 0.9405 to 1.0436, and a lower noise variance (sigma^2) of 0.0037, with a 95% CI of 0.0007 to 0.0068, demonstrating a more consistent prescription rate. This analysis, performed using Statsmodels in Python version 3.8.10, highlights the nuanced dynamics of SGLT2 inhibitor prescriptions within the cohort defined by eGFR categories.

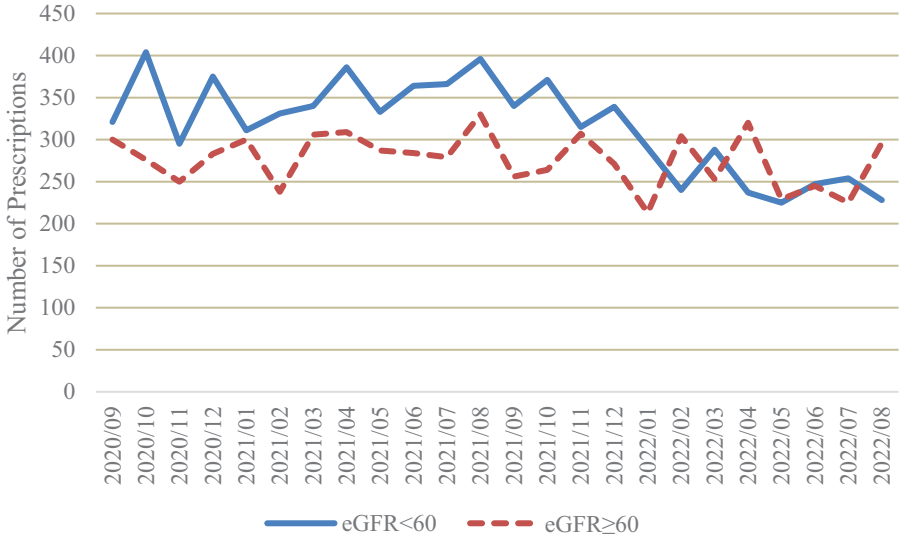

Figure 2. Trends in prescriptions of other SGLT2 inhibitors among patients with type 2 diabetes

Note: The term "Other SGLT2 Inhibitors" refers to ipragliflozin, luseogliflozin, tofogliflozin, canagliflozin, and empagliflozin.

eGFR < 60: Prescriptions for patients with eGFR less than 60 mL/min/1.73 m².

eGFR ≥ 60: Prescriptions for patients with eGFR 60 mL/min/1.73 m² or greater.

INTERPRETATION OF RESULTS

In a medium-sized hospital in Japan, dapagliflozin was prescribed to only three patients identified with renal impairment without diabetes, underscoring its limited utilisation as a CKD treatment. Despite fluctuations in dapagliflozin's prescription trends, it appeared that it was not extensively used for CKD management in patients with advancing diabetic renal impairment, indicating that dapagliflozin primarily remained a treatment for type 2 diabetes, even after its approval for CKD indications.

ANALYSIS OF INDUSTRY TRENDS, CHALLENGES, AND OPPORTUNITIES

Neuen et al. (2023) identified a notable shortfall in the prescription of SGLT2 inhibitors for patients with CKD, suggesting that targeted interventions could alleviate renal impairment. This raises the question of how the market share for SGLT2 inhibitors will evolve following the entry of generics post-patent expiration.

While SGLT2 inhibitors are predominantly prescribed for diabetes, there is concern that they may be overlooked in CKD treatment with the advent of

generics. Encouraging their prescription in clinical practices necessitates compelling evidence and strategic marketing initiatives. However, in regions with limited protection for expanded indications, the incentive for pharmaceutical companies to pursue such strategies may be minimal.

The case of dapagliflozin, developed by AstraZeneca, demonstrates that a company's strategic decisions can be greatly influenced by its comprehension of regulatory frameworks. Despite the potential for obtaining extended indication protection in Japan, the patent application PCT/EP2021/058727 remains unexamined.

The forthcoming expiration of patents for SGLT2 inhibitors might facilitate generic market entry, likely reducing diabetes-related healthcare costs. Nonetheless, this could also delay the integration of SGLT2 inhibitors in CKD treatment, posing clinical dilemmas. Moreover, the implications of the Santen ruling in Europe accentuate the risk of hastening generic introduction, potentially deterring the incentive for new drug development (Wuttke & Popp, 2020).

Ensuring exclusive rights for drugs that offer significant clinical advantages with new indications is imperative, transcending the evergreening controversy. Advocating for patent extensions based on clinical merits underscores the necessity of establishing an international consensus.

CONCLUSION

This study introduces a nuanced framework for evaluating the strategic and clinical impacts of adding new indications to SGLT2 inhibitors before the expiration of foundational patents. By incorporating legal, clinical, and market considerations, this framework enhances the discourse on pharmaceutical patent protection beyond the binary classification of innovation versus evergreening. The proposed framework emphasises the necessity for a detailed assessment of the clinical value of new indications.

The findings underscore the importance of further research into market trends and patient outcomes post-patent expiration. These insights will inform strategic planning within pharmaceutical companies and support the development of innovative treatments that address evolving healthcare needs.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted using anonymised data prepared in accordance with the ethical standards of the facility. The study utilised these pre-anonymised datasets.

AVAILABILITY OF DATA AND MATERIALS

The data underpinning this study's findings can be made available by the corresponding author upon reasonable request.

COMPETING INTERESTS

The authors declare no relevant financial or non-financial interests that could be construed as a potential conflict of interest.

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