User-life of ICS/LABA inhaler devices should be considered when prescribed as relievers

To the Editor:

Inhaled corticosteroid/formoterol (ICS/FOR) combination medications were initially developed as maintenance therapy; more recently they are also used as relievers in Europe and this use is proposed in the USA. ICS coupled with FOR (a long-acting β_2-agonist) is recommended by the 2020 Global Initiative for Asthma (GINA) guidelines [1] for steps 2–5 as maintenance and reliever (SMART) and is recommended for steps 3 and 4 in the 2020 USA National Asthma Education and Prevention Program (NAEPP) [2]. While SMART has regulatory approval in Europe, it does not in the USA.

This new usage raises concerns about ICS/FOR products, because when used solely as a reliever, an inhaler could be used for much longer than the typical 1-month period for fixed-dose maintenance treatment. Consequently, the physico-chemical stability of the formulation cannot be assured throughout use and clinical efficacy may be compromised. A study in mild asthma (step 2 GINA) reported use of approximately 0.5 puffs per day ICS/FOR when used as a reliever only [3]. Under these circumstances, a 120-dose inhaler would last about 8 months, beyond the user-life expiry for most of Europe's and the USA's ICS/FOR products (table 1). Expiry of inhalers is defined by the manufacturer in two ways; user-life and shelf-life. Regulators set the standards for inhaler stability testing and generally >80% of respirable drug must be available at the end of the reported shelf-life and user-life if stored properly [4, 5]. User-life refers to the time interval from removal of the inhaler from its packaging until the manufacturer can no longer assure potency, ranging from 3 months to 3 years for ICS/FOR and 6 months to 3 years for salbutamol (table 1) [6, 7]. User-life is required in the patient information leaflet, but not on the inhaler [6, 7]. Shelf-life refers to the time period from manufacture to expiry while remaining in the original packaging and is provided on the inhaler. Most pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) are dispensed in sealed foil packaging with a desiccant [6, 7] to protect the drug formulation from environmental moisture, resulting in a shelf-life nearly always longer than user-life. It has been reported that nearly half of all patients do not consider the inhaler shelf-life expiry [8].

For multi-dose inhalers, there is a fine balance in the physical and chemical makeup of the drug formulation, affected mainly by time, environmental moisture and temperature (>60% room humidity and >25–30°C). Not only can drug concentrations decline because of chemical changes, physical changes to crystallinity or aggregation of drug particles and/or carriers can compromise the amount of respirable drug [9]. Ingress of environmental moisture occurs through gaskets around the valve stem for pMDIs, and through blister packs and powder reservoirs with DPIs [9]. Patients with asthma are poorly informed about proper device storage; two-thirds store their inhalers improperly, half in their bathroom [10]. Although DPIs are most vulnerable to the environment, comparing budesonide (BUD)/FOR DPI and pMDI shows that wet aerosols also appear susceptible based on user-life (table 1).

While some stability data for different DPIs is available, we are unaware of such data for pMDIs. In a study comparing the *in vitro* susceptibility of Easyhaler®, Spiromax® and Turbuhaler® DPIs exposed to 75% room humidity and ambient temperature (25°C); at 0, 1.5 and 3 months, the respirable fine particle dose (FPD) of ICS and FOR were both reduced, with Easyhaler by nearly one-half at 1.5 months [11]. With

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Prescribers and asthma patients should know that ICS/LABA combination inhalers used as reliever therapy may expire under patient use sooner than the expiration shown on the inhaler, compromising effectiveness if not considered by the prescriber and patient https://bit.ly/3fhHMX2

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TABLE 1 Inhaled corticosteroids/formoterol and salbutamol inhaler products available in Europe [6] and USA [7]

Product	Device type	Number of doses in each inhaler	Drugs	User-life	Shelf-life	Storage instructions for patient
Foster NEXThaler (Chiesi)	DPI	120/180	BEC/FOR	5 months	3 years	Do not store the inhaler above 25°C (maximum of 3 months)
Foster Inhalant Solution (Chiesi)	pMDI	120/180	BEC/FOR	3 months	21 months	Before dispensing: Store in a refrigerator (maximum of 18 months) Do not store above 25°C (maximum of 3 months)
DuoResp Spiromax (Teva Pharma)	DPI	120	BUD/FOR	6 months	3 years	Do not store above 25°C
Symbicort Turbohaler (AstraZeneca UK)	DPI	60	BUD/FOR	3 years	3 years	None specific
Fobumix Easyhaler (Orion)	DPI	60	BUD/FOR	4 months	2 years	Do not store above 25°C and protect from moisture
Symbicort Inhalation Aerosol (AstraZeneca USA)	MDI	60/120	BUD/FOR	3 months	2 years	Store 20–25°C
Ventolin Accuhaler (GlaxoSmithKline UK)	DPI	200	SAL	24 months	24 months	Do not store above 30°C
Albuterol Easyhaler (Orion)	DPI	200	SAL	6 months	3 years	Store in a dry place not exceeding 25°C
Ventolin Evohaler (GlaxoSmithKline UK)	pMDI	200	SAL	3 years	3 years	Store at less than 30°C

DPI: dry powder inhaler; pMDI: pressurised metered dose inhaler; BEC: beclomethasone; FOR: formoterol; BUD: budesonide; SAL: salbutamol.

Turbuhaler, there was no change in FPD for the ICS or FOR at 3 months, and approximately a 10% decline in the ICS component with Spiromax at 3 months [10]. The reported user-life for Easyhaler is 4 months, and 6 months for Spiromax. Data about the amount of respirable drug present at the end of user-life or shelf-life is not available from the manufacturer for most products. Therefore, we do not know if 99%, 90% or the minimally acceptable 80% remains. To ensure confidence to the patient and provider that indeed the prescribed dose is available when using ICS/FOR for SMART, the user-life and the patient's inhaler usage pattern should be considered. We recommend selecting a product with a user-life long enough to minimise the likelihood of using the inhaler beyond its user-life. Patients should be instructed to replace inhalers accordingly, especially when living in settings where humidity exceeds 60% or otherwise do not store their inhaler properly.

Many important factors are recognised in inhaler selection, and we suggest that prescribers and policy makers consider inhaler stability and patient usage when recommending this "new" therapy for asthma. While there are multiple choices of ICS/FOR in Europe to accommodate for product stability and patient usage in SMART, it appears Symbicort Turbohaler may be the preferred reliever product. Yet in the USA, off-label use of Symbicort pMDI for SMART only provides a 3 month user-life [7]. These concerns could be better addressed if manufacturers provided such information or studies were published by independent researchers to define ICS/FOR stability under patient use conditions.

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