WHO Biowaiver Study Project for COVID-19 Outbreak: Dexamethasone Solubility Results for Biopharmaceutical Classification System

Dexamethasone is a corticosteroid considered today as one of the few medicines able to reduce mortality in patients infected with COVID-19 who are critically or severely ill (mortality reduction of 8.7% and 6.7% respectively at 28 days) [1,2]. It is hypothesized that its benefits are probably due to reduced inflammation which is a key component of the disease in some hospitalized patients.

According to the World Health Organization (WHO) Director-General, Dr Tedros Adhanom Ghebreyesus: "The next challenge is to increase production and rapidly and equitably distribute dexamethasone worldwide, focusing on where it is needed most" [3]. The WHO Norms and Standards for Pharmaceuticals (NSP) Team therefore conducted a high priority assessment of dexamethasone within the ongoing WHO Biowaiver Study Project to generate scientifically valid solubility data in support of regulatory decisions to improve access to this medicine in the current global public health emergency.

Valeria Gigante[1], Sabine Kopp[1], Maria del Val Bermejo Sanz[2], Giovanni M. Pauletti[3], Minghze Xu[4]

[1] *Norms and Standards for Pharmaceuticals, World Health Organization, Geneva, Switzerland*
[2] *Department of Engineering: Pharmacy section, Universidad Miguel Hernández de Elche, Alicante, Spain*
[3] *Department of Pharmaceutical and Administrative Sciences, University of Health Sciences and Pharmacy, St. Louis, Missouri, United States of America*
[4] *Institute for Chemical Drug Control, China National Institutes for Food and Drug Control, Beijing, China*

[1] The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-1: A Meta-analysis. JAMA. Published online 2 September 2020. doi:10.1001/jama.2020.17023

[2] EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation. EMA/483739/2020 (https://www.ema.europa.eu/en/documents/press-release/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation_en.pdf, accessed 1 October 2020).

[3] World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19, 22 June 2020: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---22-june-2020

Over the past four years, the WHO Biowaiver Study Project, designed in 2017 and launched in 2018 with a pilot phase, has supported the initial revision and subsequent maintenance of the *WHO Biopharmaceutical Classification System (BCS),* which is also known as *WHO Biowaiver List*[4]. Leveraging on the 1995 BCS, the WHO and several regulatory agencies from all over the world recognized the possibility of an optimized and shorter pharmaceutical development pathway by waiving the in vivo bioequivalence studies for medicines that qualify based on a set of defined criteria. This regulatory provision can be applied when developing multisource (generic) products, as well as for pre- and post- approval changes requiring bioequivalence studies.

Eligible medicines are immediate-release, solid oral dosage forms containing active pharmaceutical ingredients (APIs) Class I (highly soluble and highly permeable) or Class III (highly soluble and low permeable) according to the BSC scientific framework[5]. The intended impact of such a WHO classification is high with regards to access to the medicines, particularly for emergency situations.

The WHO Biowaiver List has been recognized by WHO and its Regional and Country Offices as a Global Public Health Good to achieve Universal Health Coverage, to contribute to the sustainable development goals and to increase access to essential medicines.

In June 2020, on the occasion of the annual meeting on regulatory guidance for multisource products hosted by the NSP Team with the Prequalification of Medicines Team - Assessment group, the NSP Team presented a set of APIs for prioritization and study within the WHO Biowaiver Study Project (study cycle IV, 2021). The proposed set included medicines that were undergoing clinical trials to address the COVID-19 emergency. During the meeting, the experts stressed the need for an urgent solubility assessment of dexamethasone for BCS purposes. In addition, it was recommended that the results of such experiments should be shared with the broader scientific community to facilitate regulatory decisions affecting production and, ultimately, the availability of dexamethasone to patients.

[4] Proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2020: Annex 12 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 23 September 2020).

[5] Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003; https://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex6.pdf?ua=1, accessed 1 October 2020).

Methods

Dexamethasone solubility was studied in parallel by three independent institutions selected from the network of laboratories that are supporting the WHO Biowaiver Project: i) the University Miguel Hernández University of Elche in Alicante, Spain; ii) the University of Health Sciences and Pharmacy in St. Louis, United States of America; and iii) the National Institutes for Food and Drug Control in Beijing, China.

Equilibrium solubility studies were performed according to the provisions specified in the WHO "*Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutical Classification System-based classification of active pharmaceutical ingredients for biowaiver*"[6]. This protocol was specifically developed and optimized for the WHO Biowaiver Project and employs a harmonized methodology that has been demonstrated to control experimental variabilities across global laboratories as illustrated in: "*Global testing of a consensus solubility assessment to enhance robustness of the WHO biopharmaceutical classification system*" [Valeria Gigante, Giovanni M. Pauletti, Sabine Kopp, Minghze Xu, Isabel Gonzalez-Alvarez, Virginia Merino, Michelle P. McIntosh, Anita Wessels, Beom-Jin Lee, Kênnia Rocha Rezende, Gerhard K.E. Scriba, Gaurav P. S. Jadaun, Marival Bermejo, ADMET and DMPK (2020), doi: http://dx.doi.org/10.5599/jese.850. Advanced online article: https://pub.iapchem.org/ojs/index.php/admet/issue/view/58].

Dexamethasone solubility was studied at the therapeutic dose of 6 mg, which is the same dosage used in the COVID-19 Recovery Trial[7] and currently recommended in adults and adolescents over 12 years of age (weighing more than 40 kg) [2,8] for the treatment of patients with severe and critical COVID-19.
Dexamethasone can be administered orally or intravenously leading to similar systemic drug exposure (i.e. high oral bioavailability).

Results

In this study, the solubility profiles of the following solid state forms of dexamethasone were evaluated: dexamethasone, dexamethasone micronized, dexamethasone phosphate and dexamethasone sodium phosphate. The experimental results for all these forms were consistent across the laboratories (Table 1).

[6] Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutical Classification System-based classification of active pharmaceutical ingredients for biowaiver. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1019, Annex 4; https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1019, accessed 23 September 2020).

[7] Dexamethasone in Hospitalized Patients with Covid-19. Preliminary Report. 2020/07/17. J New England Journal of Medicine. 10.1056/NEJMoa2021436. https://www.nejm.org/doi/full/10.1056/NEJMoa2021436

[8] Corticosteroids for COVID-19. Living Guidance. Geneva, 2 September 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1, accessed 1 October 2020).

Table 1. WHO equilibrium solubility classification of dexamethasone

Medicine [a]	Therapeutic area	Indication	Highest therapeutic dose (mg)[b]	API PQ EOI/Q	WHO classification [c]
dexamethasone	(1) Gastrointestinal medicines (2) Immunomodulators and antineoplastics (3) Medicines for pain and palliative care (4) *Corticosteroids for COVID-19**	(1) Antiemetic medicines (2) Acute lymphoblastic leukaemia (2) Multiple myeloma (3) Medicines for other common symptoms in palliative care (4) *Treatment of patients with severe or critical COVID-19**	(1) (3) 0.5 to 10 mg a day depending on the disease being treated (2) 40 mg (4) *6 mg a day **	**Yes**	**I/III**

[a] 21st *WHO Model List of Essential Medicines* (2019)
[b] According to Summary of Product Characteristics from WHO-PQ or National/Regional Regulatory Authority.
[c] According to the WHO guidelines, *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (1)*, APIs belonging to Classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (i.e. either Class I or Class III). The present solubility characterization is already sufficient to provide an indication as to whether or not an API is eligible for biowaiver.

* "*Corticosteroids for COVID-19. WHO Living guidance" September 2020)* *https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1 (accessed 30 September 2020)*

As detailed in the WHO guideline entitled "*Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*" (WHO Technical Report Series, No. 1003, Annex 7, 2017), an API is considered "highly soluble" when the highest single therapeutic dose of the API as recommended by the approved label or summary of product characteristics of the originator product is soluble in 250 mL or less of aqueous media over the entire pH-range of 1.2 – 6.8. The dose/solubility volume (DSV) is the volume of liquid necessary to completely dissolve the API.

The results from these experimental solubility assessments revealed that the DSV for dexamethasone is consistently less than 250 mL over the entire physiological pH range: pH 1.2 - pH 6.8. Thus, it is concluded that dexamethasone is a highly soluble API, consistent with the definition of a BSC Class I/III compound. Consequently, dexamethasone at doses relevant for therapeutic intervention in COVID-19 patients seems eligible for a regulatory waiver from in vivo bioequivalence studies (Table 2).

Comparative in vitro dissolution data, supported by the necessary considerations underpinning dexamethasone pharmaceutical development, are still expected to be generated and submitted to the regulatory authorities by the manufacturers.

Table 2. Experimentally determined pH-dependent API solubility using a globally harmonized protocol

Medicine	pH	Highest ter. dose (mg)	MW of the solid used	Cs mean mg/mL [a]	DSV	Solubility Class
Dexamethasone and dexamethasone micronized			392.46			Highly Soluble (BSC I/III)
	1.2	6		0.595	10.08	
	4.5	6		0.704	8.52	
	6.8	6		0.567	10.58	
Dexamethasone phosphate [b]			472.4			Highly Soluble (BSC I/III)
	1.2	7.2		3.009	2.39	
	4.5	7.2		4.027	1.79	
	6.8	7.2		3.97	1.81	
Dexamethasone sodium phosphate [c]			516.4			Highly Soluble (BSC I/III)
	1.2	7.8		0.078	100.00	
	4.5	7.8		0.109	71.56	
	6.8	7.8		0.062	125.81	

[a] Experimental data showing the mean values from the three individual experiments

[b] Used at the dose of 7.2 mg of dexamethasone phosphate corresponding to 6 mg of dexamethasone

[c] Used at the dose of 7.8 mg of dexamethasone sodium phosphate corresponding to 6 mg of dexamethasone

Conclusions

Dexamethasone is a corticosteroid (Figure 1) that has been therapeutically used since the 1960s to reduce inflammation in a range of conditions, including inflammatory disorders and certain cancers. It was first included in the WHO Model List of Essential Medicines in 1977 and listed in multiple formulations for different indications. Dexamethasone is also included in the 95% of the national essential medicines lists redacted by Member States.

Today, dexamethasone is an off-patent medicine, generally affordable and available in most countries. However, some shortages have been reported in recent years. To address the COVID-19 emergency, it is recommended to facilitate the development and production of this medicine by the pharmaceutical industry through dissemination of the outcome of these equilibrium solubility studies and the provisional BCS-based classification for regulatory purposes.

At the same time, it is important to take the globally available API quantities and manufacturing capacity into consideration to be able to estimate the impact of repurposing dexamethasone from existing indications to the recent therapeutic opportunity for use in the treatment of patients with severe and critical COVID-19. Those considerations will be critical to ensure that patients have access to the safe, effective, quality and affordable medicines they need.

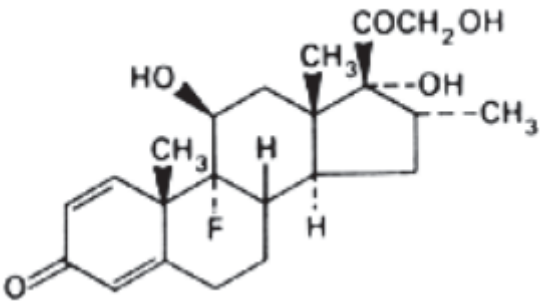

Figure 1. dexamethasone structure.
Source: The International Pharmacopoeia - Ninth Edition, 2019.