

## How to Choose the Right *Serenoa repens* Extract

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### Article info

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### Abstract

**Context:** Herbal medicines are complex mixtures of various compounds. Standardisation is essential to ensure a consistent biological effect.

**Objective:** This article reviews findings related to herbal medicines with a specific focus on *Serenoa repens*, which is available in a number of different forms.

**Evidence acquisition:** This article is based primarily on material presented at a satellite symposium entitled, “Inflammation and Prostatic Diseases: From Bench to Bedside,” held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and benign prostatic hyperplasia (BPH) were reviewed.

**Evidence synthesis:** A review of the available literature indicated that many natural products are being used in therapeutic settings such as cardiology, neurology, oncology, psychology, and urology. The need to standardise these products to ensure a consistent clinical effect is a prerequisite for good medical practice. In the case of *Serenoa repens*, which is used in the symptomatic treatment of BPH, best evidence has been published for the n-hexane lipidosterolic extract of the dwarf American palm.

**Conclusions:** This literature review highlighted the variability in the composition of the various brands of *Serenoa repens*. *Serenoa repens* hexanic extract is considered by the European Medicines Agency to be a “well-established medical use product” for symptomatic treatment of BPH.

**Patient summary:** Standardisation of herbal medicines is essential to ensure a consistent level of clinical activity and safety. In the case of *Serenoa repens*, the n-hexane lipidosterolic extract is the only formulation currently considered by the European Medicines Agency to be a “well-established medical use product.”

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### 1. Introduction

Herbs and other botanical sources of medicines have been used to treat human ailments for >5000 yr [1]. Botanical drugs, as defined by the US Food and Drug Administration, can contain ingredients from a number of sources such as fresh or dried plants, plant parts, and isolated or combined

components of plant origin, including algae and fungi [2]. In Europe, herbal medicines are defined as any medicinal product exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations or one or more such herbal substances in combination with one or more such herbal preparations. The various challenges physicians face when ascertaining the potential uses and

benefits of herbal medicines can be summed up in a few questions:

- What is the extract?
- What is it used for?
- What is the evidence for its efficacy and safety?
- Who would benefit from using it, and, conversely, who should not receive it?
- Does it have a proven place in therapy?
- Does it provide good value for cost?

Some issues associated with the use of herbal medicines include lack of quality control and standardisation; adulteration with other plants, pharmaceutical drugs, and/or heavy metals; inappropriate use; and adverse effects [1–5]. The perception that botanical products are safe because they are natural appears to be based on their traditional usage as folk remedies rather than on any formal clinical evaluation to confirm safety and tolerability [3]. Although more adverse effects are reported for conventional medicines than for herbal products, this may be explained in part by the under-reporting of herbal toxicity [1]. Herbal medicines are complex mixtures of chemicals contained within different parts of plant material. Scientists face a major challenge in standardising the final product so as to deliver a formulation with a consistent chemical profile that produces a consistent level of biological activity [2,3,5]. As noted by Liu and Wang, a long history of use, often with good evidence of efficacy, does not negate the need to validate natural products in terms of their biological authentication, chemical characterisation, process development (extraction and standardisation), safety, and efficacy before they can be accepted into mainstream medical practice [2].

Many products have achieved these standards, and the number of natural remedies, particularly from botanical sources, is increasing steadily in many therapeutic areas. Examples include cardiovascular diseases (*Digitalis purpurea*, *Achillea millefolium*), constipation (*Cassia acutifolia*, senna), depression (St. John's wort), some cancers (docetaxel, paclitaxel, vinca alkaloids), and pain and spasticity (*Cannabis sativa*) [1,4,6–8]. The use of herbal medicines is also becoming more widely established in urologic disorders such as benign prostatic hyperplasia (BPH) to minimise lower urinary tract symptoms (LUTS) [9]. In particular, extracts of the American dwarf palm (*Serenoa repens*, saw palmetto) have been widely used in this setting in Europe and the United States [4].

The aim of this review was to compare a number of commercially available brands of *Serenoa repens*, which are produced using different extraction processes, to assess whether they are consistent in terms of their composition and constituents and their biological activity.

## 2. Evidence acquisition

This article is based primarily on material presented at a satellite symposium entitled, “Inflammation and Prostatic Diseases: From Bench to Bedside,” held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH are reviewed. The article is complemented by relevant related literature identified on PubMed and by hand searches of key references.

## 3. Evidence synthesis

### 3.1. *Serenoa repens*

*Serenoa repens* is a phytopharmaceutical listed as a traditional medicinal product in the European Union herbal monographs for symptomatic treatment of BPH [10]. The dosage is 160 mg twice daily. There are numerous branded *Serenoa repens* products, and they differ both qualitatively and quantitatively because of differences in the source of the biological product and variations in the process used to extract the active ingredients. Hexanic, ethanolic, and supercritical CO<sub>2</sub> extracts of *Serenoa repens* are all commercially available in some markets in the European Union, but few clinical data are available for some products. Furthermore, a number of modern extraction techniques such as microwave-assisted, ultrasound-assisted, enzyme-assisted, and pressurised liquid or fluid extraction methods have been developed [11]; however, these techniques have not yet been applied to the extraction of *Serenoa repens*. The lipidosterolic extract of *Serenoa repens* obtained by solvent (hexane) extraction is the most widely studied product in clinical and experimental trials and forms the basis of this review. Future trials should explore the possible clinical profiles of plant extracts obtained using the various extraction processes [11].

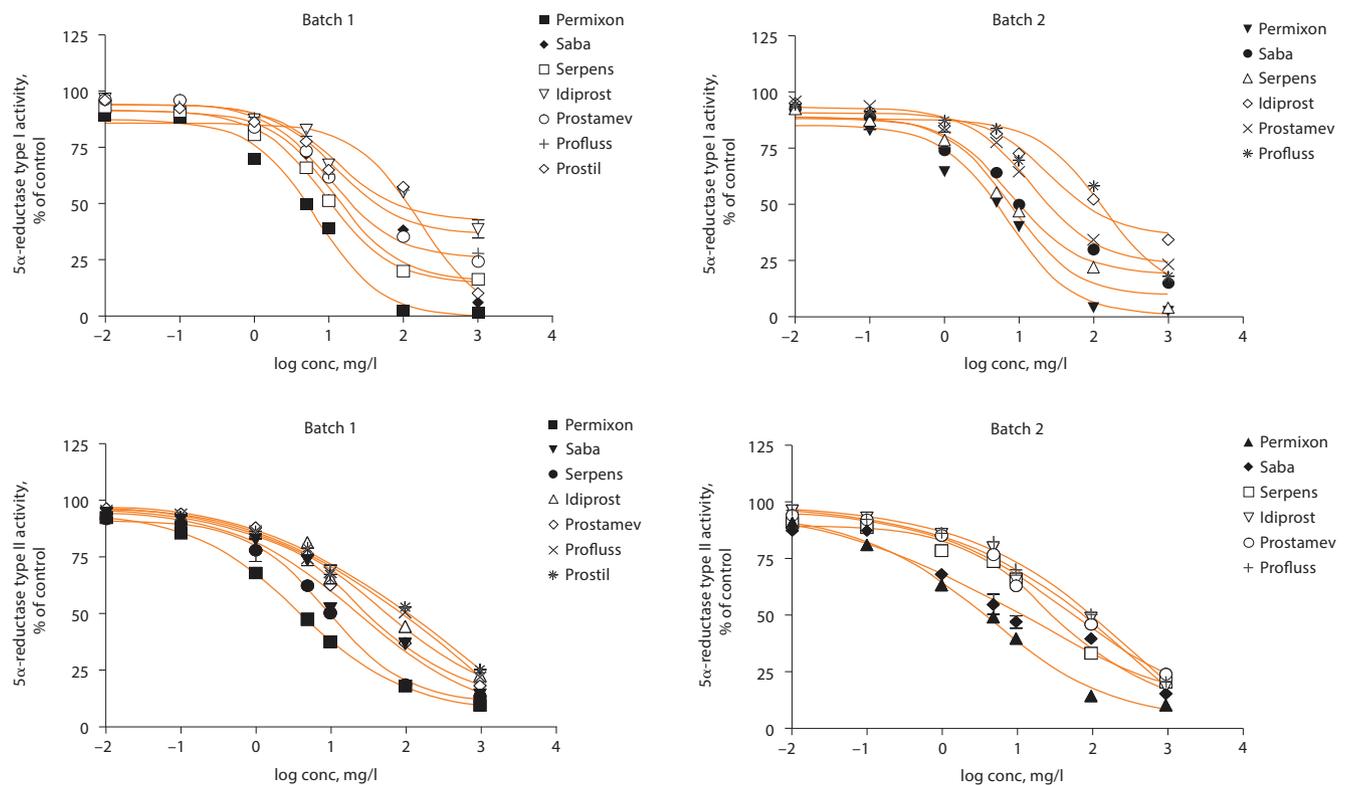
### 3.2. Composition of different brands of *Serenoa repens*

Despite being used widely for many years in numerous countries worldwide, the mechanism of action and the role of particular constituents of *Serenoa repens* are poorly understood. Studies attributing clinical benefits to any particular component of *Serenoa repens* are lacking, but pharmacologic experiments have identified the following properties: inhibition of 5 $\alpha$ -reductase, modulation of androgen-receptor binding, inhibition of  $\alpha$ -receptor binding, inhibition of eicosanoid synthesis, spasmolytic activity, and anti-inflammatory effects [4,10,12–17]; however, activity of the different extracts can vary, possibly due to compositional differences such as variation in the levels of free fatty acids. An understanding of the composition of different brands of *Serenoa repens* is essential to ascertaining whether they are likely to be bioequivalent. To this end, Habib and Wyllie compared 14 brands of *Serenoa repens* obtained from France ( $n = 1$ ), Germany ( $n = 7$ ), Italy ( $n = 3$ ), and the United States ( $n = 3$ ) [4]. The analysis highlighted significant variations in composition among the different brands (Table 1). In particular, the concentration of free fatty acids, which have been suggested as the main active ingredients of *Serenoa repens*, ranged between 40.7% (Solaray; Neutraceutical Corp, Park City, UT, USA) and 80.7% (Permixon; Pierre Fabre, Castres, France). Notably, the proportion of individual free fatty acids was found to be similar for all products tested, with lauric and oleic acids present at the highest concentrations in each sample assayed [4]. The study also highlighted potential discrepancies between the stated and actual doses of commercially available preparations due to differences in plant source, extraction process, and formulation with bioactive adjuvants.

**Table 1 – Composition of 14 different brands of *Serenoa repens***

Product	FFA (mean %)	Methyl and ethyl esters (mean %)	Long-chain esters (mean %)	Glycerides (mean %)	Unsaponified matter (mean %)
Permixon	80.7	2.5	1.36	6.8	2.27
Prosteren	74.0	3.7	1.3	10.8	2.37
Saba	70.25	2.85	1.2	14.4	2.15
Rilaprost	68.8	2.4	1.0	21.43	1.87
Prostess	68.4	9.5	1.2	10.6	2.6
Sita	62.9	9.35	1.3	13.45	2.2
Quanterra prostate	63.1	6.3	1.03	19.55	1.9
Ratiopharm uno	62.3	4.25	0.9	24.25	1.6
Talso uno	61.4	4.4	0.8	25.3	1.8
Prostamol uno	59.3	12.6	0.97	15.37	2.4
Prostagutt uno	59.2	9.25	0.85	19.7	2.0
Strogen uno	54.8	6.6	1.2	27.1	2.4
Prosta-urgenine	54.05	16.7	0.7	16.55	2.2
Solaray	40.7	1.5	0.9	52.15	1.6

Adapted from [4] with permission from Macmillan Publishers Ltd. FFA = free fatty acid.



**Fig. 1 – Inhibition of 5 $\alpha$ -reductase by various extracts of *Serenoa repens*. Enzyme activity is expressed as a percentage of the control (conversion of 1  $\mu$ M of testosterone in the absence of inhibitors is defined as 100% activity). Reproduced with permission from Karger Publishers [17]. conc = concentration.**

### 3.3. Comparison of the activity of different brands of *Serenoa repens*

In light of the different compositions of the various brands of *Serenoa repens*, a number of studies have been performed to investigate their biological activity. In 2008, our group evaluated seven brands of *Serenoa repens* available in Italy using a 5 $\alpha$ -reductase activity assay involving epithelial and fibroblast cells cocultured for 10 d [17]. All extracts tested inhibited both isoforms of 5 $\alpha$ -reductase (Fig. 1), although

there was marked variation in potency between the different extracts and between different batches of the same extracts. This is highlighted in the half maximal inhibitory concentrations, with Permixon being the most active inhibitor of both isoforms of 5 $\alpha$ -reductase and Prostil (isoform I) and Profluss (isoform II) being the least active inhibitors (Table 2). More recently, we repeated this study by comparing the potency of lipidosterolic extracts from 10 different brands of *Serenoa repens* from a number of different countries including Argentina, China, France, Mexico, Panama, Poland, Russia,

**Table 2 – Activity of *Serenoa repens* extracts on inhibition of 5 $\alpha$ -reductase types I and II (half maximal inhibitory concentration in micrograms per millilitre)**

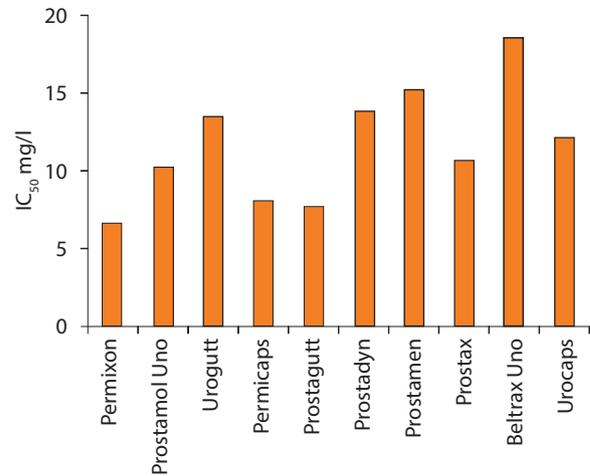
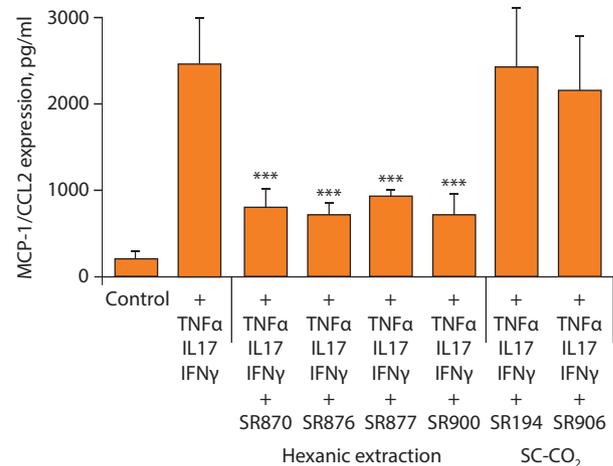
Extract	5 $\alpha$ -reductase type I	5 $\alpha$ -reductase type II
Permixon batch 1	6.836	3.841
Permixon batch 2	6.979	4.313
Saba batch 1	12.54	23.40
Saba batch 2	8.170	23.02
Serpens batch 1	9.132	9.237
Serpens batch 2	7.934	25.37
Idiprost batch 1	12.63	45.47
Idiprost batch 2	25.50	471.5
Prostamev batch 1	10.77	22.99
Prostamev batch 2	15.07	48.45
Profluss batch 1	12.95	908.4
Profluss batch 2	132.4	347.2
Prostil batch 1	161.4	513.1

Adapted from [17] with permission from Karger Publishers.

and Thailand [12]. All extracts inhibited 5 $\alpha$ -reductase I and II isoenzymes and fibroblast proliferation (after induction by human fibroblast growth factor), but there were marked differences between the various brands, with Permixon being the most potent. Figure 2 shows the inhibitory effects of the various products for 5 $\alpha$ -reductase I; Permixon was the most active extract in this model ( $p < 0.05$ – $0.001$ ). The qualitative and quantitative variation in bioactivity among the products tested is almost certainly related to differences in the levels of active constituents. This was highlighted by Raynaud and colleagues in a study that measured inhibition of 5 $\alpha$ -reductase I and II by the free fatty acid ingredients of Permixon [18]. The long-chain unsaturated fatty acids oleic and linoleic acid (two-thirds of total Permixon composition) were active against 5 $\alpha$ -reductase I and, to a lesser extent, against 5 $\alpha$ -reductase II. Saturated lauric acid was active against both isoforms of 5 $\alpha$ -reductase, whereas myristic acid was active against 5 $\alpha$ -reductase II. Palmitic and stearic acids, esterified fatty acids, alcohols, and sterols were inactive against both isoforms of 5 $\alpha$ -reductase. Although *Serenoa repens* exhibited some  $\alpha_1$ -adrenoceptor activity in vitro, at therapeutic doses it did not antagonise the  $\alpha_1$ -adrenoceptors in humans [19].

### 3.4. *Serenoa repens* in the treatment of benign prostatic hyperplasia

The prostatic inflammation observed in patients with BPH is associated with cytokine release, which creates a proinflammatory environment and a state of relative hypoxia due to the increased oxygen demand of proliferating cells [20]. Cytokines and growth factors released from inflammatory cells may interact not only with immune effectors but also with stromal and epithelial cells. In turn, epithelial cells have been shown to release inflammatory mediators [21]. Latil and colleagues compared the anti-inflammatory effects of the hexanic lipidosterolic extract of *Serenoa repens* (Permixon) with that of the supercritical CO<sub>2</sub> extract using cultured human prostate and vascular cell lines [16]. The hexanic

**Fig. 2 – Half maximal inhibitory concentration values for inhibition of 5 $\alpha$ -reductase I by 10 extracts of *Serenoa repens* [12]. IC<sub>50</sub> = half maximal inhibitory concentration.****Fig. 3 – Effects of different extracts of *Serenoa repens* on monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL-2) protein expression in prostate myofibroblastic cells. Batches 870, 876, 877, and 900 were obtained by hexanic extraction (Permixon), and batches 194 and 906 were obtained by supercritical CO<sub>2</sub> extraction. Data presented as mean plus SD (bar). \*\*\*  $p < 0.001$ . Reproduced with permission from John Wiley and Sons, Inc. [16]. IFN $\gamma$  = interferon  $\gamma$ ; IL17 = interleukin 17; SC = supercritical; SR = *Serenoa repens*; TNF $\alpha$  = tumour necrosis factor  $\alpha$ .**

extract inhibited the early steps of leukocyte infiltration in vitro by downregulating monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL-2) and vascular cell adhesion protein-1 (VCAM-1) expression. It also inhibited tumour necrosis factor  $\alpha$ -induced MCP-1/CCL-2 secretion by human vascular cells and surface VCAM-1 protein expression in a concentration-dependent manner. Under proinflammatory conditions, the hexanic extract of *Serenoa repens* produced maximal inhibition of MCP-1/CCL-2 protein expression, whereas the supercritical CO<sub>2</sub> extract did not significantly inhibit MCP-1/CCL-2 expression (Fig. 3).

Experimental findings support the potential of *Serenoa repens* in BPH, and various mechanisms of action have been postulated. These include inhibition of 5 $\alpha$ -reductase activity, modulation of androgen-receptor binding, inhibition of  $\alpha$ -receptor binding, inhibition of eicosanoid synthesis, and spasmolytic and anti-inflammatory effects. The activity

**Table 3 – Outcome of studies of *Serenoa repens* ranked by type of extract (only extracts on the European market)**

Type of extract	Outcome	Reference
Ethanol extract	Negative (PL-controlled)	[22]
Hexane extract	Equivalence (T, SR, T+SR)	[23]
	Positive (Meta-analysis: N=17)	[24]
	Equivalence (T)	[25]
	Equivalence (T, T+SR)	[26]
	Equivalence (F)	[27]
	Positive (PL-controlled)	[28]
	Negative (PL-controlled)	[29]
	Positive (PL-controlled)	[30]
	Positive (PL-controlled)	[31]
	Positive (PL-controlled)	[32]
Positive (PL-controlled)	[33]	
Positive (PL-controlled)	[34]	
Supercritical CO <sub>2</sub>	Positive (PL-controlled)	[35]

Adapted from [10] by permission from the European Medicines Agency.  
 F = finasteride; N = number of studies; PL = placebo; SR = *Serenoa repens*;  
 T = tamsulosin.

level may differ from one extract to another, probably due to the fatty acid content, which can influence the clinical efficacy of the different available brands [10]. In a recent monograph of *Serenoa repens* published by the European Medicines Agency (EMA), it was concluded that available evidence for the hexane extract (Permixon) supported its use as a “well-established medicinal product with recognised efficacy and acceptable safety,” whereas data for the ethanolic and supercritical CO<sub>2</sub> extracts were insufficient to support such a conclusion [10,22–35] (Table 3). By contrast, a recent Cochrane systematic review in which data for the various brands of *Serenoa repens* were combined reported no improvement in LUTS compared with placebo, although the authors were uncertain whether this conclusion could be extrapolated to proprietary products such as Permixon [36]. The EMA suggested that the methodology of the review was flawed, given the compositional differences of the various brands included in the analysis [10]. A review of the evidence cited on PubMed found that 51 of the 81 (63%) clinical trials of *Serenoa repens* involved the hexanic extract (Permixon).

#### 4. Conclusions

A review of current best evidence in the literature enabled a number of general recommendations to be made regarding herbal medicines. Quality assurance is a key consideration. It is important to use herbal medicines produced by larger companies because these are more likely to be of higher quality and to have been rigorously tested (to protect the company’s reputation). Standardising herbal medicines to contain specific amounts of active constituent is very important. Finally, the safety profile of herbal products needs to be clearly defined, including the potential for drug–drug interactions, because the products are not always as innocuous as might be perceived.

*Serenoa repens* is an example of an herbal medicine that highlights some general concerns in the area. Many different brands of *Serenoa repens* are available, and at least three different extraction processes are used to produce the

active medicine (hexanic, ethanolic, and supercritical CO<sub>2</sub> extraction). There are marked differences among extracts in terms of their pharmacological activity and clinical efficacy. At the present time, the EMA supports the use of only the mostly widely studied product, the hexanic lipidosterolic extract, which includes products such as Permixon.

#### Conflicts of interest

F. Scaglione has received fees for serving as a speaker and/or consultant for Astellas, Bayer, MSD, and Sanofi-Aventis within the past 3 yr.

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#### Appendix A

Manufacturers for the various *Serenoa repens* products mentioned in this article:

Beltrax Uno (Belienda, Argentina)  
 Idiprost (IdiPharma, Italy)  
 Permixon (Bago, Argentina)  
 Permixon (Pierre Fabre Médicament, France),  
 Profluss (KonPharma, Italy)  
 Prostadyn (Dr Dunner, China)  
 Prostagutt (Schwabe Pharma, Russia)  
 Prostagutt uno (Willmar Schwabe, Germany)  
 Prostamen (Ancalmo, Panama)  
 Prostamev (Farmaceutica MEV, Italy)  
 Prostamol Uno (Berlin Chemie, Poland)  
 Prostamol uno (Berlin-Chemie, Germany)  
 Prosta-urgenine (Hoyer-Madaus, Germany)  
 ProstaX (Interfarma Corporation, Panama)  
 Prosteren (Sirton Pharmaceuticals, Italy)  
 Prostess (TAD Pharmazeutisches Werk, Germany)  
 Prostil (AccaPharma, Italy)  
 Quanterra prostate (Warner-Lambert, NJ, USA)  
 Ratiopharm uno (Ratiopharm, Germany)  
 Rilaprost (Guidotti, Italy)  
 Saba (Lampugnani Farmaceutici, Italy)  
 Saba (Lampugnani, Italy)  
 Serpens (Lisapharma, Italy)  
 Sita (Hoyer-Madaus, Germany)  
 Solaray (Nutraceutical Corporation, UT, USA)  
 Strogen uno (Strathmann, Germany)  
 Talso uno (Sanofi Winthrop, PA, USA).  
 Urocaps (Division Fitoterapeutica, Mexico)  
 Urogutt (Farmasa Schwabe, Thailand)

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