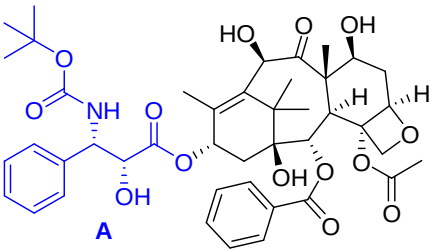
III. Case Studies-Facts

This section will discuss patent strategies that companies undertake in the course of developing a drug. This study will be conducted by highlighting the patent portfolio of two randomly selected successful drugs whose basic patent protection has been expired: Taxotere® and Xalatan®.[29]

A. Taxotere

1. General

Docetaxel (brand name Taxotere) is an "anti-mitotic agent" (Formula 1) the administration of which causes the "inability of cells to divide".[30]

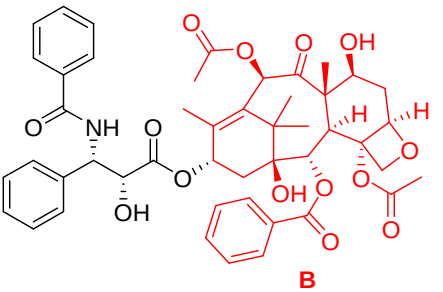


Formula 1

29 The trademarks are property of their respective owners and are used throughout the remainder of the thesis without the symbol ®.

30 A. Sulkes, J. Smyth, C. Sessa, L.Y. Dirix, J.B Vermorken, S. Kaye, J. Wanders, H. Franklin, N. LeBail, J. Verweij, *Docetaxel (Taxotere), in advance gastric cancer: results of a phase II clinical trial*, 70 British Journal of Cancer 380, (1994).

The compound has been originally disclosed in EP 0253738 A1[31] belonging to Rhone-Poulenc Santé and market approval in Europe was obtained in November 1995.[32] The patent protection for the basic compound expired in November 2010 in U.S. and European countries. The compound is obtained semi-synthetically as much of its core structure is obtained by extraction (of baccatin III or desacetyl 10-baccatin III) of the needles or bark of the European yew tree (*Taxus baccata* L.). It was designed as an alternative to the drug Taxol (paclitaxel) (Formula 2) which was obtained by extraction of the bark of the American yew tree (*Taxus brevifolia*). This tree is however less abundant, slower growing and its harvesting was strongly opposed by environmentalists and raised the issue of biodiversity conservation.[33]



Formula 2

The disclosure of docetaxel for the first time offered a sustainable access to the compound class and allowed for widespread use in the

31 The application was filed in July 1987 invoking a French application priority: FR 8610400, filing date 17 July 1986, published as FR 2601675 A1.

32 In 1995 centralized procedure for cancer drugs was optional: see Council Regulation (EEC) 2309/93, art 3(2) 1993, O.J. (L 214) 1, 163 and Part B of the Annex; now centralized procedure compulsory for cancer medicines approved after November 2005: see *supra* note 17, Annex at 51.

33 George Frisvold & Kelly Day-Rubenstein, *Bioprospecting and Biodiversity Conservation: What happens when discoveries are made?*, 50 Ariz. L. Rev. 545, 565-567, (2008).

treatment of various types of cancer, including breast, ovarian and non-small cell lung cancer.[34]

2. Patent Portfolio

a) Process

The synthetic procedure, disclosed in the basic patent family, while allowing for the production of larger amounts of docetaxel was however still far from being optimal since it involved an unselective reaction step with a consequent substantial loss of product. A company, which has to produce material for the various clinical studies and for a possible launch, therefore needs to address this issue as can be seen by the large number of successive patents in this area. E.g. EP 0336841 A1[35] disclosed an optimized synthesis which is no longer based on a late-stage reaction with poor selectivity, but introduces the synthetic fragment (A) (side-chain: Formula 1) as complete building block. Hence, any difficult reaction step potentially involving a loss of material is carried out before the valuable core (baccatin III) (B, Formula 2) extracted from the natural source is brought into play. This improved process found by the Rhone-Poulenc group demonstrates therefore a significant advantage, both from the technical (less difficult) and the economic (less material loss) point of view.

Successive patents[36] in the period from 1989 to 1994 deal with several alternative preparations of the fragment (A). Moreover, research was also directed towards the improvement of joining the two

34 O. Esposito, M. Bonfill, E. Moyano, M. Onrubia, M.H. Mirjalili, R.M. Cusidó, J. Palazón, *Biotechnological Production of Taxol and Related Taxoids: Current State and Prospects*, 9 Anti-Cancer Agents in Medicinal Chemistry 109, 110, (2009).

35 Filed in October 1989, French priority: FR 8804513, (06 April 1988).

36 WO 91/13066, WO 93/04038, WO 93/17997, WO 94/07847, WO 94/22813 and WO 94/24103.