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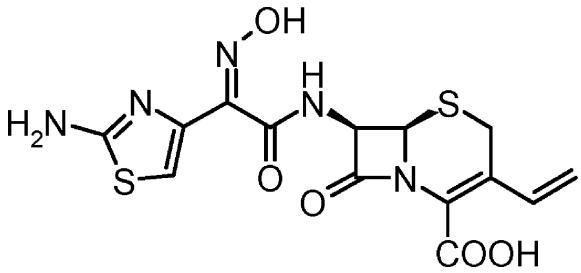

Cefdinir

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Reviews

Polymorphisms and Patent, Market, and Legal Battles: Cefdinir Case Study

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Abstract:

The ongoing patent battle relating to Cefdinir polymorphism and crystalline forms is described from a scientific point of view. This case study illustrates some of the strategies adopted by generic bulk manufacturers to challenge originator's patents on polymorphic forms.

Introduction

As the discovery of new medicines with novel modes of action becomes increasingly rare and expensive, large pharmaceutical companies are focusing ever more on the life-cycle management of their existing drug products. In this context, the filing of patents claiming new crystalline forms, usually 4−6 years after the original product patent, is a typical strategy applied by such companies to extend patent protection. This patent protection approach by big pharma forces generic bulk producers to discover and file patents on new polymorphs if they want to market the drug after expiry of the product patents. The object of this paper is to illustrate, through a case study discussion, the challenges being faced by the current Intellectual Property protection system. The case study surrounds Cefdinir (**1**) (Figure 1) and describes the strategies adopted by 8 companies in the filing of 11 patents relating to 5 possible crystalline forms.

Fujisawa and Cefdinir Crystalline Forms

Cefdinir (**1**) is a powerful antibiotic discovered by Fujisawa (now part of Astellas),[1,2] AND extensively used in antibacterial treatment with a worldwide (mainly the United States and Japan) turnover of 400 MUSD.[3] This oral cephalosporin is highly stable against β-lactamase with an excellent antibacterial activity against both Gram positive and Gram negative bacteria.[4]

Polymorphism is of paramount importance due to its effect on some physical characteristics of powders such as melting point, flowability, vapour pressure, bulk density, chemical reactivity, apparent solubility and dissolution rate, and optical and electrical properties. In other words, polymorphism can affect drug stability, manipulation, and bioavailability.[5]

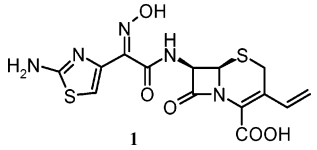

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Figure 1. **Cefdinir.**

Cefdinir (**1**) is marketed in two oral formulations: capsules and oral suspension.[2] The patent strategy adopted by Fujisawa to protect the life cycle of Cefdinir (**1**) was based on the filing of a second patent, several years after the product patent, covering the commercialised anhydrous crystalline form of the drug. As a consequence, to overcome the Cefdinir (**1**) patent protection of the U.S. and Japanese markets, generic bulk producers had to discover a new crystalline form, with the same bioavailability as the marketed one. The situation, with competition among several companies, resulted in the generation of a patent "tangle". In addition to overcoming the Fujisawa patent, the principal aim of generic bulk producers was to generate a competitive market advantage by protecting their new crystal form. In this paper we shed light on the Cefdinir (**1**) polymorphism from both a scientific and a legal point of view.

Product Patent

Cefdinir (**1**) patent protection analysis clearly shows some peculiarities. The Fujisawa Legal Office focused their attention on the main markets, namely the United States and Japan. In the original product patent, the physical properties of the powder were not fully described, and a simple IR spectra was reported.[6] The product patent expiration date was successfully extended by Fujisawa through filing a patent

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(1) Inamoto, Y.; Chiba, T.; Kamimura, T.; Takaya, T. *J. Antibiot.* **1988**, *41*, 828.

(2) NDA 50-749. [Fujisawa (Astellas) Parke Davis (Abbott)] approved by the FDA 1999. See www.fda.gov.

(3) IMS data 2004.

(4) (a) Mine, Y.; Kamimura, T.; Watanabe, Y.; Tawara, S.; Matsumoto, Y.; Shibayama, F.; Kikuchi, H.; Takaya, T. *J. Antibiot.* **1988**, *41*, 1873. (b) Mine, Y.; Yokota, Y.; Wakai, Y.; Kamimura, T.; Tawara, S.; Shibayama, F.; Kikuchi, H. *J. Antibiot.* **1988**, *41*, 1888. (c) Sakamoto, H.; Hirose, T.; Nakamoto, S.; Hatano, K.; Shibayama, F.; Kikuchi, H.; Mine, Y. *J. Antibiot.* **1988**, *41*, 1896. (d) Mine, Y.; Kamimura, T.; Sakamoto, H.; Tawara, S.; Hatano, K.; Watanabe, Y.; Kuwahara, S. *Chemotherapy* **1989**, *37*, 122. (e) Shimada, K.; Shishido, R.; Kakuno, M. *Chemotherapy* **1989**, *37*, 208.

(5) (a) Special feature section devoted to crystallization and polymorphism: *Org. Process Res. Dev.* **2000**, *6*, 957−1027. (b) Bernstein, J. *Polymorphism in Molecular Crystal*; Oxford University Press: New York, 2002. (c) Byrn, S. R.; Pfeiffer, R. R.; Stowell, J. G. *Solid State Chemistry of Drugs*; SSCI: West Lafayette, 1999.

(6) In Europe: (a) Takaya, T.; Takasugi, H.;Masugi, T.;Yamanaka, H.; Kawabata, K. EP105459 (filed September 1983, priorities UK 8323034 filed 26 August 1983, and U.S. Patent 8,323,034 filed 30 September 1982). In the United States: (b) Takaya, T.; Shirai, F.; Nakamura, H.; Inaba, Y. U.S. Patent 4,559,334 (filed 20 October 1983).

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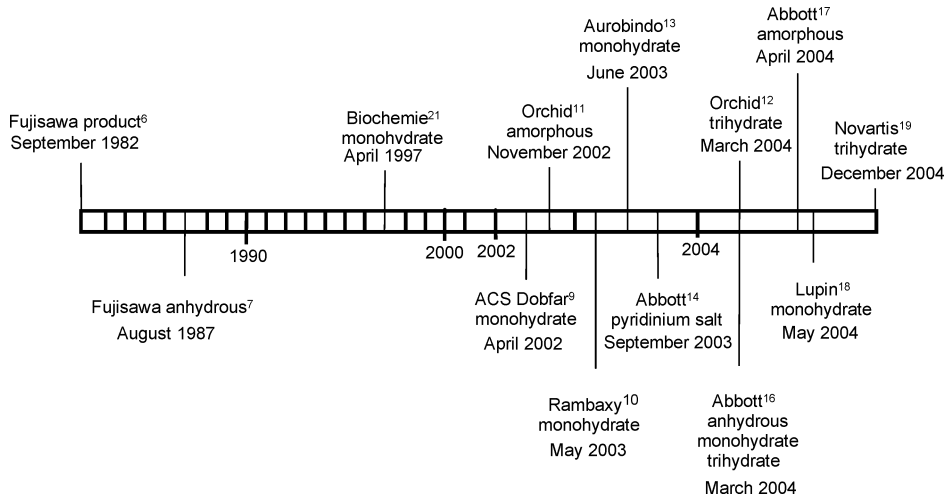


Figure 2. **The priority filing dates of all the patents claiming Cefdnir crystalline forms are reported.**

claiming the marketed crystalline form of Cefdinir (**1**), the anhydrous one.[7] The new polymorph was characterized by IR and X-ray powder diffraction (XRPD). This patent extended the protection of Cefdinir (**1**) marketed in the United States up to December 2011, 9 years after the expiration of the patent covering the structure.[6]

The aggressive market protection approach by Astellas, the new Japanese pharmaceutical giant formed by the merger of Fujisawa and Yamanouchi, was exemplified by the filing of a patent infringement lawsuit on September 15, 2005, with the Tokyo District court against Taiyo Yakuhin Co., Ltd., demanding that Taiyo stop infringing Astellas's patent rights on its oral cephalosporin antibiotic Cefdinir (**1**). In fact, Taiyo had obtained an NHI (Nation Health Insurance) price for an oral Cefdinir (**1**) capsule preparation under the trade name of CEFLOSIL in July 2005. Astellas used the patent on the crystalline form of the drug, valid until August 2008 in Japan, to prevent Taiyo commercialising CEFLOSIL.

Fujisawa adopted a completely different patent strategy in Europe, filing a European Patent in only four states (Germany, Luxembourg, Netherlands, and Sweden). In Italy and Austria, where the main bulk generic companies producing β-lactams are located, Fujisawa filed country patents.[8] The Supplementary Protection Certificate (SPC) was obtained only for the European version of the product patent. The expiration date of the SPC for the product patent claiming the structure and for the anhydrous crystal form are very close, respectively September and August 2008. In Italy and Austria, it has been possible to produce and market Cefdinir (**1**) with a crystalline form different from that of the anhydrous from 2003, as Fujisawa did not file an SPC in these countries.

The "Tangle"

A brief description of the patent applications filed by several generic companies is reported below (see also Figure 2). In addition to generic producers, Abbott, the U.S. commercial partner of Astellas, tried to protect the U.S. market from generic companies up to 2011, claiming several new polymorphs. The crystallization experiments described in the following patent applications have been repeated by us in order to verify the reproducibility of the procedures described. In Tables 1 and 2, all the data reported in the patent applications and some results of our experiments to reproduce the conditions described in the ACS Dobfar, Biochemie, and Fujisawa patents are compared.

1. ACS Dobfar US2003/0204082 (Italian priority MI2002A 000913 filed 29 April 2002).[9]

ACS Dobfar filed a patent covering a new crystal form of Cefdinir (**1**), which was characterized as having 6% water and an XRPD pattern completely different from the Fujisawa anhydrous form (see Table 2, ACS Dobfar 2Φ lines are completely different with respect to the Fujisawa anhydrous crystal form). Interestingly, ACS decided to extend the original Italian application in only three countries, namely the United States, Canada, and Japan but not in Europe. The USPTO evaluated the patent, and there are now two divisions of the original application covering respectively the new polymorph and the crystallization process. In the patent text, the Fujisawa anhydrous crystalline material was called form A, and in the ACS one it was simply the new polymorph. For unknown reasons the International Patent report on the following patents ignored this application. The reproduction in our laboratories of experiment 1 of ACS patent afforded Cefdinir (**1**) with a water content of approximately 6% and the same XRPD reported in claim 1.

2. Ranbaxy WO2004/104010 (priority IN2003DE0000711 filed 20 May 2003).[10]

The PCT application (May 2004) of Ranbaxy claimed a new crystalline form of Cefdinir (**1**) "Form R" with a moisture content of 6.19%. The powder was characterized by XRPD, IR, and DSC. The process to generate form R was reported, and the crystallization conditions appeared very

(7) In Europe: Takaya, T.; Shirai, F.; Nakamura, H.; Inaba, Y. EP304019 (filed 17 August 1988, priority JP206199 19 August 1987)). In the United States: U.S. Patent 4,935,507 (filed 8 August 1988) extended by the Waxman Hatch provision up to 4 December 2011.

(8) Italy: Antibioticos, ACS Dobfar, Pharmabios and Ribbon. Austria and Germany: Sandoz.

(9) Manca, A.; Sala, B.; Monguzzi, R. US2003/0204082 (filed 3 April 2003, priority Italy MI2002A 000913 filed 29 April 2002).

(10) Kumar, Y.; Prasad, M.; Prasad, A.; WO2004/104010 (filed 20 May 2004, priority IN2003DE0000711 filed 20 May 2003).

Table 1. **Comparison of XRPD reported in patents 1, 2, 5, 7, and 9 versus data generated by reproducing experiments described by Fujisawa U.S. Patent 4,559,334 exp 14 and/or Biochemie U.S. Patent 6,350,869 exp 2[a]**

ACS Dobfar[9] new form U.S. Patent 2003/0204082 patent 1			Fujisawa[6] Exp 14 U.S. Patent 4559334 Or Biochemie[21] U.S. Patent 6350869 Exp 2[b]		Rambaxy[10] Form R W02004/104010 patent 2	Aurobindo[13] Form B U.S. Patent 2004/0242556 patent 5			Abbott[16] lower hydrate W02005/090361 patent 7		Lupin[18] new form U.S. Patent 2005/0245738 patent 9	
d-spacing Å	relative intensity	2Φ	2Φ	relative intensity	2Φ	2Φ	*d*-spacing Å	relative intensity	2Φ	relative intensity	*d*-spacing Å	relative intensity
15.24	30	5.9	5.9	32.9		5.8	15.16	24	6.0	26	15.07	37.52
11.30	18	7.8	7.8	37.3		7.8	11.38	30			11.33	31.89
10.92	18	8.1	8.1	28.4		8.0	11.2	30	8.0	2	10.96	25.12
			11.2	20.8								
7.51	100.0	11.8	11.7	100.0	11.72	11.7	7.55	100	11.9	100	7.52	100.00
5.66	24	15.6	15.6	33.6		15.6	5.68	41			5.65	17.19
									15.9	2		
5.48	55	16.2	16.1	55.5		16.1	5.50	61	16.4	24	5.47	42.18
											4.90	10.77
4.76	96	18.6	18.6	33.1	18.58	18.6	4.77	43			4.76	43.54
4.55	44	19.4	19.4	21.6		19.4	4.58	24			4.56	18.38
4.23	71	21.0	21.0	35.6	20.92	20.9	4.24	33			4.23	38.46
4.17	85	21.2	21.2	39.5	21.2	21.2	4.19	43			4.18	33.31
3.99	74	22.3	22.3	55.9	22.28	22.3	3.99	60	22.4	21	3.98	41.54
			23.1	27.0					23.0	3		
3.74	18	23.7	23.6	11.1							3.75	5.77
3.64	78	24.5	24.4	43.5	24.42	24.4	3.64	43			3.63	35.03
3.53	24	25.1	25.1	12.1							3.54	9.09
3.46	72	25.7	25.7	33.9		25.6	3.47	37			3.46	29.93
3.39	85	26.3	26.3	44.5	26.24	26.2	3.40	41			3.39	34.30
3.26	14	27.3	27.4	9.0							3.27	3.19
3.17	21	28.0	28.1	15.9							3.18	8.88
			28.6	22.1								
3.08	37	29.0	28.8	21.3							3.08	18.07
2.96	10	30.2	30.1	13.2							2.96	5.86
2.89	23	31.0	31.0	18.7							2.88	16.56
2.82	69	31.7	31.7	21.6							2.82	16.06
2.81	42	31.7	33.3	7								
2.63	13	34.2	34.1	20.7							2.62	12.87
2.57	21	35.0	34.9	19.1							2.56	14.96
2.54	18	35.1	35.1	18.6								
			35.7	8.6								
2.39	8	37.4	37.5	16.3							2.40	7.04
			38.3	13.0								
			38.8	13.0								
2.31	17	39.1	39.0	13.0							2.30	12.91
1.99	25	45.5	45.5	10.1							1.99	5.22
1.97	10	46.0	46.1	19.1							1.97	9.12

[a] The relative standard deviation considered for 2Φ is ±0.2. [b] The XRPD pattern reported in the table was obtained from Cefdinir (**1**) generated following the experiments described by Fujisawa and Biochemie.

similar to the ones described by ACS Dobfar [Cefdinir concentration (33 g/L versus 33 g/L), temperature (3−4 °C versus 0−2 °C), and pH (2.4 versus 2)]. The only difference was the absence of any organic solvent.

3. Orchid WO2004/046154 (priorities IN848/MAS/2002 and IN152/mas/2003 filed 15 November 2002 and 26 February 2003 respectively).[11]

Orchid claimed in the PCT application a novel hydrate (4−5% of moisture) amorphous form of Cefdinir (**1**) and reported the XRPD. The reproduction in our laboratories of example 4 afforded a Cefdinir (**1**) amorphous form identical to the one described by Orchid. The water content was related to the drying conditions (temperature and time).

4. Orchid WO2005/090360(priority IN247/MAS/2004 filed 19 March 2004).[12]

In this second patent, Orchid researchers claimed, on the basis of XRPD and IR spectra, a new crystalline form of Cefdinir (**1**) with 14% moisture.

5. Aurobindo US2005/0137182 (priority IN440/MAS/2003 filed 2 June 2003).[13]

(11) Deshpande, P. B.; Khadangale, B. P.; Ramasubbu, C. WO2004/046154 (filed 10 November 2003, priorities IN848/MAS/2002 and IN152/mas/2003 filed respectively 15 November 2002 and 26 February 2003).

(12) Chandrasekaran, R.; Senthilkumar, K.; Murugan, S.; Sivaiah Sangaraju, V. R.; Reddy, G. O. WO2005/090360 (filed 15 March 2005, priority IN247/MAS/2004 filed 19 March 2004).

Table 2. **Comparison of XRPD reported in patents 4 and 7 versus data reported by ACS Dobfar monohydrate and Fujisawa anhydrous forms[a]**

ACS Dobfar[9] monohydrate U.S. Patent 2003/0204082 patent 1		Fujisawa[7] anhydrous U.S. Patent 4935507 1−2% KF		Abbott[16] W02005/090361 patent 7						Orchid[12] U.S. Patent 20050900360 patent 4		Novartis[19] U.S. Patent 2006/0122165 patent 10	
				trihemihydrate 14% KF		lower hydrate 1.7−6.1% KF		anhydrous					
2Φ	relative intensity	2Φ	relative intensity	2Φ	relative intensity	2Φ	relative intensity	2Φ	relative intensity	2Φ	relative intensity	2Φ	relative intensity
				5.4	13			5.5	66	5.3	8.4	5.3	11
5.9	30					6.0	26						
7.8	18												
8.1	18					8.0	0						
										8.4	8.3	8.4	4
				10.7	100			10.9	100	10.6	100	10.6	100
11.8	100.0	11.8	15			11.9	100			11.9	19.0		
		12.6	16					12.6	20				
				14.2	24					14.1	35.0	14.1	21
		14.7	66					14.7	62				
				15.2	8					15.1	12.7	15.1	5
15.6	24					15.9	23						
16.2	55					16.4							
		16.6	16					16.6	13				
		17.8	49										
18.6	96									18.6	10.7		
		18.9	24							19.0	7.0		
19.4	44	19.2	18										
21.0	71												
21.2	85	21.5	100	21.4	13					21.3	24.8	21.3	16
		22.0	66					21.8	8	22.2	8.2	23.7	12
22.3	74					22.4	23						
						23.0	0						
		23.4	38										
23.7	18									23.7	21.5		
										24.0	12.3	24.0	12
24.5	78	24.5	77							24.6	8.2	24.6	11
25.1	24												
		25.4	20										
25.7	72									25.8	15.2		
26.3	85											26.3	17
		26.9	8										
27.3	14							27.3	19				
		27.7	18							27.5	32.7	27.5	19
28.0	21	28.1	36										
										28.4	13.9	28.3	13
										28.6	17.7	28.6	13
29.0	37			29.2	7					29.2	7.9	29.2	12
		29.7	15										
10	30.2												
				30.6	5					30.6	6.2	30.5	7
31.0	23												
31.7	69											31.6	7
31.7	42									32.2	5.8	32.2	9
34.2	13												
35.0	21												
35.1	18												
										36.0	7.6	35.9	7
37.4	8												
39.1	17									39.0	7.2		
45.5	25												
46.0	10												

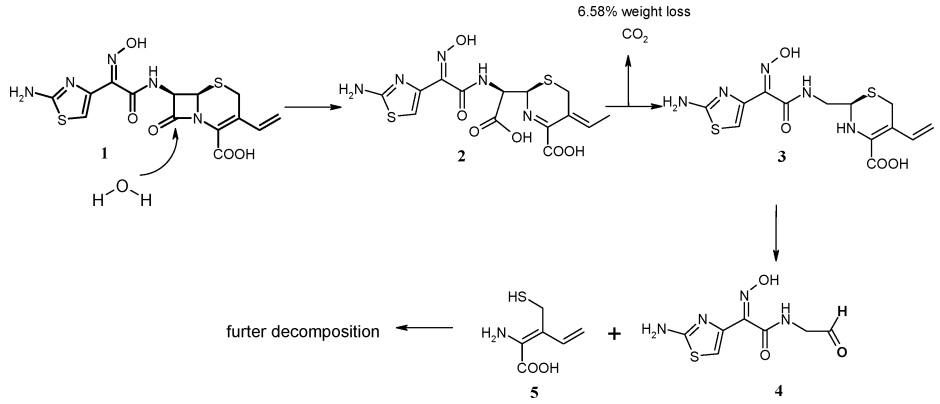
[a] The relative standard deviation considered for 2Φ is ±0.2.

The authors claimed a new crystalline form of Cefdinir called "Form B", different from the original form A described in the Fujisawa patent. The powder was characterized by X-ray and IR spectra and contained 5.5−7% moisture.

(13) Dandala, S.; Sivakumaran, S. US2005/0137182 (filed 29 October 2004, priority IN440/MAS/2003 filed 2 June 2003).

Aurobindo researchers described material obtained in the original product patent by Fujisawa (U.S. Patent 4,559,334) as: "crystalline like amorphous product, not a crystalline product". From a scientific point of view this phrase is meaningless. The patent application was extended only in the United States.

Scheme 1



6. Abbott US2005/0059818 (priority US2003000661148 filed 12 September 2003).[14]

In this U.S. application, Abbott researchers claimed a new form of Cefdinir (**1**). The product was characterized by XRPD. Interestingly, they later discovered that the product was a pyridinium salt, and the original application was subjected to a continuation in part. This last application claimed correctly the pyridine salt.[15]

7. Abbott WO2005/090361 (U.S. priority 16 March 2004).[16]

The same researcher filed a patent claiming three different forms of Cefdinir (**1**) the "trihemihydrate" (14% moisture), "anhydrate" (0% moisture), and "lower hydrate" (1.7−6.1% moisture) based on water content and XRPD. The amount of water described for the trihemihydrate form (14%) and what the XRPD reported (Table 2) were similar to that claimed for the Orchid polymorph. Abbott anticipated Orchid by 3 days, 16 March 2004 versus 19 March 2004. The procedures described by Abbott researchers to get the trihemihydrate and lower hydrate are not applicable for the claimed pharmaceutical application, and surprisingly, the protocol to obtain the "anhydrate" form was not described.

8. Abbott WO05100368 (priority US2004000821695 filed 9 April 2004).[17]

Abbott researchers claimed a novel amorphous form of Cefdinir (**1**). This patent is a replica of the one filed by Orchid (patent 4), although in this case, Orchid anticipated Abbott by a year. The process described was based on the transformation of Cefdinir (**1**) monohydrate with methanol to get the amorphous form. The definition of the polymorph by Orchid in patent 3, "amorphous hydrate" is meaningless as it is an amorphous form of a hygroscopic material.

9. Lupin US2005/0245738 (priority US10/838431 filed 3 May 2004).[18]

The authors claimed a new crystalline form of Cefdinir (**1**) with a moisture range of 6−7%. The material was characterized by XRPD and IR spectra. The reproduction in our laboratories of example 2 generated the reported crystalline form.

10. Novartis (former Biochemie) US2006/0122165 (priority GB0426837.1 filed 7 December 2004).[19]

Novartis researchers claimed a trihydrate crystalline form of Cefdinir (**1**) and the corresponding process to make it. The XRPD that is claimed is identical to the one claimed by Abbott (patent 7, " trihemihydrate") and Orchid (patent 4), see Table 2. Novartis was anticipated by both Abbott and Orchid.

Hydrates and Cephalosporins

Several cephalosporins have been isolated and commercialised as crystalline hydrate forms: ceftriaxone disodium hemiheptahydrate, ceftazidime pentahydrate, cephalexin monohydrate, cefadroxil mono- and hemihydrate, cefixime trihydrate. In the case of cephalosporins, the presence of water, not tightly coordinated and packed inside the crystal lattice, can generate several problems. In addition to the potential modification of the crystalline structure through the loss of water molecules at any step of the production process, the presence of water decreases the shelf life of the bulk even in the solid state. In fact, the main decomposition processes of cephalosporins are based on nucleophilic attack on the β-lactam nucleus, see Scheme 1. The comparison of XRPD patterns showed that Cefdinir anhydrous monohydrate and poly-(3 or 3.5 mol of H_2O)hydrate are completely different crystalline forms.[20]

The trihemihydrate or trihydrate" form described by Orchid (patent 4),[12] Abbott (patent 7),[16] and Novartis (patent 10)[19] or the amorphous one, again described by Orchid (patent 3)[11] and Abbott (patent 8),[17] contains a consistent

(14) Duerst, R. W.; Law, D.; Lou, X. US2005/0059818 (priority US2003000661148 filed 12 September 2003).
(15) Duerst, R. W.; Law, D.; Lou, X. US2005/0113355 (filed 14 September 2004 divisional of 14).
(16) Law, D.; Henry, R. F.; Lou, X. WO2005/090361 (filed 7 March 2005, priority United States 16 March 2004).
(17) Server, N. A.; Law, D. WO2005/100368 (filed 11 April 2005, priority United States 9 April 2004).
(18) Singh, G. P.; Sen, H.; Srivastava, D.; Godbole, H. M.; Singh, G. P.; Mahajan, P. R.; Rananaware, U. B.; Nehate, S. P.; Wagh, S. C. US2005/0245738 (priority U.S. Patent 10/838431 filed 3 May 2004).
(19) Daemon, O.; Hartmann, K.; Ranenburger, J. US2006/0122165 (filed 5 December 2005, priority GB0426537.1 filed 7 Dec 2004).
(20) (a) Cephalexin isomorphic solvates: Stephenson, G. A.; Groleau, E. G.; Kleeman, R. L.; Xu, W.; Rigsbee, D. R. *J. Pharm. Sci.* **1998**, *87*, 536. (b) Topotecan isomorphic solvates : Vogt, F. G.; Dell'Orco, P. C.; Diederich, A. M.; Su, Q.; Wood, J. L.; Zuber, G. E.; Katrincic, L. M.; Mueller, R. L.; Busby, D. J.; DeBrosse, C. W. *J. Pharm. Biomed. Anal.* **2006**, *40*, 1080 and references therein.

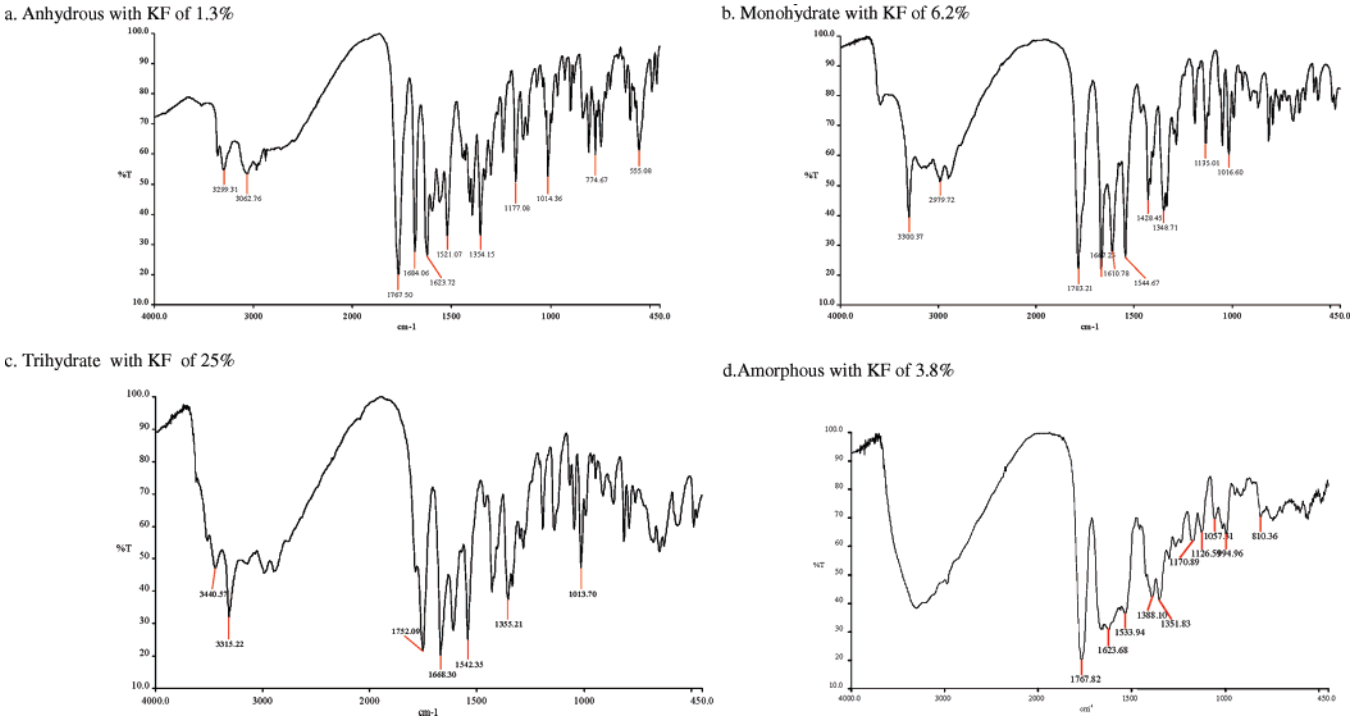


Figure 3. **IR spectra Cefdinir (1) obtained in Antibioticos labs reproducing the procedures described by Fujisawa for the anhydrous,[7] by ACS Dobfar for the monohydrate,[9] by Orchid for the trihydrate,[12] and again Orchid for the amorphous.[11] The crystalline forms were identified by XRPD FT-IR, and TGA. (a) Anhydrous with KF of 1.3%. (b) Monohydrate with KF of 6.2%. (c) Trihydrate with KF of 25%. (d) Amorphous with KF of 3.8%.**

amount of loosely bound water. Abbott researchers stated that the trihemihydrate form was unstable, being easily transformed into the lower hydrate one (monohydrate) by a simple air drying.[16] We have reproduced in our labs the Orchid procedure (example 14) and confirm the Abbott result. The water content of the wet cake was around 75%, and the XRPD was identical to the claimed one. However, this crystalline form is easily transformed into the monohydrate one. Novartis researchers clearly described the limit of the "trihydrate" form stability.[19] In fact, the product should be dried in an atmosphere with a humidity >45%. This crystalline form was described "suitable for easy handling during the manufacturing process as used in the pharmaceutical industry, particularly in countries with a humid climate".

The TGA of the amorphous material showed chemical instability. Starting from a water content of 3.8%, a 9.5% weight loss was observed between room temperature and 150 °C. A typical cephalosporin decomposition pathway under neutral conditions due to presence of water is described in Scheme 1.

Cefdinir Monohydrate XRPD

The characterization of different polymorphs is generally based on several techniques such as XRPD, IR spectra, and TGA. The only technique reported in all the patents 1−10 is the XRPD.

The XRPD of material with similar water content, around 6%, reported in the claims of application patents 1, 2, 5, 7, and 9 are almost identical. All the products obtained showed the same X-ray (Table 1), IR spectra (Figure 3), and similar TGA (Figure 4). The TGA analysis gives a lot of information with the weight loss between 25 °C and 150 °C being close to the powder water content (6.2 moisture versus 6.35 TGA weight loss, organic solvents were <0.1%). From 25 °C to 60 °C there is a weight loss corresponding to the amount of water that is not strongly bound into the crystal lattice. At 60 °C there is a clear change in the TGA slope, and the weight loss between 60 and 150 °C is around 4.35%. The amount of water in the monohydrate form corresponds to a moisture content around 4.35%.

The monohydrate form of Cefdinir (**1**) was first reported in 1997. The first CAS reference is a patent by Biochemie (now Sandoz, part of Novartis group) on Cefdinir (**1**) salts entitled "Crystalline Amine Salt of Cefdinir".[21] In example 2, Ludescher et al. stated "7-(*Z*)-[2(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-carboxylic acid (**1**) in the form of a monohydrate in a purity of 99% is obtained." The international application of the Biochemie patent was published in 1998. The reproduction of this experiment afforded Cefdinir (**1**) monohydrate identical to the powder described and obtained in the examples of patents 1, 2, 5, 7, and 9. All applicants never discussed the water content, thus avoiding any comparison with the monohydrate, and some of them invented new names or codes such as form B, form D, or lower hydrate. However, from our point of view, it is clear that the monohydrate form of Cefdinir (**1**) does not have any possibility to be claimed simply because it is not a new product.

(21) Sturm, H.; Wolf, S.; Ludescher, J. U.S. Patent 6,350,869 (filed 27 September 1999, priority AT57097 filed 4 April 1997).

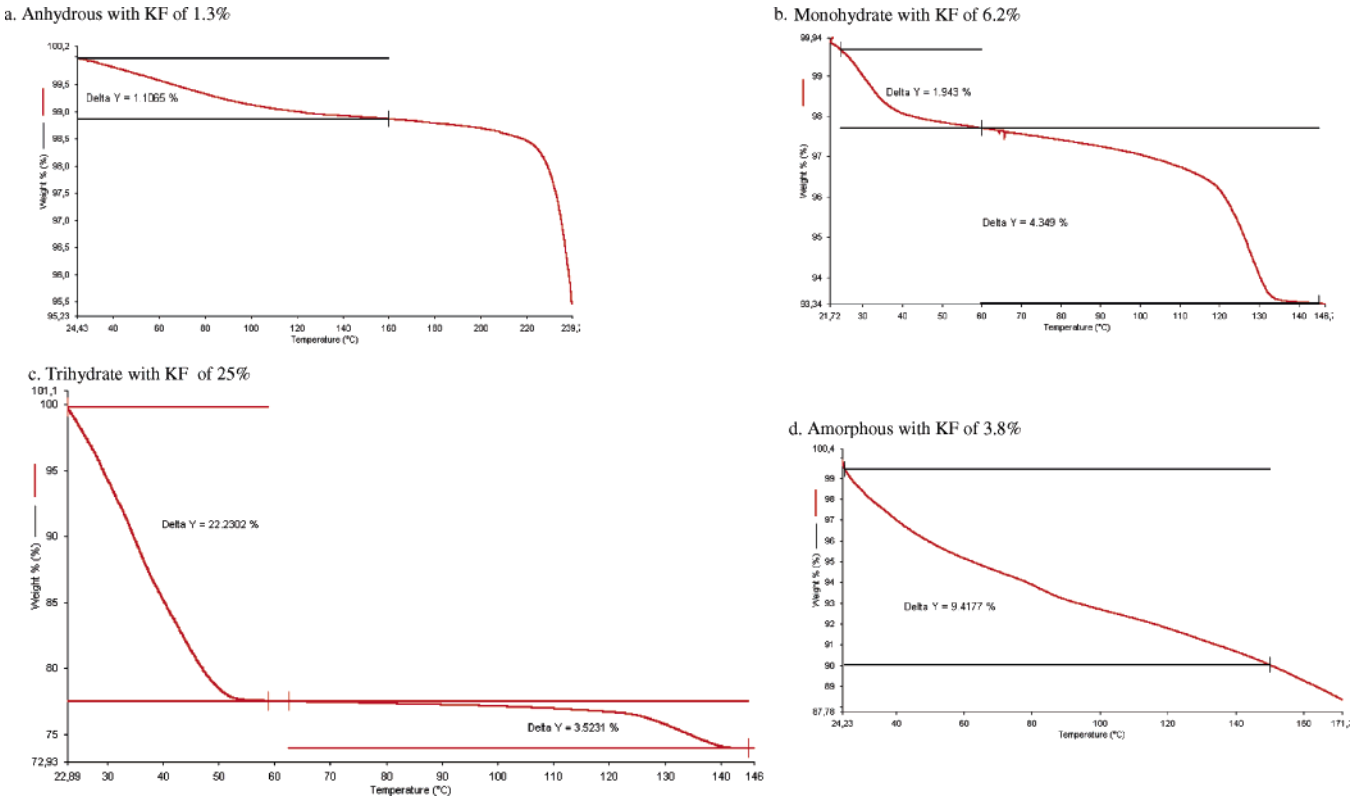


Figure 4. **TGA chromatogram of Cefdinir (1) obtained in Antibioticos labs reproducing the procedures described by Fujisawa for the anhydrous,[7] by ACS Dobfar for the monohydrate,[9] by Orchid for the trihydrate[12] and again Orchid for the amorphous.[11] The crystalline forms were identified by XRPD, FT-IR, and TGA. (a) Anhydrous with KF of 1.3%. (b) Monohydrate with KF of 6.2%. (c) Trihydrate with KF of 25%. (d) Amorphous with KF of 3.8%.**

Cefdinir Monohydrate: IR Spectra

The IR spectra described by Fujisawa in experiment 14 of the original product patent[6] showed the critical carbonyl bands of the Cefdinir (**1**) monohydrate. These infrared absorption bands were different with respect to the anhydrous or amorphous forms of Cefdinir (**1**).

The bands reported by Fujisawa: 3300, 1780, 1665, 1180, 1130 cm^{-1} are different from those seen in the spectrum of the amorphous form: 3300 (broad), 1767, 1660 (these peaks are broad and not clearly defined), 1170, 1126 cm^{-1} or from the anhydrous form: 3299, 1767, 1684, 1177, 1114 cm^{-1}. On the contrary, the Fujisawa infrared absorption bands are present in the IR spectra of the monohydrate obtained by us when reproducing Fujisawa[6]/Biochemie[21]/ACS Dobfar[9] experiments: 3300, 1785, 1667, 1190 cm^{-1}. Interestingly, Ranbaxy did not report in their claims the bands of the main peak in the carbonyl area and a 3300 cm^{-1} peak typical of the monohydrate.[10] However, in addition to the claimed peaks at 1667, 1610, 1543, 1350, 1190, 1135, 1049, 1015 cm^{-1} the IR spectra reported in the patent clearly show the peaks, typical of the monohydrate form, at 3300 and 1785 cm^{-1}.

Fujisawa researchers described Cefdinir (**1**) in the original product patent only by IR spectra. It is worth noting that the product coming from experiment 14 was identical to Cefdinir (**1**) monohydrate as determined by XRPD, FT-IR spectra, and TGA.

Cefdinir Stability

Cefdinir monohydrate is the only chemically and physically stable form that can be a valid alternative to the anhydrous form marketed by Fujisawa. In particular, we have carried out some experiments to investigate the consequences of thermal stress and exposure to moisture, to better understand the stability of the monohydrate crystalline form. The product, placed under thermal stress (75 °C for 2 h), showed a decrease in water content to 3.8%, but after direct exposure to a humid atmosphere (25 °C, 65% moisture) in less than 1 h, this rose back up to 5−6%. The monohydrate crystal can accommodate more then 1 mole of water and in fact, after 4 days exposure in a climatic chamber at 25 °C/65% humidity or 40 °C/75% humidity, the water content of the powder reached 12% and 8.5%, respectively. These processes are reversible, and under all these conditions the XRPD and IR spectra of the powder remain unchanged, showing a clear stability of the crystalline form. Even after uptake of almost 3 molecules of water (12%) the unit cell dimension was retained. This behaviour is typical of crystal structures with channels that can accommodate additional loosely bound water.[20]

The Crystallization Process

With the exception of patent 7 by Abbott,[16] patents 1, 2, 5, and 9 claimed not only the monohydrate crystal form but also the process to make it.[9,10,13,18] In our hands, the most efficient process in terms of yield and filterability was

Table 3. **Comparison of IR spectra of monohydrate forms reported in patents 2, 5, and 9, the amorphous one described by Orchid, and the spectra of the product obtained reproducing Fujisawa, Biochemie, and ACS Dobfar patents**

Fujisawa U.S. Patent 4559334	Fujisawa, exp 14[1] U.S. Patent 4,559,334 Biochemie, exp 2[21] U.S. Patent 6,350,869 ACS Dobfar, exp 1[9] US2003/0204082[a]	Rambaxy[10] patent 2	Orchid[11] patent 3 amorphous	Aurobindo[13] patent 5	Lupin[18] patent 9	Fujisawa[6] anhydrous
3300	3300	3300	3300 (broad)	3295	3297	
1780	1785	1785		1780	1781	
			1768			
						1760
1665	1667	1667	1660	1667	1666	1670
			1624			1620
1180	1188	1190		1191	1190	
1130	1134	1135		1135	1134	

[a] The IR spectra reported in the table were obtained from Cefdinir (**1**) generated by following the experiments described by Fujisawa, Biochemie, and ACS Dobfar.

described and claimed by ACS Dobfar. This result could be related to the presence in the crystallization mixture of 10% v/v of organic solvents.[9]

Patent 1, Claim 2. "A method for obtaining the crystalline form of Cefdinir claimed in claim 1, characterized in that to an aqueous solution of Cefdinir at least one organic solvent is added in a percentage v/v up to 10%, the solution is cooled to a temperature between 0 °C and +6 °C, and the pH is lower to between 1.5 and 3, to hence cause precipitation of the new Cefdinir crystal, which is isolated by known techniques."

Patent 1, Claim 3. "A method as claimed in claim 2, characterized in that said organic solvent is chosen from the group consisting of ethyl acetate and tetrahydrofuran, used individually or mixed together.

The comparison of this procedure with the one described by Fujisawa example 14 of U.S. Patent 4,559,334 is interesting[6] (see Table 3).

Example 14. "The resultant precipitate (Cefdinir crude) was collected by filtration and dissolved in a mixture of tetrahydrofuran (10 mL) and ethyl acetate (10 mL). The organic layer was extracted with an aqueous sodium bicarbonate. The aqueous extract was washed with ethyl acetate, keeping the pH value at 5 and then adjusted to pH 2.2 with 10% hydrochloridric acid. This solution was stirred for 1 h at 0 °C, and the obtained crystals were collected by filtration and dried under vacuum to give 7-(*Z*)-[2(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-carboxylic acid (syn isomer) (0.79 g)."

We have reproduced the above protocol and after extensive extraction of the aqueous phase with ethyl acetate to remove most of the tetrahydrofuran, the overall amount of organic solvents in the aqueous sodium bicarbonate solution of Cefdinir (**1**) is around 10%, mainly ethyl acetate. The process claimed and described by ACS Dobfar in 2003[9] is almost identical (solution composition/pH/temperature) to the one described by Fujisawa in 1983.[6]

The Cefdinir (**1**) monohydrate crystallization process is mainly governed by the crystallization temperature with the anhydrous crystalline form only being generated at temperatures higher than 35 °C.

Some General Observation Coming, from the Cefdinir Case Study, on Crystalline Form Patentability

Organic Volatile Impurities and Polymorphism. In several patent applications, the characterization of the final product does not allow an understanding of whether a product is a new crystalline form, a salt, or a solvate. Most of the processes described in patents 1−9 involved the use of organic solvents; however, the amount of volatile impurities has never been reported. Abbott researchers claimed the discovery of a new polymorph;[14] sometime later they discovered that the new polymorph was simply the pyridinium salt.[15] This mistake could have been avoided by a simple GC or NMR analysis.

The existence of a new crystalline form is not useful per se. The patent application should describe clearly why a particular crystalline form is useful, forf example, filterability, solubility, etc. However, all the patent applications described in this paper claimed the pharmaceutical use of the novel crystalline form. The advantages claimed in the patent applications were a better bioavailability or a more stable pharmaceutical composition or a better solubility for clinical application, etc. In this context, an active pharmaceutical ingredient (API) should meet the ICH guidelines for volatile impurities.

Characterization. The Cefdinir (**1**) case clearly shows that crystalline forms cannot be identified by a simple XRPD. From a scientific point of view, a new crystalline form must be identified by a selection of techniques adequate to establish the uniqueness of the claimed form. In the Cefdinir case XRPD, IR spectra, and DSC/TGA are sufficient to identify the crystalline form.

Crystalline Form Stability. A powder useful for a pharmaceutical application should be physically stable for a certain period of time in a range of temperature and moisture; the crystalline form must remain unchanged. Novartis researchers claimed Cefdinir trihydrate and its formulation and correctly described under which conditions the product was physically stable.[19]

Conclusions

The number of filings coming from Japan, the United States, and Europe increased by 24.9% from 2001 to 2005. It is worth noting that Patent offices are and will be under pressure in the future by the increasing number of applications from emerging countries that are and will join the WTO. In fact, PCT international applications received from developing countries in 2005 saw a 24.8% increase as compared to 2004, representing 6.9% of the international applications filed.[22] In the Cefdinir (**1**) case are involved 1 Japanese (the originator), 2 European, 1 American, and 4 Indian companies. The patent system can react by increasing patent offices staff and expenses or by looking for alternative solutions. The Cefdinir (**1**) case showed that some companies, even in the case of a clear lack of novelty, extended their patent application in the United States. Japanese and European Patent Offices are in a different position with respect to that in the United States. In Japan and Europe, during the application review, a third party can submit additional information, thus helping the patent office to complete the prior art search. The patent office's verification of all the patentability requirements is the only guarantee of a fair competition. An invention must:

A. be novel.

B. not be obvious for a person skilled in the art

C. be useful.

D. contain sufficient details to allow others to reproduce the invention.

The prior art search is one of the main issues. The international search report generated by the EPO for Ranbaxy patent application carried out in August 2004[10] did not report as a prior art the ACS Dobfar patent published almost 1 year before. The definition of simple rules for crystalline form patent applications filing could, in principle, force the authors to better evaluate the prior art and to help Patent Offices to speed up and have a better control of the evaluation process. Crystalline form patents represent a small but very important segment of product patents because of the possibility to extend the medicine market protection, thus delaying competition from generic firms. We think that for these specific types of patent applications, the following basic rules should be applied:

1. The crystalline form cannot be characterised by a single technique.

2. When a pharmaceutical application or advantage is claimed to justify the usefulness of the patent application, volatile impurities must comply with ICH guidelines,[23] and the new crystalline form must be sufficiently stable to be used as a medicine.

3. A new polymorph must have an advantage over the one previously described. All the patent applications described in this paper do not show a clear advantage of the claimed polymorph with respect to Fujisawa's anhydrous form. The claiming of a crystalline form or solvate without a clear understanding of the usefulness is common to several patent case studies. From our direct experience, an interesting example is Cabergoline (Parkinson's disease): the originator and generic companies claimed up to 14 crystalline forms and solvates.[24] What is the meaning of all these patent applications? Where is the advantage with respect to the previously reported crystalline forms or solvates?

This paper has made some observations and given some suggestions that we hope will form a useful basis for discussion on patents that claim new crystalline forms. As a result of the problems often observed in this area, it is suggested that Patent Offices adopt and enforce clear guidelines for the patenting of crystalline forms in the future, to avoid situations similar to the one of Cefdinir.

Experimental Section

All the experiments carried out in Antibioticos have been carried out according to the procedures described in the patents.

XRPD was carried out using a Philips PW1800, 45 kV/10 mA, Cu Kα, range 2Φ: 2°−40°. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000 equipped with a $LiTaO_3$ detector accumulating 64 scans at 4 cm^{-1} resolution. The sample was intimately mixed with KBr FT-IR grade to obtain a 1% mixture and a pellet was prepared using a manual press. The spectrum obtained in Nujol was almost identical to the one in KBr, showing that the powder manipulation did not modify the result. TGA were carried out using a Perkin-Elmer Pyris1 from rt to 200 °C, at a heating rate of 10 °C/min.

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(22) For IP statistics see: http://www.wipo.int/ipstats/en/.

(23) Q3C(R3): Impurities: Guideline for Residual Solvents. EU: Adopted by CPMP, September 97, issued as CPMP/ICH/283/95 MHLW: Adopted March 1998, PMSB/ELD Notification No.307 FDA: Published in the *Federal Register* **1997**, *62*(No. 247, December 24), 67377.

(24) (a) Form I by Pfizer; Sabatino, P.; Riva di Sanseverino, L.; Tonani, R. *Farmaco* **1995**, *50*, 175. (b) Form II by Pfizer; Tomasi, A.; Magenes, S.; Ramella, G.; Ungari, M.; Pandolfi, M. U.S. Patent 6,673,806 (filed 16 January 2003). (c) Form VII by Pfizer; Candiani, I.; Budelli, R.; Pandolfi, M.; Ungari, M. U.S. Patent 6,680,327 (filed 18 September 2002). (d) Amorphous form and solvates VIII, IX, XI, XII, XIV, XV, XVI, XVII, and XVIII by Ivax; Cvak, L.; Bednar, R.; Sobotik, R.; Jegorov, A. WO04101510 (filed 27 January 2004). (e) Amorphous form and solvate A by Finetech; Gutman, A.; Tishin, B.; Vilenski, A.; Agazade, A.; Pertzikov, B.; Nisnevich, G. WO04094368A (filed 20 April 2004).