

PERSPECTIVE

## Extending the market exclusivity of therapeutic antibodies through dosage patents

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### ABSTRACT

Dosage patents are one way to extend the market exclusivity of an approved drug beyond the lifetime of the patent that protects the drug as such. Dosage patents may help to compensate the applicant for the long period where the active pharmaceutical ingredient as such is already under patent prosecution, but not on the market yet, due to lengthy development and approval procedures. This situation erodes part of the time the drug is marketed under patent protection. Dosage patents filed at a later date can provide remedy for this problem. Examples of successful and unsuccessful attempts, and the reasons for the respective outcomes, are provided in this article.

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### Introduction

The rationale of granting a patent on a new dosage regimen for a given drug is that the development of such dosage regimen needs to balance patient compliance, therapeutic efficacy and side effects of said drug - a goal not always easily attained, hence requiring substantial skills. The role of dosage patents in the protection of therapeutic antibodies is substantial. However, in Europe, dosage patents have been in a rather gray area until 2008, mainly because they were considered to qualify as non-patent eligible methods of treatment. In decision T0317/95,<sup>1</sup> a claim devoted to the combination of a bismuth-containing agent and an H2-receptor blocking agent was at stake, in which the administration of the said 2 agents was effected within 5 minutes of each other. The Board of Appeal found that

“determination of the best individual treatment schedule, in particular the prescribing and modification of drug regimens used for administering a particular medicament (...), appear to be in the first place part of the typical activities and duties of the doctor in attendance in exercising his professional skills”

These, the Board continued, were typical non-commercial and non-industrial medical activities that the EPC would intend to free from restraint under the method of treatment exemption.

In decision T0056/97,<sup>2</sup> the same Board of Appeal had to decide about a claim devoted to the use of a thiazide diuretic having a predetermined diuretic effective dose, wherein a dosage unit was established that was 7–25% by weight of the predetermined diuretic effective dose. The Board rejected the claim for the same reasons as in T0317/95, and emphasized that it had

“difficulty in seeing claim 1 as more than an unsuccessful attempt to obtain protection for a method of therapeutic treatment of the human or animal body”

It appears that these decisions relied on the assumption that dosage finding was something a medical practitioner would do

in his daily practice. Obviously, these decisions ignored that a suitable dosage is today found in a clinical trial that forms part of the approval process, requires substantial input of intellectual and financial resources of different parties, and is not within the routine of a medical practitioner.

### Decision G2/08 – when it all became official

In decision G2/08, which issued February 9, 2010, the Enlarged Board of Appeal (EBA) of the European Patent Office (EPO) reversed this policy, and declared dosage regimen claims to be principally admissible:<sup>3</sup>

“Where it is already known to use a medicament to treat an illness, Article 54(5) EPC does not exclude that this medicament be patented for use in a different treatment by therapy of the same illness. Such patenting is also not excluded where a dosage regime is the only feature claimed which is not comprised in the state of the art.”

In an *obiter dictum*, the EBA also declared that they were aware that dosage regimen patents run a risk of being applied in an abusive fashion:

“The EBA does not ignore the concerns with respect to undue prolongations of patent rights potentially resulting from patent protection for claims purporting to derive their novelty and inventive step only from a not hitherto so defined dosage regime (...).”

Hence, the EBA made clear that patent claims on dosage regimens need to be examined with the same scrutiny toward novelty and inventive step as other patent claims:

“Therefore, it is important to stress that (...) for the assessment of novelty and inventive step of a claim in which the only novel feature would be the dosage regime, the whole body of jurisprudence relating to the assessment of novelty and inventive step generally also applies.”

In other words, one will not receive a patent on a dosage regimen that is obvious in view of the existing prior art, or not

sufficiently enabled or disclosed in the respective application, as will be discussed in the following sections.

### Practical relevance of dosage patents

On paper, a dosage patent may appear narrow and easy to bypass because its claims comprise a very specific dosage restriction, variation of which would draw an alternative dosage regimen out the literal scope of the claim. Further, some jurisdictions have high demands as regards a potential scope of equivalence. German courts, for example, have established a position according to which claimed ranges defined by numerical values leave no scope of equivalence. In a decision of March 12, 2002, the Federal Supreme Court stated the following:<sup>4</sup>

“For a skilled reader, features concretized by numerical values can have the meaning that the technical object of the invention is to be defined more precisely and, where appropriate, narrowly than would be the case for a mere verbal definition. As it is the applicant’s responsibility to ensure that everything for which protection is sought is recited in the patent claim, the reader of the patent specification is entitled to assume that this principle has been satisfied through the inclusion of numerical values in the claim language. This is all the more the case because an applicant, when using numerical values, has the chance to clearly consider the consequences of the chosen claim language on the scope of the protection sought for.”

Translated to dosage regimen claims, this means that, once a potential infringer modifies a claimed dosage in such way that it is just outside the claimed range, German courts would deny an infringement even under the scope of equivalence.

Notwithstanding the above drawbacks, dosage patents have an effect because they oftentimes receive substantial power from a corresponding marketing authorization. European Directive 2001/83/EC requires, under Art 11, that the Summary of Product Characteristics (SoPC) contains, *inter alia*, information as to posology (=dosage), composition (=formulation) and indication of the authorized drug.

Biosimilar manufacturers rely preferably on the authorized dosage of a branded drug because they usually do not want to establish their own dosage regimen, as this would require a completely new authorization process. If, however, the dosage for which the drug is approved is the subject of a patent, then using said dosage for the biosimilar (e.g., mentioning it in the Biosimilar SoPC) would qualify as a patent infringement. This, in turn, explains the prolonging effect dosage patents can have on the overall exclusivity of an approved antibody. Table 1 shows selected antibody dosage patents or patent applications that reflect the approved dosage.

### Carve out/skinny labeling

European Directive 2001/83/EC provides a loophole in that, under Art 11, generic manufacturers need not include those parts of the SoPC which are still covered by patents at the time when the generic medicine was marketed. The clause is meant as an attempt to incentivize the development of generics and

biosimilars. In the United States, 21 USC § 355 j (2)A (viii) has a similar provision. This so-called carve-out solution can help biosimilar manufacturers to avoid infringement of dosage patents, when there is already a dosage in the SoPC that is not patent protected. It is, however, unclear what happens if the patented dosage is the **only** dosage in the SoPC. Can a biosimilar manufacturer exclude the dosage information in such case? This would mean that the SoPC has no dosage instruction whatsoever. For safety considerations, it seems this would be unacceptable. However, caselaw does not provide any clue to solve this issue.

### Examples of dosage patents that failed in prosecution, or did not stand third party attacks

#### **Case EP1616572B1 (Rituximab): Discrepancy between the dosage that is disclosed in the patent application as originally filed, and the dosage that eventually makes it into the label**

European patent EP1616572B1, assigned to Biogen Idec, claimed the use of an escalated dosage regimen of the anti-CD20 antibody rituximab (Rituxan<sup>®</sup>/MabThera<sup>®</sup>) in chronic lymphocytic leukemia (CLL; see Table 1). Claim 1 was amended several times during prosecution, and was eventually granted as follows:

“Use of rituximab [...] for treatment of CLL [...], wherein the medicament is for administration [...] at a first dose of 375 mg/m<sup>2</sup> and subsequent dosage of 500 to 1500 mg/m<sup>2</sup>”

The granted claim was drafted in such way to faithfully reflect the dosage recommendation in the label of the European Medicines Agency (EMA), which read 375 mg/m<sup>2</sup> on day 0, followed by 500 mg/m<sup>2</sup> (6 cycles). For treating CLL, rituximab is given in combination with chemotherapy, which is usually given every 4 weeks.<sup>5</sup> To optimize patient compliance, rituximab administration is therefore adopted to that schedule.

However, the original disclosure in the patent specification (example 3) on which the amended claim relies was as follows:

“All patients receive a first dose of 375 mg/m<sup>3</sup> to minimize infusion-related side effects. Subsequent **weekly** dosages (3) remain the same but are given at an increased dose level [...] of 500–1500 mg/m<sup>3</sup>”

The point that the specification used the unity “mg/m<sup>3</sup>” instead of “mg/m<sup>2</sup>,” as eventually claimed, was considered an obvious error by the Examining Division, who admitted a respective correction (a position which later was confirmed by the Opposition Division). More importantly, however, the dosage disclosed in example 3 of the patent specification had **weekly** intervals, and only for the specific combination of **dosage and intervals** was a therapeutic effect shown. In the claims that were granted eventually, the patent proprietor had omitted the interval completely because the dosage recommendation in the label was not restricted to such weekly intervals. Therefore, a claim with weekly intervals would have left numerous bypass solutions for biosimilar manufacturers, who in such case could have relied upon the dosage recommended in the label without infringing the patent.

**Table 1.** Selected antibody dosage patents or patent applications that reflect the approved dosage.

Approved antibody	Patent	Status	Claimed dosage	Respective dosage in the EMA label
Rituximab	EP1616572B1 (Biogen)	Revoked in first instance opposition proceedings, appeal pending	Use of rituximab for treatment of CLL at a first dose of 375 mg/m <sup>2</sup> and subsequent dosage of 500 to 1500 mg/m <sup>2</sup>	CLL: The recommended dosage of MabThera in combination with chemotherapy (...) is 375 mg/m <sup>2</sup> (...) on day 0 of the first treatment cycle followed by 500 mg/m <sup>2</sup> (...) on day 1 of each subsequent cycle for 6 cycles in total. Chemotherapy should be given after MabThera infusion
Etanercept	WO2013059405, WO2013059408, WO2013059410 (Coherus)	Pending (basic patent has no dosage instruction)	Stabilized etanercept formulation comprising xylitol and optionally meglumine (WO'410), meglumine with optionally sucrose and/or sodium chloride (WO'408) or serine, with proline and/or glutamate (WO'410) Preferably, the formulation comprises about 25 to about 75 mg/ml etanercept	RA: 25 mg Enbrel administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective
Infliximab	US7179466 (Centocor)	Granted	Method of treating RA comprising a single or divided 3–5 mg/kg dose at least once every 6 weeks of an anti-TNF antibody that competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF	*RA: The recommended dose of Remicade is 3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active RA
Adalimumab	EP1406656B1 (AbbVie)	Withdrawn by patentee in opposition proceedings	Composition comprising 40 mg of adalimumab	RA: The recommended dose of Humira for adult patients with RA is 40 mg administered every other week as a single dose via subcutaneous injection
Bevacizumab	EP2478114B1 (Roche)	Granted	Method of identifying a patient with a lung cancer who may benefit from anti-angiogenic therapy comprising an anti-VEGF antibody and at least one chemotherapeutic agent. Preferably, the anti-angiogenic therapy comprises 7.5 mg/kg of bevacizumab	NSCLC: Avastin is administered in addition to platinum-based chemotherapy for up to 6 cycles (...) followed by Avastin as a single agent until disease progression. The recommended dose (...) is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion
Trastuzumab	EP1210115B1 (Roche)	Revoked by EPO in first instance opposition proceedings, appeal pending; UK part finally revoked by UK Court	Use of huMab 4D5-8 for treating breast cancer characterized by overexpression of ErbB2, comprising an initial dose of 8 mg/kg; and a plurality of subsequent doses of 6 mg/kg, wherein the doses are separated by 3 weeks	Breast cancer: Triweekly schedule; The recommended initial loading dose is 8 mg/kg (...). The recommended maintenance dose at 3-weekly intervals is 6 mg/kg (...), beginning 3 weeks after the loading dose

\*FDA label. Abbreviations: CLL: Chronic Lymphocytic Leukemia; EPO: European Patent Office; NSCLC: Non Small Cell Lung Cancer, RA: Rheumatoid Arthritis; TNF: Tumor Necrosis Factor; VEGF: Vascular Endothelial Growth Factor.

The patent was opposed by 7 parties. On September 2, 2013, it was revoked in the first instance for inadmissible amendments (Art 123 (2) EPC). The Opposition Division objected to the omission of “weekly” because it created new subject matter that was not disclosed in the application as filed, and for which no data had been provided as regards a potential effect. In fact, effects demonstrated for a given dosage regimen with weekly intervals cannot simply be extrapolated to a dosage regimen with triweekly, or unspecified, intervals. Example 3 of the patent, which allegedly provided the disclosure for the claimed escalating dosage regimen had either (1) been drafted too narrow, or (2) the application was filed too early, when the patent proprietor did not know enough about a clinically useful dosage regimen yet. The patent proprietor’s attempt to bring claims and approved dosage regimen into conformity was foredoomed.

### **US7727968 (gemtuzumab ozogamicin): Why an inventive dosage could not be protected**

The following example demonstrates that even seemingly minor changes in a dosage regimen can have a tremendous effect, thus rebutting the prejudice that the finding of a suitable dosage regimen is a matter of mere routine.

Pfizer’s gemtuzumab ozogamicin (Mylotarg®) is an antibody-drug conjugate (ADC) comprising an anti-CD33 antibody conjugated to a calicheamicin toxin. In the United States, the drug was approved in 2000 for use in patients aged 60 or older with relapsed acute myelogenous leukemia (AML), with a recommended induction dose of 9 mg/m<sup>2</sup> on days 1 and 14. The corresponding dosage patent US7727968B2 was granted June 1, 2010, and is shown in Table 2.

**Table 2.** Correlation between antibody dosage patent and approved dosage of gemtuzumab ozogamicin. The patent is broader than the approved dosage, hence anticipating later fractionated dosages that could have given rise to new patent protection.

Approved antibody	Patent	Priority date	Claimed dosage	Dosage in the FDA label
Gemtuzumab ozogamicin	US7727968B2 (withdrawn by patentee)	Nov. 6, 2002	Method of treating AML consisting essentially of: (a) administering a first course (...) of (...) about 3 to 9 mg/m <sup>2</sup> gemtuzumab ozogamicin for one day (plus chemotherapy) (b) administering a second course of (...) of about 3 to 9 mg/m <sup>2</sup> gemtuzumab ozogamicin for one day (plus chemotherapy) (...) and (c) administering a third course (chemotherapy)	9 mg/m <sup>2</sup> , infused over a 2-hour period. The recommended treatment course with Mylotarg is a total of 2 doses with 14 d between the doses

Upon request of the US Food and Drug Administration (FDA,) the drug was withdrawn in 2010 from the US market for lack of efficacy and an increase in number of fatal toxicities. Interestingly, the EMA had refused marketing authorization in 2008 because no randomized controlled trials were provided, while in Japan, the drug was approved as an orphan drug in 2005, and the Japanese authority decided to leave it on the market even after the 2010 withdrawal in the United States, provided that post-marketing surveillance was increased.<sup>6</sup> Pfizer allowed the US patent to expire by non-payment of maintenance fees, without leaving any divisionals or continuation applications behind. Counterparts in other jurisdictions do not exist.

In 2009, French researcher Sylvie Castaigne and colleagues of the Acute Leukemia French Association began a study (ALFA-0701, NCT00927498) cosponsored by Central Hospital, Versailles, which involved 280 patients between 50 and 70 y of age with previously untreated AML. To minimize the toxic side effects, the team used a fractionated dosage approach with 3 mg/m<sup>2</sup> on days 1, 4, and 7 during induction, and then another dose on day 1 on each of the 2 consolidation chemotherapy courses. Hence, the team merely subdivided the FDA dosage into 3 fractions and shortened the intervals accordingly.

The results reported in 2012 revealed that, under the new dosage regimen, gemtuzumab ozogamicin actually improves overall survival in AML when added to standard chemotherapy, without an increase in the risk of death from toxicity.<sup>7</sup> The results are consistent with those from another trial, which involved 1113 patients with *de novo* AML.<sup>8</sup> Soon after publication of these results, several authors discussed the possibility of overturning the decision to withdraw gemtuzumab ozogamicin from the market.<sup>9</sup> Reportedly, Pfizer also considered if “there is a plausible argument that the drug has benefit at an acceptable rate of toxicity.”<sup>10</sup> However, no new approval has been obtained so far.

Unfortunately, the 3 mg/m<sup>2</sup> dosage used by the group of Castaigne was already anticipated by Pfizer’s surrendered patent US7727968B2, while the timing seems to be novel over that prior art reference. The modifications the team made to the established dosage regimen had a tremendous increase in efficacy, while toxicity was not affected, a result that was undoubtedly surprising for all parties involved. In discussions with a patent examiner, the term “surprising” is often used as a buzzword to argue in support of non-obviousness. For this reason, it appears that a patent application with claims reciting that specific dosage regimen would likely have been considered non-obvious. However, a patent search carried out by the author of this article did not reveal any respective patent applications. It appears that the team of Castaigne did not file a patent application prior to

publishing their surprising results, nor did Pfizer, although Castaigne’s research was partly funded by Pfizer.<sup>11</sup>

### **Case EP1210115B1 (Trastuzumab): Obviousness of a novel dosage regimen in view of a prior art dosage regimen**

European patent EP1210115B1 related to a particular dosage regimen of the anti-human epidermal growth factor receptor (HER)2 antibody trastuzumab (Herceptin®), with 8 mg/kg loading dose and 6 mg/kg triweekly follow-up doses. The patent was opposed before the EPO by 6 opponents, and revoked on March 19, 2012 for lack of inventive step, in view of the published FDA-approved treatment regimen of a 4 mg/kg loading dose and subsequent 2 mg/kg weekly doses (see Table 3). The case is currently under appeal.

The UK part of the European patent was finally revoked on February 6, 2015 upon motion of generic company Hospira, who were also involved in the corresponding EP opposition. Like the Opposition Division of the EPO, the Courts found that the claimed treatment regimen was obvious over the published FDA-approved treatment.

In the first instance decision at the Patents Court,<sup>12</sup> Justice Birss stated that a “clinician would consult with the pharmacokinetics expert and decide to go ahead with a trial of a 3-weekly dosing schedule and select the claimed doses.” In the second instance decision at the Court of Appeal,<sup>13</sup> Justice Floyd went even further, in stating that “pharmacokinetics was not a field that was slavish to calculations and that clinical variability meant that such dosage regimens were always likely to fall within a range.” The latter statements are certainly oversimplifying the art of developing and establishing a dosage regimen that carefully weighs up patient compliance, therapeutic efficacy and side effects. Still, the ruling may generally affect the validity of dosage patents, in particular when prior art exists that discloses an earlier dosage regimen roughly similar to the claimed regimen. It is, however, not necessarily relevant for dosage patents that refer to the first dosage of an active ingredient, i.e., where there is no prior art benchmark to compete with in terms of non-obviousness.

**Table 3.** Dosage claimed in EP1210115B1 vis-a-vis prior art.

	Loading dose	Follow up doses	Interval
Prior art (FDA-approved regimen)	8 mg/kg	6 mg/kg	Triweekly
EP1210115B1	4 mg/kg	2 mg/kg	Weekly
Factor	1/2	1/3	3

## Strategies to successfully prosecute dosage regimen patents

### EP1616572B1 (Rituximab): Interplay of a new dosage and a new indication

As discussed above, the escalated rituximab dosage regimen claimed in EP1616572B1 was specifically meant for the treatment of CLL. Rituximab binds to CD20 positive cells, including lymphocytes and leukocytes. Because leukocytes are freely floating in the bloodstream, a rituximab infusion will lead to a quick onset of the cytotoxic effect on these leukocytes, by evoking antibody-dependent cell-mediated cytotoxicity (ADCC). In CLL patients with a high white blood cell count, rituximab treatment can cause severe side effects due to mass lysis of leukocytes and a subsequent cytokine storm. The claimed escalated dosage regimen was thus meant to avoid these side effects by using a lower upfront doses, followed by higher doses to ensure sustainability of the response.

Compared to the standard dosage of rituximab, the new dosage regimen was alleged to have particular advantages with respect to this specific indication. Under more favorable circumstances, an applicant could have tried to use such dosage-indication relationship as an argument in support of non-obviousness. In the opposition hearing, these questions were, however, not discussed because all claims on file were found invalid for inadmissible added matter already, a ground that is usually discussed before the inventive step. The appeal proceedings are ongoing.

### EP2459167B1 (Trastuzumab): Interplay of a new dosage and a new mode of administration

Roche's trastuzumab received a further EMA approval on 2 September 2013 for subcutaneous administration in the treatment of HER2-positive breast cancer. The recommended dose is 600 mg irrespective of the patient's body weight, administered in a 5 ml dose (hence, the administered concentration is 120 mg/ml) subcutaneously over 2–5 minutes every 3 weeks. Roche claims that, while for intravenous administration patients attend a hospital or clinic and each infusion takes 30–90 minutes to administer, the new subcutaneous formulation takes only 2–5 minutes to administer.<sup>14</sup>

On May 15, 2013, Roche received patent EP2459167B1, the priority date of which is July 31, 2009. The patent claim is a hybrid of dosage and formulation, and includes a recombinant hyaluronidase, which forms hyaluronan, a gel-like substance that creates a barrier between cells under the skin after injection.<sup>15</sup> This, Roche claims, allows the 5 ml volume of the subcutaneous formulation of the drug to be rapidly dispersed and absorbed over a greater area.

The patent is subject to an opposition by an undisclosed party, but was maintained in the first instance with the following claims 1 and 3:

1. A liquid, highly concentrated, stable pharmaceutical formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection comprising:
  - a. about 50 to 350 mg/ml anti-HER2 antibody; (...)
  - e. more than 150 to about 16,000 U/ml, about 2,000 U/ml, or about 12,000 U/ml, respectively, of a hyaluronidase enzyme.

**Table 4.** Correlation between patent claiming trastuzumab's new dosage regimen, and approved dosage.

Approved antibody	Patent	Claimed dosage	1 <sup>st</sup> Dosage in the EMA label
Trastuzumab	EP2459167B1	50 to 350 mg/ml, preferably 120 ± 18 mg/ml, for sc administration	600 mg/5 ml (equals 120 mg/ml)

3. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to claim 1 or claim 2, wherein the anti-HER2 antibody concentration is (...) 120 ± 18 mg/ml (...)

The present example again shows the close match between the approved and the claimed dosage and how regulatory aspects and aspects of Intellectual property are intertwined. Furthermore, the decision shows that a dosage regimen can be inventive if a novel interplay between dosage regimen and mode of administration is established (see Table 4 for an overview). The Opposition Division was of the opinion that the claimed combination of trastuzumab and hyaluronidase, which have opposite charges at pH5 – pH6, would not aggregate, which alone the Opposition Division found a sufficient argument for the acknowledgement of inventive step, and hence maintained the patent. An appeal is ongoing.

### EP2459167B1 (Trastuzumab): Filing of a dosage patent application only when the dosage that eventually makes it into the label is known

EP2459167B1 demonstrates another important point: The clinical trials that formed the basis for the approval of the escalating dosage of rituximab in the treatment of CLL (see above) commenced on January 24, 2006. This means the patent application, claims of which were modified in an unsuccessful attempt to cover the approved regimen, was filed **7 y before** that date. Quite obviously, the respective application was simply filed too early, i.e., when the applicant did not know enough about the clinically suitable dosage. In contrast thereto, the patent application that was used to protect the subcutaneous dosage for Trastuzumab, EP2459167B1, was filed **one day after** the respective study that formed the basis of the respective authorization began. Hence, the patent proprietor already had a clear concept of the dosage regimen for which approval was sought when filing the application. The patent application could thus be drafted accordingly to avoid any respective mismatches. An overview of this case is shown in Table 5.

## Conclusions

### The inventive step problem

As discussed above, the development of a suitable dosage regimen of a given drug needs to carefully weigh up patient compliance, therapeutic efficacy and side effects of said drug. The difficulties and implications with finding a suitable dosages have already been pointed out by renaissance physician Paracelsus (1493 – 1541), to whom the proverb “all things are poison and nothing is without poison; only the dose makes a

**Table 5.** Time lag between filing date of dosage-related patent and onset of clinical trials (when the dosage was actually established).

Patent Number	Subject matter	Priority date	Approval date	Studies	Study timeline	Delay between priority date and study onset
EP1616572B1	Rituximab for treatment of CLL	Nov. 9, 1998	Feb. 27, 2009 (EMA)	ML17102/CLL8 (NCT00281918) BO17072/Reach (NCT00090051)	First received: Jan. 24, 2006 Last verified: Sept. 9, 2013 First received: Aug. 23, 2004 Last verified: May 2013	8 years
EP2459167B1	Trastuzumab for breast cancer, sc administration	July 31, 2009	Sept. 2, 2013 (EMA)	HannaH (NCT00950300)	First received: July 30, 2009 Last verified: March 2016	–1 day

thing not poison” is ascribed.<sup>16</sup> This alone suggests that a new dosage regimen can indeed rely on an inventive step.

However, it appears that patent authorities tend to oversimplify the art of developing a specific dosage regimen, probably in obedience of the postulation the EBA made in decision G2/08, according to which “the whole body of jurisprudence relating to the assessment of novelty and inventive step generally would apply” for dosage patents.<sup>17</sup> This prejudice is reflected by the only decision of the EPO Board of Appeal 3.3.04 that is devoted to inventive step issues of antibody dosage regimen. In this case, the Board had to decide on non-obviousness of a rituximab dosage regimen in the treatment of rheumatoid arthritis (see Table 6, note that in the second decision shown in Table 6 the Board of Appeal did not opine on inventive step).

While the Mylotarg example shows that even slight modifications of an established dosage can make substantial differences, and thus give rise to inventive step according to the logic of the EPO, the inventive step discussion will continue to be difficult. Applicants should always provide experimental data showing that the newly claimed dosage has some kind of surprising properties, to have sufficiently convincing arguments for the inventive step discussion with the examining authorities. It should be noted that, in Europe and the US, experimental data that support an inventive step can still be provided post grant, in the prosecution phase, at least to some extent.

### The timing problem

The rituximab example demonstrates problems that can arise when an application is filed too early, i.e., when the applicant

does not yet know enough about the dosage that eventually is granted an approval. In such a situation, it may happen that the applicant can not adapt the claims to the actually approved dosage because this would involve the introduction of inadmissible added matter.

### The problem of own prior art

A forward-looking patent lifecycle strategy should make sure that, if possible, in the first-generation patent, which protects the drug as such, no clinically meaningful dosage regimens are disclosed. This should not be a problem in most cases because, to acknowledge an inventive step and sufficient enablement of a new antibody, the Examining Divisions of the EPO usually do not demand clinical data. In-vitro data and animal data are sufficient in most cases.<sup>18</sup> In such a strategy, a dosage regimen patent can be filed shortly before the established dosage is published, to: (1) maximize lifetime, (2) avoid prior art objections based on alleged lack of inventive step, and (3) make sure that there is an exact match between the dosage disclosed and claimed in the patent and the approved dosage.

### Disclaimer

The information provided herein reflect the personal views and considerations of the author. They do not represent legal counsel and should not be attributed to Michalski · Hüttermann and Partner Patent Attorneys or to any of its clients. Patent numbers and patent lifetimes have been verified with utmost care, but no liability is taken for their correctness.

**Table 6.** Decisions of the EPO Board of Appeal 3.3.04 that are devoted to antibody dosage regimen.

Decision	Patent/Application	Claimed dosage	Reasons why the claims were not found inventive
T 0734/12	EP1613350B1	Use of an anti-CD20 antibody which depletes B cells for treating RA which shows inadequate response to a TNF $\alpha$ -inhibitor, by administration of 2 doses of 1000 mg wherein the first dose is on day 1 and the second dose on day 15	“In the board’s view, the skilled person taking together the disclosures of documents (8) and (10) would have been motivated to use the dosage regimen of administering twice 1000 mg rituximab 2 weeks apart for the treatment of RA patients that are TNF $\alpha$ -inhibitor refractory in view of the significant therapeutic improvements achieved for RA patients being MTX refractory.”
T 0756/00	EP0755683A1	Use of a murine monoclonal antibody which (...) binds to an epitope of (...) 17-1A (...) for (...) treatment of metastases of a carcinoma (...) by (...) parenteral administration of sequential multiple doses of at least 100 mg per dose for a total dose of 0.2 to 5.0 g of antibody (...)	Board of Appeal only decided on the question of added matter, and then remanded the case to the Examining Division. The latter referred to decisions T0317/95 and T0056/97 (see introduction), and objected the claims on the basis that “the determination of the best (...) drug regime is a typical non commercial (...) medical activity.” Applicant withdrew the application thereafter. The case dates before decision G2/08, who declared dosage claims patent eligible.

## Disclosure of potential conflicts of interest

The author is involved in oppositions against some of the patent applications mentioned herein.

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