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Not So Simple Math: Calculating the Regulatory Review Period for Patent Term Extension

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This is the third article in our five-part series on PTE.

Calculating a drug's regulatory review period seems like it should be simple. The FDA even states that its regulatory review period determination is "straightforward and largely ministerial in nature." But recent court decisions coupled with prior FDA determinations demonstrate that the calculation is not so easy. Identifying the testing phase — from the effective date of the investigational new drug (IND) exemption to the filing date of the new drug application (NDA) — and the approval phase — from the filing date of the NDA to its approval date — can be tricky in certain circumstances.

Drug, biologic and medical device manufacturers should remember the following:

- If multiple INDs have been filed for a product, the first IND for the product should be used.
- If no investigational device exemption (IDE) was submitted for a device, the testing phase begins on the date on which the applicant began the first clinical investigation for the device.
- The filing date of the NDA is the date when the NDA is initially submitted.
- The approval phase may not begin until the user fees have been paid.

The regulatory review period (RRP) forms the basis for determining the length of a patent term extension (PTE). The RRP is simply the time from the date on which the IND or IDE became effective until the date on which the NDA, biologic license application (BLA) or pre-marketing authorization (PMA) was approved.[1] This period of time is broken into two phases: the testing phase and the approval phase. The length of a PTE award is equal to the sum of one-half of the time in the testing phase and the time in the approval phase, after the date the patent is issued, less any period during which the applicant was not diligent.[2] The equation is:

Period of Extension (PTE) = RRP – PGRRP – DD – ½(TP-PGTP).[3]

The FDA has jurisdiction over the calculation of the RRP.

Testing Phase Determinations

When a product is initially developed for one indication, fails that indication, and is transitioned to a new indication, the product often will have multiple INDs. In this situation, the FDA will consider the testing phase to have begun when the first IND for the approved drug product became effective.[4] Although the indication, the dose or the dosage form noted in the first IND may not be the same as when the product is approved, often there is information from the first IND — such as safety or manufacturing information — that is relevant or necessary for product approval.[5]

For a medical device, if an IDE was submitted, the testing phase begins on the effective date of the IDE. If an IDE was not submitted, the testing phase begins on the date on which the applicant began the first clinical investigation for the device.[6]

Approval Phase Determinations

The end of the testing phase and the beginning of the approval phase is "the date an application was *initially submitted* for such drug product under section 351, 505 or 507."[7] Under the FDA regulations for determining PTE, an application for approval of a product is initially submitted "on the date it contains sufficient information to allow FDA to commence review of the application."[8]

In the case of a rolling submission (in modules) of an NDA, the initial submission is usually considered the date on which the final module of the NDA is submitted to the FDA.[9] However, if the FDA responds to the applicant that the application submitted is not sufficiently complete to permit a *substantive review*, then the application for approval of the product is not yet "initially submitted," and the approval phase has not commenced.[10]

Another requirement of an application being "initially submitted" is that the filing fees must be paid, since the FDA may not review "until the correct amount of User Fee money has been received by the agency from the sponsor of the NDA."[11]

Determining the end of the approval phase is critical because it directly affects PTE calculation and starts the clock for the deadline for submitting the PTE application to the USPTO. A PTE application must be submitted to the USPTO "within the 60 day period beginning on the date the product received . . . permission for commercial marketing."[12] The date of approval of a product is not always clear. For example, if the product is a controlled substance and cannot be commercially marketed at the time of its approval due to domestic drug scheduling activities, when does approval occur for purposes of the PTE statute? Pursuant to a 2015 act, the date of approval of an NDA or BLA for a controlled substance awaiting a Drug Enforcement Administration scheduling determination is the later of the approval date and the date of issuance of the interim final rule controlling the drug.[13]

It is important for applicants to work with both patent and regulatory counsel to ensure that the RRP is calculated correctly and that the application for PTE is timely submitted. Applicants should not embark on such an analysis once their product is approved. Rather, the analysis should be started as soon as the application for approval is submitted to the FDA, if not sooner.

Endnotes

[1] 35 U.S.C. § 156(g).

[2] 35 U.S.C. § 156(c).

[3] PGRRP = pre-patent grant regulatory review period; DD = time period during which applicant did not act with due diligence; TP = regulatory review period, which is the testing phase; PGTP = pre-patent grant testing phase.

[4] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069959.htm.

[5] Brian Malkin, FDA's Role in Administering the Hatch-Waxman Act, 54 Food & Drug L.J. 211, 213 (1999). *See, e.g.,* FDA, Determination of Regulatory Review Period for Purposes of Patent Extension, MIFEPREX; Amendment, 67 Fed. Reg. 65358, 65358-59 (Oct. 24, 2002), *available at* https://www.gpo.gov/fdsys/pkg/FR-2002-10-24/pdf/02-27096.pdf (concluding that the testing phase for Mifeprex began with the first IND filed in 1983 for mifepristone alone and not the second IND filed in 1994 for mifepristone followed administration of misoprostol, which was ultimately the subject of the approved NDA).

[6] 35 U.S.C. § 156(g)(3)(B); 37 C.F.R. § 1.740(a)(10)(v)(A).

[7] 35 U.S.C. § 156(g)(1)(B) (emphasis added).

[8] 21 C.F.R. § 60.22. *See also* Letter from FDA to Arnold & Porter LLP denying its request for revision of the regulatory review period for Kepivance (March 2002); Letter from FDA to Covington & Burling LLP denying its request for revision of the regulatory review period for Zolinza, at 8 (Apr. 17, 2012).

[9] *See Boehringer Ingelheim Pharma GmbH & Co. KG v. FDA*, 195 F. Supp. 3d 366 (D.D.C. 2016).

[10] *Id.* at 380 ("The agency determined that the mere assessment of the application for completeness is not tantamount to the agency's substantive review of the application, and the Court concludes that this determination is reasonable.").

[11] *See, e.g.,* 61 Fed. Reg. 24316 (May 14, 1996) (finding that the "initial submission" date for Epivir's NDA was the date the user fees, not the NDA, were received because "[r]eview of a NDA does not begin until the correct amount of User Fee money has been received by the agency from the sponsor of the NDA").

[12] 35 U.S.C. § 156(d)(1).

[13] *See* 21 U.S.C. §§ 505(x), 512 (q); 42 U.S.C. § 351(n); *see also* 35 U.S.C. § 156(d)(1). The Improving Regulatory Transparency for New Medical Therapies Act addressed the unfairness that previously resulted in cases like *Unimed, Inc. v. Quigg*, 888 F.2d 826, 828-29 (Fed. Cir. 1989) ("[T]he Patent Term Restoration Act takes into account only the regulatory review carried out by the FDA and no other government obstacles to marketing new drugs.").

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