# APPEALS

# COORDINATED ISSUE PROGRAM

# APPEALS SETTLEMENT GUIDELINES

**INDUSTRY:** **PHARMACEUTICAL AND BIOTECHNOLOGY**

**ISSUE:** **LEGALLY MANDATED R&E EXPENSES**

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**UIL NO:** **861.08-17**

**FACTUAL / LEGAL ISSUE:** **Factual and Legal**

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**Effective Date:** **Dec. 23, 2003**

# APPEALS SETTLEMENT GUIDELINE
## LEGALLY MANDATED R&E EXPENSES

### STATEMENT OF ISSUE

Whether certain research and experimentation (R&E) expenditures in the pharmaceutical and biotechnology industries fall within the exclusive apportionment rule for legally mandated expenses provided in Treas. Reg. Section (§) 1.861-17(a)(4)?[1]

### COMPLIANCE POSITION

R&E expenditures incurred to meet legal requirements imposed by more than one political entity with respect to improvement or marketing of specific pharmaceutical and biologic products or processes do not fall within the exclusive apportionment rule for legally mandated research and experimentation (LMRE). See Treas. Reg. §1.861-17(a)(4) and Compliance's Coordinated Issue Paper on the LMRE issue.

Pursuant to Treas. Reg. §1.861-17(a)(1), expenditures that are not subject to the exclusive apportionment rule for LMRE are generally considered to be definitely related to all income reasonably connected with the relevant broad product category (or categories) of the taxpayer. Therefore, the expenditures should be allocable to all items of gross income as a class related to such product category (or categories).

### DISCUSSION

**Background**

The Food and Drug Administration (FDA) regulates the marketing of pharmaceutical and biologic products in the United States (U.S.). Before a drug can be marketed in the U.S., the manufacturer, or sponsor, must establish that the product is safe and effective. This is typically done through the filing of a New Drug Application (NDA) with the FDA that contains adequate data and information on the product's safety and "substantial evidence" of the product's effectiveness.

The manufacturer establishes a product's safety and effectiveness through testing and research. The FDA publishes regulations on pre-marketing requirements and approval procedures that are binding on all sponsors. These regulations focus on the standard of evidence needed for approval as derived from adequate and well-controlled clinical investigations. The FDA also publishes guidelines that are not legally binding on the sponsors, but are designed to provide informal guidance on specific methods through which they might satisfy regulatory requirements.

The pharmaceutical and biologic product development process is generally composed of four stages:

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[1] See Treas. Reg. § 1.861-8(e)(3)(i)(B) for tax years ending on or before 12/31/95.

- Pre-clinical or discovery research
- Clinical development
- Regulatory approval
- Post-marketing

In the pre-clinical or discovery research stage, a compound is tested on animals and non-human systems. The FDA established a set of standards, called Good Laboratory Practice, for this stage of development to ensure quality of animal testing and the resultant data. The pre-clinical or discovery stage is used to file an Investigation New Drug Application (IND). The IND is filed to permit the compound to be tested in humans.

The second stage, clinical development, is normally conducted in three phases. In Phase I the first trials in humans are conducted for safety, tolerance, and pharmacokinetics. In Phase II, testing is done to evaluate effectiveness, dosage, and safety in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented.

In Phase III, expanded clinical trials are conducted to gather additional evidence to verify dosage and effectiveness for specific indications and to better understand safety and adverse effects. These are large-scale trials typically involving thousands of patients to prove effectiveness against a specific disease or condition.

The sponsor then compiles and analyzes the Phase III data before submission of the New Drug Application (NDA). The NDA consists of clinical and non-clinical data on the product's safety and effectiveness and a full description of the methods, facilities, and quality controls employed in manufacturing and packaging. Sponsors will file an NDA with the FDA to obtain authorization to market a new pharmaceutical and biologic product and the regulatory approval stage begins at that point.

The FDA requires data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) sufficient to establish substantial evidence of effectiveness.[2] These studies are generally referred to as pivotal studies. Until the FDA grants authorization, a drug sponsor cannot market the drug in the U.S.

The final stage, post-marketing studies (also called Phase IV), occurs after the product has received FDA approval. These studies are performed to determine the long-term

[2] See FDCA 505(d); 21 C.F.R. 314.126.

effect of a drug, to study a patient population not previously studied, and to conduct marketing comparisons against other products and other uses.

**Facts**

The pharmaceutical and biotechnology industry is multinational, with most of the major companies marketing products throughout the world. According to the Pharmaceutical Research and Manufacturers of America's (PhRMA) 2000 Industry Profile, approximately 36 percent of pharmaceutical research conducted worldwide is performed in the U.S. The U.S. is the largest market for pharmaceuticals and accounts for one-third of global pharmaceutical sales. In addition, approximately 45 percent of the 152 major global drugs developed between 1975 and 1994 were of U.S. origin.

In recognition of the global market for pharmaceutical products, representatives from pharmaceutical companies and regulatory authorities from the U.S., Europe, and Japan formed the International Conference on Harmonization (ICH) in 1990. The purpose of the ICH is to make recommendations on ways to achieve harmonization in the interpretation and application of technical guidelines and requirements for drug development and approval in order to eliminate the duplication of testing in these three areas of the world.

The objective of such harmonization is a more efficient use of human, animal, and material resources, and the elimination of unnecessary and unreasonable delay in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.[3] The ICH developed a Common Technical Document, described as a "global dossier," that provides a harmonized format and content for new product applications for drug approvals in the three areas. A 1997 ICH Utilization Survey determined that the ICH guidelines affected and were used by a significant number of companies:

- 62 percent of companies in the European Union,
- 77 percent of companies in Japan, and
- 85 percent of companies in the U.S.

Under the auspices of the ICH, the U.S. FDA published guidance entitled "E5: Ethnic Factors in the Acceptability of Foreign Clinical Data" (E5: Ethnic Factors) in 1997; the guidance was effective June 10, 1998. This guidance recommends regulatory and developmental strategies to permit clinical data collected in one region to be used for support of drug and biologic registration in another region. The guidance is based on the premise that it is not necessary to repeat the entire clinical drug development process in another region. Europe and Japan have undertaken similar steps to accept clinical data collected in another region.

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[3] See "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use," www.ifpma.org.

The impact of harmonization has been analyzed by the U.S. pharmaceutical industry. In January 2000, PhRMA prepared a paper for the International Federation of Pharmaceutical Manufacturers Association (IFPMA) entitled the "Value and Benefits of ICH to Industry." This paper notes that the pharmaceutical industry has compelling reasons to support the ICH's continued efforts to further harmonize the technical requirements for the registration of innovative drugs. Thus far, harmonization has provided:

- Reduced development times and resources, including an end to duplicate clinical trials due to ethnicity differences.

- Easier simultaneous launch of a new drug in many countries (including the three ICH regions).

- ICH guidance – as a recognized standard – that will facilitate intra-company globalization.

The FDA has also begun to work with the Pan American Health Organization to encourage harmonization within the Americas.

There are several examples of the changing foreign regulatory environment due to the ICH harmonization efforts. In Japan, companies using small scale modified clinical trials have received marketing approval for products developed in other countries. For example, Dr. John Niblack, Executive Vice-President at Pfizer stated:

> "At Pfizer we've been able to use high quality data collected under GCP [good clinical practice] guidelines in one region of the world to facilitate marketing approval in another region. That gets products to patients more quickly. In the case of Viagra, for example, we did not have to repeat
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> Phase III trials in Japan. Every pharmaceutical company benefits from ICH – and patients benefit the most."[4]

Thus, Pfizer used ICH guideline E5: Ethnic Factors, which allows foreign clinical data to be submitted in any ICH region, and "E6: Good Clinical Practice: Consolidated Guideline" (E6: GCP) to gain approval of Viagra in Japan, based on R&E it had already performed in another region. ICH guideline E5: Ethnic Factors permits the use of a bridging study, rather than a full clinical trial. A "bridging study" is a small scale clinical trial designed to extrapolate a treatment's effect on another population.[5]

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[4] See "The Value and Benefits of ICH to Industry" prepared for the IFPMA by Dr. Caroline Nutley, Director of International Regulatory Affairs, PhRMA, p. 3.

[5] Ibid.

Other companies have reported changes in their development protocols to gain approval in Japan. For example, it was reported in April 2001 that Novartis plans to obtain marketing approval in Japan for Gilvec, a leukemia drug, "using virtually the same data set presented in the United States and Europe. Five years ago that would have been unthinkable."[6] It was also reported in August 2002 that Biogen was the first company to successfully use the new Common Technical Document to submit applications, based on the same R&E, to the U.S. FDA and to the European Medicines Evaluation Agency (EMEA).[7]

Isis Pharmaceuticals was the first U.S. company to submit a PDF "virtual publication" to the EMEA. Its executives agree that one of the greatest business challenges of filing in various countries is the short time period permitted for preparing each regulatory dossier for the different regions. Therefore, Isis developed a system that mixes and matches sections from different reports with different formats for an international group of regulatory boards. Nevertheless, although the format may differ, the content remains fundamentally the same.

## Meeting the Legally Mandated Standard

What happens if a drug receives approval for sale first in the U.S. and second in one or more foreign jurisdictions? To meet the legally mandated standard and allocate R&E expenditures solely to gross income from sources within the U.S., the taxpayer must establish that R&E undertaken to meet U.S. requirements was not also used to obtain foreign approval.

In contrast, what if a drug receives approval in a foreign jurisdiction prior to receiving approval in the U.S.? Then to meet the legally mandated standard and allocate R&E expenditures solely to gross income from sources within the U.S., the taxpayer must establish that R&E undertaken to meet U.S. requirements was not previously (or subsequently) used to obtain foreign approval. Whether first approved in the U.S. or in a foreign jurisdiction, the results of the R&E must not reasonably be expected to generate more than de minimis amounts of gross income outside the U.S.

## Legal Analysis

Section 901 of the IRC allows as a credit against the U.S. tax liability of a domestic corporation the amount of "any income, war profits, and excess profits paid or accrued during the taxable year to any foreign country" subject to the limitations of section 904. Section 904(a) limits the amount of foreign income taxes that a taxpayer may credit during any one year to the taxpayer's pre-credit U.S. tax on its foreign source taxable income (the foreign tax credit limitation).

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[6] See "Sun Begins to Rise for Foreign Drug Companies" by David Pilling, The Financial Times, April 26, 2001.

[7] See "Biogen's Big Picture" by Sibyl Shalo, Pharmaceutical Executive, January 2003, p. 34.

The foreign tax credit limitation is computed by multiplying the taxpayer's pre-credit U.S. income tax liability by the ratio of the taxpayer's foreign source taxable income to its worldwide taxable income. A taxpayer's foreign source taxable income (the numerator of the ratio) is determined by deducting from a taxpayer's foreign source gross income:

- The expenses, losses, and deductions properly apportioned or allocated thereto, and

- A ratable part of any expenses, losses, or other deductions that cannot definitely be allocated to some item or class of gross income.[8]

In order to determine the expenses, losses, and deductions that reduce foreign source gross income, taxpayers are generally required to allocate deductions to a class of gross income and, to the extent necessary to make the determination required by an operative Code section, to apportion deductions within the class between statutory and residual groupings of gross income.[9] A class of gross income is the gross income to which a specific deduction is definitely related. A statutory grouping is the gross income from a specific source or activity that must be determined in order to arrive at taxable income from such source or activity under an operative Code section.

General rules are provided for allocating and apportioning R&E expenditures that are deductible under section 174. These general rules recognize that R&E is an inherently speculative activity, that findings may contribute unexpected benefits, and that the gross income derived from successful R&E must bear the cost of unsuccessful R&E.[10]

R&E expenditures that a taxpayer deducts under section 174 ordinarily shall be considered deductions that are definitely related to all income reasonably connected with the relevant broad product category (or categories) of the taxpayer. Therefore, these expenditures deducted under section 174 are allocable to all items of gross income as a class (including income from sales, royalties, and dividends) related to such product category (or categories).[11] A taxpayer shall determine the relevant product categories by reference to the three-digit standard industrial classification code (SIC code).[12]

Where an expense has been allocated to a class of gross income which is included in one statutory grouping (i.e., foreign source passive income under section 904) and the residual grouping (i.e., U.S. source income), the deduction must be apportioned between the statutory grouping and the residual grouping. Where a deduction has been allocated to a class of gross income which is included in more than one statutory grouping, such deduction must be apportioned among the statutory groupings and, where necessary, the residual grouping.

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[8] See IRC §§ 862(b) and 863(b).
[9] See Treas. Reg. § 1.861-8.
[10] See Treas. Reg. §§ 1.861-17(a)(1) and 1.861-8(e)(3).
[11] See Treas. Reg. § 1.861-17(a).
[12] See Treas. Reg. § 1.861-17(a)(2)(ii).

**APPEALS SETTLEMENT GUIDELINE**
**LEGALLY MANDATED R&E EXPENSES**

In order to meet the legally mandated research and experimentation (LMRE) exception, a taxpayer must establish the following criteria as to specific products or processes:

- The expenses were incurred solely to meet legal requirements imposed by a political entity;
- The expenses were incurred with respect to improvement or marketing of specific products or processes; and,
- The R&E results cannot reasonably be expected to generate amounts of gross income, beyond de minimis amounts, outside of a single geographic source.[13]

**Example 1**

Facts: P, a multinational corporation with headquarters in the U.S., is engaged in the business of manufacturing pharmaceuticals. P generates revenues from the sale of its products in both the U.S. and foreign markets. Its global strategy is to develop products that will alleviate or cure certain conditions for the worldwide patient population. P has research facilities in the U.S. and abroad.

In year 1, P completes clinical trials of Phases I, II, and III in the U.S. for Drug A and submits Drug A for FDA approval. In its application, the research results of all clinical trials are included. As a result, the FDA approves Drug A in year 1. In year 2, P submits Drug A for approval in two foreign countries. The two foreign countries require as part of their pharmaceutical approval process all of the research data and results that were submitted to the U.S. FDA.

P submits the results of all such R&E used in the FDA approval process. As a result, the two foreign countries approve Drug A in year 2. P expects upon approval to obtain more than de minimis amounts of gross income from sales of Drug A in each country. From year 2 on, P sells Drug A with approval in the U.S. and in the two foreign countries and generates substantial amounts of gross income in each country. On its U.S. income tax return for year 1, P claims all U.S.-based clinical trials as legally mandated expenses allocated exclusively to U.S. source income.

Result: The clinical trial expenses do not qualify as legally mandated expenses because the R&E expenses were incurred to obtain regulatory approval for Drug A in all three countries and therefore were not required solely by one political entity, and because P reasonably expected the results therefrom to generate more than de minimis amounts of gross income outside a single geographic source.

[13] See Treas. Reg. § 1.861-17(a)(4).

## Example 2

Facts: In year 1, P enters into a co-marketing agreement with an unrelated foreign company to sell Drug B in the U.S. (and only in the U.S.). Drug B was developed by the foreign company outside of the U.S. and has been sold in that foreign market for several years. The co-marketing agreement requires P to perform all clinical tests necessary to obtain FDA approval for the sale of Drug B in the U.S. The co-marketing agreement also provides that the foreign company will reimburse P for one-half of the costs of the required U.S. clinical trials. On its U.S. income tax return for year 1, P claims expenses for all U.S.-based clinical trials as legally mandated expenses allocated exclusively to U.S. source income.

Result: The taxpayer incurred expenses for U.S.-based clinical trials that are required to obtain FDA approval. These R&E expenses incurred by P qualify as legally mandated expenses because they were incurred solely to meet U.S. FDA requirements and, because the co-marketing agreement is limited to the U.S., one may not reasonably expect the R&E to generate gross income (beyond de minimis amounts) outside the U.S. However, the taxpayer may only deduct those expenses for which it was not reimbursed.[14] Accordingly, only the research and experimentation expenses that are deductible under section 174 are subject to allocation and apportionment under the legally mandated rule.

Because determination of whether R&E is legally mandated is fact intensive, documentation is critical in the development of this issue. Estimates or internal interviews of company personnel may not be sufficient in and of themselves to qualify the expense for the legally mandated exception. Companies may have hundreds of projects, products, or processes that will need to be identified since only a small number will get marketing approval.

Foreign clinical data sections of foreign applications need to be provided. Research budgets, company drug review processes, strategic marketing plans, sales projections, annual reports, and FDA correspondence files need to be reviewed. Access to such data will expedite the resolution of this issue, which will ultimately benefit both the taxpayer and the Service.

Pharmaceutical and biotechnology manufacturers typically must obtain regulatory approval for each product, including different dosages, in each foreign jurisdiction in which they sell the product. The regulatory approval process frequently permits the research data amassed in order to obtain approval in one country to be used to obtain regulatory approval in other countries.

To allocate R&E expenditures solely to U.S. source gross income under the LMRE rule of Treas. Reg. §1.861-17(a)(4), a taxpayer must establish that the R&E expenditures in relation to the improvement or marketing of the specific products or processes:

[14] See IRC §§ 174 and 864.

(1) Were not required or used to obtain foreign approval in more than one jurisdiction;

(2) Were incurred with respect to improvement or marketing of specific products or processes; and,

(3) Are not reasonably expected to generate gross income beyond de minimis amounts outside of the U.S.

Failure to meet any of these requirements means that the R&E expenses will not qualify as legally mandated expenses under Treas. Reg. §1.861-8(e)(3) for tax years ending on or before December 31, 1995 and Treas. Reg. §1.861-17(a)(4) for tax years beginning after December 31, 1995.

## SETTLEMENT POSITION

We believe that, in general, LMRE is a factual issue with minimal hazards for the Service for tax years after 1990 and prior to 1998. The purpose of the drug industry initiating the International Conference on Harmonization in 1990 was to reduce costs globally. As the ICH accomplishes its harmonization objectives and as companies utilize ICH guidance and the Common Technical Document to gain approvals for products in the three ICH regions, it becomes more difficult for companies to meet the requirements imposed by Treas. Reg. §1.861-17(a)(4).

Due to the FDA's 1998 guidance, E5: Ethnic Factors, which allows foreign clinical data to be used in any ICH region, we believe that, in general, the hazards for the Service are further decreased from minimal to very minimal on this factual issue for the tax years 1998 through 2002.[15] Thus, R&E expenditures generally are no longer incurred solely to meet the legal requirements imposed by a single political entity and the results therefrom typically produce gross income in multiple countries. Pharmaceutical companies are now satisfying the regulatory and technical requirements of the three ICH regions by using data resulting from their initial R&E. Based on available public information, it is clear that the data generated by pharmaceutical or biotechnology companies will be used to gain approval in multiple jurisdictions for marketing purposes.

[15] There may be a limited exception for products marketed specifically for children between 1997 and 2002. The FDA Modernization Act of 1997 proposed a special requirement for testing pediatric populations on August 15, 1997. The final rule was not promulgated until December 2, 1998, with an effective date of April 1, 1999. On October 17, 2002, the U.S. District Court for the District of Columbia invalidated the regulations requiring pediatric testing, holding that Congress did not authorize the FDA to set a pediatric requirement when it passed the Food, Drug and Cosmetic Act. The federal government decided not to appeal. See "Bush Administration Will Seek New Legislation For Mandatory Pediatric Drug Testing," U.S. Dept. of Health & Human Services News Release, December 16, 2002. However, we note that a continuing added benefit to conducting the more rigorous pediatric testing that was formerly required under the now-invalidated regulations is an extension of the relevant product's patent life as well as six-month market exclusivity for already-patented drugs, thereby protecting them from generic competition. Thus, it may be difficult for taxpayers to establish that even special pediatric testing was performed solely to meet FDA legal requirements.

As previously noted, it was reported in August 2002 that Biogen was the first company to successfully use the CTD to submit applications to the FDA and the European Medicines Evaluation Agency. While the need for an electronic format version of the Common Technical Document (e-CTD) to replace paper submissions was still being discussed in 2002, an article entitled "E-Ticket to Global Harmonization" states, "So although global companies view the **CTD** as important – especially considering that it **is an impending requirement for 2003** – they also view it as a steppingstone to the e-CTD."[16] (Emphasis added.)

Therefore, we believe that, in general, the Service has almost no hazards for 2003 and subsequent tax years. The examples noted above demonstrate clearly that foreign regulatory agencies are accepting applications under the ICH guidelines already. The requirement of Treas. Reg. § 1.861-17(a)(4) that each product must result from research required by a single political entity is a significant hurdle for any of these companies and requires contemporaneous documentation of the data being generated.

The IRS has developed documentation guidance that has been issued in an Industry Director's Directive. The taxpayer and the Service must execute a closing agreement under section 7121 which must comply with the requirements of Rev. Proc. 68-16, 1968-1 C.B. 770.

The focus of this ASG is on R&E costs incurred in the U.S.[17] The question is what percentage of the total section 174 expenses meets the exclusive apportionment rule for LMRE. Expenditures are allocated and apportioned between the statutory and residual groupings under the following three rules:

- First, legally mandated costs imposed by a political entity are allocated directly to the gross income in the SIC code within that geographical source as a class.

- Second, non-legally mandated expenses are apportioned on a geographically based exclusive apportionment rule.

- Finally, any remaining expenditures are apportioned under either the "sales" method or the "gross income" method.

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[16] See "E-Ticket to Global Harmonization" by Wendy Hamilton, Pharmaceutical Executive, December 1, 2002.

[17] It is important to note that a potential product does not have to be successful to be subject to the LMRE and other R&E allocation and apportionment rules. Taxpayers will argue R&E that is ultimately abandoned will not give rise to any gross income outside the United States and therefore all of that R&E should be allocated to U.S. source income. While the taxpayer may not be able to identify a particular project that will be abandoned when the R&E expense is incurred, they will offer to identify statistically a percentage of projects that will be abandoned. This argument ignores the basic tenet of the regulations that research is an inherently speculative activity and that the gross income derived from successful R&E must bear the cost of unsuccessful research.

Therefore, any R&E expenses that do not meet the LMRE requirements must be included in the total R&E pool of expenses to be allocated and apportioned. [18]

[18] It should be noted that this analysis applies equally to the computation of U.S. source combined taxable income in the case of a foreign sales corporation described in sections 921 through 927, as well as in the case of a section 936 possessions corporation, two types of entities that are typically used by pharmaceutical companies.