Task Order No. 5
Contract No. 223-94-8031

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Pharmaceutical Industry Cost Savings Through Use of the Scale-up and Post-Approval Change Guidance for Immediate Release Solid Oral Dosage Forms (SUPAC-IR)

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Final Report
January 7, 1998

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SECTION ONE

EXECUTIVE SUMMARY

During the first half of 1997, the Economics Staff of the U.S. Food and Drug Administration's (FDA's) Office of Planning and Evaluation (OPE) undertook this study of the impact on and cost savings to industry of the Scale-Up and Post-Approval Change - Immediate Release (SUPAC-IR) guidance. OPE staff, with assistance from its contractor, Eastern Research Group, Inc. (ERG), interviewed representatives of six pharmaceutical companies on their experiences with the SUPAC-IR program. Besides information on cost savings, FDA and ERG solicited information on other SUPAC-IR benefits, problems or questions concerning the guidance, and recommendations for further development or enhancement of the program.

Pharmaceutical company representatives praised FDA for establishing a uniform policy for post-approval chemistry, manufacturing and control (CMC) changes, and for bringing openness, consistency, and clarity to the regulatory requirements. All company representatives stated that SUPAC-IR's greatest impact lies in enhancing industry's ability to plan and implement change and manage its resources efficiently. They noted that knowing what is required allows them to implement CMC changes more confidently, quickly, and efficiently. They further commented that SUPAC-IR provides a basis and opportunity to negotiate regulatory "gray areas" with FDA.

Company representatives stated that SUPAC-IR generates substantial savings because it permits:

- Shorter waiting times for site transfers, which reduce plant operating, overhead, and maintenance expenses
- More rapid implementation of process and equipment changes, which can improve yields and reduce the number of failure investigations
- More rapid implementation of batch size increases, which reduces quality control (QC) costs
- Production of fewer unmarketable stability test batches and reduced stability testing
- Reduced administrative costs for documentation of changes by the regulatory affairs departments.

Based on quantitative estimates provided by pharmaceutical company representatives, input from consulting experts, and a forecast of the number of SUPAC-IR submissions during calendar year 1997, ERG estimated that SUPAC-IR will save industry a total of $70.7 million for 1997 CMC changes. Pharmaceutical

companies accrue the largest savings from (1) revenues from previously unmarketable stability test batches, (2) more rapid implementation of site changes, and (3) reduced stability testing costs. Substantially larger cost savings might be realized as pharmaceutical companies become more familiar with and confident about use of SUPAC-IR and as the SUPAC principles are applied to other dosage forms. (During 1997 FDA published the SUPAC guidance for modified release solid oral dosage forms and nonsterile semisolid dosage forms.) Nevertheless, there is considerable uncertainty about the value of cost savings associated with SUPAC-IR filings. These figures represent FDA's best estimates based on the information available and the assumptions used.

All of the company representatives interviewed believe that SUPAC-IR represents an important step in applying scientific principles (along with FDA and industry collaboration) to improving the CMC supplement process. They felt that this effort should go even further and suggested the following improvements and extensions:

Make SUPAC-IR more flexible—Pharmaceutical company representatives want SUPAC-IR to address multiple changes, to expand the types of change allowable as CBEs and ARs, and to permit more effective use of existing resources (such as industry testing and validation work and field investigations) in the approval processes.

Provide more and clearer guidance—Pharmaceutical company representatives want more guidance to address remaining uncertainties with SUPAC-IR. Suggestions include establishing a SUPAC-IR hotline, periodically providing more Question & Answer information with examples of Agency advice, and publishing a preamble-like document with guidance that contains Agency thought and opinion.

Apply SUPAC science and principles more creatively—Pharmaceutical company representatives want a broader and quicker application of SUPAC initiatives. For example, company representatives stated that allowing quick implementation of site changes across dosage forms or establishment types (e.g., analytical testing laboratories, packagers) would provide substantial cost savings without compromising product quality. Further, extending SUPAC principles beyond CMC changes to bulk actives (BACPAC) and to late-stage NDA reviews would have an even greater impact than SUPAC-IR on innovation and industry savings.

Provide adequate training—Several company representatives expressed concern about the possibility of duplicative or inconsistent reviews from headquarters and field offices on certain issues, but had differing opinions on solutions. One representative suggested more training sessions for both FDA (headquarters and field personnel) and industry to assure consistent interpretation and implementation of SUPAC-IR.

SECTION TWO

INTRODUCTION AND METHODOLOGY

During the first quarter of calendar year 1997, the Economics Staff of the U.S. Food and Drug Administration's (FDA's) Office of Planning and Evaluation (OPE), and its contractor, Eastern Research Group, Inc. (ERG) interviewed representatives of six pharmaceutical companies about the Scale-Up and Post-Approval Change - Immediate Release (SUPAC-IR) guidance released in November 1995. The company representatives described the cost savings and operational impacts of this guidance on their companies.

2.1 COMPANIES PROVIDING INFORMATION

ERG contacted several major research-oriented pharmaceutical companies and generic drug manufacturers to assess their practical experience using the SUPAC-IR guidance and their willingness to discuss their experiences with FDA. Because pharmaceutical companies had not yet filed large numbers of supplements covered by SUPAC-IR, the companies were not expected to be able to provide extensive quantitative or statistically valid data on their cost savings under SUPAC-IR. Instead, FDA and ERG sought to acquire as much working knowledge, whether quantitative or not, of industry's experiences to date with this new approach to regulation of many post-approval changes. FDA and ERG held meetings or telephone conference calls with representatives of four large, research-oriented pharmaceutical companies and two generic manufacturers. Discussions lasted about 1 ½ to 2 hours.

2.2 TOPICS OF DISCUSSION

Representatives of participating companies were asked to describe all elements of their experiences with the SUPAC-IR guidance. The discussion was organized around the following topics:

- Current economic environment
- Extent of company experiences with SUPAC-IR

- Nonpecuniary benefits of SUPAC-IR
- Effect of SUPAC-IR on CMC Changes
- Recommended modifications or clarifications of SUPAC-IR

While the principal topic of discussion was the published SUPAC-IR guidance, interviewees also commented on a February 1997 "Question and Answer" (Q&A) document on SUPAC-IR released by FDA and the extension of SUPAC-IR to packaging and analytical testing site changes.

SECTION THREE

SUMMARY OF COMPANY COMMENTS

This section summarizes the comments of representatives of the six pharmaceutical companies interviewed by FDA and ERG. The section begins with a description of the economic context of pharmaceutical company operations, then summarizes representatives' comments by major topic of discussion. The resulting estimates of SUPAC-IR cost savings to industry are discussed in Section Four.

3.1 CURRENT ECONOMIC ENVIRONMENT

Pharmaceutical company interest in seeking post-approval changes stems from factors external to technical process considerations and regulatory requirements. Of primary significance is the wave of pharmaceutical company merger and acquisition activity in the mid-1990s. Major company consolidations generate applications for post-approval changes, especially for plant closings and site changes, as companies strive to avoid process duplication and redundancy in facilities.

Pharmaceutical companies have also been affected by the demands of health care providers for lower cost products. These demands have increased as the purchasing power of large health care providers has grown. In response, pharmaceutical companies have moved to leaner organizational structures. Some aspects of this reorganization involve changes requiring post-approval filings. To achieve cost savings in production, for example, some companies have moved to focus more on core production competencies and outsource less critical activities, resulting in site change requests. To minimize excess production capacity and achieve production efficiencies, companies also make other post-approval changes.

With the phase out of tax benefits for Puerto Rican operations, another wave of site changes is occurring as companies shift production operations from Puerto Rico to the mainland United States. During the interviews, some company representatives reported that they can lower production costs by shifting operations back to mainland U.S. facilities.

Pharmaceutical companies are also interested in post-approval changes for a range of other reasons that are virtually always present. For example, some companies routinely seek site changes over the life cycle of their products as their drug markets peak and ebb. Companies also seek changes to take advantage of technological changes, respond to shifts in market preferences, and respond to competitive pressures.

3.2 EXTENT OF COMPANY EXPERIENCES WITH SUPAC-IR

Pharmaceutical companies are at different points on the SUPAC-IR learning curve. Of the six pharmaceutical companies included in this study, the two generic producers have been most active in "trying out" SUPAC-IR, with each making a handful or more supplement submissions or annual report changes. The major pharmaceutical manufacturers have made only one or two submissions under SUPAC-IR, except for Company 2, which anticipates future filings for site changes.

The pharmaceutical company representatives interviewed were all broadly supportive of the SUPAC-IR program and made a number of comments on its specific benefits. They stated that SUPAC-IR provides a framework that provides consistency in filings and during the review process (Companies 1, 3, 4). They also interpreted SUPAC-IR as reflecting a shift at FDA toward greater openness and communication, and toward a willingness to discuss company strategies for obtaining approval prior to preparing submissions (Companies 1 and 3). These are considered strikingly positive developments.

The representatives of all companies anticipated important future benefits from SUPAC-IR as a result of shorter implementation periods for post-approval changes. These benefits are perhaps most significant for changes in manufacturing sites, but also apply to changes in packaging and analytical testing sites. By being able to change manufacturing sites without prior approval supplements, companies estimated that they would be able to implement changes from 6 to 24 months earlier. Cost savings accrue from several sources:

- Companies have greater and more immediate control over planning and managing change, providing efficiency gains throughout their operations.
- If the existing plant is to be closed, companies generate savings from avoiding excess overhead and capacity.

- If the existing plant is not closed, companies can consolidate production and free capacity for new products.

Companies estimated that cost savings for individual cases could be millions of dollars. One company reported that, had SUPAC-IR been in place several years earlier, the company would have saved over $10 million in unnecessary overhead expended while trying to shut down a large production facility (Company 2). Another company stated that under SUPAC-IR it had saved $4.6 million from earlier closing of a plant that manufactured 3.5 billion consumption units annually (Company 4).

The effect of SUPAC-IR on the ease of making formulation changes and scaling processes up or down seemed comparatively more important to generic companies (Companies 5 and 6), although the major research companies also mentioned these areas of increased flexibility (Companies 1, 2, and 3). Representatives of Companies 1 and 2 stated that more rapid equipment changes will eventually be an important area, although none of the companies appeared yet to have achieved significant savings in this area. Nevertheless, one company felt that SUPAC-IR was not flexible enough as currently defined to have much effect on prospects for post-approval changes, while expressing hopeful expectations for the program as a whole (Company 2).

While supportive, the companies used various approaches to address certain concerns or uncertainties about the program. For example, companies varied in their confidence that a SUPAC filing would be accepted and some companies were particularly concerned about the potential risk implicit in making CBE filings, where the company implements a change without an explicit FDA approval. Company 3 was preparing several SUPAC-IR submissions, but also had prepared sufficient data to support filing of conventional supplements should they be required. One company's representatives (Company 2) reported that they would rather submit prior approval supplements (and incur the associated regulatory wait) than risk "being wrong."

Some companies also noted potential savings because SUPAC-IR generally requires that only one batch be placed on stability testing instead of the three batches previously required (Companies 1 and 3). Also, the reduced wait for regulatory approval often means that test batches that previously became unmarketable due to "shortdating," (i.e., that they are too close to their expiration to be sold) can be successfully marketed (Companies 1, 3, 4, 6). None of the company representatives reported any savings from the reduced requirements under SUPAC-IR for invivo bioequivalency tests. The representatives noted that they generally attempted to avoid post-approval changes that might require performance of these costly tests.

Among the companies visited, innovator and generic pharmaceutical company perspectives on SUPAC-IR appeared to differ. The generic companies appeared to be more aggressive in seeking any additional flexibility that would allow them a quicker response to market conditions. Innovator companies have moved more deliberately and desired greater certainty about how their post-approval changes would be addressed. Representatives of all companies appreciated SUPAC-IR and any or all additional clarity FDA can provide.

3.3 NONPECUNIARY BENEFITS OF SUPAC-IR

Company representatives uniformly praised SUPAC-IR for its effects in (1) improving their company's ability to develop plans, manage its resources, and implement change, and (2) enhancing the clarity of regulatory requirements for post-approval changes. These effects, while generally not quantified by the companies, are substantial and as important as any other benefit from SUPAC-IR.

Company representatives welcomed the greater control over their own resources and the beneficial effect on company planning provided by SUPAC-IR (Companies 1, 2, 3, 5). Benefits also accrue from shorter waiting times for changes that can now be filed as Changes Being Effected (CBEs) or annual reports. This increased flexibility allows companies to respond more quickly to market changes, to manage internal resources more efficiently by allowing easier out-sourcing of routine tasks (especially for testing or packaging services), to reduce raw material costs by reducing batch sizes for test and/or validation batches, and to institute other improvements.

Nearly all company representatives also appreciated the clarity that SUPAC-IR brings to post-approval changes and the resulting consistency in FDA reviews (Companies 1, 3, 4, 5, and 6). Company 5 representatives noted that previously it was sometimes unclear which changes were allowed as CBEs. Also, Company 3 representatives emphasized that, by specifying test requirements, SUPAC-IR reduces the amount of testing the company performs that might not be required. SUPAC-IR guidance represents an important benchmark for FDA reviewers, for discussions between field and headquarters personnel, and for company negotiations with FDA (even about non-SUPAC changes). Company 4 representatives also noted that the new clarity helps to create a "level playing field between generic and name-brand companies." The company previously questioned whether generic companies were being held to the same standards in inspections and enforcement actions as the major research companies.

3.4 EFFECT OF SUPAC-IR ON CMC CHANGES

The pharmaceutical company representatives reported that SUPAC-IR has a slightly positive effect (Companies 1, 2, and 5) or essentially no effect (Companies 3, 4, and 6) on their willingness or ability to undertake technological changes. However, the primary consideration for making changes is cost efficiency. Some commented that investments in technological change, which are most likely to be needed for old processes, are constrained principally by the often poor return on such investments (Companies 1 and 3). Revenues from older products are often simply too small to warrant new investment. Company 3 representatives noted that validation costs for process changes are often quite significant and represent a larger share of the cost of CMC changes than regulatory requirements.

Some company representatives stated that U.S. processes do not lag behind state-of-the-art process technology used in the rest of the world (Companies 3, 4, and 5). Company 5 representatives noted that they find it easier to make process or equipment changes in their non-U.S. plants, but their U.S. facilities are still technologically up-to-date. Company 3 representatives commented that NDAs for older processes did not specify as many equipment details as more recent NDAs, so many updating changes have historically been allowed as annual report changes.

Company representatives were also asked whether SUPAC-IR created new filing or documentation requirements in any areas. Representatives of two companies (2 and 4) noted that SUPAC-IR requires dissolution tests for certain products where no such tests were previously required. They said that in some instances the dissolution tests should not be necessary. Also, Company 1 stated that under SUPAC-IR it had to submit specifications for changes in blending time that were not presented in their New Drug Application (NDA). Thus, companies making changes to older processes might have to develop specifications for certain process parameters in order to show FDA that their change can be treated within the SUPAC-IR program.

3.5 SUGGESTED MODIFICATIONS TO OR CLARIFICATIONS OF SUPAC-IR

The pharmaceutical company representatives suggested several modifications or additions to the SUPAC program. The most common suggestion was to extend SUPAC-IR concepts into new areas. For example, the representatives suggested that FDA apply SUPAC principles to all dosage forms and to the late stages of the

NDA application process. The company representatives noted that the underlying science of SUPAC suggests that the program can be applied more broadly. Several company representatives wished that SUPAC-IR addressed a broader range of possible changes, noting that process changes rarely occur in isolation and many of the comparatively simple changes addressed in the guidance must be combined with related process changes that are not addressed (Companies 1, 2, 5, and 6). Company 3 also suggested that there should be an option for filing a CBE for equipment changes. (SUPAC-IR defines equipment changes only for Level 1—annual report changes, and Level 2—prior approval supplements.)

Some representatives were frustrated that the impact of SUPAC-IR is limited by the current CFR requirements that prohibit specification changes. Thus certain process or formulation changes that lead to specification changes (that are not allowed under the CFR) cannot be made under the SUPAC-IR guidance (Companies 1 and 5). Representatives of three companies strongly encouraged FDA to broaden SUPAC to cover bulk actives, stating that potential raw material savings in this area are perhaps higher than other savings under SUPAC-IR (Companies 1, 2, and 3). Company representatives also encouraged FDA to expand the SUPAC-IR guidance to cover packaging for all dosage forms (Companies 1, 2, and 3). Company 2 representatives, for example, noted that packaging site changes among domestic locations do not cause problems. Representatives of Companies 3 and 4 also recommended that SUPAC concepts be extended to the late stages of NDA reviews.

Several company representatives (Companies 1, 2, and 4) were concerned that SUPAC does not resolve the possibility of duplicative reviews by FDA headquarters and field offices, although the company's specific concerns varied. On SUPAC-IR decisions regarding the equivalence of equipment, Company 1 representatives preferred that the decisions of headquarters' reviewers prevail, whereas Company 2 representatives preferred to see field reviews of equipment validation data be the determining review. Company 4 suggested that headquarters reviewers were better prepared to evaluate conformity with ICH guidelines for stability testing.

As well received as it is, SUPAC-IR does not quench the industry's thirst for guidance. Company representatives requested further guidance to clarify the content of SUPAC-IR (Company 2) or to clarify the "such as" terminology used in the equipment guidance and elsewhere (Company 6). FDA's efforts to date to expand on the SUPAC-IR guidance, such as the Q&A letter and the draft equipment guidance, have produced still more requests for guidance. For example, several companies did not understand or questioned the consistency of one or more elements of the Q&A letter to industry with other requirements or guidance (Companies 1, 2, 3, and 4). Similarly, some felt that the additional draft equipment guidance needed to be

clarified further and raised a number of new questions (Companies 1, 2, 4, and 5). Nevertheless, Company 4 representatives suggested that FDA provide more feedback in the form of industry Q&A releases, commenting that this type of compilation of previous industry questions is quite helpful. The representatives also encouraged site visits and other efforts such as this study of SUPAC-IR because they provide a direct conduit for industry feedback to the Agency without even the filtering through the trade associations. Company 4 also suggested that FDA provide preamble-type explanations of its SUPAC decisions to provide more background and contextual information for the Agency decisions.

Company 4 representatives also recommended more training for both industry and FDA so that the meaning and intent of SUPAC-IR is clarified further and consistently applied. Representatives of Companies 1 and 4 expressed some concern that SUPAC-IR is not consistently applied by field and headquarters offices.

Similarly, while companies appreciate the ability to effect changes more rapidly, several noted that the SUPAC-IR system is valuable as long as FDA can respond quickly to their requests. Company 3, for example, noted that if questions on SUPAC-IR requirements or interpretations take a few months to answer, they might not generate much savings compared to prior approval supplements. Company 4 representatives requested that the SUPAC-IR committee meet weekly rather than biweekly. Company 2 representatives suggested a SUPAC-IR "hotline" to speed responses to inquiries. Company 6 representatives felt that it must follow up its SUPAC-IR requests for rulings or clarifications with telephone calls to ensure a timely response. Representatives of several companies suggested that FDA should continue trying to reduce SUPAC-IR review times (Companies 1, 2, 3, 4, 6).

Additionally, company representatives (Companies 2 and 3) were concerned whether they would be able to schedule GMP inspections in time for their SUPAC-IR submissions to go forward expeditiously. The representatives requested that FDA develop a clear policy for scheduling GMP inspections.

Company representatives also wished to see clearer links between SUPAC-IR and other overlapping or related requirements. For example, Company 3 representatives noted that SUPAC-IR authorizes a wider range of CBEs but export rules do not clearly authorize shipments of pharmaceuticals that are not formally "approved."

SECTION FOUR

PHARMACEUTICAL INDUSTRY COST SAVINGS GENERATED THROUGH USE OF SUPAC-IR

This section presents an estimate of savings that industry will realize by following SUPAC-IR guidance for Chemistry, Manufacturing and Control (CMC) post-approval changes. The discussion begins with a description of the types and numbers of post-approval changes that generate savings under SUPAC-IR (Section 4.1). This is followed by estimates of savings per change and total annual savings to industry (Section 4.2). Methodology details are provided in Appendix A.

In discussing industry SUPAC submissions, it is useful to define terminology. The term "filing" is used to refer to a complete SUPAC supplement. A given filing might include several specific "changes," such as both manufacturing and packaging site changes. Most cost savings calculations are based on the count of changes forecast for all SUPAC-IR filings for 1997. The discussion also refers to the products represented in supplement filings. Individual pharmaceutical products are sometimes represented in several supplement filings.[1]

4.1 FREQUENCY AND TYPE OF SAVINGS

Table 1 presents estimates of the number of 1997 CMC changes that will be made under SUPAC-IR filings in 1997. FDA's Office of Planning and Evaluation staff estimated the total number of PA and CBE filings for 1997 based on a linear regression analysis of submissions from January through August 1997. FDA forecast the number of submission filings for 1997 at 55 prior approval supplements and 270 CBEs. To derive the total number of changes represented, ERG inflated the forecast to reflect the multiple changes (such as combined manufacturing, packaging, and testing site changes) included in many filings. ERG also estimated the total

[1]ERG determined the number of products represented in supplements by examining the NDA and ANDA application numbers and their original approval dates, as reported in a sample of supplement filings covering the first half of 1997. ERG assumed that all NDAs or ANDAs with sequential application numbers and the same original month of approval referred to the same drug product.

Table 1

Estimated Number of Post-Approval CMC Changes That Will Generate Primary Savings Under SUPAC-IR (1997)

Type of Post-Approval Change	Estimated Number of SUPAC-IR Post-Approval Changes, by Type of Filing			Changes That Will Generate Savings Under SUPAC-IR				Source of Savings
	PA	CBE	AR(a)	PA	CBE	AR	Total	
Site change Case 1 - closing manuf. facility	8	40	68		X		40	Reduced implementation time allows earlier plant closure, avoided overhead
Site change Case 2 - process consolidation	8	40	68		X	X	108	Reduced implementation time allows earlier capture of production cost savings
Site change Case 3 - testing site change	8	52	NA (b)		X		52	Reduced implementation time allows capture of lowered production costs
Site change Case 4 - packaging site change	4	58	NA (b)		X		58	Reduced implementation time allows capture of lowered production costs
Manufacturing - process	9	45	56		X	X	101	Reduced implementation time allows savings from yield improvements
Manufacturing - equipment	10	48 (c)	59		X	X	107	Reduced implementation time allows savings from yield improvements, solved equip. problems
Components and composition	2	9	11			X	11	Reduced implementation time allows savings from reduced batch failures
Batch size Scale-up	12	61	76		X	X	137	Reduced implementation time allows savings from fewer QC tests
Scale down	0	0	0		X	X	0	Reduced implementation time allows savings from validation testing on smaller batches
Total Changes	61	353	338				614	

PA= Prior Approval CBE= Change Being Effected AR= Annual report NE= Not Estimated NA= Not Applicable

(a) According to an industry study, pharmaceutical companies submit approximately 1.25 ARs for each CBE supplement filed (Shah, 1997).

(b) No AR changes for testing or packaging site changes are defined under SUPAC-IR.

(c) These equipment changes would have been classified as AR changes but were coupled with other CBE changes; as a result, they were classified as CBE changes.

Note: Totals may not add due to rounding.

number of annual report filings (338) based on data from an industry survey indicating that, under SUPAC-IR, pharmaceutical companies have prepared approximately 1.25 annual reports for each CBE filing (Shah, 1997).[2]

After generating these totals, ERG distributed the post-approval changes by type of change (site change, process change, etc.) based on CDER's data on 1997 filings to date. Because this listing does not distinguish manufacturing site changes that involve plant closures from those that are simply transfers of manufacturing between active plants, ERG distributed these changes evenly between these two categories.

Table 1 also identifies the types of changes, by regulatory category, that generate the primary savings (defined as those generated by post-approval changes to the manufacturing process) under SUPAC-IR.[3] Most savings are generated by those SUPAC-IR changes classified as CBEs or annual reports.

Under SUPAC-IR, pharmaceutical companies may also realize savings from reduced testing, reduced inventory costs, and less formal filing or documentation requirements for CMC changes. These are defined as secondary savings because they are not generated directly in the manufacturing process but indirectly in the testing and administrative efforts related to preparing regulatory submissions, and in inventory. Also, these savings apply only once for each product addressed by supplement filings (assuming the filings are roughly simultaneous), regardless of the number of supplements filed at a time or the number of changes embodied in the filings. That is because a pharmaceutical company combines simultaneous changes into its production processes and incurs only one set of stability testing costs (or one set of other expenses) related to obtaining regulatory approval for the changes. Table 2 lists the types, numbers, and sources of these secondary savings. Based on discussions with product consultants and industry personnel, ERG estimated the frequency with which secondary savings arise among products undergoing changes. Because one product may be subject to more than one

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[2]The annual reports estimate under SUPAC-IR represents about eleven percent of annual report submissions for NDAs and ANDAs for immediate release products. FDA's Center for Drug Evaluation and Research (CDER) analyzed a random sample of 140 annual reports received between July 1996 and July 1997 and found that about three percent of the 3,131 NDA and ANDA annual reports for immediate release products included SUPAC-IR changes. This finding of three percent is believed to be a lower bound of future SUPAC-IR annual report changes because (1) there is typically an 18-24 month lag between making changes and reporting those changes to FDA in an annual report, and (2) the industry use of SUPAC-IR has dramatically increased during calendar year 1997.

[3]Packaging and testing site changes are also counted as primary saving categories.

Table 2

Type, Number, and Source of
Secondary Savings Under SUPAC-IR (1997 Estimate)

Category of Savings	Ratio of Distinct Products Represented In Relevant Supplements and ARs PA	CBE	AR (a)	Percent of Products Affected (%)	Estimated Number of Changes Resulting in Savings (b)	Source of Savings
Stability testing						
Savings in testing costs	25%	60%	60%	100%	379	Testing of fewer lots required to verify safety of change
Incremental revenues from previously unmarketable batches	NA	60%	60%	50%	182	Fewer batches become unmarketable
Bioequivalence testing	NA	60%	60%	5%	18	Bioequivalence tests required less frequently
Reduced Inventory	NA	60%	60%	100%	365	Inventory costs to store stability batches are lowered
Administrative costs for change documentation	NA	NA	60%	100%	203	Less formal reporting required for documenting changes

PA= Prior Approval CBE= Change Being Effected AR= Annual report NE= Not Estimated NA= Not Applicable
(a) The ratio of products represented to number of annual reports is assumed to be the same for annual reports as for CBE supplements.
(b) Calculated by multiplying the relevant percentages of supplements or annual reports by the total number of post-approval changes forecast for 1997. The forecast is 55 Prior Approval supplements, 270 CBE supplements, and 338 annual reports.

simultaneous filing, the number of products affected is substantially smaller than the number of SUPAC-IR changes forecast. In general, the number of potentially affected products was estimated at 25 percent of the forecast of PA supplements (where PA supplements generate savings) and 60 percent of the forecast of CBE supplements and annual reports.[4] This estimate was further reduced by the likelihood (as estimated through discussions with project consultants and industry personnel) that specific types of savings would apply to products undergoing changes. For example, the potential savings under SUPAC-IR from reduced requirements for bioequivalence testing was estimated to apply to only 5 percent of products for which supplements are filed.

4.2 AGGREGATE COST SAVINGS ESTIMATE

Table 3 presents estimates of total savings to industry under SUPAC-IR, broken down by the type of post-approval change. As described above, ERG estimated the number of changes by type generating savings and the source of savings (from Tables 1 and 2). ERG also estimated the savings generated per change. Based on discussions with pharmaceutical industry personnel and project consultants, ERG developed conservative estimates of industry's avoided costs for reduced regulatory burdens under SUPAC-IR.

To reflect the distribution of manufacturers making post-approval changes, ERG prepared high, medium, and low estimates of these savings. The high estimates are for post-approval changes to relatively high-value products or otherwise reflect the circumstances that generate high savings. The medium estimates represent savings for average-value products or circumstances, while the low estimates represent savings for low value products or circumstances where savings are relatively modest. ERG assumed that the high, medium, and low estimates apply to 5 percent, 60 percent, and 35 percent of post-approval changes, respectively. This reflects the expectation that most savings fall in the low to medium range, and that the savings distribution curve has a long tail to the right (reflecting occasional very large savings).

To estimate total annual savings that industry will realize for a type of change, ERG:

[4]The 1997 SUPAC-IR submissions were reviewed to determine how many products were represented for a given sample of supplements submitted under the SUPAC-IR guidance. ERG determined that for prior approval supplements there were approximately 4 supplements for each product represented. For CBEs, ERG estimated that the number of products represented was approximately 60 percent of the number of supplements.

Table 3

Summary of Annual Pharmaceutical Industry Cost Savings Anticipated Under SUPAC-IR

Type of Post-Approval Change	Estimated Changes or Filings That Will Generate Savings	Source of Savings	Savings per Change ($000) and Share of Changes to Which Savings Apply (%) High	Medium	Low	Total Annual Savings ($000)
Primary Savings Categories						
Site change Case 1 - closing manuf. facility	40 (a)	Reduced implementation time allows earlier plant closure, avoided overhead	$1,650 5%	$990 60%	$180 35%	$9,786
Site change Case 2 - process consolidation	108	Reduced implementation time allows earlier capture of production cost savings	$375 5%	$150 60%	$38 35%	$13,126
Site change Case 3 - testing site change	52	Reduced implementation time allows capture of lowered production costs	$75 5%	$30 60%	$15 35%	$1,413
Site change Case 4 - packaging site change	58	Reduced implementation time allows capture of lowered production costs	$75 5%	$30 60%	$15 35%	$1,566
Manufacturing - process	101	Reduced impl. time allows savings from yield improvements	$125 5%	$25 60%	$3 35%	$2,252
Manufacturing - equipment	107	Reduced impl. time allows savings from yield improvements, solve equip. problems	$41 5%	$8 60%	$0 35%	$750
Components and composition	11	Reduced impl. time allows savings from reduced batch failures	$90 5%	$30 60%	$10 35%	$286
Batch size Scale-up	137	Reduced impl. time allows savings from fewer QC tests	$50 5%	$20 60%	$10 35%	$2,466
Scale down	0	Reduced impl. time allows savings from valid. testing on smaller batches	$100 5%	$50 60%	$20 35%	$0

(cont.)

Table 3 (cont.)

Summary of Annual Pharmaceutical Industry Cost Savings Anticipated Under SUPAC-IR

Type of Post-Approval Change	Estimated Changes or Filings That Will Generate Savings	Source of Savings	Savings per Change ($000) and Share of Changes to Which Savings Apply (%) High	Medium	Low	Total Annual Savings ($000)
Secondary Savings Categories						
Stability testing						
Savings in testing costs	379	Testing of fewer lots required to verify safety of change	$70 5%	$25 60%	$17 35%	$9,212
Incremental revenues from previously unmarketable batches	182	Fewer batches become unmarketable	$1,000 5%	$100 60%	$50 35%	$23,256
Bioequivalence	18	Bioequivalence tests required less frequently	$750 5%	$250 60%	$70 35%	$3,867
Inventory	365	Inventory costs to store stability batches are lowered	$27 5%	$5 60%	$3 35%	$2,019
Regulatory affairs	203	Less formal reporting required for documenting changes	$10 5%	$5 60%	Negligible 35%	$710
Total						$70,710

Totals do not add due to rounding.

(a) It was assumed that each facility closing is reflected in the supplements of several products; the number of supplements was divided by three before savings were calculated.

- Multiplied the total number of changes that will generate savings by 5 percent, 60 percent, and 35 percent to obtain the numbers of changes generating high, medium, and low savings;
- Multiplied each of these numbers by the estimated savings per change for high, medium, and low savings changes, respectively;
- Added these values to obtain total savings for the type of change (shown in the last column in Table 3.

ERG derived an overall savings to industry of $70.7 million per year. Pharmaceutical companies are expected to accrue the largest savings from (1) revenues from previously unmarketable stability test batches, (2) more rapid implementation of site changes, and (3) reduced stability testing costs. Larger cost savings might be forecast as pharmaceutical companies become more familiar with and confident about use of SUPAC-IR.

The paragraphs below briefly explain the savings estimates for each type of post-approval CMC change. ERG's methodology is described in more detail in the explanatory notes in Appendix A.

Manufacturing site closing. The site change estimate reflects savings that companies realize in being able to close manufacturing facilities more quickly under SUPAC-IR. Quicker closings reduce expenditures for plant overhead and other costs, such as building rental or depreciation, basic plant utilities, and essential building maintenance. In calculating these savings, ERG recognized that site closings generally will involve movement of several products from the closing facility. Therefore, the company would submit several site change supplements, one for each product. This pattern was also confirmed by the site visit discussions with pharmaceutical companies. ERG assumed that companies will file an average of three supplements per plant closing, so divided the number of changes by three to estimate the number of closings that generate savings.

One major brand-name manufacturer estimated that it had accrued savings at a rate of approximately $4.6 million/year under SUPAC-IR by being able to close a facility more rapidly. Project consultants estimated, however, that most site closings would generate lower savings. ERG estimated the savings to range from $1.65 million to $180,000 per change, depending on the scale of the manufacturing operation and other factors. Based on these savings per site change, ERG estimated the total annual savings to industry to be about $10 million per year.

Manufacturing site transfers. Companies often shift manufacturing locations to better utilize their existing production capacity. These changes can allow a company to (1) add products and increase production

capacity while avoiding the costs of building expansion, (2) respond to a surge in demand to avoid the use of contract manufacturing services, or (3) rationalize production operations, thereby reducing costs. To estimate savings, ERG assumed faster implementation of site transfers would save companies 5 percent of their product manufacturing costs. This estimate represents direct savings in manufacturing costs (or avoided contract manufacturing charges) and incremental savings related to the less readily quantifiable benefits from improving plant utilization. Based on this assumption, ERG estimated savings at $375,000 to $37,500 per change, for an annual industry total of $13 million.

Testing and packaging site changes. Testing and packaging changes include (1) adding a testing or packaging contractor to expand capacity, (2) moving these operations from one contractor to another, and (3) moving operations from one internal facility to another. ERG judged that, while the circumstances of packaging and testing site changes vary, these changes will result in a direct production cost savings or an indirect savings in avoided contractor charges or improved production flexibility. ERG estimated the average combined savings and benefits at 1 percent of production costs. It is unlikely that companies will realize larger savings in direct production costs because most packaging costs are irreducible raw material or labor costs and most testing costs are irreducible equipment or labor charges. This cost savings translates to $75,000 to $15,000 in savings per change. Together, testing and packaging site changes will generate an estimated savings of $3 million per year.

Process changes. Process changes improve yields and/or process or quality control. While companies can sometimes make process changes that improve yields by 2 to 3 percent, process changes classified as SUPAC-IR Level 1 or 2 changes generally will not be sufficiently dramatic to generate such yield improvements. One generic manufacturer reported making three minor process changes under SUPAC-IR that saved $10,000 in total. Based on discussions with project consultants and pharmaceutical company representatives, ERG estimated an average yield improvement of ½ percent. This translates to savings of $125,000, $25,000, and $3,000 per change for the high, medium, and low estimates, respectively. The annual industry total was calculated at $2.25 million per year.

Equipment changes. Pharmaceutical companies usually make equipment changes to address specific equipment problems that do not affect yields. Only occasionally do these changes improve yields. ERG estimated that quicker implementation of equipment changes save companies about a third of the savings they realize from process changes (except at the low end where savings were assumed to be negligible). ERG thus estimated high-

end savings at $41,000 per change and medium savings at $8,000 per change. In total, these savings amount to approximately $0.75 million per year.

Composition changes. Composition changes are most likely to occur in response to production problems and are less likely to generate yield benefits than either process or equipment changes. Assuming that most composition changes address production problems, companies benefit from reductions in the cost of failure investigations, product rework, and other quality control activities. Using an estimated avoided cost of $5,000 per failure investigation, and estimates of the number of failure investigations avoided, ERG calculated savings ranging from $90,000 to $10,000 per year. The industry total savings was calculated at approximately $0.3 million per year.

Batch scale changes. SUPAC-IR provisions for scale-up allow companies to change batch sizes more rapidly, thereby generating savings in production costs, quality control (QC) testing costs per unit of product, raw material release activities, production labor, and other production-related costs. Also, manufacturers effectively increase their production capacity by making fewer larger batches. ERG based savings estimates primarily on the reduction in the QC costs from the manufacture of fewer batches. The savings were estimated at $50,000 to $10,000 per scale-up change, resulting in total annual savings of $2.5 million per year. FDA's data did not include any submissions for scale-down changes, so ERG did not project savings for these changes.

Stability testing. SUPAC-IR reduces accelerated and long-term stability testing costs for many post-approval changes. Most significantly, SUPAC-IR reduces stability test requirements from three batches to one. For a representative batch, the per-batch cost of stability testing (for the entire gamut of accelerated testing and long-term stability tests) is approximately $10,000 to $15,000. ERG, therefore, estimated the medium-level savings from production of two fewer stability batches at $20,000 to $30,000 ($25,000 midpoint). The savings apply to each distinct pharmaceutical product addressed in CBE and annual report filings, as estimated in Table 2. Multiplying the reduction in testing costs by the number of products affected generates total annual savings estimated at $9.2 million per year.

Fewer unmarketable batches. With long regulatory leadtimes, stability batches often become "short-dated." That is, they are not released for sale until their time to expiration is too short for the batches to be marketable. Under SUPAC-IR, leadtimes are reduced, so more batches can be marketed. One company

estimated that it saved $4 million from being able to sell stability batches that otherwise would have been lost. ERG estimated total annual savings to industry to be $23.3 million per year.

Bioequivalence testing. In selected circumstances, SUPAC-IR eliminates the need to perform bioequivalence testing. Prior to SUPAC-IR, this requirement was invoked infrequently for a post-approval change, however, so that the savings from eliminating this requirement is assumed to apply to only 5 percent of the affected products. The reduced requirements for bioequivalency testing, while quite significant in individual cases, generates an aggregate industry savings of $3.9 million.

Inventory. Under SUPAC-IR, companies will incur lower inventory costs because fewer stability batches are stored for shorter periods of time. Inventory costs represent primarily the time value of money expended to manufacture batches put into storage. ERG estimated the inventory savings to range from $27,000 to $2,700 per change, resulting in total annual savings of $2.0 million.

Administrative costs to document changes. Most industry representatives and project consultants judged that preparing ARs for many SUPAC-IR changes is less time-consuming than preparing the supplement filings (CBEs or PA supplements) previously required. ARs generally require less followup with FDA (i.e., for responses to questions or requests for clarification). ERG estimated the savings to range from $10,000 to zero per change, resulting in total annual savings at $0.7 million per year.

SECTION FIVE

REPORTS ON INTERVIEWS WITH PHARMACEUTICAL INDUSTRY REPRESENTATIVES

COMPANY 1

This large pharmaceutical company manufactures products under more than 100 NDAs and approximately as many ANDAs. Overall, about half the products are solid oral dosage, immediate-release drugs.

EXTENT OF EXPERIENCE USING SUPAC-IR GUIDANCE

The company has used SUPAC as the basis for categorizing two post-approval changes as annual report changes. The company is also developing a few post-approval changes that are likely to be covered by SUPAC-IR, including a site change and a manufacturing equipment change.

The company had also considered using SUPAC-IR for a set of changes to one of its products (a manufacturing site change, a change in batch size, and a change in the blender model). It had requested case-specific guidance from FDA and was told it could proceed with the changes under SUPAC-IR but, for the equipment change, must also inform the field office about the changes. (At the time, the appropriate approach under SUPAC-IR to a group of simultaneous changes such as these was less clear.)

The company has recently made a number of site changes for which it has not been able to use SUPAC-IR because most involved a new source of the active ingredient—a type of change that SUPAC-IR does not address. For some of these site changes, the company also made fairly complex process changes because it knew that the projects would in any case be considered preapproval supplements. The company plans to make three to five site changes over the coming year. (Two or three site changes per year would be more typical.)

The company has also made more than a dozen analytical testing laboratory changes over the past year, but none were for immediate-release dosage forms. It is preparing for one more laboratory site change. Overall, it has approximately two dozen post-approval changes in the works, but they are all preapproval supplements.

Company representatives described how it will integrate the increased flexibility of SUPAC-IR into its approach to making post-approval changes. They stated that first it will make the changes SUPAC-IR would allow and then gradually make other changes as appropriate. Thus, the company might first change a manufacturing site and then upgrade the processes that were moved. The latter might include significant changes to equipment or a change in the supplier of the bulk active ingredient. The representatives expressed confidence that SUPAC-IR will help them make equipment changes much more quickly as they gain experience using it.

The representatives noted that there might be some risk inherent in pursuing modifications as Changes Being Effected (CBEs), but they are confident that their decisions and approach will be acceptable to FDA. Changes are reviewed by 10 to 12 chemists at this company before being reviewed by two more chemists at FDA.

COST SAVINGS ACHIEVED OR ANTICIPATED USING SUPAC-IR GUIDANCE

With only limited experience using SUPAC-IR, the company has relatively little quantitative data on cost savings. Nevertheless, the representatives expect to realize cost savings from reduced waiting time for post-approval changes. For site changes, the reduced wait will reduce plant overhead costs for facilities being closed and/or consolidated. It also allows considerable rationalization of manufacturing, packaging, and testing operations. For recently introduced products especially, the company's entire planning process benefits from the more clearly defined requirements. In the future, equipment changes to upgrade processes and batch size changes will also generate significant savings.

The company also expects to save on stability testing costs because fewer batches must be tested. Company representatives noted that elimination of accelerated stability testing in some cases could lead to substantial savings. Accelerated testing for a single strength and single package costs approximately $10,000 for each time interval at which testing occurs. Most products involve multiple strengths and/or packaging, however, and costs generally run $50,000 to $100,000 per product. A reasonable average cost is $65,000 to $70,000 per product. Nevertheless, the company representatives mentioned that the reduced waiting time was much more important than savings on testing costs.

Several other cost savings are anticipated:

- Company representatives noted that SUPAC-IR generates cost savings because companies are more likely to be able to sell test batches of products when they can implement changes more quickly.

- The company acknowledged the possibility that in selected cases SUPAC-IR will reduce the number of bioequivalency tests required.

- The company looks forward to improved flexibility to respond to market changes by increasing or decreasing manufacturing capacity through batch size changes.

The representatives estimated that when a post-approval change is reclassified from a preapproval supplement to an annual report item, there is no labor or cost saving for the regulatory affairs staff. The internal data-generation and report-writing requirements are essentially the same in the two cases.

ADDITIONAL BENEFITS OF THE SUPAC-IR PROGRAM

Company representatives noted that SUPAC-IR will provide savings by widening their latitude to plan changes and more efficiently manage their resources. In order of economic importance, these savings will accrue from site changes, scale changes, and equipment changes.

The representatives anticipate that the speed at which many post-approval changes are made will improve substantially. They noted that packaging site changes, for example, previously had often required as much as a year.

The representatives appreciate that in dissolution profiling, FDA allows equivalent test definitions, which had proved helpful for several products. They also appreciate that SUPAC-IR covers changes to flavorings because these are not addressed in the applicable Code of Federal Regulations (CFR).

The representatives feel SUPAC-IR provides a framework for achieving consistency in review decisions. They also noted that if user fees are not renewed, companies will have alternatives in place for implementing change more quickly.

ADDITIONAL ACTIVITIES REQUIRED UNDER SUPAC-IR

Company representatives did not describe any new testing or documentation requirements under SUPAC-IR.

EFFECT OF SUPAC-IR ON CMC CHANGES

The company expects the rate of post-approval filings to increase, although the overall effect of SUPAC-IR on technological change is not great. While equipment modifications will be made more readily, there are many new technologies that the company will not attempt to apply to its numerous older products, such as continuous coating processes. The representatives stated that most prescription products manufactured under older NDAs lack the sales volume to warrant major process changes.

RECOMMENDED MODIFICATIONS OR CLARIFICATIONS OF SUPAC-IR

Initially, company representatives felt that FDA's response to questions requesting clarifications under SUPAC-IR was too slow. More recently, however, they have not submitted many questions and do not know whether response time has improved.

The representatives expressed disappointment that under some SUPAC-IR changes companies still have to undergo double reviews—one from headquarters and one from the field. This company prefers not to deal with FDA district offices on scientific issues and remains concerned about the variability of district decisions on post-approval changes. Similarly, the representatives wondered how questions about the allowable range for equipment changes will be resolved between the field and headquarters. The representatives stated that they have moved very cautiously on some changes because of concern about the consistency of reviews in district offices.

The representatives would still like to see more consistency from the reviewing divisions. Nevertheless, they applauded FDA for the level of industry interaction in developing SUPAC-IR.

The representatives noted that many single changes, by their very nature, become multiple changes. Thus, a change in mixing time might be naturally combined with a change in the blender. Similarly, a reduction in batch size implies a change in equipment capacity. These related changes are often outside the scope of SUPAC-IR.

The representatives are also anxious to see SUPAC extended to other dosage forms, with the possible exception of sterile products. They urged FDA to think "out of the box" by extending the SUPAC concept more broadly. For example, they did not understand why the allowance for analytical testing laboratory changes could not be extended to all dosage forms.

They also noted that FDA has never disagreed with any of the company's requests for packaging site changes so handling such requests as preapproval supplements is unnecessarily time consuming. By allowing companies to more rapidly switch packaging sites, the representatives judged that the company could accrue savings from increased competition among packaging companies.

The representatives found a few items in the February 5 FDA Q&A confusing. They noted that the letter allows companies introducing a new ink to reference its uses on other products. They are confused, however, about why the reporting requirements are more extensive if the tablet ink is eliminated entirely. Similarly, they questioned why reducing a color requires a higher level of control than removing a color.

They also are eager to see the BACPAC initiative move forward and noted that the potential cost savings in production are much greater in the production of actives. If companies could shorten a synthesis process for a bulk active, for example, by changing suppliers or through some technical advance, the price of the active ingredient could be lowered significantly. Also, the representatives noted that they have considerable difficulty in controlling their suppliers of bulk actives and sometimes have to submit supplements to address changes that their suppliers are making. The potential savings are greater for unique chemical entities than for commodity drug substances.

The representatives feel that SUPAC-IR should allow company management more latitude, for example, to make innovations (such as for the dissolution guidance) that enable the company to implement changes more quickly. Confident of its own review processes, the company is willing to risk FDA reviews of such changes after the fact. FDA has never rejected a company supplement.

The representatives, looking ahead, wondered about the possibility of a paradigm shift in the reviewing process for post-approval changes. They hope for systems, for example, that would allow companies to obtain FDA reviews of their strategies or plans for post-approval changes before the company invests in data-generation work. Looking even further ahead, they also wondered whether FDA could devise systems that would allow the company to submit test results as they go, thereby keeping FDA informed throughout data development and virtually eliminating a conventional review period at the end of the project.

They also encourage development of criteria that could be applied broadly to post-approval changes of all types and that the company itself could apply when considering changes. The criteria could distinguish between stable and unstable compounds.

COMPANY 2

This company manufactures drug products covering all dosage forms under a large number of NDAs and a number of ANDAs. The company typically submits numerous supplements per year covering changes to new products.

EXTENT OF EXPERIENCE USING SUPAC-IR GUIDANCE

Company representatives stated that SUPAC-IR has not provided them with sufficient latitude to hasten post-approval changes. For example, they feel hampered in efforts to make site transfers, which generally involve multiple changes. In such cases, they stated, they sometimes have not felt comfortable deciding which requirements of SUPAC-IR are most rigorous and, therefore, should be applied.

The representatives interpreted site transfers under SUPAC-IR as requiring that old and new sites must have the same standard operating procedures (SOPs) and the same environmental conditions. SOPs and environmental conditions, however, are never the same between facilities. They mentioned that SUPAC-IR seems to require "mirror image" plants, which simply do not exist. Concerning the SOP requirement, they found it particularly daunting that FDA investigators would go through the facility with a checklist and any discrepancies would cause the supplement to be rejected. (They have not requested clarification on this topic from FDA and viewed the subject as closed.) On the environmental question, field investigators had told them that a site change would be allowed as long as the new environmental conditions are acceptable. After all, the representatives noted, the change from winter to summer anywhere is a much more dramatic change than that created by building environmental systems. The representatives still expressed concern that a CBE supplement might be rejected on this point.

The company anticipates using SUPAC-IR for its many future site changes, although given their concerns with the program, the representatives did not define how the company would approach such changes. The company generally makes at least two site changes during the product life cycle. New products are often produced at a "market-entry" plant, transferred to another plant for larger-scale production, and transferred to a final plant for smaller-scale production as a mature product. Company representatives estimated that they might have performed as many as 40 site changes over the past 3 years. At present, because regulatory

limitations have delayed a particular site change, they have had capacity limitations on their operations for 9 months.

The representatives also mentioned that the company often moves its testing facilities, and the recent FDA letter allowing such moves under SUPAC-IR will be extremely helpful. As products grow, the company finds it advantageous to outsource testing, thereby freeing personnel for other duties of more importance. For example, the company is currently moving a number of stability tests out of several North American facilities. It sees little risk in outsourcing these tests, particularly because internal staff will perform some verification testing (such as crossovers and other studies) of the results.

COST SAVINGS ACHIEVED OR ANTICIPATED USING SUPAC-IR GUIDANCE

The representatives noted that SUPAC-IR could have saved the company millions of dollars had the program been in place 8 years ago. In one situation, the company would have saved $10 million per year over a 2- to 3-year period by closing a site earlier. The company had moved approximately 30 products out of this site, but regulatory requirements prevented the last 4 products from moving as quickly. A more expeditious site closure would have generated these savings in the form of avoided facility overhead.

In general, the representatives stated that they would benefit most from the improved control over their own scheduling and staffing if site changes and other changes could be accomplished as CBEs.

The representatives noted that for level 1 changes, stability testing requirements are reduced to one lot, suggesting a possible cost savings. Nevertheless, there is no approved "bracketing" protocol for SUPAC-IR. The company normally performs stability testing for numerous strengths, and bracketing enables it to reduce the number of stability tests needed. The savings provided by SUPAC-IR are, therefore, mainly theoretical, because the company is almost always governed by a bracketing formula. The representatives had not seen any actual decline in stability testing requirements.

Company representatives estimated that reducing bioequivalence testing requirements under SUPAC-IR could generate savings of 3 to 4 months and $70,000 per study. They did not think the company had yet encountered instances of reduced bioequivalence testing requirements under SUPAC-IR, however.

For very simple changes, which are rare, or a packaging or analytical testing site change, SUPAC-IR clearly provides savings. Representatives noted that allowing level 1 equipment changes, where there was no equipment specified in the NDA, was clearly a benefit. Otherwise, the representatives remarked that much of SUPAC-IR codifies and establishes uniformity for what previously were commonly negotiated outcomes for post-approval changes.

The internal scientific and regulatory processes involved in post-approval changes are approximately the same whether they are filed as preapproval supplements or as annual report changes. The primary difference is that companies do not need to prepare a cover letter for the annual report change.

ADDITIONAL ACTIVITIES REQUIRED UNDER SUPAC-IR

Company officials have found that SUPAC-IR has added a little more testing in a few areas. They noted that SUPAC-IR added a dissolution testing requirement for one of their products where none had existed before. To meet the SUPAC-IR requirements, in fact, the company had to validate five new media dissolution test methods, which was a considerable amount of work for a one-time application.

In the Q&A letter, FDA states that it expects a validation summary to be included in a SUPAC-IR filing. This company reported that it had never previously been asked for such a summary. The representatives feel that it is the responsibility of FDA field offices to review validation work. Now the validation work is subject to dual reviews by FDA headquarters and field offices.

EFFECT OF SUPAC-IR ON CMC CHANGES

Company representatives believe that because SUPAC-IR provides a little more flexibility, it will enhance the prospects for technological improvements. But there are still too many limitations on actions, they feel, and the continued difficulty in accomplishing multiple, simultaneous changes hampers their use of SUPAC-IR. They also noted that an isolated change, such as envisioned under SUPAC-IR, is very rare.

RECOMMENDED MODIFICATIONS OR CLARIFICATIONS OF SUPAC-IR PROGRAM

In general, company representatives feel that SUPAC-IR should allow more flexibility. One representative stated that SUPAC-IR had fallen short of industry's expectations, and he noted that the number of SUPAC-IR supplements submitted by the industry has been quite small. The representatives also noted that it would be helpful if the plants involved in site transfers merely had to be "similar," instead of identical.

The representatives noted that SUPAC's flexibility in handling of packaging changes should be allowed for all dosage forms. They pointed out that a packaging move within the United States will not be fouled up. For this reason, they believe packaging site changes should be included under SUPAC as CBE supplements, assuming that a satisfactory Good Manufacturing Practices (GMP) inspection has been completed. They also suggested that streamlining the post-approval system could occur more quickly if FDA distinguished stable from unstable chemicals.

Company representatives also want to see a faster response time from FDA. They would prefer a SUPAC "Hotline" to the current arrangement for seeking clarification on SUPAC interpretations. They would like to be able to pose their questions to FDA verbally and get a response by fax. This company has twice submitted questions to FDA on SUPAC-IR and obtained one response in 30 days. The representatives noted that FDA responses through the SUPAC committee contact person were actually slower than for other questions to FDA, for which they normally call the reviewing chemist and get a rapid response. The representatives would also like FDA to continue to reduce review times for CMC supplements.

The representatives also hoped that SUPAC's flexibility could soon be extended to bulk chemical processes where the most significant technological advances of the last few years have occurred. Manufacturers can truly optimize bulk chemical synthesis processes and, for example, might sometimes be able to reduce ten manufacturing steps to three. Thus, the representatives hope that the BACPAC initiative will soon be developed and believe it will have a greater cost impact than SUPAC-IR.

With the new regulatory flexibility regarding site changes, company representatives noted that it sometimes becomes very important for a new manufacturing site to be inspected on schedule. SUPAC-IR requires that the new location show current compliance (within two years) with the GMP regulation. The representatives want to be able to request and schedule GMP inspections of facilities that are nearing the end of

the two-year inspection interval. They were particularly worried that they might have difficulty getting foreign sites inspected in a timely fashion because of the longer scheduling lead-time for foreign sites.

The representatives noted that the increased flexibility of SUPAC-IR comes with an element of risk. Although this company holds off on implementing all CBE changes for 30 days, under SUPAC-IR the risk of an error in a CBE filing appeared more significant. The representatives believed that penalties for a disallowed CBE under SUPAC-IR would, in some sense, be more stringent.

Stating also that the rules for post-approval changes remain unclear, the representatives urged FDA to provide more guidance, both to elaborate on existing elements of SUPAC and to provide further new guidance for those making post-approval changes.

Company representatives were concerned about some of the additional guidance provided in FDA's Q&A letter. They noted the FDA statement that if some item is not specified in the NDA, then a change in the item will be classified as a preapproval supplement. This statement appears to contradict the 1985 rewrite of the NDA rules. The Q&A also states that "executed batch records" are required with submissions, which the representatives stated also runs counter to earlier guidance. The company has always included a "representative batch record" in the submittal, but retained the executed batch records at the plant.

Similarly, the representatives had heard that, prior to issuance of the equipment guidance, FDA investigators sometimes require that new equipment be of the same model number as the old equipment. The equipment guidance in general will be helpful, but they would like the guidance to focus on equipment operating principles rather than lists of equipment models. In addition, they believe that equipment changes involving the same operating principle should not require preapproval. Finally, FDA should better utilize the validation work of pharmaceutical companies to allow equipment changes as CBEs regardless of the operating principle.

COMPANY 3

This company manufactures products under 50 to 100 NDAs and a few ANDAs. The company projects that it will submit approximately 40 to 50 CMC supplements in the coming year, including submissions to both CDER and CBER.

EXTENT OF EXPERIENCE USING SUPAC-IR GUIDANCE

The company characterized its experience with SUPAC-IR as limited to one and a half applications, although several more applications are being developed. The company has been in the process of decommissioning several manufacturing sites over the last few years, and SUPAC-IR was published during this process. The clearest application of SUPAC-IR for the company is occurring with the movement of all products (five in total) out of a manufacturing site. The company will make SUPAC-IR submissions for four of the five products. Moving the last product is a more complicated site change because the company is simultaneously optimizing the process, and there are also stability issues for the product.

The company has utilized SUPAC-IR for changes involving up to four simultaneous modifications to a production process. For these submissions, the company formatted its supplement based on the requirements for the most restrictive of the proposed changes, as required under SUPAC-IR.

Before the SUPAC-IR guidance was published, company representatives had sought SUPAC-type reviews from FDA through some aggressive proposals to the agency about site changes. In one case, they sought a cross-divisional review of a set of site changes. SUPAC-IR eliminates some of the negotiation that was necessary in these previous episodes.

The company expects to have a number of scale changes in the coming year that will be candidates for filing under SUPAC-IR. It also typically does not change the components or composition of its products.

COST SAVINGS ACHIEVED OR ANTICIPATED USING SUPAC-IR GUIDANCE

In moving five products out of one of its manufacturing facilities, the company documented the potential savings from SUPAC-IR. Due to some concern that the CBE supplements might not be approved, however, the company pursued regulatory approval using SUPAC-IR for four of the five products but simultaneously prepared sufficient batches to support the necessary data generation should preapproval supplements be needed. Thus, while the company calculated the savings from SUPAC-IR, it did not attempt to capture the savings.

First, the company representatives estimated the direct savings from reduced stability testing at $550,000, which represents more than one-sixth of the total budget of $3 million for the product move. The company representatives reported that bracketing of stability testing requirements, which can reduce stability testing costs by allowing fewer batches to be tested, was not an option for these products. Thus, prior to SUPAC-IR, FDA required the company to perform stability tests on three batches for each product. Under SUPAC-IR, FDA requires that only one lot be placed on stability testing. (The overall project budget includes costs that cannot be recouped from eventual product marketing, such as development work and costs beyond the normal ones incurred in process validation.)

The company reported that many products are tested 12 times during a 3-year stability program. The entire program of stability testing (covering all time intervals and required tests) might typically cost $40,000 to $50,000 per dosage strength. In this case, however, the savings are even higher—$550,000 over four products (one dosage strength each).

SUPAC-IR sometimes allows the company to do routine stability testing instead of both routine and accelerated stability testing. Also, the shorter waiting times for SUPAC-IR mean that some test batches that could not be marketed previously can now be sold. When the drug is costly, this would result in significant savings, which were not estimated by the company.

Additionally, the company could have saved substantial additional costs had it not produced the batches that would normally have been placed on stability testing. The raw material costs of the batches produced varied from about $10,000 to $250,000 per batch, with the bulk attributed to the cost of the drug substance itself. As noted, the company was concerned that the CBEs might not be approved, and therefore manufactured the additional batches to ensure it would have sufficient information to prepare preapproval supplements, if they were

needed. Thus, had the company been more confident of the workings of SUPAC-IR at the beginning of its project, it could have saved an additional sum in excess of $250,000.

Furthermore, the company representatives noted that a shorter implementation period produces additional savings in plant overhead, management overhead, and economies of scale in operations, particularly from use of more efficient production lines at the new locations. These savings are generated at the rate of approximately $1 million per year. With faster approval times, the representatives noted, the company also saves the potentially significant costs of building up product inventory prior to making a site change.

The representatives also noted the importance of SUPAC-IR's effect on the company's general flexibility to use its management and other personnel resources more effectively. Furthermore, the SUPAC-IR program enables the company to better manage personnel issues associated with plant closures. In such circumstances, the company can now give its manufacturing employees more accurate forecasts of when their jobs might end.

In addition, packaging site changes have become more economical because the change can now be filed as a CBE and implemented at the same time that stability testing begins. is not delayed for stability results and more of the product is marketable after testing.

The company noted some small savings in the time regulatory affairs personnel need to prepare submissions. When post-approval changes are described only in the annual report, the representatives noted, personnel spend slightly less time in preparing the presentation of material and less time in describing the background for the change. The supplement submission has to be reviewer-friendly. This difference is not dramatic, however, because the scientific justification for the change still needs to be prepared. The company also finds that it tends to be more cautious, and that it spends more time massaging data, for prior approval filings than for annual reports. One executive offered that the time spent by regulatory affairs personnel on an annual report filing might be only half that spent on a supplement. The regulatory affairs staff typically spends about 80 hours to prepare a prior-approval filing to FDA.

ADDITIONAL BENEFITS OF THE SUPAC-IR PROGRAM

The representatives said that the SUPAC-IR guidance gives companies a direction and opportunity to negotiate. Although SUPAC-IR contains gray areas, it assists discussion, lowers some risks, and improves the timing of some changes.

Before SUPAC-IR, the company would identify the post-approval change, conduct stability testing, assemble the data, submit, and wait for FDA approval. Now it can institute some changes almost as soon as it has acquired the data. The reduction in waiting time for preapproval by FDA means there is less risk associated with the loss of test batches.

Company representatives stated that SUPAC-IR also has clarified the requirements for making changes and brings consistency to the approval process. Previously, they had to negotiate some changes division-by-division and sometimes performed more testing than should have been necessary because of inconsistencies in division requirements. They now sense that FDA has become more open to discussing a strategy for seeking regulatory approvals before submissions are made. The timeliness of FDA responses also has helped the flow of communication.

The representatives noted that SUPAC-IR gives the company much greater flexibility to respond to changes in demand for a particular product. It also gives the company more freedom to use outside contractors, and production or packaging can be quickly moved off-site, adding substantially to production capacity. The company also appreciates the increased ability to make certain changes, such as in excipients and flavorings.

Company representatives noted that before SUPAC-IR, changes allowable within the CBE category were narrowly defined. Now a broader range of changes are allowed. The representatives feel they can now be a bit more aggressive in seeking post-approval changes because of SUPAC-IR's greater clarity on requirements and quicker regulatory approvals. Nevertheless, the broadening of this category of post-approval changes carries some risk for companies—they can submit more CBE supplements, but could be at risk if their supplements are rejected. There remain some ambiguities and guesswork about what is allowable as a CBE supplement. To address this, the representatives suggested that FDA accept or reject CBEs within 30 to 45 days of submission.

ADDITIONAL ACTIVITIES REQUIRED UNDER SUPAC-IR

Company representatives have not identified any areas where SUPAC-IR increased testing or application requirements. They noted that the clarification of requirements under SUPAC-IR might increase requirements in some cases. For example, FDA's release of the Q&A letter appeared to expand requirements for changing a technical grade of excipient. The company had not previously performed all these requirements.

EFFECT OF SUPAC-IR ON CMC CHANGES

Company representatives stated that SUPAC-IR has not affected the number of CMC changes or the rate of technological change because technical progress for U.S. operations has not been restrained by regulatory requirements. The company is more likely to incorporate new technology during product development, rather than in post-approval changes. The representatives noted that they look very critically at potential post-approval changes and implement only those that are economically sound, based on their efficiency or cost savings. Opposing potential production cost savings are the costs to validate new equipment and process changes. Validation costs tend to be more significant than the regulatory costs in considering potential changes.

For older products there is often a poor return on investments made to upgrade production equipment. In addition, NDAs for products approved in the 1970s and 1980s were less detailed and many equipment changes were, therefore, allowed in the annual reports.

RECOMMENDED MODIFICATIONS OR CLARIFICATIONS OF SUPAC-IR

Company representatives want SUPAC extended to cover changes to a packaging site, especially since it is rare for FDA to reject a packaging site change. They also want SUPAC broadened to better accommodate multiple changes, as very few changes are truly single changes.

The representatives noted that, under the equipment change guidance in SUPAC-IR, an equipment change is filed in either a preapproval supplement or an annual report. They feel that both the company and FDA would benefit if there were a middle ground, i.e., a set of equipment changes that could be filed as CBEs.

The representatives noted that substantial benefits could be generated by a SUPAC-type program to address changes to the manufacturing of the bulk active ingredient. They see that possibilities for process optimization in bulk active manufacturing are quite significant. They would also like SUPAC-type coverage of milling site changes.

In other comments:

- Company representatives feel that FDA has to respond quickly to questions under SUPAC-IR or the benefit of the program is diminished. Before SUPAC-IR, some preapproval supplements were approved within 3 or 4 months.

- Company representatives hope that SUPAC principles can be extended to late phases of the NDA review process. They believe SUPAC provides the scientific leverage to argue with FDA reviewers against the necessity of submitting as much data as now required for a site change in the late stages of NDA review.

- The representatives did not understand whether the SUPAC guidance on packaging site changes is intended to extend to secondary packaging.

- They noted that SUPAC-IR increases the emphasis on obtaining GMP inspections for facilities involved in site transfers. They want FDA to state that an applicant can ask for a GMP inspection. They are concerned that if a filing is the trigger for scheduling an inspection, it would impose a delay. They also noted that they lack experience in scheduling inspections for foreign plants.

- The representatives want to see policies evaluated and clearly linked with other overlapping laws and requirements. For example, because CBEs are not approved formally, the company executives were unsure whether they could export products from new manufacturing sites or import products from new non-U.S. sites and remain certain that the products would not be considered adulterated. The example highlights ambiguities and overlap in requirements of FDA and U.S. Customs.

- The representatives would like to know if SUPAC allows for bracketing in stability testing. Bracketing, which is often allowed in generating data for post-approval supplements, is not addressed in the SUPAC-IR guidance.

COMPANY 4

This company manufactures numerous drug products in several dosage forms under several dozen NDAs and a few ANDAs. The company has been submitting a few dozen supplements per year.

EXTENT OF EXPERIENCE USING SUPAC-IR GUIDANCE

This company used SUPAC-IR guidance for one post-approval change to the technical grade of an excipient. This level 2 change resulted in a preapproval supplement.

The company is planning three post-approval changes in the near future that will be pursued under SUPAC-IR. These will involve:

- A site change for manufacturing, analytical testing, and packaging operations
- A change in the packaging equipment of the same basic design and operating principle
- An equipment change involving the screen and blades used in granulation

The site change will involve multiple products, including some products that are relatively new (i.e., introduced within the last 5 years). The old and new sites are both domestic manufacturing locations, and the manufacturing equipment at the two sites is quite similar. These post-approval changes will be filed as CBEs under SUPAC-IR rather than as preapproval supplements, as they would previously have been classified. Company representatives stated that the site changes will enable the company to (1) focus its investments in a single site and (2) better manage its excess manufacturing capacity.

Company representatives also described several changes they hope to pursue under SUPAC-SS (for semisolid dosage forms) and BACPAC.

COST SAVINGS ACHIEVED OR ANTICIPATED USING SUPAC-IR GUIDANCE

For the first of the planned site changes, the company calculates that it would save approximately $4 million by avoiding the estimated 12-month wait for approval if SUPAC-IR were not in place. Those savings come primarily through marketing products that would have become unmarketable prior to SUPAC-IR. Specifically, the waiting period would have meant that the stability batches would be too close to expiration to be marketable by the time the supplement was approved.

The company estimates that when a site change leads to closing a facility, it could realize an additional savings of $4.6 million per year in avoided facility overhead and support costs. This estimate applies to a 50,000-square-foot facility in which 10 to 12 brands were previously manufactured. In full operation, this facility produced 3.5 billion consumption units.

Company representatives noted that SUPAC-IR introduces the possibility of avoiding bioequivalence tests in some cases. This change could produce a very significant savings, which the representatives estimated at 6 months and $250,000 in spending to outside vendors, plus approximately twice as much for internal oversight and quality control of the testing.

ADDITIONAL BENEFITS OF THE SUPAC-IR PROGRAM

The company is pleased that FDA can speak with one consistent voice under SUPAC-IR, as exemplified at the February, 1996 SUPAC training session held in College Park, MD. Company representatives are also pleased with the written feedback FDA provided on SUPAC questions submitted by the company. Also, based on two instances, they are pleased with the 3-week turnaround for questions. Despite some remaining issues, the representatives feel that SUPAC-IR is improving the consistency of agency rulings.

The representatives also feel that SUPAC-IR is helping to create a more “level playing field.” Since the rules for making post-approval changes have been clarified, this company feels that its position relative to generic companies has improved. The company representatives noted that, while generic companies can also use SUPAC-IR, the greater clarity of requirements for seeking post-approval changes helps ensure that all sectors of the industry are reviewed on equal terms.

The company representatives stated that the extension of SUPAC to laboratory and packaging site changes is quite beneficial and will affect their rate of future submissions under SUPAC. SUPAC allows the company greater flexibility to use alternative laboratory facilities to support its operations and to contract for laboratory resources to meet peak demands.

ADDITIONAL ACTIVITIES REQUIRED UNDER SUPAC-IR

In one instance, the company had to develop dissolution testing results for a product for which the results should not have been required. Thus, the company was required to perform more rather than less testing under SUPAC-IR. The company has encountered no other incremental testing requirements.

EFFECT OF SUPAC-IR ON CMC CHANGES

The representatives stated that SUPAC-IR has not affected the frequency of changes, but has made the implementation of change somewhat easier in selected circumstances. They emphasized that business decisions, not SUPAC-IR, determine whether CMC changes are pursued. They also find the increased flexibility for changes in analytical testing laboratories to be helpful. The representatives stated that from the perspective of international competition, they see no difference in technology in their U.S. and European operations.

RECOMMENDED MODIFICATIONS OR CLARIFICATIONS OF SUPAC-IR

The representatives find some of the guidance on equipment changes to be restrictive. Giving such detail on equipment specifications and types, they feel, will cause the company to be held to a tighter set of equipment specifications. While they said they are able to quickly assemble the required detail on equipment types for their submissions, the representatives are critical of FDA for using the detail in this way. They argued that companies should only have to make more comprehensive statements of operating principles in their submissions and should not have to describe all design characteristics of equipment.

They also recommend further work to ensure that FDA headquarters and field personnel are consistent in interpreting requirements for industry. Field personnel, they noted, are largely unaware of many elements of ICH agreements, such as those covering stability testing and analytical requirements. The representatives encourage FDA to invest in more training sessions for both internal and external audiences. The training sessions for industry should be more geographically distributed. The company representatives also stated that FDA's internal sessions should include reviewing chemists.

The company representatives appreciate the circulation of the Q&A summaries recently released by FDA and recommend that such releases be made regularly because they provide useful additional guidance for industry. They also requested that FDA provide preamble-type discussions of their decisionmaking logic to further industry's understanding of the Agency's decisionmaking process and criteria. They noted, however, that some of the guidance in the recent Q&A was somewhat unclear. For example, the company representatives asked if a change to a mill screen could be a level 1 change. FDA's response in the Q&A is contradictory in that it indicates that the mill screen change cannot affect the particle size distribution.

In other comments:

- The company representatives recommended that SUPAC guidance documents include a preamble-type section that describes the background, agency development processes, and agency findings or decisions that support the guidance decisions.
- The company representatives recommend that the SUPAC committee change its meeting schedule from biweekly to weekly sessions.
- The representatives also recommend that SUPAC-IR science and principles be applied to the late stages of NDA reviews.

COMPANY 5

This company manufactures two to three dozen generic products and has a large number of drug products pending approval. The company files approximately 15 to 20 CMC supplements per year. All the comments offered here were from the company manager for U.S. regulatory affairs.

EXTENT OF EXPERIENCE USING SUPAC-IR GUIDANCE

This company has used SUPAC-IR for four or five submissions thus far. It has made one submission for a change in batch sizes (of greater than ten times) and plans three or four similar changes. It has also completed a site change and is preparing about ten additional filings for site changes. It has made a formulation change within the limits allowed (i.e., +/-5 percent) under SUPAC-IR.

In some cases, the company has received an "approval" letter from FDA and in other cases has not. It has always proceeded on the implementation dates provided in the filings and has encountered no problems. The company representative was unsure whether or not the company would receive formal "approval" letters in all cases.

For one of its site changes, the company is moving a number of production processes to an entirely different campus. Under SUPAC-IR this is a level 3 change. The move is motivated by a combination of political and marketing issues, and only to a minor extent by possible economies of scale. The representative stated that the company probably would consider more site changes in the future given the greater flexibility under SUPAC-IR. Nevertheless, many of these changes will require preapproval supplements because of the combination of changes involved.

The company has submitted numerous questions to the FDA SUPAC-IR contact. FDA has responded in some cases almost immediately, and, at the longest, within two months. The company has not asked questions prior to every filing for a post-approval change, however.

COST SAVINGS ACHIEVED OR ANTICIPATED USING SUPAC-IR GUIDANCE

Under SUPAC-IR, the company can anticipate much more rapid site changes, with waiting times reduced from 6 to 9 months to approximately 4 weeks. This development has improved planning considerably.

Where SUPAC-IR has allowed more rapid changes to larger batch sizes, the company has benefited by expending fewer resources on quality control (QC). The representative explained that the company preferred to make fewer, larger batches. The QC testing costs per batch ($2,500) are roughly equivalent for the range of batch sizes considered, so QC costs per unit of product are inversely related to batch size. By doubling batch size, therefore, they can save approximately $2,500 per lot in QC costs.

This company has not encountered changes due to SUPAC-IR in the amount of stability or bioequivalence testing. As a manufacturer of generic drugs, it is able to assume that "a significant body of information" exists for its products. Therefore, as allowed under SUPAC-IR, it has always performed stability testing on one product batch. This is consistent with the mandates from the Office of Generic Drugs.

Otherwise, the company's scientific work relating to post-approval changes is based almost entirely on precedent and therefore has not changed under SUPAC-IR.

The regulatory work associated with site changes has not changed noticeably. There might be a cost savings, however, because the increased clarity of the rules means that fewer projects are tied up by conflicting regulatory interpretations within the regulatory affairs department. The company representative also suggested that perhaps less effort is spent in writing reports to explain changes.

ADDITIONAL BENEFITS OF THE SUPAC-IR PROGRAM

The company representative is highly supportive of the SUPAC-IR initiative and feels that it makes a fundamental improvement. He noted that, prior to SUPAC-IR, the types of changes allowable as CBEs were ill-defined. As a result, the representative felt that requirements for many post-approval changes were open to interpretation and that it was the company's responsibility to determine how to evaluate a change and what to submit. SUPAC has clarified these requirements.

ADDITIONAL ACTIVITIES REQUIRED UNDER SUPAC-IR

The company representative did not describe any situations in which SUPAC-IR has increased testing requirements.

EFFECT OF SUPAC-IR ON CMC CHANGES

The representative stated that the company is now much more willing to investigate possible formulation changes that are allowed for CBE or annual report filings under SUPAC-IR. The representative stated that the faster rate for implementing CMC changes in this area was important to the company, presumably because it can almost immediately capture the benefits in improved process efficiency or fewer manufacturing problems. Otherwise, the representative does not expect SUPAC-IR to influence the rate at which the company undertakes technological advances in its processes. Although SUPAC-IR specifies a certain range of equipment changes within categories, the company has not realized any particular benefits from this definition of allowable changes.

In its non-U.S. production facilities, the representative reported, the company is able to make equipment improvements more quickly. Many equipment changes are allowed as long as the relevant equipment specifications are met. Nevertheless, the U.S. operations of the company are not significantly behind the Canadian processes in their technological characteristics.

Some restrictions on equipment changes have proven binding to the company, however. As part of a major site change, the company was unable to modernize some outdated process equipment. In this case, the company wanted to replace very old ribbon blending equipment with modern equipment. This substitution, however, would have made the entire change a preapproval supplement. Despite the fact that today ribbon blenders are rarely sold to pharmaceutical companies and are difficult to validate, the company has had to find and purchase new ribbon blenders and install them in the new facility. It did this in order to avoid having to change its filing for the move to a preapproval supplement.

RECOMMENDED MODIFICATIONS OR CLARIFICATIONS OF SUPAC-IR

The company representative expressed some frustration with unsuccessful efforts to make certain process or composition changes within the purview of SUPAC-IR. Some proposed changes, which initially appear to be addressed by SUPAC-IR, have by their nature created other changes that are not addressed. For a change in an excipient, for example, there was also a change in tablet weight, which created a specification change. A specification cannot be changed without a preapproval supplement. Also, the limit on allowable specification changes is defined in the CFR and therefore beyond the scope of SUPAC-IR guidance. Thus, the apparent liberalization of changes under SUPAC-IR is sometimes canceled out by the limitation on specification changes.

The company was also frustrated in attempting to change from outdated manual methods of wetting in wet granular processes to newer spray methods. Unfortunately, the newer spray methods, by virtue of their greater efficiency, use less of the wetting solution, and this change is outside the specification limit.

The company views the equipment guidance document as adding restrictions to the range of allowable changes. In the past, the company has judged the equivalence of equipment after testing it within the process, validating its use, and testing the final product. The company representative believes that the draft equipment guidance, by distinguishing between equipment types based on operating principles, will be too narrowly interpreted and result in a more restrictive basis for considering changes. Some of the changes that the company had previously considered to be annual report items now could be deemed preapproval changes. The company recommends that “operating principles” be better defined.

COMPANY 6

This company manufactures generic drugs under approximately two to three dozen ANDAs and a few old NDAs. Most of its output is immediate-release products. The company typically submits six or seven CMC supplements per year.

EXTENT OF EXPERIENCE USING SUPAC-IR GUIDANCE

The company has made a number of SUPAC-IR submissions, including several for scale up and scale down of product batches, and others for site changes and process optimization changes. Company representatives noted that they had been frustrated in efforts to make a packaging site change for a powdered product. (This product is not systemically absorbed and, therefore, not included within the SUPAC-IR definition of an immediate-release solid oral product. The company's original assumption that this product is covered under SUPAC-IR was incorrect).

The company had more success with SUPAC-IR changes to optimize products. In one case it was preparing the validation batches for a new product when it encountered a problem with the product mixing time. Under SUPAC-IR the company was able to submit a CBE supplement and quickly adjust the mixing time. It simultaneously made a change that helped to provide proper lubrication for the drug.

COST SAVINGS ACHIEVED OR ANTICIPATED USING SUPAC-IR GUIDANCE

The company has also realized cost savings by using SUPAC-IR to scale down production batch sizes. For products with a small sales forecast, the company can now do its validation testing on a scaled-down batch. With this step the company avoids both the raw material costs and inventory costs of larger batches that cannot be sold. In the past, much of the product from validation batches became short-dated and unmarketable. The company representatives reported having saved a total of $57,000 from scale-down changes for certain products.

For scale-up changes, the company can more quickly realize the savings that result from making fewer, larger batches and performing less laboratory testing per unit of product. The company representatives explained

that they perform essentially the same amount of testing per batch across a range of batch sizes. By increasing batch size, therefore, the cost of laboratory QC testing is spread over a much larger quantity of product. Also, producing fewer batches results in savings because there are fewer procedures performed, such as the release of components into manufacturing. As with the other post-approval changes, the company accrued savings over the 8 to 9 months it would previously have been waiting for approval. The company estimated the savings from scale-up changes across five different products at $80,000. This company generated most of these savings by reducing the number of batches for a very large volume product that previously had been manufactured in over 100 batches per year.

The company representatives had not observed any instances in which stability testing requirements for post-approval changes had been reduced under SUPAC-IR.

When the company was able to quickly modify the mixing time for its new product, as mentioned above, it was able to initiate marketing 8 to 9 months earlier than before SUPAC-IR. The company had not made this drug previously so there was no product inventory. Without SUPAC-IR the company would not have been able to begin marketing until a preapproval supplement was accepted.

The greater flexibility to optimize manufacturing processes also helps reduce the frequency and severity of QC investigations of failures in the affected processes. Company representatives estimate that with each failure in a nonoptimized process, the company's testing costs triple. The company immediately repeats the tests in question and then performs a "refereed" testing. In some cases shipment of the batch is delayed and, if the batch is held up too long, the time to expiration shown on the label might need to be shortened. The company did not quantify these savings.

The company representatives noted three instances in which the company implemented minor manufacturing changes, such as changing from manual to automated process operations, under SUPAC-IR. The combined savings for these changes on manufacturing costs was estimated at $10,000. (These savings do not appear to include the benefits from earlier marketing of products or reduced testing costs.)

ADDITIONAL BENEFITS OF SUPAC-IR PROGRAM

Company representatives find the equipment guidance document helpful. Overall, they think the SUPAC-IR program is lively and dynamic. They do feel, however, that further clarification would be helpful, as is discussed below.

ADDITIONAL ACTIVITIES REQUIRED UNDER SUPAC-IR

The company has not encountered situations in which SUPAC-IR has increased the testing or documentation requirements for a post-approval change.

EFFECT OF SUPAC-IR ON CMC CHANGES

The representatives do not feel that SUPAC-IR has influenced the company's rate of technological innovation. Some of the changes they would like to pursue, such as those needed to update screening processes, will not be covered by SUPAC-IR.

RECOMMENDED MODIFICATIONS OR CLARIFICATIONS OF SUPAC-IR

Company representatives feel that SUPAC-IR should be extended to powdered products, such as the product they are manufacturing. They feel their product should be regulated in the same manner as immediate release products.

Despite the substantial clarification provided by SUPAC-IR, the guidance document includes a number of uses of "such as" terminology. This phrase creates a good deal of ambiguity and uncertainty about the specific post-approval changes to which the phrases apply. The document could be improved considerably, the company representatives stated, if such terminology were avoided and concrete guidance provided in these areas.

The representatives stated that they had to perform considerable follow-up work with FDA to ensure that questions to the SUPAC-IR committee were addressed. They estimated that they had generally received responses within 4 to 6 weeks, although these response times reflect the fact that follow-up telephone calls were made for approximately 90 percent of the questions they submitted.

The representatives would like to see more latitude in the application of SUPAC-IR. For example, SUPAC-IR does not allow changes to an excipient when it would produce a change in a specification.

APPENDIX A

EXPLANATORY NOTES TO ESTIMATES OF COST SAVINGS UNDER SUPAC-IR

(See Tables 1, 2, and 3)

A.1 General Notes on Methodology

SUPAC-IR establishes the framework and requirements for Chemistry, Manufacturing and Control (CMC) post-approval changes. Cost savings attributable to SUPAC-IR are described in terms of the primary cost savings, defined as those generated by the reduction in time to implement changes defined in CBE and annual report filings, and secondary costs savings, defined as those that are generated by reductions in the testing and administrative requirements to justify changes. The latter include reductions in stability and bioequivalence test requirements, efficiency gains from inventory management, and administrative savings in documentation of changes. Cost saving estimates are described below for each primary and secondary cost saving category.

Pharmaceutical companies are assumed to save six months in implementation time for supplements that can now be filed as CBEs (six months of regulatory review time for a prior approval supplement versus essentially immediate implementation for a CBE). For convenience, the 6-month reduction in implementation time is also assumed to apply to annual report changes.

In the preparation of cost saving estimates, common scenarios are defined for each category of CMC change. The scenarios are intended to be representative of those that would commonly occur, i.e., they do not represent exceptional circumstances.

A.2 Assumptions About Product Values and Production Costs

Manufacturers of both brand name and generic pharmaceuticals are making submissions under SUPAC-IR and the cost savings generated by many SUPAC-IR changes vary directly with the scale of the manufacturing operation. To reflect the distribution of manufacturers making post-approval changes, ERG defined high, medium, and low estimates of the savings for each category of change. The estimates represent the judgments

of ERG staff, with inputs from project consultants. The high savings estimate is intended to be representative of cost savings accruing for post-approval changes to relatively high-value brand name products. In some cases, the highest-priced, largest-volume generic products would generate equivalent revenues. ERG assumed that the high end cost savings will be generated for products that generate from $25 million to perhaps $1 billion or more per year. ERG selected a conservative value of $50 million per year per product to represent the annual revenue estimate for these products. In other cases, the high-end estimate of cost savings is defined to represent the largest manufacturing operations (regardless of product value) or the circumstances that produce the largest cost savings, regardless of either product or plant characteristics.

The medium estimates are intended to represent savings accruing to average revenue-generating products, or simply the average cost savings, regardless of product or plant characteristics. ERG assumed the medium cost savings are generated by post-approval changes for products that generate revenues of approximately $10 million per year. The low end estimates represent savings for low market value brand-name or generic products, which were assumed to be generating annual revenues of $5 million.

For the high end products, ERG estimated that production costs represent 30 percent of revenues, or $15 million per year. This estimate is most representative of major brand name products. Project consultants estimated that the direct annual production costs for medium- and low-value products, many of which are generics, represent 60 percent of product revenues, or $6 million and $3 million per year, respectively. Department of Commerce data are reasonably consistent with these estimates of the relationship of product revenues to product costs. Specifically, the 1992 Census of Manufactures reports that production worker wages and cost of materials in SIC 2834, pharmaceutical preparations, represented 33 percent of the value of shipments in 1992 (Census Bureau, 1995).

ERG also asked industry personnel and project consultants to describe the production costs and market value of representative product batches. While this value is extremely variable among products, based on the discussions held, ERG selected $150,000 as the cost per batch of high-value products, $30,000 for medium-value products, and $15,000 for low-value batches. The market value of these batches are estimated at $500,000 (assuming production costs are 30 percent of revenues) for high-value products, $50,000 (assuming production costs are 60 percent of revenues) for medium-value products, and $25,000 (assuming production costs are 60 percent of revenues) for low-value products.

The high, medium, and low cost saving estimates were assumed to apply to 5 percent, 60 percent, and 35 percent of the post-approval changes, respectively. This distribution of savings reflects the expectation that the distribution of savings is centered among the circumstances that generate low to medium savings. Additionally, the distribution has a long tail to the right, reflecting occasional circumstances in which very large savings will accrue to pharmaceutical companies. This distribution, although quite conservative, reflects the range of data generated during the analysis.

A.3 Primary Cost Saving Categories

The primary cost-saving categories are:

- Manufacturing site changes (either to close a facility or to transfer a process between facilities)
- Analytical laboratory testing site changes
- Packaging site changes
- Process changes
- Equipment changes
- Composition and component changes
- Scale-up and scale-down

A.3.1 Closing of Manufacturing Facility

The site change estimates reflect savings that companies realize in being able to close manufacturing facilities more quickly under SUPAC-IR. The estimates represent essential plant overhead and other costs that are eliminated with more timely plant closure. The costs eliminated include building rental or depreciation, basic plant utilities (excluding utility costs in operating process equipment), and essential building maintenance.

ERG estimated the aggregate cost savings for this and other categories by multiplying the forecasted number of SUPAC-IR changes by the unit costs savings for each change. The number of site change supplements filed, however, was divided by 3 before cost savings were calculated to reflect the fact that most site closures will

involve the transfer of numerous products. That is, it is assumed that on average 3 supplements will be generated for each site closure.

Project consultants estimated that the high-end savings from plant closures under SUPAC-IR will range from $1.5 to $2.5 million over a year per plant closure ($2 million midpoint). (Most company personnel and project consultants estimated that SUPAC-IR allowed the company to avoid a regulatory implementation period of a year, while in this study, ERG assumed that the avoided regulatory implementation period was 6 months. Cost saving estimates based on a regulatory implementation period of a year were, therefore, reduced by one-half.) One major brand-name manufacturer estimated that it had accrued savings at a rate of approximately $4.6 million/year under SUPAC-IR by being able to close a facility more rapidly. ERG averaged the two estimates to derive a rate of savings of $3.3 million per closure per year. Assuming that the reduced implementation time is 6 months, the high-end cost savings estimate was reduced to $1.65 million ($3.3 million times 6/12ths of the year). For the medium cost savings estimate, the high-end savings estimate was scaled down by 40 percent to reflect the approximate relative scale of brand name (which are more representative of the high-value products) and generic manufacturing facilities (which are more representative of medium-value products). This produces a cost savings estimate of $1.0 million. The low end estimate is derived below.

ERG also considered the cost savings for an alternative scenario under which manufacturers build up product inventory to continue marketing throughout the regulatory implementation period. Under this approach, a manufacturer would build sufficient inventory to supply customers over an extended period, then close his manufacturing facility without waiting for regulatory approval.

The costs of an inventory buildup are substantial. The required buildup would need to cover the 6-month regulatory implementation period. Industry consultants estimated the cost of carrying inventory at 12 to 17 percent per annum, a value which reflects the industry's cost of capital. For this calculation, ERG used the conservative estimate of 12 percent.

Under SUPAC-IR, CBE supplements can be filed and the inventory expense is avoided. Assuming an annual production cost for the high-value product of $15 million and a 12 percent cost of capital for pharmaceutical companies, the inventory cost savings for the high-value product would be $0.9 million ($15 million x 12 percent x 6/12ths of the year). The inventory cost savings for the medium-value product would be

$360,000 ($6 million x 12 percent x 6/12ths of the year), and for the low-end product $180,000 ($3 million x 12 percent x 6/12ths of the year).

While in theory any pharmaceutical manufacturer could choose to build inventory to circumvent the regulatory delay for closing a facility, many practical difficulties can intervene. For example, manufacturers might have difficulty obtaining sufficient raw material to allow a buildup of inventory, or they might lack the capability to expand batch size or frequency sufficiently to generate the additional production. For this analysis, ERG assumed that the inventory buildup scenario was applicable only to the low-end cost savings, and the savings estimate of $180,000 was used for that case.

A.3.2 Site Changes To Capture Productivity/Capacity Increase (No Plant Closure)

Companies often shift manufacturing locations to better utilize their production capacity. In these changes companies do not close facilities but improve their use of existing plant and equipment. For example, a company might consolidate the manufacturing of two or more products that (1) can be made on the same process equipment and (2) that are not selling at the previously forecasted production levels. The change in manufacturing locations provides several types of benefits, including:

- Allowing a company to add products and increase production capacity while avoiding the costs of building expansion,
- For a company responding to a surge in demand for one or more products, allowing a change to avoid the use of contract manufacturing services, and
- Rationalizing production operations, thereby reducing costs.

While project consultants agreed that savings from process consolidation are significant, no direct, quantitative relationship could be defined to represent the relevant savings. Nevertheless, avoidance of contract manufacturing charges and/or the rationalization of production operations suggest that cost savings can be estimated as a share of production costs. To capture these values, ERG assumed that companies save 5 percent of the product manufacturing cost for the 6 month reduction in implementation time. This estimate is intended to reflect both the direct savings in manufacturing costs (or avoided contract manufacturing charges) and the incremental savings related to the less readily quantifiable savings from improving plant utilization. Using this

estimate, ERG calculated the savings for the high-value product savings at $0.375 million (5 percent x $15 million x 6/12ths of the year). The savings for the medium-value product was estimated at $150,000 (5 percent x $6 million x 6/12ths of the year). For the low end estimate, ERG assumed only a 2.5 percent reduction in production costs would occur, generating savings of $37,500 (2.5 percent x $3 million x 6/12ths).

A.3.3 Packaging and Testing Site Changes

Packaging and testing site changes resemble other site changes in that they release capacity for alternative uses. Packaging costs represent up to 10 percent of the production costs, although for high-value products their contribution can be much smaller. That is, if the cost per bottle of tablets is high, the share of costs represented by packaging is likely to be very small. Census of Manufactures data show that plastic components, capsules, bottles, and labels combined represent approximately 20 percent of the cost of materials consumed by the pharmaceutical industry (Bureau of the Census, 1994). Testing costs typically represent less than one percent of the production cost.

While many pharmaceutical companies representatives lauded the benefits of easier packaging and testing site changes, none provided estimates of the resulting cost savings. Also, the circumstances of packaging and testing site changes are quite variable, so benefits will vary. For packaging, for example, a site change might mean the company is (1) adding a packaging contractor to expand its capacity, (2) moving packaging operations from one contractor to another, or (3) moving the packaging operation from one internal facility to another. Nevertheless, ERG judged that, while the circumstances of packaging and testing site changes will vary, these changes must result in a direct production cost savings, or an indirect savings in avoided contractor charges, or improved production flexibility. It was further judged that the combined savings and benefits would average 1 percent of production costs. It is unlikely that the companies will realize larger savings purely in direct production costs because most packaging costs are irreducible raw material or labor costs, and most testing costs are irreducible equipment or labor charges. The additional benefits of indirect cost savings and improved production flexibility are not readily quantifiable and are not captured. The savings are calculated for the high-value products at $75,000 (1 percent x $15 million x 6/12ths of the year), for medium-value products at $30,000 (1 percent x $6 million x 6/12ths of the year), and for low-value products at $15,000 (1 percent x $3 million x 6/12ths of the year).

A.3.4 Process and Equipment Changes

Process changes improve yields and/or process or quality control. Project consultants suggested that, in the best cases, companies can make process changes that improve yields by 2 to 3 percent, with the exceptional change improving yields by 5 percent. Process changes classified as SUPAC-IR Level 1 or 2 changes, however, generally will not be sufficiently dramatic to generate such yield improvements. One generic manufacturer reported making three minor process changes under SUPAC-IR that saved $10,000 in total. Representatives of brand-name manufacturers anticipated benefits from process changes under SUPAC-IR but did not provide quantitative estimates of the savings.

Based on the discussions with project consultants and the generic company estimate, a yield improvement of ½ percent was credited for the high-value case. Thus, it was calculated that a brand name manufacturer with a revenue stream of $50 million per year will generate on average a ½ percent increase in yield, resulting in a $0.25 million increase in revenues over a year, or $0.125 million over the 6-month reduction in the regulatory implementation period. For the medium-value product, a 0.5 percent yield improvement was assumed for a product generating $10 million per year in revenues, generating a savings of $25,000 ($10 million X 0.5 percent X 6/12ths of the year). For the low-value case, it was estimated that savings are generated at the rate of $3,000 per process change, based approximately on the savings reported by the generic manufacturer.

Equipment changes are less likely to improve yields, but will occasionally do so. Nevertheless, pharmaceutical companies make equipment changes most commonly to address specific equipment problems that do not affect yields. The cost savings for equipment changes were estimated at 33 percent of the benefits of the process changes except at the low end where savings were assumed to be negligible.

Yield improvements will increase packaging and other costs that are related output. These incremental costs were not considered significant enough to include in these estimates.

A.3.5 Composition and components

Composition changes are most likely to occur in response to production problems, and are less likely to generate yield benefits than either process or equipment changes. Some project consultants suggested that

pharmaceutical companies might also make composition changes in response to changes in the market prices of components, although others felt that the frequency of such changes is quite limited. Assuming that most composition changes address production problems, companies would benefit from reductions in the cost of failure investigations, product rework, and other quality control activities.

Failure investigation costs vary with the extent of documentation and investigation needed. Based on discussions with project consultants, however, it was assumed that failure investigations costing $2,000 to $10,000 due to the specific problem addressed by the post-approval change occur periodically. The number of batches produced, however, is also quite variable. For the high-end estimate, ERG assumed that 3 failures per month are occurring (due to the specific composition problem being addressed) at a cost of $5,000 per investigation and an aggregate $90,000 over the 6-month regulatory implementation period. (The estimated number of failing batches is intended to reflect a high-volume product for which a large number of batches are produced. Nevertheless, the number of batches and the frequency of failures could vary widely.) For the medium-value case, failures were assumed to occur once per month for a cost savings of $30,000. For the low-value estimate, 2 failure investigations over the regulatory implementation period are assumed to be avoided for a total savings of $10,000. No estimates were made for the savings from reduced product rework.

A.3.6 Scale-Up and Scale-Down

The SUPAC-IR provisions for scale-up allow companies to change batch sizes more rapidly, thereby generating savings in production costs, quality control testing costs per unit of product, raw material release activities, production labor, and other production-related costs. Furthermore, by making fewer, larger batches, manufacturing capacity is increased.

ERG estimated manufacturer cost savings based on several sources, although none capture all aspects of the possible savings. One generic manufacturer reviewed its manufacturing costs and estimated that scale-up provisions had allowed the company to save $80,000 for 5 processes, for an average of $16,000 per process. A single large-volume process, however, generated most of the savings. This estimate does not cover imputed savings for released production capacity. A second generic manufacturer estimated the savings for quality control testing alone from scale-up provisions at $2,500 per batch. If it is assumed that the manufacturers reduce the

number of batches produced by 5 to 20 batches per year, SUPAC-IR generates a savings of $12,500 to $50,000. Brand-name manufacturers provided no quantitative estimates on scale changes.

Alternatively, project consultants estimated representative QC costs at approximately 1 percent of production costs, and this estimate also can be used to estimate the savings for scale-up changes. Assuming companies reduce the number of batches by 2/3rds, they achieve a savings in quality control costs approaching 2/3rds of one percent of production costs. The value of 2/3rds was chosen based on the company comments regarding the number of batches they sought to consolidate. For the high-value product, this savings is calculated at $50,000 ($15 million x 1 percent x 2/3 x 6/12ths of the year). For the medium-sized product (with annual production costs of $6 million per year), this savings would be $20,000 ($6 million x 1 percent x 2/3 x 6/12ths), which is within the average estimated by the second generics manufacturer and more than the average savings reported by the first manufacturer. For the low-end estimate, the cost savings is estimated at $10,000 ($3 million x 1 percent x 2/3 x 6/12ths). Given their consistency with the data from the generic manufacturers, and with the consultants' estimates, these values were used to characterize the cost savings. These savings estimates do not capture the benefits from increased production capacity from scale-up changes and probably do not represent all savings from economies of scale in production.

For scale-down, manufacturers save production costs for batches that cannot be sold, such as validation batches or commercial batches that will exceed market demand by a wide margin. Based on discussions with consultants, ERG assumed that the bulk of the savings are from reduced raw material costs (i.e., production labor is not significantly changed from reducing the production scale), and that a substantial share of the raw material costs could be avoided. One generic manufacturer estimated savings of $57,000 from scale-down of several processes. No other quantitative estimates were obtained, and FDA has received very few scale-down SUPAC-IR submissions. Based on the single estimate, the savings were estimated at $100,000, $50,000, and $20,000, respectively for high, medium, and low estimates.

A.4 Secondary Cost Savings

The secondary cost savings are generated in the areas of:

- Stability testing costs

- Fewer unmarketable test batches
- Bioequivalence test batches
- Inventory management costs
- Administrative cost savings in documenting changes

Secondary savings were considered potentially applicable to each product represented in CMC supplement filings and annual reports. Because some filings address more than one change to a product (e.g., a site change and a manufacturing process change in the same CBE supplement), and there are sometimes multiple filings for an individual product, the total number of changes used in calculating the primary savings was reduced to reflect the number of distinct products. Therefore, secondary savings were considered potentially applicable to 25 percent of all prior approval supplements and 60 percent of the CBE and annual report changes based on the patterns of changes indicated in a sample of SUPAC-IR filings. The specific applicability of the secondary savings are described in each section below.

A.4.1 Stability Testing

SUPAC-IR reduces stability testing costs for many post-approval changes. In general, savings accrue from clarification of testing requirements and from relaxed accelerated and long term stability testing requirements. SUPAC-IR generates the most significant savings by requiring that only 1 batch be put on long term stability testing where FDA had previously required three batches.

Stability savings were credited to all distinct prior approval, CBE, and annual report filings. (These are the only savings applicable to prior approval supplements since they do not generate any primary savings from faster implementation time.)

A representative per batch cost of stability testing (for the entire gamut of accelerated testing and long-term stability tests) is approximately $10,000 to $15,000. Where stability testing imposes exceptional analytical requirements, however, the per batch testing cost can increase by a factor of 2 or 3. With the shift in stability requirements from 3 batches to 1 for most post-approval changes, ERG estimated the medium estimate of the prospective savings at $20,000 to $30,000 ($25,000 midpoint) for two fewer stability batches (based on the

average range estimated at $10,000 to $15,000). The high-end estimate was set at $70,000 to reflect cases with relatively extensive testing requirements. The low end estimate was estimated at 2/3rds the medium estimate because stability testing costs per batch do not generally fall far below the $10,000 to $15,000 range estimated for the medium case.

A.4.2 Fewer Unmarketable Batches

As noted above, FDA has generally expected 3 commercial scale batches to be produced for stability testing, although for certain changes only 1 stability batch was required. With long regulatory leadtimes, these batches often became "short-dated," that is, they are not released for sale until their time to expiration is too short for the batches to be marketable. Under SUPAC-IR, FDA generally requires only 1 stability batch, and with shorter leadtimes, such batches are more likely to be marketable.

Based on discussions with project consultants, ERG estimated that prior to SUPAC-IR pharmaceutical companies were able to sell approximately 50 percent of their stability batches, while the remainder became unmarketable. Pharmaceutical companies can market their stability batches despite the wait for regulatory approval in cases where: (1) regulatory approval comes fairly quickly, (2) they are able to delay the production of the stability batches until relatively late in the approval process, or (3) they are able to extend the product life estimate and avoid shortdating of the product. ERG applied the estimate to the number of distinct CBE and annual report filings.

Pharmaceutical companies might also avoid the production cost of the two additional batches that are no longer required for stability purposes. These batches might still be produced for process validation purposes, however, and simply not placed on stability testing. Validation batches can be, but might not be, the same as stability batches. Either validation and/or stability batches can become unmarketable if there is a lengthy wait for implementation of changes. Companies can reduce their losses in various ways, however, such as by negotiating to use pilot scale rather than commercial scale batches for some validation batches, or, under SUPAC-IR, using the scale-down provision to produce small batches for testing or validation.

As noted above, individual batches of the high, medium, and low value products are estimated to generate revenues of $500,000, $50,000, and $25,000, respectively. Companies are forecast, therefore, to save this amount

for each previously unmarketable batch. While the exact arrangements for production of stability and validation batches can vary, it was judged that SUPAC-IR allows companies to recover the market value on average of 2 batches, generating savings of $1 million, $100,000, and $50,000, respectively. The high end estimate is consistent with a large pharmaceutical company's estimate that under SUPAC-IR it had generated approximately $4 million in incremental revenues over four of its products by selling previously unmarketable batches.

A.4.3 Bioequivalence testing

In selected circumstances, SUPAC-IR eliminates the need to perform bioequivalence testing. Nevertheless, prior to SUPAC-IR, this requirement was invoked infrequently for a post-approval change so the savings from eliminating this requirement were estimated to apply for only 5 percent of the products addressed in CBE and annual report filings.

Pharmaceutical company representatives described a wide range for the costs of bioequivalence testing. At the high end, one company estimated its vendor costs at $250,000, with internal costs to monitor the bioequivalency study adding an additional $500,000. At the low end, one company estimated the costs at approximately $70,000. Commercial laboratories contacted for this study confirmed that the possible cost range for bioequivalency tests was quite large. Many variables, including the necessary number of test subjects, the cost of the drug, the nature of testing required, and numerous others, contribute to the wide range of possible costs. Based on these estimates, therefore, bioequivalency testing costs were estimated to range from $750,000 to $70,000.

A.4.4 Inventory

As explained earlier, inventory costs are estimated based on the time value of the funds invested in product batches placed in inventory while companies await regulatory approval. The cost of inventory was estimated at 12 percent per annum. Inventory savings were judged to apply to all distinct CBE and annual report filings.

Companies will save on inventory for validation/stability batches that previously had to be stored pending regulatory approval. The inventory savings was applied to all three of the previously prepared stability batches. Under SUPAC-IR, the regulatory implementation period is much shorter. For the high-end estimate, the inventory savings were estimated at $27,000 ($150,000 production cost per batch x 12 percent x 3 batches x 6/12ths of the year). The medium savings for inventory savings was estimated at $5,400 ($30,000 production cost per batch x 12 percent x 3 batches x 6/12ths of the year). The low estimate was calculated at $2,700 ($15,000 production cost per batch x 12 percent x 3 batches x 6/12ths of the year).

A.4.5 Administration Costs to Document Changes

To estimate this savings category, the principal issue is whether preparing the annual report entries required for many SUPAC-IR changes are as time-consuming as the supplement filings (CBEs or prior approval supplements) previously required. Pharmaceutical company executives interviewed for this study disagreed on whether personnel of the regulatory affairs department will now spend less time to document post-approval changes. Project consultants estimated, however, that SUPAC-IR will consistently reduce costs because annual reports do not require the same followup efforts with FDA, such as for responding to questions and to requests for clarification. Also, based on all inputs, ERG judged that most regulatory affairs departments inevitably spend more time on submissions made to FDA (whether CBEs or prior-approval supplements) than annual report changes, which need not be made quite so "reviewer friendly." The project consultants also provided specific quantitative estimates of the savings. At the high end, the savings were estimated at $10,000 to reflect approximately 4 days of additional work in preparing the regulatory submittal and 8 days in followup work to respond to FDA queries and other communications (approximately 100 hours at $100 per hour). The medium estimate was set at $5,000, and reflects cases where less followup work with FDA is required. The low end estimate was set at zero to reflect the opinion of those industry executives that see no savings. These executives judged that the annual report changes produced under SUPAC-IR are virtually as time-consuming to prepare as supplement filings. The administrative savings were applied to all distinct annual report filings.

References

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