A１９

措置報告及び研究報告は、従来どおり、治験依頼者から直ちに治験責任医師及び実施医療機関の長に通知する必要がある。

別添２

治験副作用等症例の規制当局への報告事項並びに治験責任医師及び実施医療機関の長への通知事項について

本一覧表は、平成２１年４月１日から施行される治験副作用等症例（措置報告、研究報告を除く）の取扱いについて、治験関係者等に理解を深めていただくために参考として作成したものである。
実際の取扱いについては、規制当局への報告にあっては規則を、治験責任医師及び実施医療機関の長への通知についてはＧＣＰ省令を遵守すること。

１．治験中副作用等症例の規制当局への報告事項（規則第２７３条）

（１）新有効成分、その他下記（２）以外の治験の場合

予測性	重篤性	国内症例（国内治験）	外国症例（外国臨床試験・外国市販後自発報告等）
予測できない（未知）	死亡・死亡につながる恐れのある症例	個別（　７日以内）・定期（半年ごと）	個別（　７日以内）・定期（半年ごと）
	その他重篤な症例	個別（１５日以内）・定期（半年ごと）	個別（１５日以内）・定期（半年ごと）
予測できる（既知）	死亡・死亡につながる恐れのある症例	個別（１５日以内）・定期（半年ごと）	個別（１５日以内）・定期（半年ごと）
	その他重篤な症例	―　・定期（半年ごと）	―　・定期（半年ごと）

（２）一変治験（用法・用量又は効能・効果の追加、変更又は削除に係るものに限る）の場合

予測性	重篤性	国内症例（国内治験）	外国症例（外国臨床試験・外国市販後自発報告等）
予測できない（未知）	死亡・死亡につながる恐れのある症例	個別（　７日以内）・定期（半年ごと）	―※　・定期（半年ごと）
	その他重篤な症例	個別（１５日以内）・定期（半年ごと）	―※　・定期（半年ごと）
予測できる（既知）	死亡・死亡につながる恐れのある症例	個別（１５日以内）・定期（半年ごと）	―　・定期（半年ごと）
	その他重篤な症例	―　・定期（半年ごと）	―　・定期（半年ごと）

※　未知の外国症例については、市販後安全対策の枠組みにおいて報告された情報を活用

2．治験中副作用等症例の治験責任医師及び実施医療機関の長への通知事項（ＧＣＰ省令第２０条第２項及び第３項）

予測性	重篤性	国内症例（国内治験）	外国症例（外国臨床試験・外国市販後自発報告等）
予測できない（未知）	死亡・死亡につながる恐れのある症例	個別（直ちに）・定期（半年ごと）	個別（直ちに）・定期（半年ごと）
	その他重篤な症例	個別（直ちに）・定期（半年ごと）	個別（直ちに）・定期（半年ごと）
予測できる（既知）	死亡・死亡につながる恐れのある症例	―　・定期（半年ごと）	―　・定期（半年ごと）
	その他重篤な症例	―　・定期（半年ごと）	―　・定期（半年ごと）

厚生労働科学研究費補助金
（医薬品・医療機器等レギュラトリーサイエンス総合研究事業）

分担研究報告書

米国における治験審査委員会のあり方の研究

研究分担者：小野俊介（東京大学大学院薬学系研究科　准教授）
研究分担者：斉藤和幸（（独）医薬品医療機器総合機構　審査役）

研究要旨
米国における治験審査委員会（IRB）の現状について、主として IRB を取り巻く規制環境及び近年実施されている治験の様態や特徴の観点から調査・研究を行った。
日本が ICH-GCP を受け容れ、施行した 1997 年よりずっと以前から、米国ではその臨床研究環境の中で、IRB による審査をはじめとする治験実施の仕組みを独自に発達させてきた。米国の仕組みの多くの要素は ICH-GCP を含む国際ガイドライン等に盛り込まれているが（米国主導でガイドラインが策定されることが多い実情を考えれば当然である）、一方で米国内では、米国固有の医療・社会背景が IRB 運用の実態に色濃く反映されていることが本研究で明らかになった。例えば、州によってインフォームドコンセントや IRB の情報公開の規定の内容及びその厳格さが全く異なるという事実は、米国の治験関連規制を誤って画一的・ステレオタイプに取扱うことへの注意を喚起する。また 2009 年になって初めて IRB の登録制度が法的に導入されたこと、有害事象等の IRB への報告に関して種々の混乱が現在でも続いているおり、2009 年に混乱の一部を解消するためのガイダンスが示されたこと等は、米国の治験実施の仕組みを我々が参照するに際して、制度の利点だけでなく欠点・問題点を随時把握する必要があることを示すものである。

A. 研究目的

治験実施に際して倫理的な観点からの審査を行う治験審査委員会（IRB）については、2006 年 3 月及び 2008 年 2 月 GCP 省令の IRB 関連規定の大幅な改定が行われたところである。

これらの改定は主として IRB の設置、運営、そして活用の自由度を高めることにより、近年の治験とその環境変化に対応したより効率的・高度な IRB 審査を目指すことを目的としている。具体的な改定内容は、IRB 設置可能者の拡大、外部 IRB の活用可能性の拡大、IRB の自施設設置原則の撤廃、IRB 審議内容の公開等である。こうした施策の実施（言い換えると従来の方針の変更）が日本の今後の IRB そして IRB による治験審査にどのような影響を与えるかについては時間を置いた評価が必要である。

ICH-GCP の導入・実施（1997 年）をはじめとして、日本の治験実施の現在の仕組みは欧米の仕組みを骨格として導入し、それを日本の環境に合わせて改変することで成り立っている。IRB に係る仕組みも同様である。しかし一概に「欧米の治験制度」と言っても、実は欧米各国固有の医療制度や経済・歴史・文化等の背景を踏まえて発達し、固有の環境において運営されていることは明らかである。外国の制度の外形的な仕組みをそのまま日本に導入するのではなく、各国の制度がいかなる経緯をたどって現在の姿となったのか、現時点の制度は各国の当

事者にとって本当に満足のいくレベルで機能しているのか、機能していないとすればその理由は何か等を検討し、検討結果の日本の状況への含意を踏まえて日本固有の仕組みを構築しなければならない。

こうした問題意識に立ち、本分担研究では、米国の IRB の実態、IRB をめぐる制度、IRB の運営について現地関係者からの事情聴取及び文献調査を行い、我が国の IRB において現在検討されている論点についての考察を行った。

B. 研究方法

分担研究者 2 名が米国において次の関連施設及び製薬企業の IRB 関連業務担当者に直近の事情を聴取した。現地調査結果に基づき、日本の IRB に係る規制環境の今後のあり方を考察した。

(1) ジョージワシントン大学
Dr Anne N. Hirshfield, PhD （Associate Vice President for Health Research, Compliance & Technology）

(2) 米国被験者保護局（Office for Human Research Protection, OHRP）及び米国医薬品食品局（Food and Drug Administration, FDA）
OHRP：
Capt. Melody H. Lin, PhD （Deputy Director, Director of International Activities）
Glen D. Drew, MS, JD （Health Policy Analyst）

FDA：
Mathew T. Thomas, MD （Chair of IRB）

(3) Pfizer, Inc.
吉川宗治氏 （Quality Assurance, Global Research & Development）
（注：吉川氏のコメント等は Pfizer Inc としての公式見解ではない。現地で氏が Quality Assurance 業務を担当しての個人的意見・印象、及び Pfizer 社の General Council、GCP auditors からの一般的な情報等である。）

（倫理面への配慮）

今回の研究は関係者からの事情聴取、研究班における議論、文献調査に基づくものであり、ヒト組織や個人情報を扱うものではない。

C. 研究結果

C-1. 治験実施医療機関における IRB の現状について

ジョージワシントン大学（GWU）IRB 担当者から聴取した米国の臨床試験（含治験）の実施状況、IRB の運営状況、現時点での問題点等は次のとおりである。（なお分担研究者が重要と判断した論点に下線を付した。以下同じ。）

<GWU の臨床試験実施状況>

- GWU IRB での臨床研究の審査は年間 700 試験程度。そのうちの多くが social science 試験なのが GWU の特徴。

<情報公開 public disclosure について>

- 州ごとに、また、大学ごとに異なるのが現状。例えば Univ of Maryland は State of Maryland の下にあるので、すべての情報は public が入手可能であるべきという考え方で、多くの情報はオープンにされている。一方私立大学ではオープンにするという発想が少ないと考えられる。
- 州によってインフォームドコンセントの規定が異なるように、情報公開の規定も異なる。
- Ellen Roche の事件等の後で、情報をオープンにする動きが州法で（連邦法ではなく）進んだ。
- ただし公開といっても制約はある。例えば個人情報は除く、企業秘密に係る情報も除く等。IRB 委員名は公開していない。
- また公開することで IRB メンバーに世間からの圧力がかからないように、議事録への記載には特に注意している。「xx 委員がこう発言した」とは議事録には決して書かない。IRB 委員としての総意を載せるようにしている。また外部からの問い合わせに対しては IRB 事務局が対応し、IRB 委員が対応することはない。
- IRB の議事録は倫理的な論点に関しては

求められればすべて出す。透明性は保証されている。

- 健康人での第 I 相試験については、それを公開することの意味・意義を踏まえての話となるが、一般的には公開しないという方針になるだろう。
- IRB の標準業務手順書（SOP）はすべて公開されている。企業の人々にもすべて見せている。SOP は常に最新版に改定されており、秘密でない部分はすべて公開されることになる。
- 情報公開においては OHRP が各 IRB の代わりに情報を公開してくれる意味がある。IRB で起きたことを OHRP に報告すると、OHRP は FOI の規定により全ての情報を公開するというのが常識である。
- Common rules、FDA regulations ですべての研究がカバーされていないのは常識。例えば Ca 強化剤のようなもので HHS から資金を受けていない研究はいくつもあり、これらはどちらの規制下にも置かれていない。また政府の研究でも HHS 以外の役所（例えば教育省）は必ずしも Common rule に従わないことがある。 これらの研究を無理矢理に common rule や FDA rules の下に持ってきて、不要な事務仕事を生むことは、研究のインセンティブにねじれを生む可能性はある。
- AAHRPP の認定 accreditation システムが、common rule と FDA rule のねじれ（違い。例えば有害事象報告に関するもの）を含め、様々な規制やルールをハーモナイズする役割を果たしている。AAHRPP が独自のルール、独自の定義を定め（それらは十分に立派なものである必要がある）、それを活用することで、ルールのねじれや食い違いが生じた場合に「AAHRPP のルールに従っているのだからそれでよい」とする対応も可能になる。

<OHRP と FDA>

- 簡単に言うと OHRP は IRB 関連の規制、FDA は治験実施医師と依頼者の規制を担当しているが、GWU は HHS をスポンサーとする試験と製薬企業をスポンサーとする試験を両方実施しているので、両方の役所と定常的にコンタクトしている。
- FDA はだいたい 3 年に 1 回程度査察 inspection にやってくる。ルーチンの査察である。査察要項にもとづく具体的な項目を一つ一つ確認していく査察を行う。
- 一方 OHRP（その前身の OPRR）は for-cause inspection が多い。Duke 大で OHRP の inspection の結果すべての研究が停止させられた前例はよく知られている。
- 1998 年に Duke 大で問題が起き、National Biosafety Advisory Committee が問題提起して、インフォームドコンセントの取得が困難なヒト（例：いわゆる adult children）の試験をどうするかでヒアリング、公聴会が開かれた。各施設に OPRR から査察が入ったことがある。3 日間程度の集中的な査察が実施されたと聴いている。

<Central IRB としての役割>

- 中央 IRB（CIRB）の審査で各施設固有の状況をどう把握し、審査でどう決定するかは重要な問題で、Dr Hirshfield も様々な機会に発言してきている。
- CIRB はそもそも IRB 審議のダブり・繰り返しの非効率の問題に端を発しており、法律的な根拠もあるが、しかし他の IRB の判断に頼り切るのはやはり難しいと思う。現在まだ議論の真っ最中である。
- 外部の基準（例えば AAHRPP の認定やルールに従っているか）を判断基準にするのは、複数の IRB の様々な食い違いを解決する一つの方策である。
- 困ったことが起きた場合（何か wrongdoing があったとき）には、どの IRB が責任を有すると考えるのかという問題がある。例えば他の大学が CIRB として審査を行っている試験で、参加機関の一つの GWU で不祥事が起きたようなときに、GWU の IRB はやはり黙っているわけにはいかないだろう（IRB がある以上、問題を放置するわけにはいかない）。倫理面を含めた全体的な承認を CIRB が行い、各施設の IRB が各施設で実行していることの承認をするというのは一つの方向である。
- 多施設試験では独立系の IRB（independent IRB 等）を使うこともある。

・ IRB ショッピングの問題は表面にはなかなか出てこない、潜在的に危険な問題と認識している。

C-2. 米国規制当局担当者の視点から見た IRB 関連諸規制の現状と課題

IRB 関連諸規制を管轄する OHRP 及び FDA 担当者から関連規制の現状と課題を聴取した。

<IRB の登録制度に関して>

・ OHRP が IRB 登録制度を運用しているが、Federalwide Assurance (FWA) の制度とは別立てである。IRB の登録制度が先にあって、それに基づいて（その適切な活用を前提にして）FWA の認定がおりるということになる。
・ かねての懸案事項（2004 年 7 月にパブリックコメントを求めて以来）であった IRB の正式な登録制度については、OHRP 側、FDA 側双方に登録の規定が設けられることになった（2009 年 1 月 15 日の Federal Register）。調整に長い時間を要した。実施は 2009 年 7 月 14 日からである。
・ ただし OHRP ルールと FDA ルールには登録すべき事項等において若干の差異がある。FDA への登録には IRB の委員名を提出する必要がない（委員長、コンタクトパーソンがあれば良い）が、OHRP への登録は IRB の委員名が必要、等。
・ 具体的には FDA に登録する事項は、IRB 名、所在地、コンタクト先、IRB 委員長、過去 12 ヶ月で何本アクティブな試験があるか、どんなタイプのモノか（医薬品、機器、色素、食品添加物、程度のレベル）等である。
・ OHRP 管轄の試験、FDA 管轄の試験といった縦割りは変わっていない。OHRP の管轄の試験を審査する IRB は OHRP に登録、FDA の管轄の試験を審査する IRB は FDA に登録、両者の試験を審査する IRB は両者に IRB を登録することになる。
・ IRB データベースは OHRP（HHS）に集約するらしい。OHRP のデータベースを FDA が利用することになる。これで米国の IRB 全体の状況を誰も把握していないという批判（米国議会での答弁でそのことが露呈して問題になった）に初めて公的な対応ができたことになる。
・ 登録方法として、FDA は書類ベースでの申請を受け付けるが、OHRP は電子申請のみとするといった違いがある。
・ なお 2009 年現在、米国に存在する IRB は約 4500 である。OHRP に登録されている IRB の総数は約 6000（海外の IRB を含む）。2006 年の OIG 報告では約 3000 としているが、これは古い数字を引用しているから。

<商業的第 1 相試験施設について>

・ 基本的には FDA が把握している。大学などでは NIH fund 試験をやっているのが普通だから、OHRP も把握しているはず。
・ このような施設で特段、被験者保護に問題が生じているとは認識していない。

<IRB の情報公開について（規制当局からの情報公開と各 IRB の情報公開の両方）>

・ OHRP に登録された内容を web に載せることはしていない。ただし FOIA で要求があったら、その都度応じるというスタンスをとっている。
・ 情報公開の程度・方法は州によって完全に異なる。インフォームドコンセントの要件が各州で異なっているのと同様である。一部の Sunshine state と呼ばれる州（eg. Georgia）では委員長、委員リストを含めすべて公開されており、また、審議自体に誰でも（一般市民が）参加可能というやり方をとっている。
・ また各 IRB も、自分たちがどこまで情報を公開するのかを決めうる。一律のルールは存在しない。
・ （当方が、FDA が Bioresearch Monitoring Information System File として IRB の委員 or chair を公開している件について指摘したところ）、Form 1572 に IRB と関連付けられている investigator が掲載されているものだと思われるが、当該 investigator が委員長か、メンバーか等は把握していないので、確認する。FDA が IRB メンバーを公開する方針にあるという事実はない。

<査察結果, disqualification の公開に関して>

- なお、FDA が disqualification list として公開しているいわゆるブラックリスト（IRB も含む）は、これまで話してきた情報公開とは話が別。Web に載せる対応と、FOIA に基づく対応がある。
- OHRP にはブラックリストは存在しないが、それぞれの違反等の案件ごとに、対応をすべて公開するという方針である。
- なお OHRP は FWA（施設の認定）を通じて違反等に対応するので、処分等は施設単位で行われる。（商業試験との住み分けに関しては）施設次第となる。施設がすべての試験を FWA 下の要求に基づいてやると宣言していたら、例えば研究の停止 suspension 等の処分は企業治験を含むすべての研究が対象となり、間接的に処分が適用されることになる。多くの場合、企業治験は別、と割り切ることは難しいのではないか。
- FDA の処分対象は基本的には個人（IRB は別だが）である点が OHRP の処分とは異なる。
- （当方から Office of Inspector General (OIG)が inspection を行うのはどういう場合か?と尋ねたところ）OIG が行っているのは OHRP/FDA と同様の意味での査察と呼ぶべきではない。OIG が IRB を調査するのはあくまで IRB 制度やシステムの評価 evaluation を行い、その改革案等を提言するのが目的。なお政府機関での機密の漏洩に対する捜査的な意味合いでの調査を行うこともあるが、これも査察と呼ぶにはなじまない。

<IRB の設置に関して>

- 要件を満たす IRB を設立できるのであれば、「誰でも（個人でも、製薬企業でも）」IRB を設立可能。日本とは大きく異なる。

<IRB shopping について>

- proposed guidance を出して comment を求めているところである。

<民間の認定機関について>

- AAHRPP の認定等の活用はあくまで自発的なものであり、OHRP/FDA の規制との直接の関係はない。製薬企業等がその質を判断する根拠あるいは prestige として活用されるべきものである。
- AAHRPP, PRIM&R（CIP）といった認証機関の側は OHRP のお墨付きがほしいと思っているかもしれないが、それは無理である。海外の当局や治験責任医師から、例えば CIP だから採用・活用しても良いか?といった問い合わせが来るが、OHRP としては回答することはできない。
- ただし、これらの専門家集団の活動を通じて、各種ガイドラインが策定され、レビューされることの意義は高い。
- OHRP/FDA はこれらの団体のシンポジウム、講演会等には協力している。（例えば Drug Information Association に対する協力と同様。）
- なお、NCQA はもう活動していない。ARENA もそれ自体としてはもう活動していない。

<有害事象等の報告について>

- IRB 等への有害事象等の報告については 2009 年 1 月に FDA がガイダンスを出している（Adverse Event Reporting to IRBs – Improving Human Subject Protection Jan 2009）。OHRP も 2007 年 10 月に予測できない有害事象等にかかるガイダンスを出している。
- 本件に関しては Federal task force が活動していた。
- 従来から問題視されている FDA の定義と OHRP の定義が乖離していることについては、運用を両者が近づけることで解決を目指している（CFR の規定そのものを変えるのではない模様）。これで食い違いは小さくなりつつあると思う。
- 有害事象報告を web 化する等の活動は Medwatch、clinicaltrial.gov 等の活動となる。
- NCI は各施設をファイバーでつなぐプロジェクトを実施している。

C-3. 製薬企業の視点から見た米国の治験・IRB の状況

<情報公開、IRB の議事録公開について>
- 米国では IRB の議事録を企業担当者には見せてくれないのが普通である。
- 一般論として製薬企業は IRB 議事録を公開することについては否定的な見解を持っているのではないか。理由は個人情報の観点（法務が特に気にする）と企業の競争の観点からである。企業の競争の観点からは、他社の臨床開発に関する情報収集の目的で使われることになると推察される。

<IRB 全般>
- Central IRB（independent IRB）に関しては企業側も活用のメリットがあると考えている。特に大規模でよく知られた IRB が好まれる。理由は、煩雑さの回避、専門性の蓄積、開催頻度（の多さ）等である。
- 企業としては central IRB を勧めても、実際にそれを使うかどうかは研究者・施設の判断となる。施設によっては（例えば大学病院、一般的に大病院）ローカル IRB を必須とするところもある。
- IRB 審議では研究者代表が説明を行うこともある。また IRB 委員の一人がプロトコルごとに事前にレビューを割り当てられて、審議時に他の委員にブリーフィングをするという審議の効率化もある。
- （米国では誰が IRB を設立しても良いことについて）IRB が研究者・医療機関から独立した判断ができることが根幹にあるので、自律の精神が保たれている限り、あまり違和感がないのではないか。

<FDA の査察に関して>
- 企業担当者が立ち会うことはない。施設の準備の手伝いはする。
- FDA は Form 1572 から IRB に関する情報を集めているが、情報が最新のものとならないことがあった。それが今般の IRB 情報登録と随時更新へとつながっている。
- FDA の査察で問題あり（OAI 等）と判断されることはもちろんあり（年間 100 件程度の IRB への査察を実施しているはず）、結果 IRB の閉鎖等にまで至ることもあるかもしれないが、普通は指摘に対する適切な対応で済む。
- IRB 査察の結果に基づいて申請データを削除するという発想は米国ではあまりない。IRB の活動・存在意義と申請におけるデータの integrity とをリンクさせるのは不自然である。

<認定について>
- AAHRPP 等の認定については、一つの目安にはなるが、質の完全な保証にはならないという印象。認定されていても問題がある施設を経験している。
- 企業としては、(1) FDA と OHRP は共同して GCP や HSP (Human Subject Protection) トレーニング に関する、統一された標準的な内容を確立してほしい、(2)これらのトレーニングには信頼のできる第三者的な団体の利用を推奨すべき、(3) これらトレーニングの Certificate や Accreditation system を FDA や OHRP はサポートすべき、と要望している。
- NCQA の認定は止めたようだが、AAHRPP 等によるこうした認定には一定の需要は存在し続けている。

D. 考察

米国の治験実施状況や IRB の運用状況については過去に多数の報告があり、それらを参照しながら日本の制度構築の議論は行われてきている。しかし、例えば米国内においては自国の治験に係る監督・監視体制が期待されているほど堅固ではないこと等も報告されているにもかかわらず、こうした報告に取り上げられた事実を具体的に取り上げて、日本の治験関係者が十分に議論する機会はあまりない。[1]

今回の調査では従来の日本の議論ではあまり表面に出てこない事実をあわせて確認し、また、それらの点に関しての日米関係者の興味深い見解の相違が明らかになった。

D-1. IRB に係る情報公開について

日本では 2008 年の GCP 省令改定において

IRB 委員名を含む各種 IRB 情報を公開する旨が義務付けられたが、米国では統一された規定はなく、各州によって情報公開の程度はかなり異なることが明らかになった。例えば IRB 委員の氏名等の公開が審議内容に好ましくない影響を与える可能性を事情聴取した関係者が度々指摘しており、この論点に関する議論は米国においても依然決着がついていないことがうかがわれた。

D-2. IRB の設置者について

米国では IRB の設置者に関して何ら制約が存在しないこと（要件を満たす IRB が運営できるのであれば何人でも IRB を設立可能なこと）が再確認された。ICH-GCP 導入時、日本では IRB を誰がどのように設置するかという根本的なところから検討が行われ、策定された GCP 省令において IRB 設立可能者に係る厳密な規定が設けられているが、それとは好対照である。

各国間での IRB の運営様態の違いを考える上で、設立母体に係る制約の有無・違いはきわめて重要である。例えば、欧州における公的な倫理委員会のあり方と、米国型あるいは日本型 IRB のあり方を比較する上での根幹となりうる背景情報である。

D-3. いわゆる中央 IRB について

多施設共同試験において一つの IRB が全体の審査を行うという文脈でのいわゆる中央 IRB については、日本と同様に米国でも依然運用において難しい点が残っていることが明らかになった。中央 IRB 審査の法的な根拠は明確であり、かつ、中央審査に係るガイダンスも存在するものの、実際に中央 IRB 審査を行うと、各施設の IRB と中央 IRB の間の役割及び責任分担に不明確な部分が残っていることが判明した。

D-4. IRB の登録制度について

これまで OHRP が FWA にあわせて実施していた IRB 登録に FDA も参加し、米国の IRB 登録制度と呼べるものがようやく動き始めることとなった。従来は IRB 登録制度の直接の法的根拠がなく、2004 年に新たな制度の提案（パブリックコメント募集）を行っていたが、その後の進展がはっきりしない状況が長く続いていた。[2]

日本でも医薬品医療機器総合機構に IRB 情報を登録する試みが開始されるが、これを公的制度としてどのように発展させていくかについては、こうした米国の状況を参考とすることができる。

D-5. IRB への有害事象の報告について

治験中に発生した（又は情報収集された）有害事象等について、どのようなものを IRB に報告すべきかについてのガイダンスが 2009 年 1 月に発出された。[3] ガイダンスにはすべての情報を一律に報告するのではなく適切な取捨選択を行う必要があること、取捨選択に際しては被験薬の特性やすべての実施機関での治験実施状況を包括的に把握している治験依頼者（製薬企業）の判断が重要であることが記載されている。

日本でも ICH-GCP の施行後、各施設への有害事象等の報告のあり方について主として治験実施医師・医療機関からの改善要望が起こり、規制当局による報告範囲の合理化が段階的に進んでいる。これらの合理化で報告に係る要求の形式的な透明性は明らかに高くなった。しかし、被験者の安全を守る観点で治験実施医師・医療機関・IRB にとってどのような情報がどの程度必要なのかについての考え方の基本は明らかになっておらず、例えば「さらに報告を合理化することができるのではないか」という医療機関・製薬産業の双方からの提案に対していかに対応すべきかの議論が依然続いている。

今般発出された米国のガイダンスは今後の日本の議論を建設的なものにするための参考になる。

（参考文献）

[1] DHHS. Office of Inspector General. The Food and Drug Administration's Oversight of Clinical Trials. September 2007.
[2] Federal Register. Vol.74, No.10. January 15,

2009.
[3] US FDA. Adverse Event Reporting to IRBs. Improving Human Subject Protection. January 2009.

E. 結論

日本が ICH-GCP を受け容れ、施行する 1997 年のはるか以前から、米国ではその独自の治験環境の中で IRB による審査をはじめとする治験実施の仕組みを独自に発達させてきた。米国の仕組みの多くの要素は ICH-GCP を含む国際ガイドライン等に盛り込まれているが（米国が主導でガイドラインが策定されることが多いことを考えれば当然である。）、一方で米国固有の背景が IRB 運用の現状に色濃く反映されていることが本研究で明らかになった。例えば、州によってインフォームドコンセントや IRB の情報公開の規定や厳格さが全く異なるという事実は、米国の治験関連規制を誤って画一的に取扱うことへの注意を喚起する。また、2009 年になって初めて IRB の登録制度が法的に導入されたこと、有害事象等の IRB への報告に関して種々の混乱が現在でも続いているおり、2009 年にガイダンスが示されたこと等は、米国の治験実施の仕組みを参照するに際して、制度の利点だけでなく欠点・問題点を随時把握する必要があることが判明した。

F. 健康危険情報

該当する情報なし。

G. 研究発表

なし。

I. 知的財産権の出願・登録状況

1. 知的所有権の取得状況
   なし。

2. 実用新案登録
   なし。

【参考資料】

party listed in Appendix A to 31 CFR Chapter V with the bracketed suffix [NPWMD] of an item subject to the EAR. If OFAC authorizes an export from the United States or an export or reexport by a U.S. person to a party listed in Appendix A to 31 CFR Chapter V with the bracketed suffix [NPWMD], such authorization constitutes authorization for purposes of the EAR as well.

(ii) U.S. persons must seek authorization from BIS for the export or reexport to a party listed in Appendix A to 31 CFR Chapter V with the bracketed suffix [NPWMD] of any item subject to the EAR that is not subject to OFAC's regulatory authority pursuant to Executive Order 13382.

(iii) Non-U.S. persons must seek authorization from BIS for any export from abroad or reexport to a party listed in Appendix A to 31 CFR Chapter V with the bracketed suffix [NPWMD] of any item subject to the EAR.

(iv) Any export or reexport to a party listed in Appendix A to 31 CFR Chapter V with the bracketed suffix [NPWMD] of any item subject to the EAR and not authorized by OFAC is a violation of the EAR.

(v) Any export or reexport by a U.S. person to a party listed in Appendix A to 31 CFR Chapter V with the bracketed suffix [NPWMD] of any item subject to the EAR that is not subject to regulation by OFAC and not authorized by BIS is a violation of the EAR. Any export from abroad or reexport by a non-U.S. person to a party listed in Appendix A to 31 CFR Chapter V with the bracketed suffix [NPWMD] of any item subject to the EAR and not authorized by BIS is a violation of the EAR.

(3) *Relation to other EAR license requirements.* The license requirements in this section supplement any other requirements set forth elsewhere in the EAR.

(b) *License exceptions.* No license exceptions are available for the EAR license requirements imposed in this section.

(c) *Licensing policy.* Applications for EAR licenses required by this section generally will be denied. You should consult with OFAC concerning transactions subject to OFAC licensing requirements.

(d) *Contract sanctity.* Contract sanctity provisions are not available for license applications reviewed under this section.

PART 746—[AMENDED]

■ 7. The authority citation for part 746 continues to read as follows:

Authority: 50 U.S.C. app. 2401 *et seq.*; 50 U.S.C. 1701 *et seq.*; 22 U.S.C. 287c; Sec 1503, Public Law 108–11, 117 Stat. 559; 22 U.S.C. 6004; 22 U.S.C. 7201 *et seq.*; 22 U.S.C. 7210; E.O. 12854, 58 FR 36587, 3 CFR, 1993 Comp., p. 614; E.O. 12918, 59 FR 28205, 3 CFR, 1994 Comp., p. 899; E.O. 13222, 3 CFR, 2001 Comp., p. 783; Presidential Determination 2003–23 of May 7, 2003, 68 FR 26459, May 16, 2003; Presidential Determination 2007–7 of December 7, 2006, 72 FR 1899 (January 16, 2007); Notice of July 23, 2008, 73 FR 43603 (July 25, 2008).

■ 8. Revise § 746.7 to read as follows:

§ 746.7 Iran.

The Treasury Department's Office of Foreign Assets Control (OFAC) administers a comprehensive trade and investment embargo against Iran. This embargo includes prohibitions on exports and certain reexport transactions involving Iran, including transactions dealing with items subject to the EAR. These prohibitions are set forth in OFAC's Iranian Transactions Regulations (31 CFR part 560). In addition, BIS maintains licensing requirements on exports and reexports to Iran under the EAR as described in paragraph (a)(1) of this section or elsewhere in the EAR (*See, e.g.*, § 742.8—Anti-terrorism: Iran).

(a) *License requirements.*

(1) *EAR license requirements.* A license is required under the EAR to export or reexport to Iran any item on the CCL containing a CB Column 1, CB Column 2, CB Column 3, NP Column 1, NP Column 2, NS Column 1, NS Column 2, MT Column 1, RS Column 1, RS Column 2, CC Column 1, CC Column 2, CC Column 3, AT Column 1 or AT Column 2 in the Country Chart Column of the License Requirements section of an ECCN or classified under ECCNs 0A980, 0A982, 0A983, 0A985, 0E982, 1C355, 1C395, 1C980, 1C981, 1C982, 1C983, 1C984, 2A994, 2D994, 2E994, 5A980, 5D980, or 5E980.

(2) *BIS authorization.* To avoid duplication, exporters or reexporters are not required to seek separate authorization from BIS for an export or reexport subject both to the EAR and to OFAC's Iranian Transactions Regulations. Therefore, if OFAC authorizes an export or reexport, such authorization is considered authorization for purposes of the EAR as well. Transactions that are not subject to OFAC regulatory authority may require BIS authorization.

(b) *Licensing Policy.* Applications for licenses for transactions for humanitarian reasons or for the safety of civil aviation and safe operation of U.S.-origin aircraft will be considered on a case-by-case basis. Licenses for other purposes generally will be denied.

(c) *License Exceptions.* No license exceptions may be used for exports or reexports to Iran.

(d) *EAR Anti-terrorism controls.* The Secretary of State has designated Iran as a country that has repeatedly provided support for acts of international terrorism. Anti-terrorism license requirements and licensing policy regarding Iran are set forth in § 742.8 of the EAR.

(e) *Prohibition on exporting or reexporting EAR items without required OFAC authorization.* No person may export or reexport any item that is subject to the EAR if such transaction is prohibited by the Iranian Transactions Regulations (31 CFR part 560) and not authorized by OFAC. The prohibition of this paragraph (e) applies whether or not the EAR requires a license for the export or reexport.

Dated: January 9, 2009.

Christopher R. Wall,

Assistant Secretary for Export Administration.

[FR Doc. E9–726 Filed 1–14–09; 8:45 am]

BILLING CODE 3510–33–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 56

[Docket No. FDA–2004–N–0117] (formerly Docket No. 2004N–0242)

RIN 0910–AB88

Institutional Review Boards; Registration Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, we) is issuing a final rule to require institutional review boards (IRBs) to register through a system maintained by the Department of Health and Human Services (HHS). The registration information includes contact information (such as addresses and telephone numbers), the number of active protocols involving FDA-regulated products reviewed during the preceding 12 months, and a description of the types of FDA-regulated products involved in the protocols reviewed. The IRB registration requirements will make it easier for FDA to inspect IRBs and to convey information to IRBs.

DATES: This rule is effective July 14, 2009. This effective date is necessary to allow refinement of the electronic

registration system so that it corresponds to this final rule. All IRBs must comply with the initial registration requirement and, if necessary, make required revisions to their registrations by September 14, 2009.

FOR FURTHER INFORMATION CONTACT: Erik Mettler, Office of Policy, Planning and Preparedness, Food and Drug Administration, WO1, rm. 4324, Silver Spring, MD 20993–0002, 301–796–4830.

SUPPLEMENTARY INFORMATION:

I. Introduction

What Led Us to Issue This Rule?

IRBs are "boards, committees, or groups formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects" (see 21 CFR 56.102(g)). An IRB's primary purpose during such reviews is to assure the protection of the rights and welfare of human subjects (id.). FDA's general regulations pertaining to IRBs are at part 56 (21 CFR part 56). (While section 520(g) of the Federal Food, Drug, and Cosmetic Act ("the act") (21 U.S.C. 360j(g)) refers to "institutional review committees" rather than IRBs, FDA considers institutional review committees to be IRBs and to be subject to the IRB regulations.)

Even though IRBs play an important role in the conduct of clinical investigations regulated by FDA, we have never compiled a comprehensive list of IRBs involved in reviewing clinical investigations regulated by FDA. Existing FDA regulations have required some, but not all, clinical investigators or sponsors of clinical investigations to provide IRB names and addresses to FDA, and the requirements differ slightly among the different types of products regulated by FDA. For example, for human drug products, the sponsor must disclose the name and address of "each reviewing" IRB (see 21 CFR 312.23(a)(6)(iii)(b)). For medical devices, the sponsor must disclose the names and addresses of IRBs that "have been asked *or will be asked*" to review the investigation (see 21 CFR 812.20(b)(7)) (emphasis added). For other types of clinical investigations regulated by FDA (such as food additive studies involving human subjects), the regulations do not expressly require the sponsor or the clinical investigator to disclose or keep records showing an IRB's name and address, and they make no distinction between "reviewing IRBs" and IRBs that have been asked or will be asked to review a study.

In 1998, the Department of Health and Human Services' Office of the Inspector General (OIG) issued several reports on IRBs. The OIG sought to identify the challenges facing IRBs and to make recommendations on improving Federal oversight of IRBs. One recommendation was that all IRBs should register with the Federal Government on a regular basis as part of an effort to develop more streamlined, coordinated, and probing means of assessing IRB performance and to enhance the Federal Government's ability to identify and respond to emerging problems before they result in "serious transgressions" (see Office of the Inspector General, Department of Health and Human Services, *Institutional Review Boards: a Time for Reform*, pages 20 and 21, June 1998).

After reviewing the OIG's recommendation, we concluded that IRB registration would serve several important goals. IRB registration would:

- Enable us to identify more precisely those IRBs reviewing clinical investigations regulated by FDA. At present, much of our knowledge about the identities and numbers of IRBs reviewing clinical investigations regulated by FDA is based on information from persons conducting or sponsoring clinical investigations rather than from IRBs themselves. This information may be obsolete (because there may be no obligation to update the information) or incomplete (because the requirements to report the names and addresses of IRBs are not uniform across all FDA-regulated products);
- Enable us to send educational information and other information to IRBs. Because we lack an accurate list of IRBs, our outreach and educational efforts are not as efficient as they might be. Changes in IRB addresses result in returned mail, and newly formed IRBs may not appear in FDA's mailing lists; and
- Help us identify IRBs for inspection, because we would have a more accurate list of IRBs.

Consequently, FDA, in consultation with the Department of Health and Human Services, Office for Human Research Protections (OHRP), published a proposed rule in the **Federal Register** of July 6, 2004 (69 FR 40556), that would require IRB registration for IRBs reviewing clinical investigations involving FDA-regulated products. OHRP issued a companion proposed rule which appeared in the **Federal Register** of July 6, 2004 (69 FR 40584) that would require registration for IRBs reviewing federally supported research. The final OHRP IRB registration rule is published elsewhere in this issue of the **Federal Register**.

The goal of the two rules is to create a simple, electronic registration system that all IRBs, regardless of whether they review clinical investigations regulated by FDA or federally supported research, can use.

II. What Comments Did We Receive?

A. How Many Comments Did We Receive, and Who Submitted Comments?

We received over 15 comments in response to the proposed rule. Individuals, IRB members, IRB associations, an IRB accreditation association, government, health, academic or trade associations, a university system, and drug companies submitted comments. In general, the comments supported IRB registration, although some disagreed with specific aspects of the proposal or with other issues that were discussed in the preamble to the proposed rule. To make it easier to identify comments and our responses, the word "Comment," in parentheses, will appear before the comment's description, and the word "Response," in parentheses, will appear before our response. We have also numbered each comment to help distinguish between different comments. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was received.

B. Who Must Register? (Section 56.106(a)).

Proposed § 56.106(a) would require the following IRBs to register:

- Each IRB in the United States that reviews clinical investigations regulated by FDA under sections 505(i) (21 U.S.C. 355(i)) or 520(g) of the act; and
- Each IRB in the United States that reviews clinical investigations that are intended to support applications for research or marketing permits for FDA-regulated products.

The preamble to the proposed rule invited comment on whether there are circumstances in which foreign IRBs should be required or invited to register (see 69 FR 40556 at 40558).

(Comment 1) One comment stated that foreign IRBs are not needed in America.

(Response) The comment may have misinterpreted the preamble. The issue is not whether foreign IRBs should or should not review studies, but rather whether foreign IRBs should be included in the IRB registration system.

(Comment 2) Several comments differed as to whether foreign IRBs should have to register. One comment would require foreign IRBs to register if they review research conducted in the

United States; the same comment would give foreign IRBs the option to register if they review research conducted outside the United States that may be used to support a future marketing application in the United States.

Several comments would allow for voluntary registration of foreign IRBs or ethical review committees. Two comments explained that registering foreign IRBs would enable them to have access to educational materials and other information. However, one comment would limit such registration to foreign IRBs reviewing research conducted in the United States, and another comment noted that local privacy laws in foreign countries might affect a foreign IRB's ability to provide certain registration information.

In contrast, one comment said that we should respect oversight of ethical review committees by foreign authorities and that we should not impose "additional bureaucracy." Similarly, another comment opposed registering foreign IRBs, stating that such registration could pose "significant difficulties" for clinical investigators and sponsors and that foreign laws and regulations might make it difficult for foreign IRBs to register.

(Response) We agree in part with the comments. We agree that foreign IRBs would benefit from educational and other materials that would be sent to registered IRBs. Therefore, we have revised § 56.106(a) to allow for voluntary registration by foreign IRBs and by any domestic IRB that is not otherwise required to register.

We decline to require registration by foreign IRBs that review research to be conducted in the United States. We do not believe a significant number of foreign IRBs review research that is to be conducted in the United States. Furthermore, requiring registration by foreign IRBs that review research conducted in the United States could lead to arguments over the validity of our regulatory authority when applied to actions occurring in a foreign country.

As for possible problems foreign IRBs might encounter in registering information due to foreign laws and regulations, the comments did not identify specific registration elements that would be a problem. Consequently, we lack sufficient information to determine whether we should modify certain IRB registration elements to accommodate foreign IRBs.

(Comment 3) One comment asked us to clarify whether the reference to section 520(g) of the act was limited to research done under an investigational device exemption (IDE) or encompassed all investigational devices in a clinical investigation.

(Response) The reference to section 520(g) of the act encompasses all investigational devices in a clinical investigation, regardless of whether FDA approval of an IDE is needed in accordance with 21 CFR part 812 for the clinical investigation.

(Comment 4) One comment asked us to clarify whether the rule applied to "non-local" or "commercial" IRBs.

(Response) The comment did not explain what it meant by the terms "non-local" or "commercial" IRB. For purposes of this response, we will assume that a "non-local" IRB is one that is physically located away from the clinical trial site(s) and that a "commercial" IRB is one that is paid to review research.

If the "non-local" or "commercial" IRB is located in the United States and:

- Reviews clinical investigations regulated by FDA under sections 505(i) or 520(g) of the act; or
- Reviews clinical investigations that are intended to support applications for research or marketing permits for FDA-regulated products, then the non-local or commercial IRB must register under § 56.106(a). If the non-local or commercial IRB does not perform any of the reviews described immediately above or is outside the United States, then it may register voluntarily.

C. What Information Must an IRB Register? (Section 56.106(b))

Proposed § 56.106(b) would describe the information that IRBs would provide as part of the registration process. For example, proposed § 56.106(b)(1) would require the name and mailing address of the institution operating the IRB and the name, mailing address, phone number, facsimile number, and electronic mail address of the senior officer of that institution who is responsible for overseeing the IRB's activities. (A facsimile number also is known more commonly as a "fax number.")

(Comment 5) Several comments addressed the registration information in proposed § 56.106(b) generally. Two comments said that the registration information that OHRP and FDA would require should either be the same or that information required by OHRP, but not by FDA, should be clearly delineated and marked as optional for IRBs that are subject to FDA regulation. Similarly, one comment said that questions relating to research funded by HHS, which were part of OHRP's proposed registration system, should be identified clearly so IRBs that do not review HHS-funded research are not obliged to answer those questions.

Another comment said the proposed registration information is appropriate.

One comment urged us to reexamine the registration information to assure that the information is necessary to support the rule's stated goals.

(Response) We coordinated our rule with OHRP and tailored our respective registration information elements to be as consistent as possible and to use the same internet-based registration system.

We agree that the IRB registration system should specify whether certain registration information is optional or not required for IRBs subject only to our jurisdiction. The preamble to the proposed rule stated that, "In those instances where the Internet registration site would seek more information than FDA would require under this proposal, the site would clarify that IRBs regulated solely by FDA may, but are not required to, provide the additional information" (69 FR 40556 at 40558). The Internet registration site will be structured so that required information will be identified or marked as such, and IRBs indicating that they are registering pursuant to FDA's regulation also will be directed to questions requesting information required only under FDA's regulation.

(Comment 6) Proposed § 56.106(b)(1) would require IRBs to provide the name and mailing address of the institution operating the IRB and the name, mailing address, phone number, facsimile number, and electronic mail address of the "senior officer of that institution who is responsible for overseeing activities performed by the IRB." The preamble to the proposed rule explained that the senior officer "must not be an IRB member, IRB staff, or a sponsor or investigator participating in an investigation under review by that IRB" (see 69 FR 40556 at 40558).

Several comments addressed this provision. Two comments supported the proposed requirement, but two other comments stated that our interpretation of "senior officer" was too prohibitive or too restrictive. These comments said that if a senior officer is on the IRB, his or her membership should not invalidate registration or subject the IRB to enforcement action.

Another comment questioned what we meant when we referred to "IRB staff." The comment said that some IRBs distinguish staff from IRB members to ensure the IRB's integrity and independence. The comment suggested that we list persons who cannot be a "senior officer" and that we delete "IRB staff" from that list.

(Response) We agree, in part, with the comments. We recognize that, in some cases, it may not be feasible to identify

a "senior officer" who is not also an IRB member or IRB staff. However, our experience indicates that IRBs sometimes form subcommittees or other groups and that the institutions overseeing the IRBs may not be aware of these subcommittees or other groups. Thus, when we said that the "senior officer" should not be an IRB member or IRB staffer, our goal was to ensure that the institution overseeing the IRB's activities is truly aware of those activities. For these reasons, where feasible, we recommend that the senior officer not be an IRB member or an IRB staffer.

Additionally, as the preamble to the proposed rule stated, information regarding the institution will enable us to identify the institution and to determine whether problems that might exist for one IRB at that institution exist at other IRBs affiliated with that institution (see 69 FR 40556 at 40558).

Additionally, on our own initiative, we have revised § 56.106(b)(1) to require the street address for the institution if the street address is different from the institution's mailing address.

(Comment 7) One comment said we should ensure that any addresses and telephone numbers are current and are kept current. The comment suggested that we issue fines and penalties if IRBs fail to keep such information current.

(Response) Section 56.106(e) requires IRBs to revise their registration information within 90 days if a contact person or chairperson information changes; this would encompass changes in the contact person's or chairperson's telephone number.

As for the comment's suggestion of imposing fines and penalties, we do not have legal authority to impose fines for failure to maintain IRB registration information. As for other penalties, we discuss the consequences of failing to register in comment 24 of this document.

(Comment 8) Proposed § 56.106(b)(2) would require IRBs to provide the IRB's name, the names of each IRB chair person and each contact person (if one exists) for the IRB, and the IRB's mailing address, street address (if different from the mailing address), phone number, facsimile number, and electronic mail address.

One comment supported the proposal. However, another comment noted that the OHRP proposal would require IRBs to provide the name, gender, degree, scientific or nonscientific specialty, and affiliation of each IRB member and suggested that we revise our rule to require the same information as the OHRP rule.

(Response) We agree, in part, and disagree, in part, with the comment's suggestion that we require the same information as OHRP's rule. We decline to revise the rule as requested by the comment. Unlike OHRP, we have never required IRBs to give us the names, educational background, and qualifications of all IRB members. Our rule does not include this information because our regulatory emphasis has been on the IRB's overall composition. Consequently, our final rule does not require such information about individual IRB members.

We have, however, revised § 56.106(b)(2) to replace "chair person" with "chairperson." This change reflects the common spelling for this noun and does not alter the application or interpretation of § 56.106(b)(2). Additionally, we have revised § 56.106(b)(2) to require the phone number and electronic mail address for the IRB chairperson; this will enable us to communicate with the IRB chairperson quickly if such a need arises.

On our own initiative, we have revised § 56.106(b)(2) to delete the parenthetical of "(if one exists)" after "the contact person's name" and to require and the name, mailing address, phone number, facsimile number, and electronic mail address of the contact person providing the registration information. This information will enable us to communicate with the contact person if any questions arise regarding the IRB or its registration information, and the information now required is similar to that required for the contact person under OHRP's rule. We also have reorganized the provision to make it easier to understand what information is required.

(Comment 9) Proposed § 56.106(b)(3) would require IRBs to provide the "number of active protocols (small, medium, or large) involving FDA-regulated products reviewed." The proposal explained that a "small" number of protocols is 1 to 25 protocols; "medium" is 26 to 499 protocols, and "large" is 500 protocols or more.

Several comments interpreted this provision in different ways or sought clarification as to its meaning. In brief:

- One comment asked us to define "protocol" because it said questions would arise regarding multi-site studies involving a single protocol.
- Another comment would redefine the numerical ranges so that "small" would be 1 to 99 protocols, "medium" would be 100 to 499 protocols, "large" would be 500 to 1,999 protocols, and "very large," a new category, would be 2,000 protocols or more. The comment explained that a "substantial number" of organizations oversee thousands of protocols and that these organizations operate differently compared to those that review 500 protocols.
- Another comment expressed concern about the protocol numbers, stating that it was unclear how useful or accurate the data would be due to complexities in IRB review and "protocol driven research activities," the level of IRB review (such as full IRB review or expedited review), and frequent or daily changes in protocol review numbers.

Similarly, another comment stated that protocols are neither uniform nor uniformly complex, so that protocol activity is not a reasonable basis for determining IRB activity. A third comment said that we should consider the protocol ranges to be only approximations of IRB workloads and use the information carefully and cautiously in evaluating or characterizing IRBs.

- Another comment disputed the need for protocol review information, arguing that compliance with regulatory requirements is an issue regardless of the number of protocols reviewed by an IRB.

(Response) The preamble to the proposed rule explained that information regarding the number of protocols reviewed would enable us to determine how active an IRB is and to assign our inspection resources based on IRB activity levels (see 69 FR 40556 at 40558). Our intent was not to get an exact or precise figure, and the proposal's use of "small," "medium," and "large" protocol ranges reflected that intent.

Consequently, we decline to revise the rule to define "protocol" in the final rule. *Webster's II—New Riverside University Dictionary* defines "protocol," in relevant part, as "the plan for a scientific experiment or treatment" (see *Webster's II—New Riverside University Dictionary* at page 947 (1988)). Thus, in the comment's scenario, if an IRB conducts one review for a multi-site study, that single review could be considered as one "protocol." If an IRB conducts separate reviews for individual study sites, then it conceivably could have reviewed multiple "protocols" notwithstanding the fact that the study plan remains essentially the same for all sites.

However, on our own initiative, we have amended § 56.106(b)(3) to define what the term "active protocol" means. The final rule defines "active protocol" as "any protocol for which an IRB conducted an initial review or a continuing review at a convened

meeting or under an expedited review procedure during the preceding 12 months." We have made this change to be consistent with changes made by OHRP in its final rule.

With respect to the proposal's numerical ranges and their usefulness to us, we reiterate that our intent was to get a general—rather than a precise—sense of how active IRBs are and to assign our limited inspectional resources more efficiently and effectively. We recognize that there are different types of IRB review and that changes in an IRB's workload could make an IRB's protocol estimate outdated or obsolete at a later point in time. However, given the protocol ranges were created simply to give us an idea about an IRB's activity, we have revised the rule to eliminate the "small," "medium," and "large" ranges. Instead, the final rule requires an approximate number of active protocols reviewed, but we neither expect nor want IRBs to constantly change or update their protocol numbers whenever their protocol numbers fluctuate. If the approximate number of protocols changes after initial IRB registration, the IRB should report the new protocol number as part of the re-registration process which takes place every 3 years.

As for compliance activities, we believe the comment may have misinterpreted the preamble to the proposed rule. We did not state that we would base inspections solely on an IRB's self-reported level of "small," "medium," or "large" numbers of protocols reviewed. We simply said that the information would help us assign inspection resources based on IRB activity levels.

To put it another way, we have limited inspectional resources, and our field staffs that inspect IRBs are also responsible for many other types of inspections and activities. We must prioritize our routine IRB inspections in some manner to make the most efficient use of our resources. Such prioritization of IRB inspections is not tantamount to declaring, as the comment suggests, that IRBs reviewing "small" or "medium" numbers of protocols do not have to comply with FDA regulations or that we enforce our requirements differently depending on whether an IRB reviews a "small," "medium," or "large" number of protocols. Nevertheless, given that the final rule does not contain the "small," "medium," or "large" protocol ranges, the issue is largely moot.

(Comment 10) Proposed § 56.106(b)(4) would require IRBs to describe the types of FDA-regulated products, such as biological products, color additives, food additives, human drugs, or medical devices, involved in the protocols that they review.

Two comments addressed this provision. One comment stated that it had no objection to the requirement provided that the description could be simple or generic without numerical ranges associated with each product type. Another comment said the descriptions would be appropriate only if we used the information for purposes of sending useful and targeted information to IRBs. The comment also said that the description should be generic and without numerical ranges associated with product types.

(Response) We agree with the comments. Section 56.106(b)(4) merely seeks a generic description of the FDA-regulated products in the protocols reviewed by the IRB. So, for example, if the IRB reviews protocols for human drug studies, the description, to satisfy § 56.106(b)(4), could simply be "human drugs." If the IRB reviews protocols for human drug and medical device studies, the description would be "human drugs" and "medical devices." We also note that the electronic registration system will list the types of FDA-regulated products and allow individuals to check the appropriate boxes relating to those products and to check "other" and explain what the "other" FDA-regulated products are.

Furthermore, § 56.106(b)(4) does not require IRBs to assign numerical values to the FDA-regulated product types. As the comments noted, our intent is to use this information to send product-specific information to IRBs, and we can do so with a simple description of product types.

(Comment 11) Proposed § 56.106(b)(5) would require an indication whether the IRB is accredited and, if so, the date of the last accreditation and the name of the accrediting body or organization. The preamble to the proposed rule stated that we recognized that IRB accreditation is a developing concept and invited comment on "the perceived value of collecting information on the accreditation status of IRBs" (see 69 FR 40556 at 40558).

We received more than 10 comments on IRB accreditation issues, and the comments reflected a considerable difference of opinion regarding IRB accreditation and whether we should require information about such accreditation. In brief, the comments stated:

- IRB accreditation information may give FDA useful information in deciding which IRBs to inspect and may help us decide whether to focus educational activities on certain areas. One comment added that accreditation information would help us evaluate the value of IRB accreditation. In contrast, one comment said that IRB accreditation information will not give FDA new information that will be useful in assessing accreditation's value;
- FDA should refer to accreditation of human research protection programs rather than accreditation of IRBs;
- FDA should require information about the name of the accrediting organization under which the IRB functions or collect information about accreditation type or level. One comment explained that one body has two different accreditation categories;
- The additional reporting burden should not be passed on to the institution;
- FDA should delete the provision because accreditation information can be collected without the need for a regulation or is publicly available from accrediting organizations. One comment added that accreditation information, if it were part of the IRB registration requirement, might be unreliable because our rule would require re-registration every 3 years; and
- Accreditation does not accurately represent a measure of compliance with human subject protection requirements. Similarly, an IRB's lack of accreditation could be misconstrued as reflecting on the quality of the IRB's human subject protection program. In contrast, one comment strongly encouraged IRBs to become accredited, and another comment said that accreditation implies that a certain standard has been achieved.

(Response) The final rule omits accreditation information from the IRB registration requirements. We agree that, if necessary, we can obtain accreditation information from the accreditation organizations themselves and that the resulting information may be more reliable or accurate, given that the rule does not require certain registration information to be updated until re-registration. We also agree that, as a general matter, accreditation does not ensure or demonstrate that a particular action was done correctly; instead, accreditation may increase one's confidence that the accredited body is capable of performing a particular action correctly.

Furthermore, we continue to believe that accreditation, insofar as human subject protection is concerned, is still a developing concept. Consequently, we will continue to follow such accreditation activities, but will not require accreditation information as part of IRB registration.

Finally, because the final rule does not require accreditation information, the comment regarding reporting burdens is moot.

D. When Must an IRB Register? (Section 56.106(c))

Proposed § 56.106(c) would have IRBs register once and to renew their registrations every 3 years. Initial IRB registration would occur within 30 days before the date when the IRB intends to review clinical investigations regulated by FDA. IRB registration would become effective upon HHS posting of the registration information on its Web site.

(Comment 12) One comment would have us consider IRBs to be registered as soon as they complete submitting the registration information regardless of whether the IRB submitted the information electronically or in writing. Another comment suggested that the electronic registration system acknowledge or document that the IRB has registered. Another comment stated that, if IRB registration is to identify IRBs for future inspections, there is no need for a 30-day "waiting" period.

A different comment said that the 30-day time period might interfere with IRB review, particularly expedited reviews and full IRB reviews that take less than 30 days. The comment suggested that we revise the rule so that IRBs may not issue a determination on FDA-regulated research until they have registered.

Another comment asked us to clarify when IRBs must register. The comment explained that the codified provision directed IRBs to submit an initial registration within 30 days before the date when the IRB intends to review clinical investigations regulated by FDA. The comment said that the word "within" could mean that an IRB could register "anytime between one and 30 days before reviewing a protocol," but that the preamble to the proposed rule interpreted proposed § 56.106(c) as requiring registration at least 30 days before reviewing the protocol. The comment preferred giving IRBs the ability to register any time between 1 and 30 days before reviewing protocols in FDA-regulated research.

(Response) We agree, in part, with the comments. For IRBs that register electronically, the registration system will notify them that they are registered. This notification will be sent to the electronic mail address that the IRB provides as part of the registration process. The IRB's registration will be effective after review and acceptance by HHS. We have amended § 56.106(c) regarding the time at which IRB registration becomes effective to correspond to changes made by OHRP in its final rule which is published elsewhere in this issue of the **Federal Register**. OHRP revised a comparable provision in its rule to clarify when IRB registration would become effective.

For IRBs that submit their registration information in writing, our experience with written forms in other contexts suggests that some individuals will not complete the forms or omit required information. As a result, we may need to contact individuals to obtain the missing information. Therefore, it would be more practical for us to consider IRBs who submit their registration information in writing to be registered only after they have submitted all required registration information, we have entered that information into the electronic registration system, and the information is reviewed and accepted by HHS.

As for the comments concerning the 30-day timeframe and the suggestion that we amend the rule so that IRBs cannot issue decisions on FDA-regulated research until they have registered, we have decided to eliminate the 30-day timeframe from the final rule. We note that IRB registration, alone, does not address issues regarding an IRB's competence or expertise, nor does it require IRBs to meet a particular standard in order to conduct a review. However, because it is important to FDA to assemble an accurate IRB database, we have revised § 56.106(c) to state that: "Each IRB must submit an initial registration. The initial registration must occur before the IRB begins to review a clinical investigation described in paragraph (a) of this section. Each IRB must renew its registration every 3 years. IRB registration becomes effective after review and acceptance by HHS."

(Comment 13) One comment would require IRBs to renew their registration every year instead of every 3 years. The comment said that 3 years would be too long a time period.

(Response) We decline to revise the rule as suggested by the comment. IRB registration does not confer any particular status on IRBs, nor does registration, alone, reflect upon an IRB's competence or capabilities. Moreover, given that the information we seek through IRB registration is quite basic (as in names and addresses) and that § 56.106(e) describes how and when IRBs are to revise their registration information, annual registration would not appear to confer any advantages or make registration information more accurate or reliable. Consequently, we decline to require IRBs to register annually.

E. Where Can an IRB Register? (Section 56.106(e))

Proposed § 56.106(e) would direct IRBs to register at a specific Internet address or, if an IRB lacked the ability to register electronically, to send its registration information to a specific mail address. We indicated that we would provide the Internet address and mail address in the final rule. We also invited comment on whether we should discontinue written IRB registration procedures after some time period has elapsed, because we did not know how widespread Internet access is among IRBs (see 69 FR 40556 at 40558).

(Comment 14) Several comments pertained to the registration site(s). One comment said we should maintain one common registration site with OHRP and that the registration system should automatically include currently registered IRBs. The comment said the registration system should also allow such IRBs to retain their assigned numbers. The comment acknowledged the intent to create a single registration site, but implied that the proposed rule's omission of a specific Internet address created concern. Another comment supported creation of a simple, electronic registration system.

(Response) We agree that a single Internet registration site should be used for electronic registrations and have always worked with OHRP towards that end. We were unable to provide a specific Internet address at the time of the proposed rule because the electronic registration system was still under development. The final rule now states that the Internet registration address is *http://ohrp.cit.nih.gov/efile*.

Additionally, as we stated in the preamble to the proposed rule, OHRP will continue to recognize previous IRB registrations (see 69 FR 40556 at 40558).

(Comment 15) One comment asked whether entities that have more than one IRB at the same location need to register more than once or whether they could register once and provide multiple pieces of information in connection with a single registration.

(Response) The electronic registration system will assign an organization number to each entity, and this will enable the entity to register several IRBs without having to enter the same data repeatedly for each IRB.

(Comment 16) Two comments encouraged us to have the electronic registration system consider IRBs to be registered automatically once an IRB completes the electronic registration process or to send acknowledgements to the IRBs once they complete the electronic registration process.

(Response) As we stated in our response to comment 12 of this document, when an IRB completes the electronic registration process and HHS has reviewed and accepted the information, the electronic registration system will notify IRBs that they are registered.

(Comment 17) Several comments responded to our question whether we should discontinue written IRB registrations after some time period has elapsed. One comment supported conversion to electronic registration as soon as possible, but said it is important to allow small organizations the time to acquire the necessary technology. The comment agreed that not all institutions have electronic capabilities or Internet access.

Another comment supported giving IRBs the option to submit registration information in writing for a predetermined period of time, but did not suggest any time period. A different comment also supported the written registration option, but suggested that it be available only for 2 years.

Another comment opposed discontinuing written IRB registration. The comment said that there are adverse consequences to both the IRB and any sponsor or investigator that might use an unregistered IRB (which appeared to be a reference to a later discussion, in the preamble to the proposed rule, about "What Happens if an IRB Does Not Register?" (see 69 FR 40556 at 40559)), so we should continue to make written IRB registration possible.

(Response) While we continue to believe that most IRBs will use the electronic registration system, we do not know how many IRBs will use the written registration option, and the administrative record for this rulemaking does not give us sufficient basis to set a deadline at which we would end the written registration option. (We realize that one comment suggested a 2-year period, but, given that IRBs have 3 years to renew registrations, discontinuing written registrations after 2 years would not give IRBs the opportunity to renew their registrations in writing.) Consequently, until we become more experienced with IRB registrations, we will continue to offer written registration as an alternative to electronic registration, and the final rule states that IRBs that lack the ability to register electronically must send their registration information, in writing, to the Good Clinical Practice Program (HF–34), Office of Science and Health Coordination, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

F. How Does an IRB Revise Its Registration Information? (Section 56.106(e))

Proposed § 56.106(e) would have IRBs revise their registration information within specific timeframes if certain changes occurred. For example, if the IRB's contact or chair person information changes, proposed § 56.106(e) would require the IRB to change its registration information within 90 days of the change. If the IRB decided to disband or to discontinue reviewing FDA-regulated clinical investigations, it would report that change within 30 days. All other information changes would be reported when the IRB renews its registration.

(Comment 18) Two comments pointed out a discrepancy between the proposed rule and its preamble. The comments noted that the preamble to the proposed rule said that if an IRB reviews new types of FDA-regulated products, it would revise its registration information within 30 days (see 69 FR 40556 at 40559), yet proposed § 56.106(e) was silent regarding such changes. The comments suggested that we reconcile the codified text with the preamble.

(Response) The comments were correct. We inadvertently omitted changes in the IRB's review of FDA-regulated research from proposed § 56.106(e), and we have revised the rule so that IRBs must revise their registration information within 30 days if they review new types of FDA-regulated products. Additionally, on our own initiative, we have added a parenthetical phrase to clarify that a decision to review "new types of FDA-regulated products" should be interpreted as a decision to review a different category of FDA-regulated products, such as a decision to review studies pertaining to food additives when the IRB previously reviewed studies pertaining to drug products. We do not want IRBs to revise their registration information if they decide to review studies pertaining to subcategories within the same class of FDA-regulated products; for example, if an IRB previously reviewed studies pertaining to drugs intended to treat cardiac conditions and then decided to review studies pertaining to drugs intended to treat cancer, both types of studies would still pertain to drug products, so there would be no "new type" of FDA-regulated product within § 56.106(e).

(Comment 19) One comment addressed IRBs that have decided to disband. The comment said that the process of closing an IRB may take longer than 30 days, so requiring IRBs to revise their registration information within 30 days of a decision to disband would put an "undue burden" on IRBs and the institutions responsible for the IRBs.

(Response) We agree in part, and disagree in part with the comment. We agree that, in some cases, closing an IRB may take more than 30 days, but, in other cases, the process may take less time. In other words, IRBs vary in size, resources, organization, and complexity, and, as a result, different IRBs will take different amounts of time to perform the same or similar functions.

The comment also may have misinterpreted the proposed rule. Proposed § 56.106(e) stated that an IRB's decision to disband or to discontinue reviewing FDA-regulated clinical investigations is a change that must be reported within 30 days of that change; thus, the proposal would begin the time period when IRB decides to close, not when the IRB finally closes. Nevertheless, for consistency with OHRP's final rule (which appears elsewhere in this issue of the **Federal Register**), we have revised § 56.106(e) to state that an IRB's decision to disband is a change that must be reported "within 30 days of permanent cessation of the IRB's review of research." In the preamble to the OHRP final rule, OHRP states that "the date of permanent cessation of the IRB's review of * * * research would occur on or after the IRB's decision to disband, but not before the IRB's decision to disband was made."

Furthermore, given the simplicity of the electronic registration system, we do not believe that IRBs or their institutions will find it "unduly" burdensome to report the IRB's decision to disband.

(Comment 20) One comment would shorten the time period for reporting changes in the IRB's contact or chair person information from 90 days to 60 days.

(Response) We decline to revise the rule as suggested by the comment. The comment did not identify any advantage in shortening the timeframe, and we do not believe that reducing the timeframe by 30 days will confer any significant benefit.

G. What Other Comments Did We Receive?

1. What Information Will Be Publicly Available?

The preamble to the proposed rule referred to the OHRP proposal for information regarding public disclosure of IRB registration information, the Freedom of Information Act (FOIA), and

the Privacy Act of 1974 (see 69 FR 40556 at 40557). It also stated that, insofar as FDA's registration system was concerned, the name of the institution operating the IRB and the IRB's name will be publicly accessible, and all other IRB registration information would be subject to public disclosure under FOIA and our public information regulations at part 20 (21 CFR part 20) (see id.).

(Comment 21) One comment said that, in addition to the institution's name and the IRB's name, we should make the following information publicly available:

- The name, address, and telephone number of the IRB contact; and
- For accredited IRBs, information relating to that accreditation.

Another comment asked us to clarify what information would be publicly available under FOIA.

(Response) All registration information required under this rule will be subject to FOIA and any other applicable statutes and regulations pertaining to public disclosure. Please note that certain information may be withheld from public disclosure or may require an individual's consent to public disclosure (see, e.g., § 20.63(e) (stating that a request for all records relating to a specific individual will be denied as a clearly unwarranted invasion of personal privacy unless accompanied by the written consent of the individual named)).

As for accreditation information, accreditation status is not required under the final rule, so that information will not be publicly available from us or from OHRP.

(Comment 22) One comment suggested that sponsors and investigators have access to the IRB registration database. The comment said that sponsors and investigators currently have access to Federal-wide assurances data and suggested that, if sponsors and investigators could not have access to the IRB registration database, we or OHRP should issue a report of IRB registrations or issue certificates to individual IRBs.

(Response) OHRP currently posts all registered IRBs on its Web site, including the name and location of the organization operating the IRB(s) and the name and location of each IRB.

We decline to issue reports on IRB registration or certificates to show that an IRB is registered. As we stated in our response to comment 12 of this document, IRB registration, alone, does not address issues regarding an IRB's competence or expertise, nor does it require IRBs to meet a particular standard in order to conduct a review.

(Comment 23) One comment said we should establish a link to the publicly available IRB registration information from the portion of our own Web site that pertains to "Good Clinical Practices in FDA-Regulated Clinical Trials," located at *http://www.fda.gov/oc/gcp/default.htm*.

(Response) We agree with the comment and have modified our Web site accordingly.

2. What Happens if an IRB Does Not Register?

The preamble to the proposed rule stated that sponsors and investigators who used unregistered IRBs might be using IRBs that "would not have had the benefit of receiving educational materials from FDA and would not have been identified on an FDA IRB registration list for future inspection" (see 69 FR 40556 at 40559). Thus, the preamble to the proposed rule added that, "to the extent that any existing FDA regulation requires a sponsor or investigator to comply with [part 56] or to use an IRB that complies with part 56, FDA will consider sponsors and investigators using an unregistered IRB to be in conflict with their regulatory obligations" (id.).

The preamble to the proposed rule also noted how we considered other options to require sponsors and investigators to use only registered IRBs, such as refusing to consider information from an application for a research permit for a clinical investigation that is reviewed or is to be reviewed by an unregistered IRB (id.). The preamble to the proposed rule also invited comment on what sanctions or administrative mechanisms, if any, should or might be used against sponsors and investigators who use unregistered IRBs and whether any additional changes to our regulations were necessary.

(Comment 24) We received many comments relating to sanctions, other regulatory changes, and ensuring that sponsors and investigators use only registered IRBs. The comments reflected a considerable difference of opinion. For example:

- One comment said we should impose and enforce "high fines" for failure to follow human subject protection regulations;
- Several comments said that the forms investigators currently use (Form FDA 1572) could be used to reinforce or otherwise highlight the need to use only registered IRBs, but the comments differed as to whether investigators should be subject to any sanctions if they use an unregistered IRB. For example, one comment said failure to use a registered IRB should be treated the same as any other breach of an investigator's responsibilities, but others said that IRBs, rather than sponsors or investigators, should be responsible for any failure to register. One comment also opposed placing an investigation on clinical hold because, the comment argued, clinical holds are appropriate when the rights and/or safety of human subjects are in jeopardy or other material, noncompliance concerns are evident; the comment said that failure to register does not mean improper oversight by the IRB or by the sponsor. Some comments argued that sponsors and investigators should not be obliged to monitor an IRB's registration status. In contrast, one comment would have us amend the investigational new drug (IND) application regulations to authorize us to place a study on clinical hold if the sponsor or investigator uses an unregistered IRB. The same comment suggested that we consider additional enforcement options, such as "refusing to consider information from an application for a research permit for a clinical investigation that is reviewed or is to be reviewed by an unregistered IRB."
- Several comments, mostly from pharmaceutical firms or trade associations, opposed any changes outside the IRB regulations. The comments, in general, felt that the existing IND regulations were sufficient and clear regarding a sponsor's or investigator's obligation to use IRBs that comply with part 56. Some comments said we should not expend resources on revising the IND regulations but should promote awareness of the IRB registration requirements instead. Another comment, from an association of medical colleges, also opposed revisions to the IND regulations, stating that clinical holds would be unworkable because, if an unregistered IRB had reviewed a clinical study and the clinical study had proceeded, retroactive review of the study would be impermissible. The comment said we should refuse to consider information from an application for a research permit that is reviewed or is to be reviewed by an unregistered IRB.
- One comment suggested a "flexible" approach whereby we would start by sending a certified letter to an unregistered IRB regarding its failure to register and include registration instructions. If the IRB remained unregistered, the comment suggested that we inspect the IRB. The comment said that this approach would allow us to take appropriate action against unregistered IRBs without "unnecessarily penalizing" sponsors and investigators who have attempted to

follow our regulations in good faith. Similarly, another comment advocated sending letters to IRBs or notices to sponsors rather than imposing sanctions.

- One comment agreed with us that an IRB's failure to register would not justify disqualification of the IRB under § 56.121 absent the extreme circumstances described in § 56.121(b)(1) (the IRB has refused or repeatedly failed to comply with regulatory requirements) or § 56.121(b)(2) (the noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation).

(Response) We agree in part and disagree in part with the comments. We agree that the existing IND regulations, as well as the IDE regulations, are sufficient and clear regarding a sponsor's or investigator's obligation to use IRBs that comply with part 56. We also agree that an IRB's failure to register, alone, should not lead to disqualification proceedings under § 56.121 absent extreme circumstances. We intend to educate IRBs, sponsors, and investigators about the IRB registration requirements and to encourage sponsors and investigators to use registered IRBs for the same reasons we stated in the preamble to the proposed rule.

Given the existing IND and IDE regulations and our intent to pursue educational efforts, we disagree with those comments that would have us impose fines or place clinical investigations on clinical hold if the sponsor or investigator used an unregistered IRB. We believe that it would be premature for us to consider the use of such sanctions before we and the regulated community have gained sufficient experience with the IRB registration program.

3. What Other Issues Did the Comments Raise?

Several comments addressed issues that were either not part of the rulemaking or not material to the proposed codified text.

(Comment 25) One comment disagreed with the preamble to the proposed rule when we stated that our knowledge about the identities and numbers of IRBs reviewing FDA-regulated clinical research is obsolete or incomplete (see 69 FR 40556 at 40557). The comment said that we require sponsors to identify IRBs and that, for 20 years, OHRP has maintained a list of IRBs that have filed assurances (under 45 CFR part 46). The comment said that such past practices were apparently sufficient for purposes of conducting inspections.

(Response) We disagree with the comment. As we stated in the preamble to the proposed rule, existing FDA regulations have required some, but not all, clinical investigators and sponsors to provide IRB names and addresses to us, and those regulatory requirements differ slightly (see 69 FR 40556 at 40557). Consequently, because of differences within our own regulations, we do not have a comprehensive list of IRBs that review FDA-regulated research. Additionally, because our pre-existing regulations do not require sponsors and investigators to revise or update IRB information if and when the IRB changes its address, contact person, or chair person, or even, in some cases, to provide addresses, contact information, or chair person information to us, the IRB information we do have is not as detailed as the information we seek under this rule.

As for institutions that have filed assurances with OHRP under 45 CFR part 46, the IRBs associated with such institutions are not necessarily identical to those that review FDA-regulated research. OHRP's regulations apply to institutions that are engaged in human subjects research conducted or supported by HHS. In contrast, our IRB regulations apply to clinical investigations regulated by us, regardless of whether those investigations are conducted or supported by HHS. Thus, the fact that OHRP has operated an assurance system for decades does not necessarily mean that the OHRP list of institutions that have filed assurances can serve as a list of IRBs that review FDA-regulated research.

(Comment 26) One comment said that registration and re-registration fees should be set at $5,000 to cover costs. The comment said that taxpayers should not have to pay the fees or fund the costs of "profiteers," and that pharmaceutical companies should not "get away" with low fees when "they can pay their executives $150,000,000 at retirement."

(Response) We decline to revise the rule as suggested by the comment. We have no express authority to impose registration or re-registration fees on IRBs. Additionally, the rule is directed at IRBs themselves rather than pharmaceutical firms, so issues relating to pharmaceutical executives' salaries are not relevant to this rulemaking.

(Comment 27) One comment asked us to confirm that our IRB inspections will adhere to the guidelines described in the "Guidance for Institutional Review Boards and Clinical Investigators."

(Response) This rulemaking does not affect how we conduct IRB inspections. We may, however, use IRB registration information to help us prioritize inspections. Additionally, our receipt of more accurate IRB addresses and contact information due to IRB registration should make it easier and more efficient to schedule IRB inspections.

H. What Other Amendment Did We Propose?

The proposal would also make a non-substantive amendment to part 56. The proposal would revise the definition of "An Application for an Investigational Device Exemption," at § 56.102(b)(12), to eliminate its reference to 21 CFR part 813. The preamble to the proposed rule explained that this change is necessary because we removed the regulations at part 813 (which had pertained to intraocular lenses) in 1997 (see 62 FR 4164, January 29, 1997).

We received no comments on this aspect of the proposal. Consequently, the final rule deletes a reference to part 813.

III. Implementation

This rule is effective July 14, 2009. This protracted effective date is necessary to allow refinement of the electronic registration system so that it corresponds to this final rule and to OHRP's final rule.

IV. Legal Authority

In general, the act authorizes us to issue regulations pertaining to investigational uses of FDA-regulated products (see, e.g., sections 409(j) (21 U.S.C. 348(j)) (investigations involving food additives); 505(i) (investigations involving human drugs); 520(g) (investigations involving devices); and 721(f) (21 U.S.C. 379e(f)) of the act (investigations involving color additives)).

The act also requires the submission of a petition or application to FDA (see, e.g., sections 409(b) (food additive petitions); 505(b) (new drug applications); 505(j) (abbreviated new drug applications); 513(f) (premarket notification for devices); 515(c) (premarket approval applications for devices); 520(m) (humanitarian device exemption applications); and 721(b) of the act (color additive petitions)) before marketing begins.

To implement these provisions of the act, section 701(a) of the act gives us the authority to issue regulations for the efficient enforcement of the act. By requiring IRB registration, the final rule will aid in the efficient enforcement of the act's provisions regarding the