

**STATE OF MICHIGAN
IN THE 30TH JUDICIAL CIRCUIT COURT
INGHAM COUNTY**

MICHAEL A. COX, Attorney General of
the State of Michigan, *ex rel* STATE OF
MICHIGAN,

Plaintiffs,

v

BAYER CORPORATION,

Defendant.

Suzanne D. Sonneborn (P55511)
Assistant Attorney General
Consumer Protection Division
Michigan Department of Attorney General
P.O. Box 30213
Lansing, MI 48909
(517) 335-0855

Hon. REVERLEY NETTLES-NICKERSON

Case No. 07-79-CP

CONSENT JUDGMENT

Plaintiff, State of Michigan, acting by and through Attorney General MICHAEL A. COX, has brought this action pursuant to the Michigan Consumer Protection Act, MCL 445 901, *et seq.*, having filed a complaint against the Defendant, Bayer Corporation. ("Bayer") and the parties having consented to the entry of this Consent Judgment ("hereinafter referred to as "Consent"), NOW THEREFORE, upon the consent of the parties hereto, IT IS ORDERED:

PREAMBLE

This Consent is entered into between the Attorneys General or other entities¹ of the States and Commonwealths of Arizona, Arkansas, California, Connecticut, Delaware, Florida, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nevada, North Carolina, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont, Virginia, Washington, and Wisconsin (hereinafter referred to as “Signatory Attorneys General”), acting on behalf of their respective states, and pursuant to their respective consumer protection statutes; and Bayer

I. DEFINITIONS

The following definitions shall be used in construing this Consent:

A. “Adverse Events” shall mean an adverse event associated with the use of a drug in humans. “Serious Adverse Events” are those that, at any dose, are fatal, life-threatening, disabling or incapacitating; result in hospitalization; prolong a hospital stay; or are associated with congenital abnormality. In addition, any event not meeting the above criteria may still be deemed Serious if such an event jeopardizes the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

B. “Baycol[®]” shall mean cerivastatin sodium.

¹ For the purposes of this agreement, when the entire group is referred to as “Signatory Attorneys General,” such designation, as it pertains to CONNECTICUT, shall refer to the Commissioner of the Department of Consumer Protection, who enters this Consent pursuant to the Connecticut Unfair Trade Practices Act, Conn. Gen. Stat. Sec. 42-110j, acting by and through his counsel, Richard Blumenthal, Attorney General for the State of Connecticut. For MONTANA, the acting agency is the Consumer Protection Office. For MONTANA, such designation shall refer to the Consumer Protection Office of the Department of Justice who enters into this settlement pursuant to the Montana Unfair Trade and Consumer Protection Act of 1973 MCA 30-14-101 et al., acting by counsel, Mike McGrath, Attorney General for the State of Montana.

C “Bayer” shall mean the Bayer Corporation and its U.S.-based affiliates, subsidiaries, predecessors, successors, and assigns.

D “Bayer Website” shall mean Bayer’s main Internet site, currently <http://www.pharma.bayer.com>, or a link from that site.

E “Bayer-Sponsored” shall mean Bayer is responsible for regulatory approvals, site selection, protocol development, initiation, monitoring, safety reporting, and Data analysis, even if some or all of these activities are transferred to another party (e.g. Clinical Research Organization). A Clinical Study is not “Bayer-Sponsored” if it is initiated by a third party for which Bayer provides some support, for example by way of a grant or supply of medication, but with sponsor responsibilities for study initiation and management agreed in writing to reside with the third party. For purposes of this Consent only, studies conducted by Bayer’s parent entity and its foreign affiliates shall be considered Bayer-Sponsored.

F “Clinical Study” shall mean any research project that prospectively assigns human subjects to intervention and concurrent comparison/control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. The term “Clinical Study” is not limited to a research study that is randomized or blinded; and is not limited to studies conducted in the United States.

G “Clinical Study Report” shall mean a description of the Protocol, a summary of all the Data, a description and the results of statistical analyses of the Data, a listing of the common Adverse Events and a more detailed listing of the Serious Adverse Events, and the clinically relevant conclusions drawn from the Data in a Bayer-Sponsored Clinical Study, including the answers to the questions posed in the Protocol.

H “Compliance Provisions” shall mean Paragraphs 6 through 16 of this Consent.

I. “Covered Conduct” shall mean Bayer’s promotional and marketing practices regarding the prescription drug Baycol®

J. “Data” shall mean all of the results and outcome measurements obtained from a Clinical Study.

K. “Effective Date” shall mean the date by which all Parties have executed the Consent.

L. “Exploratory Phase II Clinical Study” shall mean a study with less than fifty (50) participants and where a health outcome is not a predefined endpoint of the study.

M. “Individual State” and “State” shall mean each Signatory Attorney General who is participating in the Multistate Working Group

N “Multistate Working Group” (“MSWG”) shall mean the Attorneys General and their staffs representing the States and Commonwealths of Arizona, Arkansas, California, Connecticut, Delaware, Florida, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nevada, North Carolina, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont, Virginia, Washington, and Wisconsin.

O “Non-Exploratory Phase II Clinical Study” shall mean a study with fifty (50) or more participants or where a health outcome is a pre-defined endpoint of the study.

P “Parties” shall mean Bayer and the Individual States

Q. “Post” information shall mean to provide access to the information on an Internet site that provides no-cost and unrestricted access to both the site and the information Bayer has provided through the site. The Posting obligations exclusively reside with Bayer as defined in paragraph C, not Bayer’s parent entity or its foreign affiliates Bayer does not fulfill a

requirement to Post information under this Consent if it does so on an Internet site, other than the Bayer Website, that contains any advertisement by any pharmaceutical company or for any pharmaceutical product.

R. “Products” shall mean any pharmaceutical or biological product manufactured, distributed, sold, marketed or promoted in any way by Bayer, solely or in conjunction with other companies in the United States.

S. “Protocol” shall mean the investigational plan that is used to conduct the Clinical Study. The Protocol for an acute phase of a Clinical Study is separate from the Protocol of a continuation or extension phase of a Clinical Study.

T. “Signatory Attorney General” shall mean the Attorney General, or his or her designee, of each state in the Multistate Working Group investigating Bayer’s promotion and marketing practices regarding Baycol.[®]

U. “State Consumer Protection Laws” shall mean the consumer protection laws under which the Signatory Attorneys General have conducted their investigation²

² ARIZONA Consumer Fraud Act, Ariz. Rev. Stat. §44-1521, *et seq.*; ARKANSAS - Deceptive Trade Practices Act, Ark. Code Ann. § 4-88-101 *et seq.*; CALIFORNIA Business and Professions Code § 17200 *et seq.* 17500 *et seq.*; CONNECTICUT – Connecticut Unfair Trade Practices Act, Conn. Gen. Stat. §42-110 *et seq.*; DELAWARE - Consumer Fraud Act, 6 Del. C. Section 2511, *et seq.*, UDIPA, 6 Del. C. Section 2531, *et seq.*; FLORIDA - Deceptive and Unfair Trade Practices Act, Fla. Stat. Ch. 501.201 *et seq.*; IDAHO - Consumer Protection Act, Idaho Code § 48-601 *et seq.*; ILLINOIS - Consumer Fraud and Deceptive Business Practices Act, 815 ILCS § 505/1 *et seq.* (2002); IOWA - Iowa Consumer Fraud Act, Iowa Code Section 714.16; KANSAS – Kansas Consumer Protection Act, K.S.A. 50-623, *et seq.*; KENTUCKY - Consumer Protection Statute, KRS 367.170; MAINE – Unfair Trade Practices Act, 5 M.R.S.A. section 205-A *et seq.*; MARYLAND - Consumer Protection Act, Maryland Commercial Law Code Annotated § 13-101 *et seq.*; MASSACHUSETTS - Consumer Protection Act, M.G.L. c. 93A *et seq.*; MICHIGAN - Consumer Protection Act, Mich. Comp. Laws §445.901 *et seq.* (2004); MISSISSIPPI - Consumer Protection Act, Miss. Code Ann. § 75-24-1 *et seq.*; MONTANA - Mont. Code Ann. § 30-14-101 *et seq.*; NEVADA - Deceptive Trade Practices Act, Nevada Revised Statutes 598.0903 *et seq.*; NORTH CAROLINA - Unfair and Deceptive Trade Practices Act, N.C.G.S. § 75-1.1 *et seq.*; OHIO - Consumer Sales Practices Act, R.C. § 1345.01 *et seq.*; OREGON - Unlawful Trade Practices Act, ORS 646.605 to 646.656; PENNSYLVANIA - Unfair Trade Practices and Consumer Protection Law, 73 P.S. § 201-1 *et seq.*; SOUTH CAROLINA - Unfair Trade Practices Act, Sections 39-5-10 *et seq.*; SOUTH DAKOTA – Deceptive Trade Practices and Consumer Protection

V. “Subject Matter of this Consent” shall mean the Signatory Attorneys’ General investigation under the State Consumer Protection Laws of Bayer’s promotional and marketing practices regarding the prescription drug Baycol®

W. “Study Completion Date” shall mean the date on which the last observation is made either of the last patient who remains enrolled in the Clinical Study or following a decision to terminate the Clinical Study early, whichever happens first.

II. BACKGROUND

1. Bayer is in the business of, among other things, researching, developing, manufacturing, distributing, selling, and promoting drugs for use in treating various illnesses and diseases.

2. Baycol®, a prescription drug, was approved initially by the FDA in 1997 as safe and effective as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary cholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures alone was not adequate. Bayer voluntarily withdrew Baycol® from the market in August 2001

Law, SDCL Chapter 37-24; TENNESSEE - Consumer Protection Act, Tenn. Code Ann § 47-18-101 *et seq.*, (1977); TEXAS - Deceptive Trade Practices and Consumer Protection Act, Tex Bus. And Com Code § 17.41 *et seq.*, (Vernon 2002); VERMONT - Consumer Fraud Act, 9 V S A § 2451 *et seq.*; VIRGINIA - Virginia Consumer Protection Act, 59.1 -196 *et seq.*; WASHINGTON – Washington Consumer Protection Act, RCW 19 86 *et seq.*; WISCONSIN - Wis Stat § 100.18 (Fraudulent Representations)

3. The States have concerns that Bayer failed to adequately warn prescribers and consumers of potential adverse side effects of Baycol®, and, in particular, that such failure violated the States' Consumer Protection Laws.

4. Bayer denies that it failed to adequately warn prescribers and consumers of potential adverse side effects of Baycol® and denies that it violated any of the State Consumer Protection Laws.

5. Bayer enters into this Consent for the purpose of resolving the Signatory Attorneys' General investigation into Bayer's promotional and marketing practices regarding Baycol®, arriving at a complete and total settlement and resolution of any disagreement as to the matters addressed in this Consent to avoid unnecessary expense, inconvenience, and uncertainty, without admitting any violation of law and without admitting any wrongdoing, and for settlement purposes only.

III. COMPLIANCE PROVISIONS

6. Bayer shall comply with all applicable laws and regulations relating to the marketing, sale and promotion of its Products. Bayer shall not make any false, misleading or deceptive representation regarding any of its Products in violation of all applicable laws and regulations

7. Any terms that are not defined above in Section I shall be interpreted to have the same meaning as they have in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Industry: Structure and Content of Clinical Study Reports (July 1996), which is annexed as Exhibit 1

8. Bayer shall register all Non-Exploratory Phase II, and all Phase III and IV Bayer-Sponsored Clinical Studies on ClinicalTrials.gov in accordance with the following requirements:

- a. Bayer shall register Non-Exploratory Phase II, and all Phase III and IV Bayer-Sponsored Clinical Studies on ClinicalTrials.gov at the time such studies are initiated.
- b. At the time of registration of a Non-Exploratory Phase II Bayer-Sponsored Clinical Study, Bayer will post 15 of the 20 data set items established by the World Health Organization (“WHO”), attached as Exhibit 2, to ClinicalTrials.gov (that is, all data set items except 10, 13, 17, 19 and 20) and, if there is a change in status, update data set 18 in a timely manner. Bayer will populate the remaining five WHO data fields either when the Product reaches Phase III (and a Phase III Bayer-Sponsored Clinical Study is initiated), or when the Summary of the Clinical Study Report is Posted, whichever occurs first. In the event that a Non-Exploratory Phase II Bayer-Sponsored Clinical Study of a Bayer Product that is approved for marketing and is commercially available in the United States is terminated prior to one or more of its endpoints, Bayer will populate the remaining five WHO data fields no later than 30 days following termination of the study.
- c. At the time of registration of a Phase III or IV Bayer-Sponsored Clinical Study, Bayer will post all 20 data set items to ClinicalTrials.gov

9. Bayer shall Post on ClinicalStudyResults.org Summaries of Clinical Study Reports (“Summaries of Clinical Study Reports”) for all Phase II, III and IV Bayer-Sponsored Clinical Studies of Bayer Products that are approved for marketing and are commercially

available in the United States. Should a publicly funded website for such postings become available after the Date of this Consent, Bayer shall also Post on that website as well. Such summaries shall conform to ICH E3 principles and to the template published in the Federal Register, Vol 61, July 17, 1996, Page 37320 et seq.

10 For studies initiated after the date of this Consent, Bayer will also make all reasonable efforts to encourage the publication of, or in the alternative, secure the right to Post, Summaries of Clinical Study Reports in which Bayer had significant participation but did not sponsor.

11 The Summaries of Clinical Study Reports that Bayer Posts shall accurately reflect the methodology used to conduct the Clinical Study and summaries of the Data obtained during the Clinical Study. The Summaries of Clinical Study Reports that Bayer Posts shall include not only the generic and brand names of the Bayer Products, but also a listing of all aliases under which the Bayer Products may be known at the time of Posting, including the serial numbers, code names and chemical descriptions

12. Bayer shall Post the Summaries of Clinical Study Reports in accordance with the following time requirements:

a With respect to Products approved for marketing and commercially available in the United States for any indication prior to the Date of this Consent:

i. Studies completed prior to the Date of this Consent: Summaries of Phase II, III and IV Clinical Study Reports and summaries of any other studies material to a physician's judgment in relation to prescribing Products in the United States, with a Study Completion Date that occurred between July 1, 2005, and the Date of this Consent will be posted within 120 days of the

Effective Date of this Consent or within twelve months of the Study

Completion Date, whichever is later

- ii. Studies completed after the Date of Consent: Summaries of Clinical Study Reports for Phase II, III and IV Clinical Studies and summaries of any other studies material to a physician's judgment in relation to prescribing Products in the United States, completed after the Date of this Consent will be Posted within twelve months of the Study Completion Date
- b With respect to Products approved for marketing and commercially available in the United States for an initial indication after the Date of this Consent, Summaries of Clinical Study Reports and summaries of any other studies material to a physician's judgment in relation to prescribing Products in the United States will be posted within twelve months of the Study Completion Date or first marketing, whichever is later
- c. The parties recognize that, in some instances, there may be a delay in Posting complete Summaries of Clinical Study Reports because Bayer must seek intellectual-property protection or comply with policies of Peer Reviewed Journals to which manuscripts have been submitted for publication; and, further, that Bayer may be required to withhold certain Summaries of Clinical Study Reports to comply with confidentiality provisions in agreements with other parties.
- d. In regard to confidentiality agreements, in all future Clinical Studies Bayer will use reasonable efforts to exclude provisions limiting the publication of Summaries of Clinical Study Reports. For all past Clinical Studies with such

confidentiality agreements, Bayer will make reasonable efforts to secure the right to Post the Summaries of Clinical Study Reports.

- e The Signatory Attorneys General and Bayer do not intend Bayer's determination of materiality for posting to be admissible in private litigation or to constitute an admission by Bayer that the information posted is in fact material to prescribing decisions.

13. Bayer shall clearly and conspicuously state on the Home Page of the Bayer Website that the Posted information is available at ClinicalTrials.gov and ClinicalStudyResults.org and shall prominently feature links to those websites on the Home Page of the Bayer Website

14. Within two weeks of the Date of this Consent, Bayer shall arrange and pay for the publication of the advertisement annexed hereto as Exhibit 3 to run in the next available print and electronic editions (for at least one month on the electronic editions) of each of the following journals: Journal of the American Medical Association, New England Journal of Medicine, Annals of Internal Medicine, Journal of the American Board of Family Practice, Pharmacotherapy, Annals of Pharmacotherapy, and the Journal of Clinical Pharmacology & Therapeutics. Bayer shall arrange and pay for each of the advertisements to be placed between the front cover and the first article in each journal. Letters to the editor do not constitute articles for the purpose of this paragraph. Each advertisement must be at least one-half page in size.

- 15. Nothing in this Consent shall require Bayer to:
 - a. take an action that is prohibited by the FDCA or any regulation promulgated thereunder, or by FDA; or

- b. fail to take an action that is required by the FDCA or any regulation promulgated thereunder, or by FDA. Any written or oral promotional claim subject to this Consent which is the same or substantially the same as the language prescribed by FDA shall not constitute a violation of this Consent.

16. Bayer shall:

- a. provide a copy of the Compliance Provisions of this Consent Decree to all current employees having direct responsibility for Posting Clinical Study information; and will make this Consent Decree accessible on Bayer's intranet site to all current employees having responsibility for marketing and promoting its Products. ("Relevant Persons");
- b. obtain certifications from the Relevant Persons that they have received and/or reviewed a copy of the Compliance Provisions of this Consent, have read them, understand their responsibilities and duties in accordance therewith, and will abide by the Compliance Provisions; and
- c. submit to each Signatory Attorney General, on the anniversary of the Effective Date of this Consent, a written affirmation setting forth Bayer's compliance with this paragraph.

**IV. DISBURSEMENT OF PAYMENTS:
PAYMENT TO THE STATES**

17. Within thirty (30) days of the Effective Date of this Consent, Bayer shall pay \$8,000,000.00 to the States by electronic fund transfer made payable to the Oregon Attorney General's Office which shall divide and distribute these funds as designated by and in the sole discretion of the Signatory Attorneys General as part of the consideration for the termination of

their respective investigations under the State Consumer Protection Laws regarding the Subject Matter of this Consent. Said payment shall be used by the States as and for attorneys' fees and other costs of investigation and litigation, or to be placed in, or applied to, the consumer protection enforcement fund, consumer education, litigation or local consumer aid fund or revolving fund, used to defray the costs of the inquiry leading hereto, or for other uses permitted by state law, at the sole discretion of each Signatory Attorney General.³

V. GENERAL PROVISIONS

18 This Consent shall be governed by the laws of the above-named states.

19. This Consent is entered into by the Parties as their own free and voluntary act and with full knowledge and understanding of the nature of the proceedings and the obligations and duties imposed by this Consent.

20. Nothing in this Consent constitutes any agreement by the Parties concerning the characterization of the amounts paid pursuant to this Consent for purposes of the Internal Revenue Code or any state tax laws.

³ For ARKANSAS, the money shall be placed in the Arkansas Attorney General's Consumer Education and Enforcement Fund and held in trust for purposes directly related to Arkansas consumer protection efforts. For CALIFORNIA, payment will go to the California Unfair Competition Fund. For DELAWARE, payment will go to the Consumer Protection Fund. In MASSACHUSETTS, the money shall be deposited into the Local Consumer Aid Fund pursuant to M.G.L. c. 12, section 11G. In OREGON, the money shall be deposited to the Consumer Protection and Education Revolving Account established pursuant to ORS 180.095. In PENNSYLVANIA, funds distributed to the Pennsylvania Office of Attorney General may be used for costs of investigation, attorney fees and for future consumer protection and public protection purposes. For WASHINGTON state, in lieu of direct restitution, the funds may be used for recovery of costs and fees and consumer education by pres.

21 This Consent does not constitute an approval by the Signatory Attorneys General of any of Bayer's business practices, including its promotional or marketing practices, and Bayer shall make no representation or claim to the contrary

22 This Consent sets forth the entire agreement between the Parties hereto and supersedes all prior agreements or understandings, whether written or oral, between the Parties and/or their respective counsel with respect to the subject matter hereof. This Consent may be amended by written agreement between the Parties, subject to any further requirements under an individual Signatory Attorney General's state law.

23 This Consent may be executed in counterparts, and by different signatories on separate counterparts, each of which shall be deemed to constitute an original counterpart hereof, and all of which shall together constitute one and the same Consent. One or more counterparts of this Consent may be delivered by facsimile or electronic transmission with the intent that it or they shall constitute an original counterpart hereof.

24 This Consent shall become effective on the Effective Date and Bayer's obligations to Post information and otherwise publish its Clinical Study Reports shall remain in effect for Ten (10) years following the Effective Date.

VI. REPRESENTATIONS AND WARRANTIES

25 Bayer acknowledges that it is a proper party to this Consent. Bayer further warrants and represents that the individual signing this Consent on behalf of Bayer is doing so in his or her official capacity and is fully authorized by Bayer to enter into this Consent and to legally bind Bayer to all of the terms and conditions of the Consent.

26 Each of the Parties represents and warrants that it negotiated the terms of this Consent in good faith.

27. Each of the Signatory Attorneys General warrants and represents that he or she is signing this Consent in his or her official capacity, and that he or she is fully authorized by his or her state to enter into this Consent, including but not limited to the authority to grant the release contained in Paragraphs 29-31 of this Consent, and to legally bind his or her state to all of the terms and conditions of this Consent.

28. Bayer acknowledges and agrees that the Signatory Attorneys General have relied on all of the representations and warranties set forth in this Consent and that, if any representation is proved false, deceptive, misleading, or inaccurate in any material respect, the Signatory Attorneys General have the right to seek any relief or remedy afforded by law or equity in their respective states.

VII. RELEASE

29. Based upon their investigation into Bayer's promotional and marketing practices regarding Baycol, the Signatory Attorneys General have concluded that this Consent is the appropriate resolution of any alleged violations of the State Consumer Protection Laws. The Signatory Attorneys General acknowledge by their execution hereof that this Consent terminates their investigation under the State Consumer Protection Laws into Bayer's promotional practices regarding Baycol® prior to the Effective Date of this Consent.

30. In consideration of the Compliance Provisions, payments, undertakings and acknowledgments provided for in this Consent, and conditioned upon Bayer's full payment of the amount specified in Paragraph 17 and subject to the reservations set forth in Paragraph 31 by its execution of this Consent, each Signatory Attorney General, as defined in Section I, Paragraph I, releases and forever discharges, to the fullest extent permitted by law, Bayer and all of its past and present officers, directors, shareholders, employees, subsidiaries, affiliates,

predecessors, assigns and successors (hereinafter referred to collectively as the “Released Parties”), from the following: all civil claims, causes of action, counterclaims, set-offs, demands, actions, suits, rights, liabilities, damages, restitution, fines, costs and penalties under the above-cited statutes arising from the Covered Conduct, also defined as the Subject Matter of this Consent in Section I, Paragraph V, as described in Section II, Paragraph 3 of the Consent, that were or could have been asserted against the Released Parties by the Signatory Attorneys General on or after February 18, 1998. This release does not apply to any conduct occurring after the Effective Date of this Consent

31. Notwithstanding any term of this Consent, specifically reserved and excluded from the Released Claims as to any entity or person, including Released Parties, are any and all of the following:

- a. Any criminal liability that any person or entity, including Released Parties, has or may have to any or all of the Signatory Attorneys General;
- b. Any civil or administrative liability that any person or entity, including Released Parties, has or may have to any or all of the Signatory Attorneys General, under any statute, regulation or rule not expressly covered by the release in Paragraph 30 above, including, but not limited to, any and all of the following claims:
 - i. State or federal antitrust violations;
 - ii. Reporting practices, including “best price”, “average wholesale price” or “wholesale acquisition cost”;

- iii. Medicaid violations, including federal Medicaid drug rebate statute violations, Medicaid fraud or abuse, and/or kickback violations related to any State's Medicaid program;
 - iv. State false claims violations; and,
 - v. Claims to enforce the terms and conditions of this Consent.
- c. Any liability under the above-cited consumer protection laws of any or all of the Signatory Attorneys General which any person or entity, including Released Parties, has or may have to individual consumers or State program payors of said Individual States, and which have not been specifically enumerated as included herein.

VIII. NO ADMISSION OF LIABILITY

32. This Consent does not constitute an admission by Bayer for any purpose, of any fact or of a violation of any state law, rule, or regulation, nor does this Consent constitute evidence of any liability, fault, or wrongdoing. Bayer enters into this Consent for the purpose of resolving the concerns of the Signatory Attorneys General regarding Bayer's promotional and marketing practices for Baycol®. Bayer does not admit any violation of the State Consumer Protection Laws, and does not admit any wrongdoing that could have been alleged by the Signatory Attorneys General.

33. This Consent shall not be construed or used as a waiver or any limitation of any defense otherwise available to Bayer. This Consent is made without trial or adjudication of any issue of fact or law or finding of liability of any kind. Nothing in this Consent, including this paragraph, shall be construed to limit or to restrict Bayer's right to use this Consent to assert and maintain the defenses of res judicata, collateral estoppel, payment, compromise and settlement,

accord and satisfaction, or any other legal or equitable defenses in any pending or future legal or administrative action or proceeding

IX. DISPUTES REGARDING COMPLIANCE

34. For the purposes of resolving disputes with respect to compliance with this Consent, should any of the Signatory Attorneys General have cause to believe that Bayer has violated a provision of this Consent subsequent to the Effective Date of this Consent, then such Attorney General shall notify Bayer in writing of the specific objection, identify with particularity the provisions of this Consent and/or the State Consumer Protection Law that the practice appears to violate, and give Bayer thirty (30) business days to respond to the notification; provided, however, that a Signatory Attorney General may take any action where the Signatory Attorney General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action.

35. Upon giving Bayer thirty (30) business days to respond to the notification described in Paragraph 34 above, the Signatory Attorney General shall be permitted to serve a document request for relevant, non-privileged, non-work-product records and documents in the possession, custody or control of Bayer that relate to Bayer's compliance with each provision of this Consent as to which legally sufficient cause has been shown. In response to that document request, Bayer will make responsive documents available to the Signatory Attorneys General.

X. PENALTIES FOR FAILURE TO COMPLY

36. The State may assert any claim that Bayer has violated this Consent in a separate civil action to enforce this Consent, or to seek any other relief afforded by law. In any such action or proceeding, relevant evidence of conduct that occurred before the Effective Date shall be admissible on any material issue, including alleged willfulness, intent, knowledge, contempt

or breach, to the extent permitted by law. Bayer does not waive any objection it may have to the admissibility of any such evidence, as permitted by law.

XI. COMPLIANCE WITH ALL LAWS

37. Except as expressly provided in this Consent, nothing in this Consent shall be construed as:

- a. relieving Bayer of its obligation to comply with all applicable state laws, regulations or rules, or granting permission to engage in any acts or practices prohibited by such law, regulation or rule; or
- b. limiting or expanding in any way any right the State may otherwise have to obtain information, documents or testimony from Bayer pursuant to any applicable state law, regulation or rule, or any right Bayer may otherwise have to oppose any subpoena, civil investigative demand, motion, or other procedure issued, served, filed, or otherwise employed by the State pursuant to any such state law, regulation, or rule.

XII. NOTICES UNDER THIS CONSENT

38. Any notices that must be sent to the State or to Bayer under this Consent shall be sent by overnight United States mail. The documents shall be sent to the following addresses:

For the MSWG:

Suzanne D. Sonneborn
Assistant Attorney General, Consumer Protection Division
525 West Ottawa Street
Post Office Box 30213
Lansing, Michigan 48909
Telephone: 517.335.0855
Facsimile: 517.335.1935

David Anthony Hart
Assistant Attorney General
1162 Court Street NE
Salem, Oregon 97301-4096
Telephone: 503 947-4333
Facsimile: 503 378-5017

For Bayer:

Kristin Graham Koehler, Esquire
Sidley Austin LLP
1501 K Street, N W
Washington, D C. 20005
Telephone: 202 736 8359
Facsimile: 202 736 8711

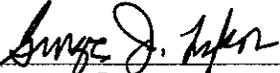
and

Chief Legal Officer
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205
Telephone: 412 777 5774
Facsimile: 412 777 4417

**SECTION XIII. SIGNATURES FOLLOW ON NEXT PAGE
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SIGNATURES

FOR BAYER:

By:  Date: January 17, 2007

George J. Lykos
Chief Legal Officer
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205
Telephone: 412 777.5774

Approved as to form:

By: *Kristin Graham Koehler* Date: *January 17, 2007*
Kristin Graham Koehler, Partner
Sidley Austin LLP
1501 K Street, N W.
Washington, D.C 20005
Telephone: 202.736.8359

Approved as to form:

By: _____

Jeffrey Feikens P42816

Feikens, Stevens, Kennedy & Galbraith, P.C.

660 Woodward, Suite 700

Detroit, MI 48226

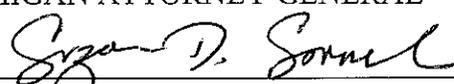
313-962-8869

Date: _____

July 11, 2007

FOR THE STATE OF MICHIGAN:

MICHAEL A. COX
MICHIGAN ATTORNEY GENERAL

By: 

Date: 1/11/07

Suzanne D. Sonneborn
Assistant Attorney General
Consumer Protection Division
525 West Ottawa Street
Post Office Box 30213
Lansing, Michigan 48909
517-335-0855 Telephone
517-335-1935 Facsimile

APPROVED BY THE COURT:

JAMES R. GIDDINGS

Date: **JAN 23 2007**

Judge

S:\Consumer Protection\Assignment Control\Cases\Open\Sonneboms\2006\Baycol\Consent Judgment - Michigan specific 1 18 07.DOC

Exhibit
1

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
USE

ICH HARMONISED TRIPARTITE GUIDELINE

STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS
E3

Current *Step 4* version
dated 30 November 1995

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA

EXHIBIT

1

E3
Document History

First Codification	History	Date	New Codification November 2005
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Current *Step 4* version

E3	Approval by the Steering Committee under <i>Step 4</i> and recommendation for adoption to the three ICH regulatory bodies	30 November 1995	E3
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STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 30 November 1995, this guideline is recommended for adoption to the three regulatory parties to ICH

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STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS

INTRODUCTION TO THE GUIDELINE

The objective of this guideline is to allow the compilation of a single core clinical study report acceptable to all regulatory authorities of the ICH regions. The regulatory authority specific additions will consist of modules to be considered as appendices, available upon request according to regional regulatory requirements.

The clinical study report described in this guideline is an "integrated" full report of an individual study of any therapeutic, prophylactic or diagnostic agent (referred to herein as drug or treatment) conducted in patients, in which the clinical and statistical description, presentations, and analyses are integrated into a single report, incorporating tables and figures into the main text of the report, or at the end of the text, and with appendices containing the protocol, sample case report forms, investigator related information, information related to the test drugs/investigational products including active control/comparators, technical statistical documentation, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output etc. The integrated full report of a study should not be derived by simply joining a separate clinical and statistical report. Although this guideline is mainly aimed at efficacy and safety trials, the basic principles and structure described can be applied to other kinds of trials, such as clinical pharmacology studies. Depending on the nature and importance of such studies, a less detailed report might be appropriate.

The guideline is intended to assist sponsors in the development of a report that is complete, free from ambiguity, well organised and easy to review. The report should provide a clear explanation of how the critical design features of the study were chosen and enough information on the plan, methods and conduct of the study so that there is no ambiguity in how the study was carried out. The report with its appendices should also provide enough individual patient data, including the demographic and baseline data, and details of analytical methods, to allow replication of the critical analyses when authorities wish to do so. It is also particularly important that all analyses, tables, and figures carry, in text or as part of the table, clear identification of the set of patients from which they were generated.

Depending on the regulatory authority's review policy, abbreviated reports using summarised data or with some sections deleted, may be acceptable for uncontrolled studies or other studies not designed to establish efficacy (but a controlled safety study should be reported in full), for seriously flawed or aborted studies, or for controlled studies that examine conditions clearly unrelated to those for which a claim is made. However, a full description of safety aspects should be included in these cases. If an abbreviated report is submitted, there should be enough detail of design and results to allow the regulatory authority to determine whether a full report is needed. If there is any question regarding whether the reports are needed, it may be useful to consult the regulatory authority.

In presenting the detailed description of how the study was carried out, it may be possible simply to restate the description in the initial protocol. Often, however, it is possible to present the methodology of the study more concisely in a separate document. In each section describing the design and conduct of the study, it is particularly important to clarify features of the study that are not well-described in

the protocol and identify ways in which the study as conducted differed from the protocol, and to discuss the statistical methods and analyses used to account for these deviations from the planned protocol

The full integrated report of the individual study should include the most detailed discussion of individual adverse events or laboratory abnormalities, but these should usually be reexamined as part of an overall safety analysis of all available data in any application.

The report should describe demographic and other potentially predictive characteristics of the study population and, where the study is large enough to permit this, present data for demographic (e.g., age, sex, race, weight) and other (e.g., renal or hepatic function) subgroups so that possible differences in efficacy or safety can be identified. Usually, however, subgroup responses should be examined in the larger database used in the overall analysis.

The data listings requested as part of the report (usually in an appendix) are those needed to support critical analyses. Data listings that are part of the report should be readily usable by the reviewer. Thus, although it may be desirable to include many variables in a single listing to limit size, this should not be at the expense of clarity. An excess of data should not be allowed to lead to overuse of symbols instead of words or easily understood abbreviations or to too small displays etc. In this case, it is preferable to produce several listings.

Data should be presented in the report at different levels of detail: overall summary figures and tables for important demographic, efficacy and safety variables may be placed in the text to illustrate important points; other summary figures, tables and listings for demographic, efficacy and safety variables should be provided in section 14; individual patient data for specified groups of patients should be provided as listings in Appendix 16 2; and all individual patient data (archival listings requested only in the US) should be provided in Appendix 16 4.

In any table, figure or data listing, estimated or derived values, if used, should be identified in a conspicuous fashion. Detailed explanations should be provided as to how such values were estimated or derived and what underlying assumptions were made.

The guidance provided below is detailed and is intended to notify the applicant of virtually all of the information that should routinely be provided so that post-submission requests for further data clarification and analyses can be reduced as much as possible. Nonetheless, specific requirements for data presentation and/or analysis may depend on specific situations, may evolve over time, may vary from drug class to drug class, may differ among regions and cannot be described in general terms; it is therefore important to refer to specific clinical guidelines and to discuss data presentation and analyses with the reviewing authority, whenever possible. Detailed written guidance on statistical approaches is available from some authorities.

Each report should consider all of the topics described (unless clearly not relevant) although the specific sequence and grouping of topics may be changed if alternatives are more logical for a particular study. Some data in the appendices are specific requirements of individual regulatory authorities and should be submitted as appropriate. The numbering should then be adapted accordingly.

In the case of very large trials, some of the provisions of this guideline may be impractical or inappropriate. When planning and when reporting such trials, contact with regulatory authorities to discuss an appropriate report format is encouraged.

The provisions of this guideline should be used in conjunction with other ICH guidelines.

STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS

1. TITLE PAGE

The title page should contain the following information:

- study title
- name of test drug/ investigational product
- indication studied
- if not apparent from the title, a brief (1 to 2 sentences) description giving design (parallel, cross-over, blinding, randomised) comparison (placebo, active, dose/response), duration, dose, and patient population
- name of the sponsor
- protocol identification (code or number)
- development phase of study
- study initiation date (first patient enrolled, or any other verifiable definition)
- date of early study termination, if any
- study completion date (last patient completed)
- name and affiliation of principal or coordinating investigator(s) or sponsor's responsible medical officer
- name of company/sponsor signatory (the person responsible for the study report within the company/sponsor. The name, telephone number and fax number of the company/sponsor contact persons for questions arising during review of the study report should be indicated on this page or in the letter of application.)
- statement indicating whether the study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents
- date of the report (identify any earlier reports from the same study by title and date).

2. SYNOPSIS

A brief synopsis (usually limited to 3 pages) that summarises the study should be provided (see Annex I of the guideline for an example of a synopsis format used in Europe). The synopsis should include numerical data to illustrate results, not just text or p-values.

3 TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

The table of contents should include:

- the page number or other locating information of each section, including summary tables, figures and graphs;
- a list and the locations of appendices, tabulations and any case report forms provided

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

A list of the abbreviations, and lists and definitions of specialised or unusual terms or measurements units used in the report should be provided. Abbreviated terms should be spelled out and the abbreviation indicated in parentheses at first appearance in the text.

5 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

It should be confirmed that the study and any amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. A list of all IECs or IRBs consulted should be given in appendix 16.1.3 and, if required by the regulatory authority, the name of the committee Chair should be provided.

5.2 ETHICAL CONDUCT OF THE STUDY

It should be confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

5.3 PATIENT INFORMATION AND CONSENT

How and when informed consent was obtained in relation to patient enrolment, (e.g., at allocation, pre-screening) should be described.

Representative written information for the patient (if any) and a sample patient consent form should be provided in appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The administrative structure of the study (e.g., principal investigator, coordinating investigator, steering committee, administration, monitoring and evaluation committees, institutions, statistician, central laboratory facilities, contract research organisation (C.R.O.), clinical trial supply management) should be described briefly in the body of the report.

There should be provided in appendix 16.1.4 a list of the investigators with their affiliations, their role in the study and their qualifications (curriculum vitae or equivalent). A similar list for other persons whose participation materially affected the conduct of the study should also be provided in appendix 16.1.4. In the case of large trials with many investigators the above requirements may be abbreviated to consist of general statements of qualifications for persons carrying out particular roles in the study with only the name, degree and institutional affiliation and roles of each investigator or other participant.

The listing should include:

- a) Investigators
- b) Any other person carrying out observations of primary or other major efficacy variables, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. It is not necessary to include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for any of the above
- c) The author(s) of the report, including the responsible biostatistician(s)

Where signatures of the principal or coordinating investigators are required by regulatory authorities, these should be included in appendix 16.1.5 (see Annex II for a sample form). Where these are not required, the signature of the sponsor's responsible medical officer should be provided in appendix 16.1.5

7. INTRODUCTION

The introduction should contain a brief statement (maximum: 1 page) placing the study in the context of the development of the test drug/investigational product, relating the critical features of the study (e.g., rationale and aims, target population, treatment, duration, primary endpoints) to that development. Any guidelines that were followed in the development of the protocol or any other agreements/meetings between the sponsor/company and regulatory authorities that are relevant to the particular study, should be identified or described

8. STUDY OBJECTIVES

A statement describing the overall purpose(s) of the study should be provided

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN - DESCRIPTION

The overall study plan and design (configuration) of the study (e.g., parallel, cross-over) should be described briefly but clearly, using charts and diagrams as needed. If other studies used a very similar protocol, it may be useful to note this and describe any important differences. The actual protocol and any changes should be included as appendix 16.1.1 and a sample case report form (unique pages only; i.e., it is not necessary to include identical pages from forms for different evaluations or visits) as appendix 16.1.2. If any of the information in this section comes from sources other than the protocol, these should be identified.

The information provided should include:

- treatments studied (specific drugs, doses and procedures);
- patient population studied and the number of patients to be included;
- level and method of blinding/masking (e.g., open, double-blind, single-blind, blinded evaluators and unblinded patients and/or investigators);
- kind of control(s) (e.g., placebo, no treatment, active drug, dose-response, historical) and study configuration (parallel, cross-over);
- method of assignment to treatment (randomisation, stratification);
- sequence and duration of all study periods, including pre-randomisation and post-treatment periods, therapy withdrawal periods and single- and double-blind treatment periods. When patients are randomised should be specified.

It is usually helpful to display the design graphically with a flow chart which includes timing of assessments (see Annexes IIIa and IIIb for an example);

- any safety, data monitoring or special steering or evaluation committees;
- any interim analyses.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The specific control chosen and the study design used should be discussed, as necessary. Examples of design issues meriting discussion follow

Generally, the control (comparison) groups that are recognised are placebo concurrent control, no treatment concurrent control, active treatment concurrent control, dose comparison concurrent control, and historical control. In addition to the type of control, other critical design features that may need discussion are use of a cross-over design and selection of patients with particular prior history, such as response or non-response to a specific drug or member of a drug class. If randomisation was not used, it is important to explain how other techniques, if any, guarded against systematic selection bias.

Known or potential problems associated with the study design or control group chosen, should be discussed in light of the specific disease and therapies being studied. For a crossover design, for example, there should be consideration, among other things, of the likelihood of spontaneous change in the disease and of carry-over effects of treatment during the study.

If efficacy was to be demonstrated by showing equivalence, i.e., the absence of a specified degree of inferiority of the new treatment compared to an established treatment, problems associated with such study designs should be addressed. Specifically there should be provided a basis for considering the study capable of distinguishing active from inactive therapy. Support may be provided by an analysis of previous studies similar to the present study with respect to important design characteristics (patient selection, study endpoints, duration, dose of active control, concomitant therapy etc) showing a consistent ability to demonstrate superiority of the active control to placebo. How to assess the ability of the present study to distinguish effective from ineffective therapy should also be discussed. For example, it may be possible to identify a treatment response (based on past studies) that would clearly distinguish between the treated population and an untreated group. Such a response could be the change of a measure from baseline or some other specified outcome like healing rate or survival rate. Attainment of such a response would support the expectation that the study could have distinguished the active drug from an inactive drug. There should also be a discussion of the degree of inferiority of the therapy (often referred to as the delta value) the study was intended to show was not exceeded.

The limitations of historical controls are well known (difficulty of assuring comparability of treated groups, inability to blind investigators to treatment, change in therapy/disease, difference due to placebo effect etc) and deserve particular attention.

Other specific features of the design may also deserve discussion, including presence or absence of washout periods and the duration of the treatment period, especially for a chronic illness. The rationale for dose and dose-interval selection should be explained, if it is not obvious. For example, once daily dosing with a short half-life

drug whose effect is closely related in time to blood level is not usually effective; if the study design uses such dosing, this should be explained, e.g., by pointing to pharmacodynamic evidence that effect is prolonged compared to blood levels. The procedures used to seek evidence of "escape" from drug effect at the end of the dose-interval, such as measurements of effect just prior to dosing, should be described. Similarly, in a parallel design dose-response study, the choice of doses should be explained.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

The patient population and the selection criteria used to enter the patients into the study should be described, and the suitability of the population for the purposes of the study discussed. Specific diagnostic criteria used, as well as specific disease requirements (e.g., disease of a particular severity or duration, results of a particular test or rating scale(s) or physical examination, particular features of clinical history, such as failure or success on prior therapy, or other potential prognostic factors and any age, sex or ethnic factors) should be presented.

Screening criteria and any additional criteria for randomisation or entry into the test drug/investigational product treatment part of the trial should be described. If there is reason to believe that there were additional entry criteria, not defined in the protocol, the implications of these should be discussed. For example, some investigators may have excluded, or entered into other studies, patients who were particularly ill or who had particular baseline characteristics.

9.3.2 Exclusion Criteria

The criteria for exclusion at entry into the study should be specified and the rationale (e.g., safety concerns, administrative reasons or lack of suitability for the trial) provided. The impact of exclusions on the generalisability of the study should be discussed in section 13 of the study report, or in an overview of safety and efficacy.

9.3.3 Removal of Patients from Therapy or Assessment

The predetermined reasons for removing patients from therapy or assessment observation, if any, should be described, as should the nature and duration of any planned follow-up observations in those patients.

9.4 TREATMENTS

9.4.1 Treatments Administered

The precise treatments or diagnostic agents to be administered in each arm of the study, and for each period of the study, should be described including route and mode of administration, dose and dosage schedule.

9.4.2 Identity of Investigational Product(s)

In the text of the report, a brief description of the test drug(s)/investigational product(s) (formulation, strength, batch number(s)) should be given. If more than one batch of test drug/investigational product was used, patients receiving each batch should be identified in appendix 16.1.6.

The source of placebos and active control/comparator product(s) should be provided. Any modification of comparator product(s) from their usual commercial state should

be noted, and the steps taken to assure that their bioavailability was unaltered should be described.

For long-duration trials of investigational products with limited shelf-lives or incomplete stability data, the logistics of resupply of the materials should be described. Any use of test materials past their expiry date should be noted, and patients receiving them identified. If there were specific storage requirements, these should also be described.

9.4.3 Method of Assigning Patients to Treatment Groups

The specific methods used to assign patients to treatment groups, e.g., centralised allocation, allocation within sites, adaptive allocation (that is, assignment on the basis of earlier assignment or outcome) should be described in the text of the report, including any stratification or blocking procedures. Any unusual features should be explained.

A detailed description of the randomisation method, including how it was executed, should be given in appendix 16.1.7 with references cited if necessary. A table exhibiting the randomisation codes, patient identifier, and treatment assigned should also be presented in the appendix. For a multicentre study, the information should be given by centre. The method of generating random numbers should be explained.

For a historically controlled trial, it is important to explain how the particular control was selected and what other historical experiences were examined, if any, and how their results compared to the control used.

9.4.4 Selection of Doses in the Study

The doses or dose ranges used in the study should be given for all treatments and the basis for choosing them described (e.g., prior experience in humans, animal data).

9.4.5 Selection and Timing of Dose for each Patient

Procedures for selecting each patient's dose of test drug/investigational product and active control/comparator should be described. These procedures can vary from simple random assignment to a selected fixed drug/dose regimen, to some specified titration procedure, to more elaborate response-determined selection procedures, e.g., where dose is titrated upward at intervals until intolerance or some specified endpoint is achieved. Procedures for back-titration, if any, should also be described.

The timing (time of day, interval) of dosing and the relation of dosing to meals should be described, and if it was not specified, this should be noted.

Any specific instructions to patients about when or how to take the dose(s) should be described.

9.4.6 Blinding

A description of the specific procedures used to carry out blinding should be provided (e.g., how bottles were labelled, labels that reveal blind-breakage, sealed code list/envelopes, double dummy techniques), including the circumstances in which the blind would be broken for an individual or for all patients, e.g., for serious adverse events, the procedures used and who had access to patient codes. If the study allowed for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Measures taken to ensure that test drug/investigational product and placebo were indistinguishable and

evidence that they were indistinguishable, should be described, as should the appearance, shape, smell, and taste of the test material. Measures to prevent unblinding by laboratory measurements, if used, should be described. If there was a data monitoring committee with access to unblinded data, procedures to ensure maintenance of overall study blinding should be described. The procedure to maintain the blinding when interim analyses are performed should also be explained.

If blinding was considered unnecessary to reduce bias for some or all of the observations, this should be explained; e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Holter tapes are often read by automated systems that are presumably immune to observer bias. If blinding was considered desirable but not feasible, the reasons and implications should be discussed. Sometimes blinding is attempted but is known to be imperfect because of obvious drug effects in at least some patients (dry mouth, bradycardia, fever, injection site reactions, changes in laboratory data). Such problems or potential problems should be identified and if there were any attempts to assess the magnitude of the problem or manage it (e.g., by having some endpoint measurements carried out by people shielded from information that might reveal treatment assignment), they should be described.

9.4.7 Prior and Concomitant Therapy

Which drugs or procedures were allowed before and during the study, whether and how their use was recorded, and any other specific rules and procedures related to permitted or forbidden concomitant therapy should be described. How allowed concomitant therapy might affect the outcome due either to drug-drug interaction or to direct effects on the study endpoints should be discussed, and how the independent effects of concomitant and study therapies could be ascertained should be explained.

9.4.8 Treatment Compliance

The measures taken to ensure and document treatment compliance should be described, e.g., drug accountability, diary cards, blood, urine or other body fluid drug level measurements, or medication event monitoring.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The specific efficacy and safety variables to be assessed and laboratory tests to be conducted, their schedule (days of study, time of day, relation to meals, and the timing of critical measures in relation to test drug administration, e.g., just prior to next dose, two hours after dose), the methods for measuring them, and the persons responsible for the measurements should be described. If there were changes in personnel carrying out critical measurements, these should be reported.

It is usually helpful to display graphically in a flow chart (see Annex III of the guideline) the frequency and timing of efficacy and safety measurements; visit numbers and times should be shown, or, alternatively, times alone can be used (visit numbers alone are more difficult to interpret). Any specific instructions (e.g., guidance or use of a diary) to the patients should also be noted.

Any definitions used to characterise outcome (e.g., criteria for determining occurrence of acute myocardial infarction, designation of the location of the infarction, characterisation of a stroke as thrombotic or haemorrhagic, distinction between TIA

and stroke, assignment of cause of death) should be explained in full. Any techniques used to standardise or compare results of laboratory tests or other clinical measurements (e.g., ECG, chest X-ray) should also be described. This is particularly important in multicentre studies.

If anyone other than the investigator was responsible for evaluation of clinical outcomes (e.g., the sponsor or an external committee to review X-rays or ECG's or to determine whether the patient had a stroke, acute infarction, or sudden death) the person or group should be identified. The procedures, including means of maintaining blindness, and centralising readings and measurements, should be described fully.

The means of obtaining adverse event data should be described (volunteered, checklist, or, questioning), as should any specific rating scale(s) used and any specifically planned follow-up procedures for adverse events or any planned rechallenge procedure.

Any rating of adverse events by the investigator, sponsor or external group, (e.g., rating by severity or, likelihood of drug causation) should be described. The criteria for such ratings, if any, should be given and the parties responsible for the ratings should be clearly identified. If efficacy or safety was to be assessed in terms of categorical ratings, numerical scores etc., the criteria used for point assignment (e.g., definitions of point scores) should be provided. For multicentre studies, indicate how methods were standardised.

9.5.2 Appropriateness of Measurements

If any of the efficacy or safety assessments was not standard, i.e., widely used and generally recognised as reliable, accurate, and relevant (able to discriminate between effective and ineffective agents), its reliability, accuracy and relevance should be documented. It may be helpful to describe alternatives considered but rejected.

If a surrogate end point (a laboratory measurement or physical measurement or sign that is not a direct measure of clinical benefit) was used as a study end point, this should be justified e.g., by reference to clinical data, publications, guidelines or previous actions by regulatory authorities.

9.5.3 Primary Efficacy Variable(s)

The primary measurements and endpoints used to determine efficacy should be clearly specified. Although the critical efficacy measurements may seem obvious, when there are multiple variables, or when variables are measured repeatedly, the protocol should identify the primary ones, with an explanation of why they were chosen, or designate the pattern of significant findings or other method of combining information that would be interpreted as supporting efficacy. If the protocol did not identify the primary variables, the study report should explain how these critical variables were selected (e.g., by reference to publications, guidelines or previous actions by regulatory authorities) and when they were identified (i.e., before or after the study was completed and unblinded). If an efficacy threshold was defined in the protocol, this should be described.

9.5.4 Drug Concentration Measurements

Any drug concentrations to be measured, and the sample collection times and periods in relation to the timing of drug administration, should be described. Any relation of drug administration and sampling to ingestion of food, posture and the possible

effects of concomitant medication/alcohol/caffeine/nicotine should also be addressed. The biological sample measured the handling of samples and the method of measurement used should be described, referring to published and/or internal assay validation documentation for methodological details. Where other factors are believed important in assessing pharmacokinetics (e.g., soluble circulating receptors, renal or hepatic function), the timing and plans to measure these factors should also be specified.

9.6 DATA QUALITY ASSURANCE

The quality assurance and quality control systems implemented to assure the quality of the data should be described in brief. If none were used, this should be stated. Documentation of inter-laboratory standardisation methods and quality assurance procedures, if used, should be provided under appendix 16.1.10.

Any steps taken at the investigation site or centrally to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data, such as training sessions, monitoring of investigators by sponsor personnel, instruction manuals, data verification, cross-checking, use of a central laboratory for certain tests, centralised ECG reading, or data audits, should be described. It should be noted whether investigator meetings or other steps were taken to prepare investigators and standardise performance.

If the sponsor used an independent internal or external auditing procedure, it should be mentioned here and described in appendix 16.1.8; and audit certificates, if available, should be provided in the same appendix.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

The statistical analyses planned in the protocol and any changes made before outcome results were available should be described. In this section emphasis should be on which analyses, comparisons and statistical tests were planned, not on which ones were actually used. If critical measurements were made more than once, the particular measurements (e.g., average of several measurements over the entire study, values at particular times, values only from study completers, or last on-therapy value) planned as the basis for comparison of test drug/investigational product and control should be specified. Similarly, if more than one analytical approach is plausible, e.g., changes from baseline response, slope analysis, life table analysis, the planned approach should be identified. Also, whether the primary analysis is to include adjustment for covariates should be specified.

If there were any planned reasons for excluding from analysis patients for whom data are available, these should be described. If there were any subgroups whose results were to be examined separately, these should be identified. If categorical responses (global scales, severity scores, responses of a certain size) were to be used in analysing responses, they should be clearly defined.

Planned monitoring of the results of the study should be described. If there was a data monitoring committee, either within or outside the sponsor's control, its composition and operating procedures should be described and procedures to maintain study blinding should be given. The frequency and nature of any planned interim analysis, any specified circumstances in which the study would be terminated and any

statistical adjustments to be employed because of interim analyses should be described.

9.7.2 Determination of Sample Size

The planned sample size and the basis for it, such as statistical considerations or practical limitations, should be provided. Methods for sample size calculation should be given together with their derivations or source of reference. Estimates used in the calculations should be given and explanations provided as to how they were obtained. For a study intended to show a difference between treatments, the difference the study is designed to detect should be specified. For a positive control study intended to show that a new therapy is at least as effective as the standard therapy, the sample size determination should specify the difference between treatments that would be considered unacceptably large and therefore the difference the study is designed to be able to exclude.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any change in the conduct of the study or planned analyses (e.g., dropping a treatment group, changing the entry criteria or drug dosages, adjusting the sample size etc.) instituted after the start of the study should be described. The time(s) and reason(s) for the change(s), the procedure used to decide on the change(s), the person(s) or group(s) responsible for the change(s) and the nature and content of the data available (and to whom they were available) when the change was made should also be described, whether the change was documented as a formal protocol amendment or not (Personnel changes need not be included). Any possible implications of the change(s) for the interpretation of the study should be discussed briefly in this section and more fully in other appropriate sections of the report. In every section of the report, a clear distinction between conditions (procedures) planned in the protocol and amendments or additions should be made. In general, changes in planned analyses made prior to breaking the blind have limited implications for study interpretation. It is therefore particularly critical that the timing of changes relative to blind breaking and availability of outcome results be well characterised.

10. STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

There should be a clear accounting of all patients who entered the study, using figures or tables in the text of the report. The numbers of patients who were randomised, and who entered and completed each phase of the study, (or each week/month of the study) should be provided, as well as the reasons for all post-randomisation discontinuations, grouped by treatment and by major reason (lost to follow-up, adverse event, poor compliance etc.). It may also be relevant to provide the number of patients screened for inclusion and a breakdown of the reasons for excluding patients during screening, if this could help clarify the appropriate patient population for eventual drug use. A flow chart is often helpful (see Annexes IVa and IVb of the guideline for example). Whether patients are followed for the duration of the study, even if drug is discontinued, should be made clear.

In appendix 16.2.1, there should also be a listing of all patients discontinued from the study after enrolment, broken down by centre and treatment group, giving a patient identifier, the specific reason for discontinuation, the treatment (drug and dose),

cumulative dose, (where appropriate), and the duration of treatment before discontinuation. Whether or not the blind for the patient was broken at the time of discontinuation should be noted. It may also be useful to include other information, such as critical demographic data (e.g., age, sex, race), concomitant medication, and the major response variable(s) at termination. See Annex V for an example of such a listing.

10.2 PROTOCOL DEVIATIONS

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment should be described.

In the body of the text, protocol deviations should be appropriately summarised by centre and grouped into different categories, such as:

- those who entered the study even though they did not satisfy the entry criteria;
- those who developed withdrawal criteria during the study but were not withdrawn;
- those who received the wrong treatment or incorrect dose;
- those who received an excluded concomitant treatment.

In appendix 16.2.2, individual patients with these protocol deviations should be listed, broken down by centre for multicentre studies

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

Exactly which patients were included in each efficacy analysis should be precisely defined, e.g., all patients receiving any test drugs/investigational products, all patients with any efficacy observation or with a certain minimum number of observations, only patients completing the trial, all patients with an observation during a particular time window, only patients with a specified degree of compliance etc. It should be clear, if not defined in the study protocol, when, (relative to study unblinding), and how inclusion/exclusion criteria for the data sets analysed were developed. Generally, even if the applicant's proposed primary analysis is based on a reduced subset of the patients with data, there should also be for any trial intended to establish efficacy an additional analysis using all randomised (or otherwise entered) patients with any on-treatment data.

There should be a tabular listing of all patients, visits and observations excluded from the efficacy analysis provided in appendix 16.2.3 (see Annex VI of the guideline for an example). The reasons for exclusions should also be analysed for the whole treatment group over time (see Annex VII of the guideline for an example).

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Group data for the critical demographic and baseline characteristics of the patients, as well as other factors arising during the study that could affect response, should be presented in this section and comparability of the treatment groups for all relevant characteristics should be displayed by use of tables or graphs in section 14.1. The data for the patient sample included in the "all patients with data" analysis should be given first. This can then be followed by data on other groups used in principal analyses, such as the "per-protocol" analysis or other analyses, e.g., groups defined by compliance, concomitant disease/therapy, or demographic/baseline characteristics

When such groups are used, data for the complementary excluded group should also be shown. In a multicentre study where appropriate, comparability should be assessed by centre, and centres should be compared.

A diagram showing the relationship between the entire sample and any other analysis groups should be provided.

The critical variables will depend on the specific nature of the disease and on the protocol but will usually include:

- demographic variables
 - age
 - sex
 - race
- disease factors
 - specific entry criteria (if not uniform), duration, stage and severity of disease and other clinical classifications and sub-groupings in common usage or of known prognostic significance
 - baseline values for critical clinical measurements carried out during the study or identified as important indicators of prognosis or response to therapy
 - concomitant illness at trial initiation, such as renal disease, diabetes, heart failure
 - relevant previous illness
 - relevant previous treatment for illness treated in the study
 - concomitant treatment maintained, even if the dose was changed during the study, including oral contraceptive and hormone replacement therapy; treatments stopped at entry into the study period (or changed at study initiation)
- other factors that might affect response to therapy (e.g., weight, renal status, antibody levels, metabolic status)
- other possibly relevant variables (e.g., smoking, alcohol intake, special diets) and, for women, menstrual status and date of last menstrual period, if pertinent for the study.

In addition to tables and graphs giving group data for these baseline variables, relevant individual patient demographic and baseline data, including laboratory values, and all concomitant medication for all individual patients randomised (broken down by treatment and by centre for multicentre studies) should be presented in by-patient tabular listings in appendix 16.2.4. Although some regulatory authorities will require all baseline data to be presented elsewhere in tabular listings, the appendix to the study report should be limited to only the most relevant data, generally the variables listed above.

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Any measurements of compliance of individual patients with the treatment regimen under study and drug concentrations in body fluids should be summarised, analysed by treatment group and time interval, and tabulated in Appendix 16 2 5

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 Analysis of Efficacy

Treatment groups should be compared for all critical measures of efficacy (primary and secondary end-points; any pharmacodynamic end points studied), as well as benefit/risk assessment(s) in each patient where these are utilised. In general, the results of all analyses contemplated in the protocol and an analysis including all patients with on-study data should be performed in studies intended to establish efficacy. The analysis should show the size (point estimate) of the difference between the treatments, the associated confidence interval, and where utilised, the results of hypothesis testing.

Analyses based on continuous variables (e.g., mean blood pressure or depression scale score) and categorical responses (e.g., cure of an infection) can be equally valid; ordinarily both should be presented if both were planned and are available. If categories are newly created, (i.e., not in the statistical plan) the basis for them should be explained. Even if one variable receives primary attention (e.g., in a blood pressure study, supine blood pressure at week x), other reasonable measures (e.g., standing blood pressure and blood pressures at other particular times) should be assessed, at least briefly. In addition, the time course of response should be described, if possible. For a multicentre study, where appropriate, data display and analysis of individual centres should be included for critical variables to give a clear picture of the results at each site, especially the larger sites.

If any critical measurements or assessments of efficacy or safety outcomes were made by more than one party (e.g., both the investigator and an expert committee may offer an opinion on whether a patient had an acute infarction), overall differences between the ratings should be shown, and each patient having disparate assessments should be identified. The assessments used should be clear in all analyses.

In many cases, efficacy and safety endpoints are difficult to distinguish, (e.g., deaths in a fatal disease study). Many of the principles addressed below should be adopted for critical safety measures as well.

11.4.2 Statistical/Analytical Issues

The statistical analysis used should be described for clinical and statistical reviewers in the text of the report, with detailed documentation of statistical methods (see section Annex IX) presented in appendix 16 1 9. Important features of the analysis including the particular methods used, adjustments made for demographic or baseline measurements or concomitant therapy, handling of drop-outs and missing data, adjustments for multiple comparisons, special analyses of multicentre studies, and adjustments for interim analyses, should be discussed. Any changes in the analysis made after blind-breaking should be identified.

In addition to the general discussion the following specific issues should be addressed (unless not applicable):

11.4.2.1 Adjustments for Covariates

Selection of, and adjustments for, demographic or baseline measurements, concomitant therapy, or any other covariate or prognostic factor should be explained in the report, and methods of adjustment, results of analyses, and supportive information (e.g., ANCOVA or Cox regression output) should be included in the detailed documentation of statistical methods. If the covariates or methods used in these analyses differed from those planned in the protocol, the differences should be explained and where possible and relevant, the results of planned analyses should also be presented. Although not part of the individual study report, comparisons of covariate adjustments and prognostic factors across individual studies may be an informative analysis in a summary of clinical efficacy data

11.4.2.2 Handling of Dropouts or Missing Data

There are several factors that may affect dropout rates. These include the duration of the study, the nature of the disease, the efficacy and toxicity of the drug under study, and other factors that are not therapy related. Ignoring the patients who dropped out of the study and drawing conclusions based only on patients who completed the study can be misleading. A large number of dropouts, however, even if included in an analysis, may introduce bias, particularly if there are more early dropouts in one treatment group or the reasons for dropping out are treatment or outcome related. Although the effects of early dropouts, and sometimes even the direction of bias, can be difficult to determine, possible effects should be explored as fully as possible. It may be helpful to examine the observed cases at various time points or, if dropouts were very frequent, to concentrate on analyses at time points when most of the patients were still under observation and when the full effect of the drug was realised. It may also be helpful to examine modelling approaches to the evaluation of such incomplete data sets.

The results of a clinical trial should be assessed not only for the subset of patients who completed the study, but also for the entire patient population as randomised or at least for all those with any on-study measurements. Several factors need to be considered and compared for the treatment groups in analysing the effects of dropouts: the reasons for the dropouts, the time to dropout, and the proportion of dropouts among treatment groups at various time points.

Procedures for dealing with missing data, e.g., use of estimated or derived data, should be described. Detailed explanation should be provided as to how such estimations or derivations were done and what underlying assumptions were made.

11.4.2.3 Interim Analyses and Data Monitoring

The process of examining and analysing data accumulating in a clinical trial, either formally or informally, can introduce bias and/or increase type I error. Therefore, all interim analyses, formal or informal, pre-planned or ad hoc, by any study participant, sponsor staff member, or data monitoring group should be described in full, even if the treatment groups were not identified. The need for statistical adjustment because of such analyses should be addressed. Any operating instructions or procedures used for such analyses should be described. The minutes of meetings of any data monitoring group and any data reports reviewed at those meetings, particularly a meeting that led to a change in the protocol or early termination of the study, may be

helpful and should be provided in appendix 16.1.9. Data monitoring without code-breaking should also be described, even if this kind of monitoring is considered to cause no increase in type I error.

11.4.2.4 Multicentre Studies

A multicentre study is a single study under a common protocol, involving several centres (e.g., clinics, practices, hospitals) where the data collected are intended to be analysed as a whole (as opposed to a post-hoc decision to combine data or results from separate studies). Individual centre results should be presented, however, where appropriate, e.g., when the centres have sufficient numbers of patients to make such analysis potentially valuable, the possibility of qualitative or quantitative treatment-by-centre interaction should be explored. Any extreme or opposite results among centres should be noted and discussed, considering such possibilities as differences in study conduct, patient characteristics, or clinical settings. Treatment comparison should include analyses that allow for centre differences with respect to response. If appropriate, demographic, baseline, and post-baseline data, as well as efficacy data, should be presented by centre, even though the combined analysis is the primary one.

11.4.2.5 Multiple Comparison/Multiplicity

False positive findings increase in number as the number of significance tests (number of comparisons) performed increases. If there was more than one primary endpoint (outcome variable), more than one analysis of particular endpoint, or if there were multiple treatment groups, or subsets of the patient population being examined, the statistical analysis should reflect awareness of this and either explain the statistical adjustment used for type I error criteria or give reasons why it was considered unnecessary.

11.4.2.6 Use of an "Efficacy Subset" of Patients

Particular attention should be devoted to the effects of dropping patients with available data from analyses because of poor compliance, missed visits, ineligibility, or any other reason. As noted above, an analysis using all available data should be carried out for all studies intended to establish efficacy, even if it is not the analysis proposed as the primary analysis by the applicant. In general, it is advantageous to demonstrate robustness of the principal trial conclusions with respect to alternative choices of patient populations for analysis. Any substantial differences resulting from the choice of patient population for analysis should be the subject of explicit discussion.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

If an active control study is intended to show equivalence (i.e., lack of a difference greater than a specified size) between the test drug/investigational product and the active control/comparator, the analysis should show the confidence interval for the comparison between the two agents for critical end points and the relation of that interval to the prespecified degree of inferiority that would be considered unacceptable. (See 9.2, for important considerations when using the active control equivalence design.)

11.4.2.8 Examination of Subgroups

If the size of the study permits, important demographic or baseline value-defined subgroups should be examined for unusually large or small responses and the results presented, e.g., comparison of effects by age, sex, or race, by severity or prognostic groups, by history of prior treatment with a drug of the same class etc. If these analyses were not carried out because the study was too small it should be noted. These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc. Where there is a prior hypothesis of a differential effect in a particular subgroup, this hypothesis and its assessment should be part of the planned statistical analysis.

11.4.3 Tabulation of Individual Response Data

In addition to tables and graphs representing group data, individual response data and other relevant study information should be presented in tables. Some regulatory authorities may require all individual data in archival case report tabulations. What needs to be included in the report will vary from study to study and from one drug class to another and the applicant must decide, if possible after consultation with the regulatory authority, what to include in appendix to the study report. The study report should indicate what material is included as an appendix, what is in the more extensive archival case report tabulations, if required by the regulatory authority, and what is available on request.

For a controlled study in which critical efficacy measurements or assessments (e.g., blood or urine cultures, pulmonary function tests, angina frequency, or global evaluations) are repeated at intervals, the data listings accompanying the report should include, for each patient, a patient identifier, all measured or observed values of critical measurements, including baseline measurements, with notation of the time during the study (e.g., days on therapy and time of day, if relevant) when the measurements were made, the drug/dose at the time (if useful, given as mg/kg), any measurements of compliance, and any concomitant medications at the time of, or close to the time of, measurement or assessment. If, aside from repeated assessments, the study included some overall responder vs non-responder evaluation(s), (bacteriologic cure or failure), it should also be included. In addition to critical measurements, the tabulation should note whether the patient was included in the efficacy evaluation (and which evaluation, if more than one), provide patient compliance information, if collected, and a reference to the location of the case report form, if included. Critical baseline information such as age, sex, weight, disease being treated (if more than one in study), and disease stage or severity, is also helpful. The baseline values for critical measurements would ordinarily be included as zero time values for each efficacy measurement.

The tabulation described should usually be included in appendix 16.2.6 of the study report, rather than in the more extensive case report tabulations required by some regulatory authorities, because it represents the basic efficacy data supporting summary tables. Such a thorough tabulation can be unwieldy for review purposes, however, and it is expected that more targeted displays will be developed as well. For example, if there are many measurements reported, tabulations of the most critical measurements for each patient (e.g., the blood pressure value at certain visits might be more important than others) will be useful in providing an overview of each individual's results in a study, with each patient's response summarised on a single line or small number of lines.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

When the dose in each patient can vary, the actual doses received by patients should be shown and individual patient's doses should be tabulated. Although studies not designed as dose-response studies may have limited ability to contribute dose-response information, the available data should be examined for whatever information they can yield. In examining the dose response, it may be helpful to calculate dose as mg/kg body weight or mg/m² body surface

Drug concentration information, if available, should also be tabulated (Appendix 16.2.5), analysed in pharmacokinetic terms and, if possible, related to response.

Further guidance on the design and analysis of studies exploring dose-response or concentration response can be found in the ICH Guideline "Dose-Response Information to Support Drug Registration".

11.4.5 Drug-Drug and Drug-Disease Interactions

Any apparent relationship between response and concomitant therapy and between response and past and/or concurrent illness should be described

11.4.6 By-Patient Displays

While individual patient data ordinarily can be displayed in tabular listings, it has on occasion been helpful to construct individual patient profiles in other formats, such as graphic displays. These might, for example, show the value of (a) particular parameter(s) over time, the drug dose over the same period, and the times of particular events (e.g., an adverse event or change in concomitant therapy). Where group mean data represent the principal analyses, this kind of "case report extract" may offer little advantage; it may be helpful, however, if overall evaluation of individual responses is a critical part of the analysis.

11.4.7 Efficacy Conclusions

The important conclusions concerning efficacy should be concisely described, considering primary and secondary end points, pre-specified and alternative statistical approaches and results of exploratory analyses.

12. SAFETY EVALUATION

Analysis of safety-related data can be considered at three levels. First, the extent of exposure (dose, duration, number of patients) should be examined to determine the degree to which safety can be assessed from the study. Second, the more common adverse events, laboratory test changes etc should be identified, classified in some reasonable way, compared for treatment groups, and analysed, as appropriate, for factors that may affect the frequency of adverse reactions/events, such as time dependence, relation to demographic characteristics, relation to dose or drug concentration etc. Finally, serious adverse events and other significant adverse events should be identified, usually by close examination of patients who left the study prematurely because of an adverse event, whether or not identified as drug related, or who died

The ICH Guideline on Clinical Safety Data Management, Definitions and Standards for Expedited Reporting defines serious adverse events as follows: a "serious adverse event" (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect

For the purpose of this guideline, "other significant adverse events" are marked haematological and other laboratory abnormalities and any adverse events that led to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy.

In the following sections, three kinds of analysis and display are called for:

- 1) summarised data, often using tables and graphical presentations presented in the main body of the report
- 2) listings of individual patient data, and
- 3) narrative statements of events of particular interest.

In all tabulations and analyses, events associated with both test drug and control treatment should be displayed

12.1 EXTENT OF EXPOSURE

The extent of exposure to test drugs/investigational products (and to active control and placebo) should be characterised according to the number of patients exposed, the duration of exposure, and the dose to which they were exposed.

- *Duration.* Duration of exposure to any dose can be expressed as a median or mean, but it is also helpful to describe the number of patients exposed for specified periods of time, such as for one day or less, 2 days to one week, more than one week to one month, more than one month to 6 months etc. The numbers exposed to test drug(s)/investigational product(s) for the various durations should also be broken down into age, sex, and racial subgroups, and any other pertinent subgroups, such as disease (if more than one is represented), disease severity, concurrent illness.
- *Dose.* The mean or median dose used and the number of patients exposed to specified daily dose levels should be given; the daily dose levels used could be the maximum dose for each patient, the dose with longest exposure for each patient, or the mean daily dose. It is often useful to provide combined dose-duration information, such as the numbers exposed for a given duration (e.g., at least one month) to the most common dose, the highest dose, the maximum recommended dose etc. In some cases, cumulative dose might be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/m² basis as appropriate. The numbers of patients exposed to various doses should be broken down into age, sex, and racial subgroups, and any other pertinent subgroups.
- *Drug concentration.* If available, drug concentration data (e.g., concentration at the time of an event, maximum plasma concentration, area under curve) may be helpful in individual patients for correlation with adverse events or changes in laboratory variables. (Appendix 16.2 5)

It is assumed that all patients entered into treatment who received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

12.2 ADVERSE EVENTS (AEs)

12.2.1 Brief Summary of Adverse Events

The overall adverse event experience in the study should be described in a brief narrative, supported by the following more detailed tabulations and analyses. In these tabulations and analyses, events associated with both the test drug and control treatment should be displayed.

12.2.2 Display of Adverse Events

All adverse events occurring after initiation of study treatments (including events likely to be related to the underlying disease or likely to represent concomitant illness, unless there is a prior agreement with the regulatory authority to consider specified events as disease related) should be displayed in summary tables (section 14.3.1). The tables should include changes in vital signs and any laboratory changes that were considered serious adverse events or other significant adverse events

In most cases, it will also be useful to identify in such tables "treatment emergent signs and symptoms" (TESS; those not seen at baseline and those that worsened even if present at baseline).

The tables should list each adverse event, the number of patients in each treatment group in whom the event occurred, and the rate of occurrence. When treatments are cyclical, e.g., cancer chemotherapy, it may also be helpful to list results separately for each cycle. Adverse events should be grouped by body system. Each event may then be divided into defined severity categories (e.g., mild, moderate, severe) if these were used. The tables may also divide the adverse events into those considered at least possibly related to drug use and those considered not related, or use some other causality scheme (e.g., unrelated or possibly, probably, or definitely related). Even when such a causality assessment is used, the tables should include all adverse events, whether or not considered drug related, including events thought to represent intercurrent illnesses. Subsequent analyses of the study or of the overall safety data base may help to distinguish between adverse events that are, or are not, considered drug related. So that it is possible to analyse and evaluate the data in these tables, it is important to identify each patient having each adverse event. An example of such a tabular presentation is shown below.

**ADVERSE EVENTS: NUMBER OBSERVED AND RATE,
WITH PATIENT IDENTIFICATIONS**

Treatment Group X

N=50

	Mild		Moderate		Severe		Total		Total
	Related*	NR*	Related	NR	Related	NR	Related	NR	R+NR
Body System A									
Event 1	6 (12%)	2 (4%)	3 (6%)	1 (2%)	3 (6%)	1 (2%)	12 (24%)	4 (8%)	
	N11**	N21	N31	N41	N51	N61			
	N12	N22	N32		N52				
	N13		N33		N53				
	N14								
	N15								
	N16								
Event 2									

*NR = not related, related could be expanded, e.g., as definite, probable, possible

**Patient identification number

In addition to these complete tables provided in 14.3.1, an additional summary table comparing treatment and control groups, without the patient identifying numbers limited to relatively common adverse events (e.g., those in at least 1% of the treated group), should be provided in the body of the report

In presenting adverse events, it is important both to display the original terms used by the investigator and to attempt to group related events (i.e., events that probably represent the same phenomena) so that the true occurrence rate is not obscured. One way to do this is with a standard adverse reaction/events dictionary

12.2.3 Analysis of Adverse Events

The basic display of adverse event rates described in section 12.2.2 (and located in section 14.3.1) of the report, should be used to compare rates in treatment and control groups. For this analysis it may be helpful to combine the event severity categories and the causality categories, leading to a simpler side-by-side comparison of treatment groups. In addition, although this is usually best done in an integrated analysis of safety, if study size and design permit, it may be useful to examine the more common adverse events that seem to be drug related for relationship to dosage and to mg/kg or mg/m² dose, to dose regimen, to duration of treatment, to total dose, to demographic characteristics such as age, sex, race, to other baseline features such as renal status, to efficacy outcomes, and to drug concentration. It may also be useful to examine time of onset and duration of adverse events. A variety of additional analyses may be suggested by the study results or by the pharmacology of the test drug/investigational product.

It is not intended that every adverse event be subjected to rigorous statistical evaluation. It may be apparent from initial display and inspection of the data that a significant relation to demographic or other baseline features is not present. If the studies are small and if the number of events is relatively small, it may be sufficient to limit analyses to a comparison of treatment and control.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude adverse event rates. When treatments are cyclical, e.g., cancer chemotherapy, it may also be helpful to analyse results separately for each cycle

12.2.4 Listing of Adverse Events by Patient

All adverse events for each patient, including the same event on several occasions should be listed in appendix 16.2.7, giving both preferred term and the original term used by the investigator. The listing should be by investigator and by treatment group and should include:

- Patient identifier
- Age, race, sex, weight (height, if relevant)
- Location of CRFs, if provided
- The adverse event (preferred term, reported term)
- Duration of the adverse event
- Severity (e.g., mild, moderate, severe)
- Seriousness (serious/non-serious)
- Action taken (none, dose reduced, treatment stopped, specific treatment instituted etc.)
- Outcome (e.g., CIOMS format)
- Causality assessment (e.g., related/not related). How this was determined should be described in the table or elsewhere
- Date of onset or date of clinic visit at which the event was discovered
- Timing of onset of the adverse event in relation to last dose of test drug/investigational product (when applicable)
- Study treatment at time of event or most recent study treatment taken
- Test drug/investigational product dose in absolute amount, mg/kg or mg/m² at time of event
- Drug concentration (if known)
- Duration of test drug/investigational product treatment
- Concomitant treatment during study.

Any abbreviations and codes should be clearly explained at the beginning of the listing or, preferably, on each page.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

Deaths, other serious adverse events, and other significant adverse events deserve special attention.

12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

Listings, containing the same information as called for in section 12.2.4 above, should be provided for the following events.

12.3.1.1 Deaths

All deaths during the study, including the post treatment follow-up period, and deaths that resulted from a process that began during the study, should be listed by patient in section 14.3.2.

12.3.1.2 Other Serious Adverse Events

All serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be listed in section 14.3.2. The listing should include laboratory abnormalities, abnormal vital signs and abnormal physical observations that were considered serious adverse events.

12.3.1.3 Other Significant Adverse Events

Marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events, should be listed in section 14.3.2.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

There should be brief narratives describing each death, each other serious adverse event, and those of the other significant adverse events that are judged to be of special interest because of clinical importance. These narratives can be placed either in the text of the report or in section 14.3.3, depending on their number. Events that were clearly unrelated to the test drug/investigational product may be omitted or described very briefly. In general, the narrative should describe the following:

the nature and intensity of event, the clinical course leading up to event, with an indication of timing relevant to test drug/investigational product administration; relevant laboratory measurements, whether the drug was stopped, and when; countermeasures; post mortem findings; investigator's opinion on causality, and sponsor's opinion on causality, if appropriate.

In addition, the following information should be included:

- Patient identifier
- Age and sex of patient; general clinical condition of patient, if appropriate
- Disease being treated (if the same for all patients this is not required) with duration (of current episode) of illness
- Relevant concomitant/previous illnesses with details of occurrence/duration
- Relevant concomitant/previous medication with details of dosage
- Test drug/investigational product administered, drug dose, if this varied among patients, and length of time administered.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

The significance of the deaths, other serious adverse events and other significant adverse events leading to withdrawal, dose reduction or institution of concomitant therapy should be assessed with respect to the safety of the test drug/investigational product. Particular attention should be paid to whether any of these events may represent a previously unsuspected important adverse effect of the test drug/investigational product. For serious adverse events that appear of particular

importance, it may be useful to use life table or similar analyses to show their relation to time on test drug/investigational product and to assess their risk over time.

12.4 CLINICAL LABORATORY EVALUATION

12.4.1 Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)

When required by regulatory authorities, the results of all safety-related laboratory tests should be available in tabular listings, using a display similar to the following, where each row represents a patient visit at which a laboratory study was done, with patients grouped by investigator (if more than one) and treatment group, and columns include critical demographic data, drug dose data, and the results of the laboratory tests. As not all tests can be displayed in a single table, they should be grouped logically (haematological tests, liver chemistries, electrolytes, urinalysis etc.). Abnormal values should be identified, e.g., by underlining, bracketing etc. These listings should be submitted as part of the registration/marketing application, when this is required, or may be available on request.

LIST OF LABORATORY MEASUREMENTS

Patient	Time	Age	Sex	Race	Weight	Dose	Laboratory Tests		
							SGOT	SGPT	AP . . . X
# 1	T0	70	M	W	70 kg	400mg	V1*	V5	V9
	T1						V2	V6	V10
	T2						V3	V7	V11
	T3						V4	V8	V12
# 2	T10	65	F	B	50 kg	300mg	V13	V16	V19
	T21						V14	V17	V20
	T32						V15	V18	V21

* Vn = value of a particular test

For all regulatory authorities, there should be a by-patient listing of all abnormal laboratory values in section 14.3.4, using the format described above. For laboratory abnormalities of special interest (abnormal laboratory values of potential clinical importance), it may also be useful to provide additional data, such as normal values before and after the abnormal value, and values of related laboratory tests. In some cases, it may be desirable to exclude certain abnormal values from further analysis. For example, single, non-replicated, small abnormalities of some tests (e.g., uric acid or electrolytes) or occasional low values of some tests (e.g., transaminase, alkaline phosphatase, BUN etc.) can probably be defined as clinically insignificant and excluded. Any such decisions should be clearly explained, however, and the complete list of values provided (or available to authorities on request) should identify every abnormal value.

12.4.2 Evaluation of Each Laboratory Parameter

The necessary evaluation of laboratory values must in part be determined by the results seen, but, in general, the following analyses should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate, and as compatible with study size. In addition, normal laboratory ranges should be given for each analysis.

12.4.2.1 Laboratory Values Over Time

For each parameter at each time over the course of the study (e.g., at each visit) the following should be described: the group mean or median values, the range of values, and the number of patients with abnormal values, or with abnormal values that are of a certain size (e.g., twice the upper limit of normal, 5 times the upper limit; choices should be explained). Graphs may be used.

12.4.2.2 Individual Patient Changes

An analysis of individual patient changes by treatment group should be given. A variety of approaches may be used, including:

- I. "Shift tables" - These tables show the number of patients who are low, normal, or high at baseline and then at selected time intervals.
- II. Tables showing the number or fraction of patients who had a change in parameter of a predetermined size at selected time intervals. For example, for BUN, it might be decided that a change of more than 10 mg/dL BUN should be noted. For this parameter, the number of patients having a change less than this or greater than this would be shown for one or more visits, usually grouping patients separately depending on baseline BUN (normal or elevated). The possible advantage of this display, compared to the usual shift table, is that changes of a certain size are noted, even if the final value is not abnormal.
- III. A graph comparing the initial value and the on-treatment values of a laboratory measurement for each patient by locating the point defined by the initial value on the abscissa and a subsequent value on the ordinate. If no changes occur, the point representing each patient will be located on the 45° line. A general shift to higher values will show a clustering of points above the 45° line. As this display usually shows only a single time point for a single treatment, interpretation requires a time series of these plots for treatment and control groups. Alternatively the display could show baseline and most extreme on-treatment value. These displays identify outliers readily (it is useful to include patient identifiers for the outliers).

12.4.2.3 Individual Clinically Significant Abnormalities

Clinically significant changes (defined by the applicant) should be discussed. A narrative of each patient whose laboratory abnormality was considered a serious adverse event and, in certain cases, considered an other significant adverse event, should be provided under sections 12.3.2 or 14.3.3. When toxicity grading scales are used (e.g., WHO, NCI), changes graded as severe should be discussed regardless of seriousness. An analysis of the clinically significant changes, together with a recapitulation of discontinuations due to laboratory measurements, should be provided for each parameter. The significance of the changes and likely relation to the treatment should be assessed, e.g., by analysis of such features as relationship to dose, relationship to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy.

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs, other physical findings, and other observations related to safety should be analysed and presented in a way similar to laboratory variables. If there is evidence of a drug effect, any dose-response or drug concentration-response relationship or relationship to patient variables (e.g., disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events.

12.6 SAFETY CONCLUSIONS

The overall safety evaluation of the test drug(s)/investigational product(s) should be reviewed, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk should be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of drug metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the drug should be described.

13. DISCUSSION AND OVERALL CONCLUSIONS

The efficacy and safety results of the study and the relationship of risks and benefit should be briefly summarised and discussed, referring to the tables, figures, and sections above as needed. The presentation should not simply repeat the description of results nor introduce new results.

The discussion and conclusions should clearly identify any new or unexpected findings, comment on their significance and discuss any potential problems such as inconsistencies between related measures. The clinical relevance and importance of the results should also be discussed in the light of other existing data. Any specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies should be identified. Alternatively, such discussions may be reserved for summaries of safety and efficacy referring to the entire dossier (integrated summaries).

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Figures should be used to visually summarise the important results, or to clarify results that are not easily understood from tables.

Important demographic, efficacy and safety data should be presented in summary figures or tables in the text of the report. However, if these become obtrusive because of size or number they should be presented here, cross-referenced to the text, along with supportive, or additional, figures, tables or listings.

The following information may be presented in this section of the core clinical study report:

14.1 DEMOGRAPHIC DATA

Summary figures and tables

14.2 EFFICACY DATA

Summary figures and tables

14.3 SAFETY DATA

Summary figures and tables

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (Each Patient)

15. REFERENCE LIST

A list of articles from the literature pertinent to the evaluation of the study should be provided. Copies of important publications should be attached in an appendix (16.1.11 and 16.1.12). References should be given in accordance with the internationally accepted standards of the 1979 Vancouver Declaration on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" or the system used in "Chemical Abstracts".

16. APPENDICES

This section should be prefaced by a full list of all appendices available for the study report. Where permitted by the regulatory authority, some of the following appendices need not be submitted with the report but need to be provided only on request.

The applicant should therefore clearly indicate those appendices that are submitted with the report.

N.B. In order to have appendices available on request, they should be finalised by the time of filing of the submission.

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms

16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

- 16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)
- 16.1.8 Audit certificates (if available) (see Annex IVa and IVb of the guideline)
- 16.1.9 Documentation of statistical methods
- 16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used
- 16.1.11 Publications based on the study
- 16.1.12 Important publications referenced in the report
- 16.2. PATIENT DATA LISTINGS**
 - 16.2.1 Discontinued patients
 - 16.2.2 Protocol deviations
 - 16.2.3 Patients excluded from the efficacy analysis
 - 16.2.4 Demographic data
 - 16.2.5 Compliance and/or drug concentration data (if available)
 - 16.2.6 Individual efficacy response data
 - 16.2.7 Adverse event listings (each patient)
 - 16.2.8 Listing of individual laboratory measurements by patient, when required by regulatory authorities
- 16.3 CASE REPORT FORMS**
 - 16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE
 - 16.3.2 Other CRFs submitted
- 16.4. INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)**

SYNOPSIS

ANNEX I

Name of Sponsor/Company:	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use only)</i>
Name of Finished Product:		
Name of Active Ingredient:		
Title of Study:		
Investigators:		
Study centre(s):		
Publication (reference):		
Studied period (years): (date of first enrolment) (date of last completed)	Phase of development:	
Objectives:		
Methodology:		
Number of patients (planned and analysed):		
Diagnosis and main criteria for inclusion:		
Test product dose and mode of administration, batch number:		
Duration of treatment:		
Reference therapy dose and mode of administration, batch number:		

**PRINCIPAL OR COORDINATING
INVESTIGATOR(S) SIGNATURE(S)
OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER**

STUDY TITLE:

STUDY AUTHOR(S):

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR: _____ SIGNATURE(S) _____
OR SPONSOR'S RESPONSIBLE
MEDICAL OFFICER

AFFILIATION: _____

DATE: _____

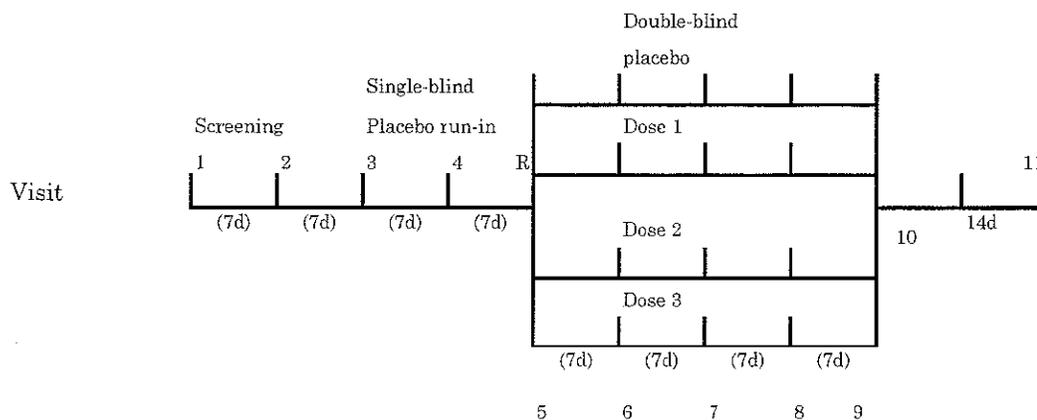
STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

TREATMENT PERIOD	A	B		C		
		B1	B2	C1	C2	
		Test Drug/ Investigational Product A 5 mg 10 mg		Test Drug/ Investigational Product A 5 mg 10 mg		
	Run-in	Test Drug/ Investigational Product B 5 mg 10 mg		Test Drug/ Investigational Product B 5 mg 10 mg		
Weeks	-2 (-3)	0	3	6	9	12
Visit	1	2	3	4	5	6
Exercise test 24 h		x ¹	x ²	x	x	x
Medical history	x					
Physical examination	x					x
ECG	x					x
Lab. invest.	x					x
Adverse events			x	x	x	x

1 = 14-20 days after visit 1

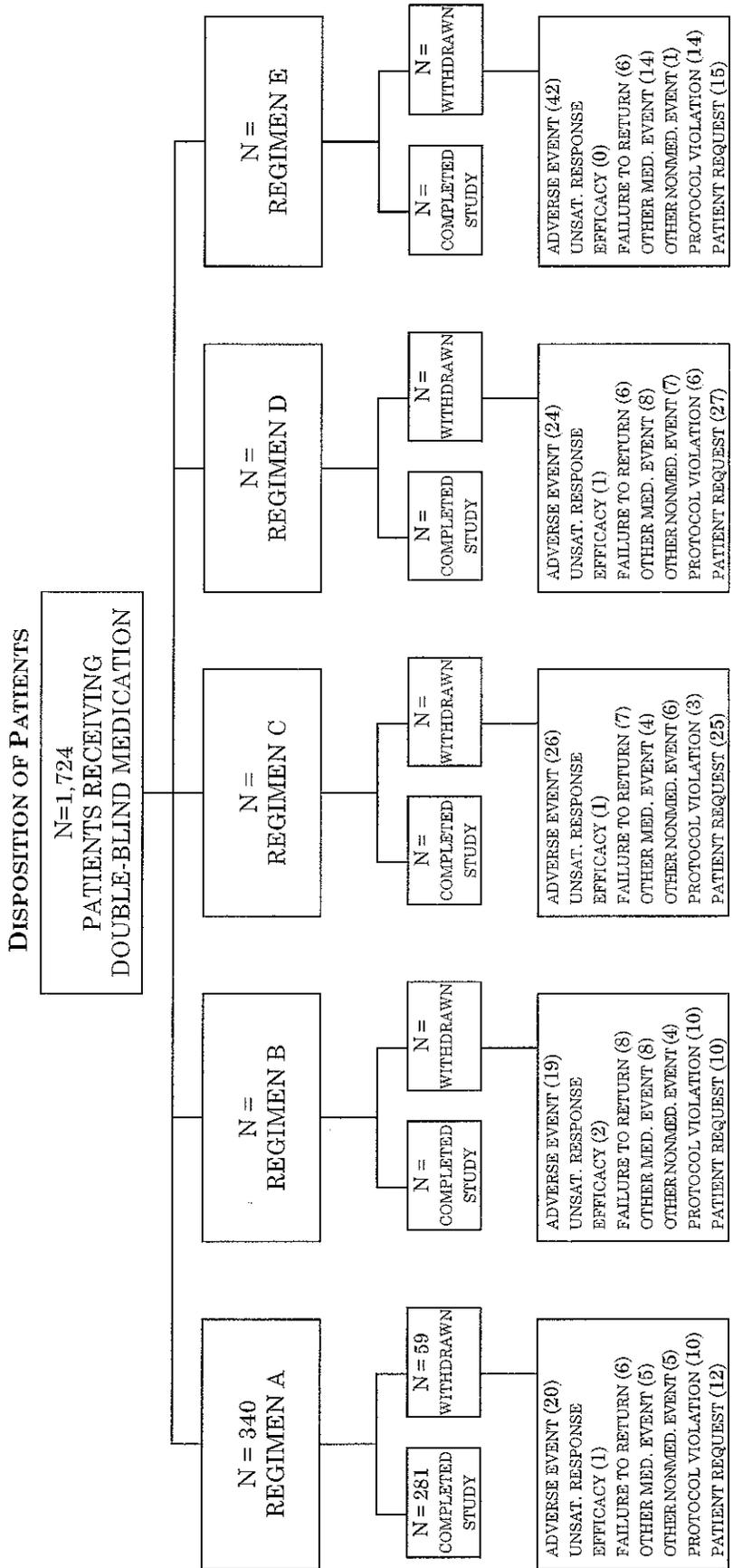
2 = 1-7 days after the first exercise test

STUDY DESIGN AND SCHEDULE OF ASSESSMENTS



Assessment	Screening	Run-in	Baseline	Treatment	Follow-up					
Study Week	-2	-1	0	1	2	3	4	5	6	8
Informed consent	x									
History	x									
Physical exam	x									x
Effectiveness:										
Primary variable	x	x	x	x	x	x	x	x	x	x
Secondary variable	x	x	x	x		x			x	x
Safety:										
Adverse events	x	x	x	x	x	x	x	x	x	x
Lab tests	x	x	x			x		x	x	
Body weight	x		x						x	x

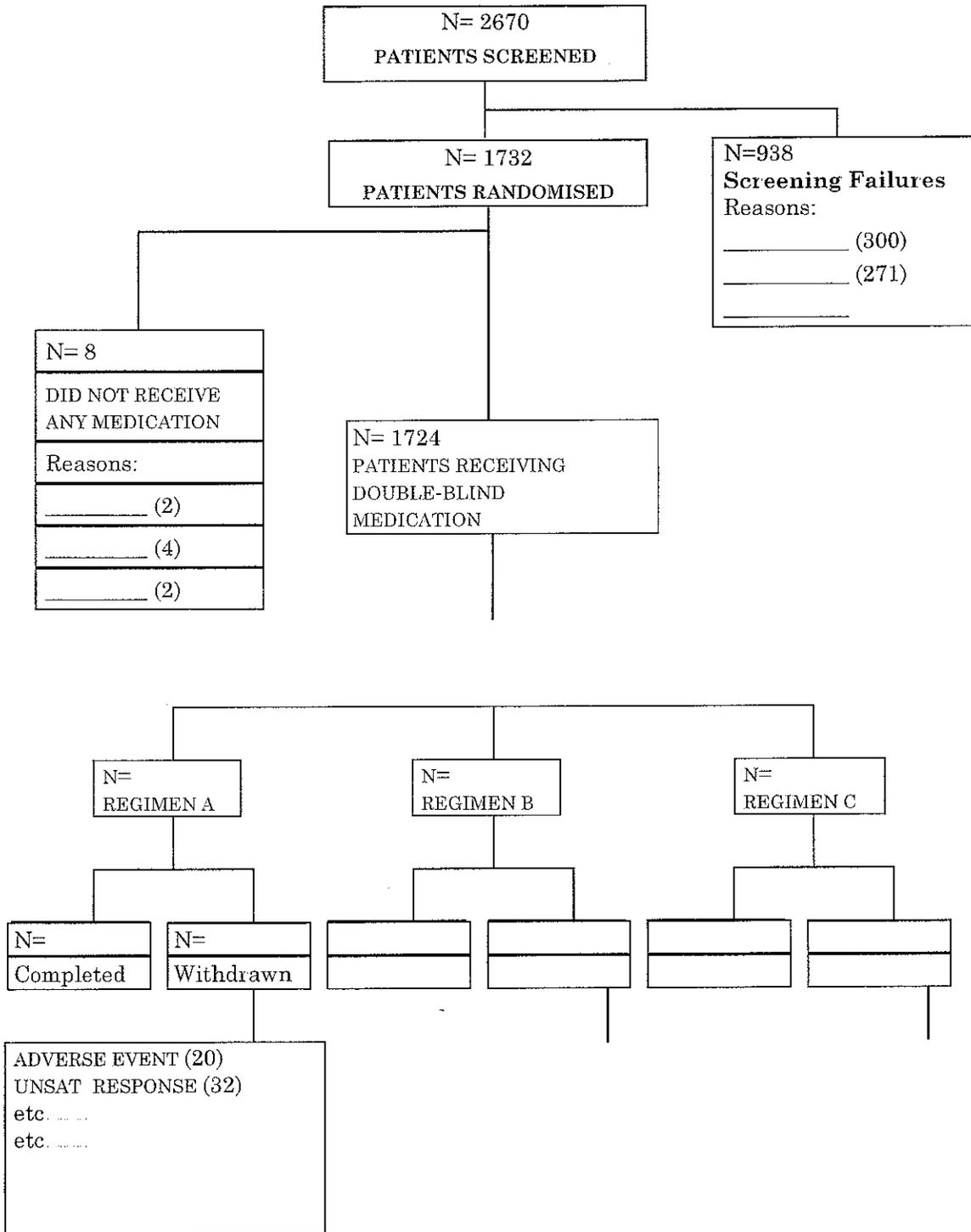
ANNEX IV a



N=1,861
PATIENTS COMPLETING STUDY

DISPOSITION OF PATIENTS

ANNEX IV b



STUDY #
(Data Set Identification)

LISTING OF PATIENTS WHO DISCONTINUED THERAPY

Centre:

<u>Treatment</u>	<u>Patient #</u>	<u>Sex</u>	<u>Age</u>	<u>Last Visit</u>	<u>Duration</u>	<u>Dose</u>	<u>Concomitant Medication</u>	<u>Reason for Discontin.</u>
Test Drug/ investigational product								Adverse reaction*

-
-
-

Therapy
failure

<u>Treatment</u>	<u>Patient #</u>	<u>Sex</u>	<u>Age</u>	<u>Last Visit</u>	<u>Duration</u>	<u>Dose</u>	<u>Concomitant Medication</u>	<u>Reason for Discontin.</u>
Active Control/ Comparator								

<u>Treatment</u>	<u>Patient #</u>	<u>Sex</u>	<u>Age</u>	<u>Last Visit</u>	<u>Duration</u>	<u>Dose</u>	<u>Concomitant Medication</u>	<u>Reason for Discontin.</u>
Placebo								

*The specific reaction leading to discontinuation

(Repeat for other centres)

STUDY #
(Data Set Identification)

**LISTING OF PATIENTS AND OBSERVATIONS EXCLUDED
FROM EFFICACY ANALYSIS**

Centre

<u>Treatment</u>	<u>Patient #</u>	<u>Sex</u>	<u>Age</u>	<u>Observation Excluded</u>	<u>Reason(s)</u>
------------------	------------------	------------	------------	-----------------------------	------------------

Test Drug/Investigational Product

<u>Treatment</u>	<u>Patient #</u>	<u>Sex</u>	<u>Age</u>	<u>Observation Excluded</u>	<u>Reason(s)</u>
------------------	------------------	------------	------------	-----------------------------	------------------

Active Drug/Comparator

<u>Treatment</u>	<u>Patient #</u>	<u>Sex</u>	<u>Age</u>	<u>Observation Excluded</u>	<u>Reason(s)</u>
------------------	------------------	------------	------------	-----------------------------	------------------

Placebo

(Repeat for other centres)

Reference Tables

Summary:

STUDY #
(Data Set Identification)

NUMBER OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

Test Drug/Investigational Product	N =			
	Week			
Reason	1	2	4	8
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
Total	_____	_____	_____	_____

Similar tables should be prepared for the other treatment groups

**GUIDANCE FOR SECTION 11.4.2 - STATISTICAL/ANALYTICAL ISSUES AND
APPENDIX 16.1.9**

A. Statistical Considerations

Details of the statistical analysis performed on each primary efficacy variable should be presented in an appendix. Details reported should include at least the following information:

- a) The statistical model underlying the analysis. This should be presented precisely and completely, using references if necessary.
- b) A statement of the clinical claim tested in precise statistical terms, e.g., in terms of null and alternative hypotheses.
- c) The statistical methods applied to estimate effects, construct confidence intervals etc. Literature references should be included where appropriate.
- d) The assumptions underlying the statistical methods. It should be shown, insofar as statistically reasonable, that the data satisfy crucial assumptions, especially when necessary to confirm the validity of an inference. When extensive statistical analyses have been performed by the applicant, it is essential to consider the extent to which the analyses were planned prior to the availability of data and, if they were not, how bias was avoided in choosing the particular analysis used as a basis for conclusions. This is particularly important in the case of any subgroup analyses, because if such analyses are not preplanned they will ordinarily not provide an adequate basis for definitive conclusions.
 - (i) In the event data transformation was performed, a rationale for the choice of data transformation along with interpretation of the estimates of treatment effects based on transformed data should be provided.
 - (ii) A discussion of the appropriateness of the choice of statistical procedure and the validity of statistical conclusions will guide the regulatory authority's statistical reviewer in determining whether reanalysis of data is needed.
- e) The test statistic, the sampling distribution of the test statistic under the null hypothesis, the value of the test statistic, significance level (i.e., p-value), and intermediate summary data, in a format that enables the regulatory authority's statistical reviewer to verify the results of the analysis quickly and easily. The p-values should be designated as one- or two-tailed. The rationale for using a one-tailed test should be provided.

For example, the documentation of a two-sample t-test should consist of the value of the t-statistic, the associated degrees of freedom, the p-value, the two sample sizes, mean and variance for each of the samples, and the pooled estimate of variance. The documentation of multi-centre studies analysed by analysis of variance techniques should include, at a minimum, an analysis of variance table with terms for centres, treatments, their interaction, error, and total. For crossover designs, the documentation should include information regarding sequences, patients within sequences, baselines at the

start of each period, washouts and length of washouts, dropouts during each period, treatments, periods, treatment by period interaction, error, and total. For each source of variation, aside from the total, the table should contain the degrees of freedom, the sum of squares, the mean square, the appropriate F-test, the p-value, and the expected mean square.

Intermediate summary data should display the demographic data and response data, averaged or otherwise summarised, for each centre-by-treatment combination (or other design characteristic such as sequence) at each observation time.

B. Format and Specifications for Submission of Data Requested by Regulatory Authority's Statistical Reviewers

In the report of each controlled clinical study, there should be data listings (tabulations) of patient data utilised by the sponsor for statistical analyses and tables supporting conclusions and major findings. These data listings are necessary for the regulatory authority's statistical review, and the sponsor may be asked to supply these patient data listings in a computer-readable form.

Exhibit

2



Trial Registration Data Set

Introduction

The Registry Platform has finalized the Trial Registration Data Set. In order to register a trial, Responsible Registrants must complete Items #3 to #20 for submission to a Primary or Associate Register. The previous list of 20 items will be acceptable for registration until further notice. The WHO encourages all registers to transition to the new data set as soon as possible.

The "form" on the next page is just an example to illustrate the data values, **and is NOT an interface for submitting data to the WHO or to any register**. Actual register submission interfaces will be different from this illustration. All entries can be in free text (i.e., do not have to be terms from a controlled vocabulary), although some registers may require or encourage coded entries. The Registry Platform is considering MeSH as the common vocabulary for any coding of register entries.

Please note that this Data Set applies only to interventional trials.

Registration Data Set (Version 1.0)

This WHO Trial Registration Data Set is now finalized. Specific implementation details remain to be resolved and will be codified in a guidance document that is being developed (e.g., specific pick list options, whether age criteria will be collected in structured form, etc). The "field value" column given below is just an example to illustrate the data fields, and does not reflect an actual interface for submitting data to the WHO or to any register. This Data Set will be reviewed in 2 years.

For a trial to be properly registered, all items must be recorded as applicable in a Primary Register. All entries should accurately reflect the study protocol. Entries can be in free text (i.e., do not have to be terms from a controlled vocabulary), although some registers may require or encourage coded entries. The Registry Platform is considering MeSH as the common vocabulary for coding Conditions, Interventions, and Primary Outcomes.

	Item	Field Value	Definition/Explanation
1	Primary Register and Trial ID #	<input type="text"/> Trial ID # <input type="text"/>	Name of Primary Register, and the unique ID number assigned by the Primary Register to this trial.
2	Date of Registration in Primary Register	<input type="text"/> <input type="text"/> <input type="text"/>	Date when trial was officially registered in the Primary Register YYYY/MM/DD.
3	Secondary ID#s	Issuing Authority <input type="text"/> ID Number <input type="text"/> Click to add more ...	Other identifying numbers and issuing authorities besides the Primary Register, if any. Include the sponsor name and sponsor-issued trial number (e.g., protocol number) if available. Also include other trial registers that have issued an ID number to this trial. There is no limit on the number of Secondary ID numbers that can be provided.
	Source(s) of		Major source(s) of monetary or material

4	Monetary or Material Support	Name <input type="text"/> Click to add more...	support for the trial (e.g., funding agency, foundation, company).
5	Primary Sponsor	Name <input type="text"/>	The individual, organization, group or other legal person taking responsibility for securing the arrangements to initiate and/or manage a study (including arrangements to ensure that the study design meets appropriate standards and to ensure appropriate conduct and reporting). In commercial trials, the primary sponsor is normally the main applicant for regulatory authorization to begin the study. It may or may not be the main funder.
6	Secondary Sponsor (s)	Name <input type="text"/> Click to add more...	Additional individuals, organizations or other legal persons, if any, that have agreed with the primary sponsor to take on responsibilities of sponsorship A secondary sponsor may have agreed <ul style="list-style-type: none"> • to take on all the responsibilities of sponsorship jointly with the primary sponsor; or • to form a group with the primary sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or • to act as the sponsor's legal representative in relation to some or all of the trial sites; or • to take responsibility for the accuracy of trial registration information submitted.
7	Contact for Public Queries	Email, telephone number, or address <input type="text"/>	Email address, telephone number, or postal address of the contact who will respond to general queries, including information about current recruitment status
8	Contact for Scientific Queries	Email, telephone number, or address <input type="text"/> Affiliation <input type="text"/>	Email address, telephone number, or postal address, and affiliation of the person to contact for scientific queries about the trial (e.g., principal investigator, medical director employed by the sponsor). For a multi-center study, enter the contact information for the lead Principal Investigator or overall scientific director.
9	Public Title	<input type="text"/>	Title intended for the lay public in easily understood language.
10	Scientific Title	<input type="text"/> Acronym <input type="text"/>	Scientific title of the study as it appears in the protocol submitted for funding and ethical review. Include trial acronym if available.
11	Countries of Recruitment	<input type="text"/>	The countries from which participants will be, are intended to be, or have been recruited.
			Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error) If the study is conducted in

12	Health Condition(s) or Problem(s) Studied	<input type="text"/>	<p>healthy human volunteers belonging to the target population of the intervention (e.g., preventative or screening interventions), enter the particular health condition(s) or problem(s) being prevented. If the study is conducted in healthy human volunteers not belonging to the target population (e.g., a preliminary safety study), an appropriate keyword will be defined for users to select.</p>
13	Intervention(s)	<p>Intervention name(s) <input type="text"/></p> <p>Other details (e.g., dose, duration, etc) <input type="text"/></p> <p>Click to add more experimental interventions</p> <p>Control Intervention name <input type="text"/></p> <p>Other details of control (e.g., dose, duration, etc) <input type="text"/></p> <p>Click to add more control interventions</p>	<p>Enter the specific name of the intervention(s) and the comparator/control(s) being studied. Use the International Non-Proprietary Name if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable. If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g., "low-fat diet, exercise").</p> <p>The control intervention(s) is/are the interventions against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, be sure to enter in the name(s) of that intervention, or enter "placebo" or "no treatment" as applicable.</p> <p>For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc)</p>
14	Key Inclusion and Exclusion Criteria	<p>Inclusion Criteria <input type="text"/></p> <p>Exclusion Criteria <input type="text"/></p>	<p>Inclusion and exclusion criteria for participant selection, including age and sex.</p>
15	Study Type	<p>Choose one <input type="text"/></p>	<p>A single arm study is one in which all participants are given the same intervention. Trials in which participants are assigned to receive one of two or more interventions are NOT single arm studies. Crossover trials are NOT single arm studies.</p> <p>A trial is "randomized" if participants are assigned to intervention groups using a method based on chance (e.g., random number table, random computer-generated sequence, minimization, adaptive randomization).</p>
16	Date of First Enrollment	<input type="text"/> <input type="text"/>	<p>Anticipated or actual date of enrollment of the first participant (YYYY/MM).</p>
17	Target Sample Size	<input type="text"/>	<p>Number of participants that this trial plans to enroll.</p>
			<p>Recruitment status of this trial.</p> <ul style="list-style-type: none"> • Pending: participants are not yet being recruited or enrolled at any site

18	Recruitment Status	<input type="text"/>	<ul style="list-style-type: none"> • <u>Active</u>: participants are currently being recruited and enrolled • <u>Temporary halt</u>: there is a temporary halt in recruitment and enrollment • <u>Closed</u>: participants are no longer being recruited or enrolled
19	Primary Outcome(s)	<p>Outcome Name</p> <input type="text"/> <p>Timepoints</p> <input type="text"/> <p>Click to add more outcomes</p>	<p>Outcomes are events, variables, or experiences that are measured because it is believed that they may be influenced by the intervention. The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effects of the intervention(s).</p> <p>Enter the names of all primary outcomes in the trial as well as the pre-specified timepoint (s) of primary interest. Be as specific as possible with the metric used (e.g., "% with Beck Depression Score > 10" rather than just "depression") Examples:</p> <p>Outcome Name: all-cause mortality, Timepoints: 5 years; or Outcome Name: Mean Beck Depression Score, Timepoint: 18 weeks</p>
20	Key Secondary Outcomes	<p>Outcome Name</p> <input type="text"/> <p>Timepoints</p> <input type="text"/> <p>Click to add more outcomes</p>	<p>Secondary outcomes are events, variables, or experiences that are of secondary interest or that are measured at timepoints of secondary interest. A secondary outcome may involve the same event, variable, or experience as the primary outcome, but measured at timepoints other than those of primary interest (e.g., Primary outcome: all-cause mortality at 5 years; Secondary outcome: all-cause mortality at 1 year, 3 years), or may involve a different event, variable, or experience altogether (e.g., Primary outcome: all-cause mortality at 5 years; Secondary outcome: hospitalization rate at 5 years)</p> <p>Enter the name and timepoint(s) for all secondary outcomes of clinical and/or scientific importance. Be as specific as possible with the metric used (e.g., "% with Beck Depression Score > 10" rather than just "depression"). Examples: Outcome Name: all-cause mortality, Timepoint: 6 months, 1 year; or Outcome Name: Mean glycosylated hemoglobin A1C, Timepoint: 4 and 8 weeks</p>

Non-drug Trials Examples

Here are some examples of non-drug trials which apply the WHO Minimum 20 Items Trial Registration Data Set. These examples refer to trials dealing with procedures, behavioral treatments, devices, or process-of-care changes.

A. Early trials (Phase 1 and Phase 2)

Non-exhaustive List

- 1 A randomised controlled trial of an intervention to improve communication with patients suffering acute chest pain: [click here](#)
- 2 The prevention of developmental and behavioral problems of very preterm infants and parental stress through the use of development care: an intervention program for infants and parents: [click here](#)
- 3 New Technologies for Cervical Cancer screening: [click here](#)
- 4 A Randomised Controlled Trial of goal setting and pacing for cardiac patients not suitable for group based cardiac rehabilitation: [click here](#)
- 5 Group Counseling for Smoking Cessation: [click here](#)
- 6 Cell Repair in Heart Failure: [click here](#)
- 7 Phase 1 Study of the Biologic Lung Volume Reduction (BLVR) System in Patients With Advanced Upper Lobe Predominant Emphysema: [click here](#)

B Phase 3 and above

Non-exhaustive List

- 1 Feasibility study of the effect of price discounts and nutrition education on food purchases in supermarkets: [click here](#)
- 2 Domiciliary versus centre-based rehabilitation of older community dwellers: Randomised trial with economic evaluation: [click here](#)
- 3 Cluster-randomised trial of general practitioners to evaluate the effects of education versus no specific education about depression and self-harm behaviour in later life: [click here](#)
- 4 Promoting Physical Activity in Later Life: Impact on Memory and Mood: [click here](#)
- 5 The effects of Tea Tree oil on acne: [click here](#)
- 6 House dust mite allergen avoidance and omega 3 fatty acid supplementation to reduce the incidence of asthma in children with a family history [click here](#)

C Other non-randomised trials

Non-exhaustive List

- 1 Evaluation of an interdisciplinary assessment service to evaluate new prosthetic prescriptions for trauma related trans-femoral amputees: [click here](#)
- 2 Study of Decision Making in Patients Participating in Phase I Clinical Trials: [click here](#)
- 3 Evaluating Patient Participation in Phase I Clinical Trials: [click here](#)

Exhibit
3

Exhibit 3

Multi-State Attorney General Consent Judgment with Bayer Corporation

PUBLIC ACCESS TO SUMMARIES OF BAYER CLINICAL
STUDIES ON CLINICALSTUDYRESULTS.ORG

Bayer Corporation announced that Bayer will post on ClinicalStudyResults.org summaries of the clinical study reports for all Phase II, III and IV Bayer-sponsored clinical studies conducted on Bayer's drugs.

Access to this information is unrestricted and free-of-charge. The content of the summaries will conform to the principles required by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Industry: Structure and Content of Clinical Study Reports (ICH's E-3 Guidance). The content of the summaries will also conform to the template published in the Federal Register, Vol 61, July 17, 1996, Page 37320 *et seq.*

Bayer will make all reasonable efforts to post within the next four months, the summaries of clinical study reports that were completed since July 1, 2005. Bayer shall, in general, post the summaries of clinical studies that are completed in the future within 12 months of the study completion date or upon first marketing. In some cases, the timing may be affected by the policies of a peer reviewed journal that has accepted an article about the study.

There may be a delay in posting complete summaries of clinical study reports because Bayer may seek intellectual-property protection or comply with policies of peer-reviewed journals to which manuscripts have been submitted for publication. Further, Bayer may be required to withhold certain summaries of clinical study reports to comply with confidentiality provisions in agreements with other parties. In regard to confidentiality agreements, in all future clinical studies, Bayer will use reasonable efforts to exclude provisions limiting the publication of summaries of clinical study reports. For all past clinical studies with such confidentiality agreements, Bayer will make reasonable efforts to secure the right to post the summaries of clinical study reports.

Questions concerning Bayer's registry should be directed to: Bayer Clinical Communications at 800-288-8371.

**STATE OF MICHIGAN
IN THE 30TH JUDICIAL CIRCUIT COURT
INGHAM COUNTY**

MICHAEL A. COX, Attorney General of
the State of Michigan, *ex rel* STATE OF
MICHIGAN,

Plaintiffs,

v

BAYER CORPORATION,

Defendant.

Hon. Rosemarie Aquilina

Case No. 07-79-CP

Suzanne Hassan (P67620)
Assistant Attorney General
Consumer Protection Division
Michigan Department of Attorney General
P.O. Box 30213
Lansing, MI 48909
(517) 335-0855
_____ /

ORDER MODIFYING CONSENT DECREE

This cause coming before the Court on a Joint Motion to Modify the Consent Decree, due notice having been given, and the Court being fully advised in the premises,

IT IS HEREBY ORDERED:

1. The Joint Motion To Modify the Consent Decree is hereby granted;
2. The Consent Decree entered on January 23, 2007, remains in full force and effect.

In addition to the terms contained therein, the Consent Decree is modified to add the following terms as set forth below which shall be incorporated into the Consent Decree by this reference as though set forth fully therein:

- a. Section I. Definitions is modified to add Paragraphs X and Y as follows:

- i. Paragraph X. "Modification Signatory Attorneys General" shall mean the Attorney General, or his or her designee, of each of the following states that have agreed to this modification of the Consent Decree: Arizona, Arkansas, California, Connecticut, Delaware, Florida, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nevada, North Carolina, Ohio, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Washington, and Wisconsin.
 - ii. Paragraph Y. "YAZ®" shall mean the oral contraceptive product composed of a combination of drospirenone and ethinyl estradiol approved for marketing by FDA pursuant to NDAs 21-676, 21-873, and 22-045 under the brand name "YAZ®."
- b. Section II. Background is modified to add Paragraphs 6 and 7 as follows:
- i. Paragraph 6. Bayer enters into this Modification solely for the purpose of resolving the Modification Signatory Attorneys General's investigation under both the Consent Decree and their respective states consumer protection statutes into the issues identified in the Warning Letter issued by FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC") dated October 3, 2008 (attached as Exhibit 1 and hereafter referred to as "Warning Letter"), to avoid unnecessary expense, inconvenience, and uncertainty without admitting any violation of the Consent

Decree or state consumer protection statutes and without admitting any wrongdoing and for settlement purposes only.

- ii. Paragraph 7. This Modification is made without adjudication of any issue of fact or law or finding of wrongdoing or liability of any kind. It is the intent of both Bayer and the Modification Attorneys General that this Modification shall not be admissible in any other matter or proceeding, and shall not bind Bayer in any respect other than in connection with the enforcement of this Modification.

Except in an action by the Modification Attorneys General to enforce this Modification, this Modification shall not be construed or used as a waiver or limitation of any defense otherwise available to Bayer or of Bayer's right to defend itself, or make arguments, in any other matter related to the issues identified in the Warning Letter.

- c. In addition to the terms contained in the Consent Decree, "Section XIII. YAZ® Advertising" is added with the following Paragraphs:

- i. Bayer shall disseminate corrective advertising that addresses the issues identified in the Warning Letter. The corrective advertising campaign shall consist of a television advertisement and a print advertisement that have been approved by DDMAC and reviewed by the Modification Signatory Attorneys General prior to submission of this Joint Motion. The television advertisement shall be broadcast on national cable and network television and the

print advertisement shall be published in magazines with national distribution. The specific content and timing of this advertising campaign shall be as specified and approved by DDMAC and reviewed by the Modification Signatory Attorneys General prior to the submission of this Joint Motion. Bayer shall spend at least \$20 million on this corrective advertising campaign. Bayer's dissemination of the advertising described in this paragraph shall not be construed as an admission by Bayer that the advertisements identified in the Warning Letter were false, misleading, or deceptive in any manner. Nor shall Bayer's dissemination of the advertising described in this paragraph be considered evidence of any liability, wrongdoing, or fault by Bayer.

- ii. Bayer agrees to submit all new Direct to Consumer ("DTC") television advertising campaigns for YAZ® to FDA for pre review, wait until Bayer receives a response from FDA prior to running the advertising campaign, and to modify such advertising consistent with any final written comments received from FDA. Non-material modifications to existing advertising campaigns are not covered by this paragraph.
- iii. Bayer shall not run print advertising for YAZ suggesting or marketing YAZ®'s effectiveness at treating selected symptoms of the FDA-approved indication(s) unless the drug's specific FDA-

approved indication(s) is/are stated as clearly and conspicuously in the same promotional spread as the symptoms referenced.

- iv. Bayer's obligations with respect to paragraphs ii and iii shall remain in effect for six years following the date this Order Modifying Consent Decree is entered by the court.
 - v. Bayer shall submit to each Modification Signatory Attorney General on the anniversary of the Effective Date of this Modification a written affirmation setting forth Bayer's compliance with Section XIII.
- d. In addition to the terms contained in the Consent Decree, Section XIV RELEASE RE YAZ® is added and with the following paragraphs.
- i. Section XIV shall pertain to the product YAZ® only and does not alter or modify the release set forth in Section VII of the Consent Decree.
 - ii. Based upon their investigation into Bayer's promotional and marketing practices regarding YAZ® and whether those practices violate the Consent Decree, the Modification Signatory Attorneys General have concluded that the Consent Decree as modified per this Order Modifying Consent Decree is the appropriate resolution of any alleged violations of the Consent Decree by Bayer regarding its marketing and promotion of the product YAZ® as described by

the Warning Letter attached as Exhibit 1 and incorporated by this reference as though set forth in full.

- iii. In Consideration of the terms set forth in Section XIII, by execution of this modification of Consent Decree, each Modification Signatory Attorney General, as defined in Section I, Paragraph X, releases and forever discharges, to the fullest extent permitted by law, Bayer and all of its past and present officers, directors, shareholders, employees, affiliates, subsidiaries, predecessors, assigns and successors (hereinafter referred to collectively as the "Released Parties"), from contempt proceedings that were or could have been asserted against the Released Parties by the Modification Signatory Attorneys General for the marketing and promotion of YAZ® by engaging in only the specific conduct described in the Warning Letter attached hereto as Exhibit 1 and incorporated by this reference as though set forth in full.
- iv. The Modification Signatory Attorneys General also release and forever discharge, to the fullest extent permitted by law, the Released Parties from any other claims or causes of action under the following consumer protection statutes: ARIZONA - Consumer Fraud Act, A.R.S. § 44-1521, et seq.; ARKANSAS - Deceptive Trade Practices Act, Ark. Code Ann. § 4-88-101 et seq.; CALIFORNIA - Bus. & Prof. Code, § 17200 et seq.; CONNECTICUT - Connecticut Unfair Trade Practices Act, Conn.

Gen. Stat. § 42- 110a et seq.; DELAWARE - Delaware Consumer Fraud Act, 6 Del. C. § 2511, et seq. and Deceptive Trade Practices Act, 6 Del. C. §2532 et seq.; FLORIDA - Deceptive and Unfair Trade Practices Act, Fla. Stat. Ch. 501.201 et seq.; IDAHO - Consumer Protection Act, Idaho Code § 48-601 et seq.; ILLINOIS - Consumer Fraud and Deceptive Business Practices Act, 815 ILCS § 505/1 et seq.; IOWA - Iowa Consumer Fraud Act, Iowa Code Section 714.16; KANSAS - Consumer Protection Act, K.S.A. 50-623 et seq.; KENTUCKY - Consumer Protection Statute, KRS 367.170; MAINE - Unfair Trade Practices Act, 5 M.R.S.A. § 205-A et seq.; MARYLAND - Consumer Protection Act, Md. Code Ann., Com. Law § 13-101 et seq.; MASSACHUSETTS - Consumer Protection Act, M.G.L. c. 93A et seq.; MICHIGAN - Consumer Protection Act, Mich. Comp. Laws § 445.901 et seq.; MISSISSIPPI - Consumer Protection Act, Miss. Code Ann. § 75-24-1 et seq.; MONTANA - Mont. Code Ann. § 30-14-101 et seq.; NEVADA - Deceptive Trade Practices Act, Nevada Revised Statutes 598.0903 et seq.; NORTH CAROLINA - Unfair and Deceptive Trade Practices Act, N.C. Gen. Stat. § 75-1.1 et seq.; OHIO - Consumer Sales Practices Act, R.C. 1345.01 et seq.; OREGON - Unlawful Trade Practices Act, ORS 646.605 et seq.; PENNSYLVANIA - Unfair Trade Practices and Consumer Protection Law, 73 P.S. § 201-1 et seq.; SOUTH DAKOTA -

Deceptive Trade Practices Act, S.D. Codified Laws § 37-24, et seq.; TENNESSEE - Tennessee Consumer Protection Act, Tenn. Code Ann. §§ 47-18-101 et seq.; TEXAS - Deceptive Trade Practices - Consumer Protection Act, Tex. Bus. and Com. Code § 17.47, et seq.; WASHINGTON - Unfair Business Practices/Consumer Protection Act, R.C.W. 19.86 et seq.; WISCONSIN - Wis. Stat. § 100.18 et seq. (Fraudulent Representations) and Wis. Stat. § 100.182 et seq. (Fraudulent Drug Advertising) that were or could have been asserted against the Released Parties by the Modification Signatory Attorneys General for the marketing and promotion of YAZ® by engaging in only the specific conduct described in the Warning Letter attached hereto as Exhibit 1 and incorporated by this reference as though set forth in full. This release does not extend to conduct or advertisements by the Released Parties that were not specifically described in the Warning Letters attached hereto as Exhibit 1 including, but not limited to, conduct that occurred prior to or subsequent to the described conduct, conduct pertaining to advertisements not addressed in the Warning Letter, or conduct beyond the scope of what is described in the Warning Letter.

- e. Notwithstanding any term of this Modification, specifically reserved and excluded from the Released Claims as to any entity or person, including Released Parties, are any and all of the following:

- i. Any criminal liability that any person or entity, including Released Parties, has or may have to any or all of the Modification Signatory Attorneys General;
- ii. Any civil or administrative liability that any person or entity, including Released Parties, has or may have to any or all of the Modification Signatory Attorneys General, under any statute, regulation or rule not expressly covered by the release in Paragraph iii. above, including, but not limited to, any and all of the following claims:
 1. State or federal antitrust violations;
 2. Reporting practices, including "best price", "average wholesale price" or "wholesale acquisition cost";
 3. Medicaid violations, including federal Medicaid drug rebate statute violations, Medicaid fraud or abuse, and/or kickback violations related to any State's Medicaid program;
 4. State false claims violations; and,
 5. Claims to enforce the terms and conditions of this Modification.
- iii. Any liability under the above-cited consumer protection laws of any or all of the Modification Signatory Attorneys General which any person or entity, including Released Parties, has or may have to individual consumers or State program payors of said Individual

States, and which have not been specifically enumerated as included herein.

3. Notice and hearing on the above Order is waived.
4. The Clerk is ordered to enter this Order Modifying Consent Decree forthwith.

IT IS SO ORDERED

APPROVED:

PLAINTIFF, THE PEOPLE OF THE
STATE OF MICHIGAN

By: MICHAEL A. COX
Michigan Attorney General

Suzanne Hassan

Suzanne Hassan (P67620)
Assistant Attorney General
Michigan Dept. of Attorney
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Date: Jul 9, 2009

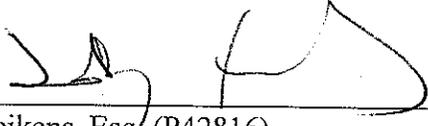
APPROVED:
DEFENDANT, BAYER CORPORATION



George J. Lykes
Chief Legal Officer
Bayer Corporation
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(412) 777-5774 (telephone)
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Date: Feb. 2, 2009

Approved as to form:



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Attorney for Bayer Corporation

Date: July 30, 2009

DATED this 9th day of February, 2009

JUDGE ROSEMARIE E. AQUILINA

Honorable Rosemarie Aquilina

CIRCUIT COURT JUDGE, Ingham County, Michigan

EXHIBIT 1



TRANSMITTED BY FACSIMILE

Reinhard Franzen
President & Chief Executive Officer
Bayer HealthCare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000

**Re: NDA # 21-676, 21-873, 22-045
YAZ® (drospirenone and ethinyl estradiol) Tablets
MACMIS ID# 16473**

WARNING LETTER

Dear Mr. Franzen:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed two 60-second direct-to-consumer (DTC) broadcast television advertisements (TV Ads) entitled "Not Gonna Take it" (ZYRA-6323) and "Balloons" (ZYRA-6567) for YAZ® (drospirenone and ethinyl estradiol) Tablets (YAZ) submitted by Bayer HealthCare Pharmaceuticals, Inc. (Bayer) under cover of separate Forms FDA-2253. The TV Ads are misleading because they broaden the drug's indication, overstate the efficacy of YAZ, and minimize serious risks associated with the use of the drug. Thus, the TV Ads misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n), 352(f)(1) & 321(n), and FDA's implementing regulations. 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5)(iii) & (e)(6)(i). These violations are concerning from a public health perspective because they encourage use of YAZ in circumstances other than those in which the drug has been approved, over-promise the benefits and minimize the risks associated with YAZ.

Background

According to the INDICATIONS AND USAGE section from the FDA-approved product labeling (PI), YAZ is approved for the following indications (in pertinent part):

[F]or the prevention of pregnancy in women who elect to use an oral contraceptive. . . .

[F]or the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated.

The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

YAZ has not been evaluated for the treatment of premenstrual syndrome (PMS) [emphasis added].

[F]or the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

Additionally, the BRIEF SUMMARY PATIENT PACKAGE INSERT and DETAILED PATIENT PACKAGE INSERT state that:

... YAZ has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious cluster of symptoms occurring before menstruation. If you or your healthcare provider believes you have PMS, you should only take YAZ if you want to prevent pregnancy; and not for the treatment of PMS. . . .

The PI for YAZ includes a BOXED WARNING that states (in pertinent part):

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

Additionally, there are numerous warnings associated with the use of YAZ including, but not limited to, venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, stroke), hepatic neoplasia, gallbladder disease, and hypertension.

Moreover, YAZ has additional risks because it contains the progestin, drospirenone. Drospirenone has antimineralocorticoid properties which can lead to hyperkalemia in high risk patients, which may result in potentially serious heart and health problems. Women taking YAZ must be concerned about the drug interactions that could increase potassium, in addition to the drug interactions common to all combination oral contraceptives. This additional risk is described in the bolded WARNINGS section of YAZ's PI.

Broadening of Indication

Premenstrual Dysphoric Disorder (PMDD)

"Not Gonna Take It" (ZYRA-6323) & "Balloons" (ZYRA-6567)

The TV Ads misleadingly suggest that YAZ is effective in a broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, given the overlap in certain symptoms between premenstrual syndrome (PMS) and PMDD, and the material limitation on YAZ's PMDD indication (that it has not been evaluated for the treatment of the less serious condition, PMS), the TV Ads misleadingly suggest that YAZ is appropriate for treating women with PMS, who may not be appropriate candidates for this drug. We note that despite listing certain symptoms of PMDD, nowhere do the TV Ads use the full phrase "premenstrual dysphoric disorder," to more completely distinguish PMDD from PMS, thereby increasing the likelihood that a viewer, in light of the claims and presentations described below, will understand it to be the same as, or substantially similar to, PMS.

The TV Ad "Not Gonna Take It" starts by stating:

- "We all know that birth control pills are 99% effective and can give you shorter, lighter periods. But did you know there's a Pill that could do more?"

It then displays images of energetic, euphoric, playful women singing "We're Not Gonna Take It" as they kick, punch, and push words describing symptoms such as "IRRITABILITY," "MOODINESS," "BLOATING," and "FEELING ANXIOUS," away from the screen, followed by the claim "It's YAZ! And there's no other birth control like it." The screen then displays a listing of symptoms including: irritability; increased appetite; moodiness; fatigue; feeling anxious; headaches; bloating; and muscle aches.

Similarly, the TV Ad "Balloons" starts by stating:

- "All birth control pills are 99% effective and can give you shorter, lighter periods. But there's one Pill that goes beyond the rest. It's YAZ."

It then displays numerous balloons throughout the ad with symptoms, such as, "IRRITABILITY," "MOODINESS," "FEELING ANXIOUS," "BLOATING," "FATIGUE," "MUSCLE ACHES," "HEADACHES," "INCREASED APPETITE," and "ACNE."

The symptoms displayed in these ads are commonly seen in women with PMS, which is a less serious and more common condition than PMDD. PMDD is a disorder whose hallmarks

include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features of PMDD include decreased interest in usual activities, difficulties concentrating, lack of energy, change in appetite or sleep, and feeling out of control. As discussed in the PI, for a diagnosis of PMDD:

... the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to the DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

The TV Ads entirely omit the material limitation from the PI of the drug's PMDD indication – i.e., that "YAZ has not been evaluated for the treatment of premenstrual syndrome (PMS)" – and fail to convey that the drug is only indicated for women who experience the symptoms presented to such a degree that they have PMDD, rather than PMS. As a result of the failure to convey these material facts, and the failure to explain what PMDD is, in contrast to PMS, the TV Ads misleadingly suggest that YAZ is approved to treat women with any severity of the symptoms presented, regardless of whether their symptoms are actually severe enough to constitute PMDD.

We note that the list of symptoms displayed in the TV Ads are accompanied by the text "YAZ treats PMDD" along with a SUPER reading "PMDD is a mood disorder related to the menstrual cycle." However, these disclosures do not suffice to communicate the material fact that YAZ is not approved for treatment of PMS or to overcome the implication created by the totality of the visuals and images in the ads that YAZ is appropriate for any woman who experiences the symptoms presented. We also note that the voiceover states that "YAZ is the only birth control pill proven to treat the emotional and physical premenstrual symptoms that are severe enough to impact your life." However, this claim also fails to communicate that YAZ is not approved for treatment of PMS, and fails to distinguish between PMS and PMDD.

The totality of the visual and audio presentations in both TV ads suggest that YAZ is approved to treat women with any severity of the symptoms presented, including women with PMS, when this is not the case. Thus, the TV Ads misleadingly broaden the indication of the drug.

Acne

In addition, the TV Ads suggest that YAZ is approved for acne of all severities when this is not the case. Specifically, in "Not Gonna Take it," the word "ACNE" appears in large print in the middle of the screen along with the audio claim "It can also help keep your skin clear," which is accompanied by a close-up visual of a woman with completely clear skin. Similarly, in "Balloons," the "ACNE" balloon is prominently displayed on the screen, as it floats by a smiling woman with obviously clear skin, along with the audio claim that YAZ "... also helps keep skin clear." These presentations fail to adequately convey that, as noted in the PI, "YAZ is indicated for the treatment of moderate acne vulgaris..." (emphasis added). While the TV Ads do include a SUPER which refers to "improvement in ... moderate acne" in small,

unbolded print, this does not mitigate the misleading impression created by the prominent audio and visual claims in the TV Ads that YAZ is indicated for acne of all severities.

Overstatement of Efficacy

PMDD

"Balloons" (ZYRA-6567)

The TV Ad is misleading because it suggests that YAZ is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The totality of the audio and visual claims and presentations misleadingly suggests that treatment with YAZ will allow women to say "good-bye" to their symptoms completely. For example, the TV Ad's theme song "Good-Bye to you" plays in the background as energetic, euphoric, playful women release balloons into the air displaying certain symptoms (e.g., irritability, moodiness, feeling anxious, bloating, fatigue, muscle aches, headaches, increased appetite, and acne). The balloons then float up and away from the women misleadingly suggesting that these women are saying, "goodbye" to their symptoms and are now symptom-free, when such an elimination of symptoms has not been demonstrated by substantial evidence or substantial clinical experience. According to the PI, in the primary clinical trial that served as the basis for approval of YAZ in the PMDD population, "...the average decrease (improvement) from baseline was 37.5 points in women taking YAZ, compared to 30.0 points in women taking placebo" (added emphasis). These results do not support the implication that YAZ will result in a complete cessation of PMDD symptoms.

Acne

"Not Gonna Take It" (ZYRA-6323) & "Balloons" (ZYRA-6567)

The TV Ads include close-up images of women with completely clear, acne-free skin. In the TV Ad "Not Gonna Take It," there is an image of a woman with the word "ACNE" prominently displayed on the screen before the word "ACNE" fades away from view. The woman turns her face to the side showing viewers that she has no visible signs of acne on her face, in conjunction with the audio claim "It can also help keep your skin clear." In "Balloons," a woman with obviously clear skin smiles and acknowledges the "ACNE" balloon as it floats away from the center of the screen and disappears into the sky, in conjunction with, the background song "Good-bye to you" and the audio claim that YAZ "...also helps keep skin clear." The overwhelming impression conveyed by the TV Ads is that treatment with YAZ results in clear, acne-free skin for those women suffering from acne when this has not been demonstrated by substantial evidence or substantial clinical experience. As illustrated by Table III in the PI, the percentage of subjects assessed by the Investigator's Static Global Assessment (ISGA) with a 'clear' or 'almost clear' rating at day 15 of cycle 6 was 15% and 21% for subjects receiving YAZ versus 4% and 9% of placebo subjects in Studies 1 and 2, respectively. Furthermore, the mean percent reduction of total lesions at day 15 of cycle 6 was 42% and 46% for subjects receiving YAZ versus 25% and 31% of placebo subjects in studies 1 and 2, respectively. Although these results are significant, they do not demonstrate that YAZ results in clear, acne-free skin for a typical woman; rather, these results demonstrate that it reduces the amount of acne lesions more than placebo but does not

result in completely clear skin for these women. Thus, the TV Ads misleadingly overstate the efficacy of the drug.

Minimization of Risk

“Not Gonna Take It” (ZYRA-6323) & “Balloons” (ZYRA-6567)

The audio communication of serious risk disclosures during the “major statement” is minimized by distracting visuals, numerous scene changes, and other competing modalities such as the background music which combine to interfere with the presentation of the risk information. In “Not Gonna Take It”, the fast-paced visuals depict various women looking at pictures, trying on clothes, chatting at a cafe, stretching/exercising in a park, and walking down the street while the audio component describes the major risks associated with YAZ. Similarly, in “Balloons,” the background music plays as fast-paced visuals depict various women running in a park, sitting on a scenic waterfront, smiling, walking out of a coffee shop, driving and singing, walking out on a balcony, using an elevator, walking through the street to join friends, in addition, to a pigeon on a building ledge and balloons being released and floating away. These complex presentations distract from and make it difficult for viewers to process and comprehend the important risks being conveyed. This is particularly troubling as some of the risks being conveyed are serious, even life-threatening. The overall effect of the distracting visuals, graphics, concurrent supers and background music is to undermine the communication of important risk information, minimizing these risks and misleadingly suggesting that YAZ is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, the promotional piece misbrands YAZ in violation of the Act, 21 U.S.C. 352(n), 352(f)(1), & 321(n), and FDA implementing regulations. 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5)(iii) & 202.1(e)(6)(i).

DDMAC asks Bayer to immediately cease dissemination of violative promotional materials for YAZ that are the same as or similar to those described above. Please submit a written response to this letter on or before October 20, 2008, describing your intent to comply with this request, listing all promotional materials for YAZ that are the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS ID # 16473 in addition to the NDA number(s). If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for YAZ comply with each applicable requirement of the Act and FDA implementing regulations. Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Abrams
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