Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 21, 1993

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approvable and/or Approval Action Memorandum
NDA 20-272: Risperdal™, Janssen brand of risperidone

TO: File NDA 20-272
&
Robert Temple, M. D.
Director,
Office of Drug Evaluation I
HFD-100

Introduction:

The Division review team has concluded that Risperdal™ will be safe in use and effective for use if marketed for the 'management of the manifestations of psychotic disorders' under the conditions of use described and recommended in the professional product labeling drafted by the Division's review team

For reasons explicated in the body of this memorandum, the Division believes that the issuance of an approvable action letter is unnecessary and recommends that the Office issue the attached approval action letter that grants Janssen permission to market Risperdal™ under the labeling developed by the Division.

Background:

Negotiations on the final form and content of drug product labeling ordinarily do not take place until a sponsor of an NDA has received and responded to an approvable action letter. Although it has advantages, the sequence of approvable action, labeling negotiations, and final approval action can needlessly extend the time to an approval action, especially in

those circumstances where the approvable action step is largely a formality (e.g., as when virtually all substantive issues affecting approval are already resolved at the time the approvable action issues).

Accordingly, believing that Division and Janssen were largely in agreement about the conditions of use under which Risperdal™ would be safe and effective for use, the Division initiated negotiations with the firm on product labeling. It was our expectation that agreement on a final draft of labeling would be reached readily, making it possible to approve the Risperdal™ NDA without having to go through the usual approvable action step.

Despite protracted deliberations with Janssen's representatives, this goal has not been realized. Rather than reaching speedy agreement, the Division and the firm have become embroiled in a dispute over aspects of product labeling that have nothing at all to do with the safe and effective use of Risperdal™.

Janssen insists that labeling for Risperdal™ provide information about the degree of therapeutic response among, and adverse reactions suffered by, patients randomized to the haloperidol control arm that is incorporated in each of the 3 clinical studies that provide substantial evidence of Risperdal's™ effectiveness. The Division has refused to accede to Janssen's demands because it believes that the side by side presentation of data obtained on Risperdal™ and haloperidol assigned subjects invites a comparison that leads to the conclusion that Risperdal™ has been shown to be superior to haloperidol when, in fact, it has not.

In the Division's view, none of the 3 studies that are a source of the data bearing on the two products is by design capable of adducing the kind and quality of evidence necessary to support a robust, externally valid, conclusion about their relative benefits or risks.

The firm, although acknowledging the validity of the Division's critique of the design of their 3 investigations, will not alter its position. Janssen's view is that the haloperidol data, provided they are accompanied by a statement which warns they cannot serve as a basis for a valid comparison of the relative risks and benefits of Risperdal™ and

haloperidol, may be presented without risk of misleading prescribers.

Negotiations, thus, are at an impasse, one that will not be overcome through further discussions.

The result, in my opinion, is perverse. The agency, publicly committed to expedite the approval of safe and effective drug products, finds its approval of a drug product that has evoked considerable interest in the psychiatric community and among psychiatric patients and their families being delayed solely because of a sponsor's desire for labeling that will facilitate the promotion of the product.

Accordingly, the Division, having concluded that Risperdal™ is 'safe in use' and 'effective for use' under the conditions of use recommended in the labeling drafted by the Division recommends that the NDA be approved. If Janssen finds the labeling under which the approval is made unacceptable, it does not have to market the product, but, given such a decision, the firm will be unable to claim that FDA is responsible for the delay in the product's approval.

The Division's recommendation notwithstanding, I are mindful that the Office may wish to proceed in a more traditional manner. Thus, an approvable action letter notifying the sponsor that the Risperdal™ NDA may be approved provided that Risperdal™ is marketed under the labeling developed by the Division has also been prepared. Although the Division believes the issuance of an approvable letter is unnecessary, it would not object if the Office elects to issue it rather than the approval action.

The remaining sections of this memorandum provide a number of observations that I want to offer for the record about the evidence bearing on the Division's recommendation as well as some comments about the kind and quality of evidence that would be required to make a valid comparison of the risks and benefits of two drug products.

Basis for the approval of Risperdal™:

The case for the approval of the Risperdal™ NDA, provided it is marketed under the labeling drafted by agency's review team, is straight forward

and is explicated in comprehensive detail in Dr. Laughren's excellent Approval Action Memorandum of 12/20/93.

The sponsor has provided results from more than one adequate and well controlled clinical investigation (i.e., Studies 201, 204 and 024) that, upon review, have been found to provide 'substantial evidence' that risperidone is 'effective in use' for the management of the manifestations of psychotic disorders. The Psychopharmacological Drugs Advisory Committee [PDAC] has considered the evidence and has endorsed the Division's conclusions.

The conclusion that Risperdal™ is 'safe for use' derives from reviews of reports of clinical experience involving approximately 2600 patients who participated in phase 2 and 3 trials. Although this experience does not show Risperdal™ to be free of risk, it is more than sufficient, given the nature of alternative modes of treatment available, and the natural history of psychotic illness, to support a conclusion that the risks associated with the use of Risperdal™ do not outweigh the benefits associated with that use. The PDAC shares this view.

Accordingly, the other requirements of the FD&C Act being satisfied, Risperdal™ may be approved for use under the conditions of use described in the draft labeling proposed by the Division.

Comments about the clinical studies that provide 'substantial evidence' of risperidone's effectiveness

Three clinical investigations (Studies 201, 204 and 024) have been identified as sources of substantial evidence of risperidone's short term effectiveness as an antipsychotic agent.

Each of the three studies was conducted at multiple sites, entered actively psychotic, hospitalized, schizophrenic patients and employed a randomized, parallel control design. Two studies (201 and 204), conducted in North America, employed placebo controls; the third study (024) conducted at multiple sites in 15 countries around the world, did not. Two studies (204 and 024) randomized subjects to a fixed dose of drug.

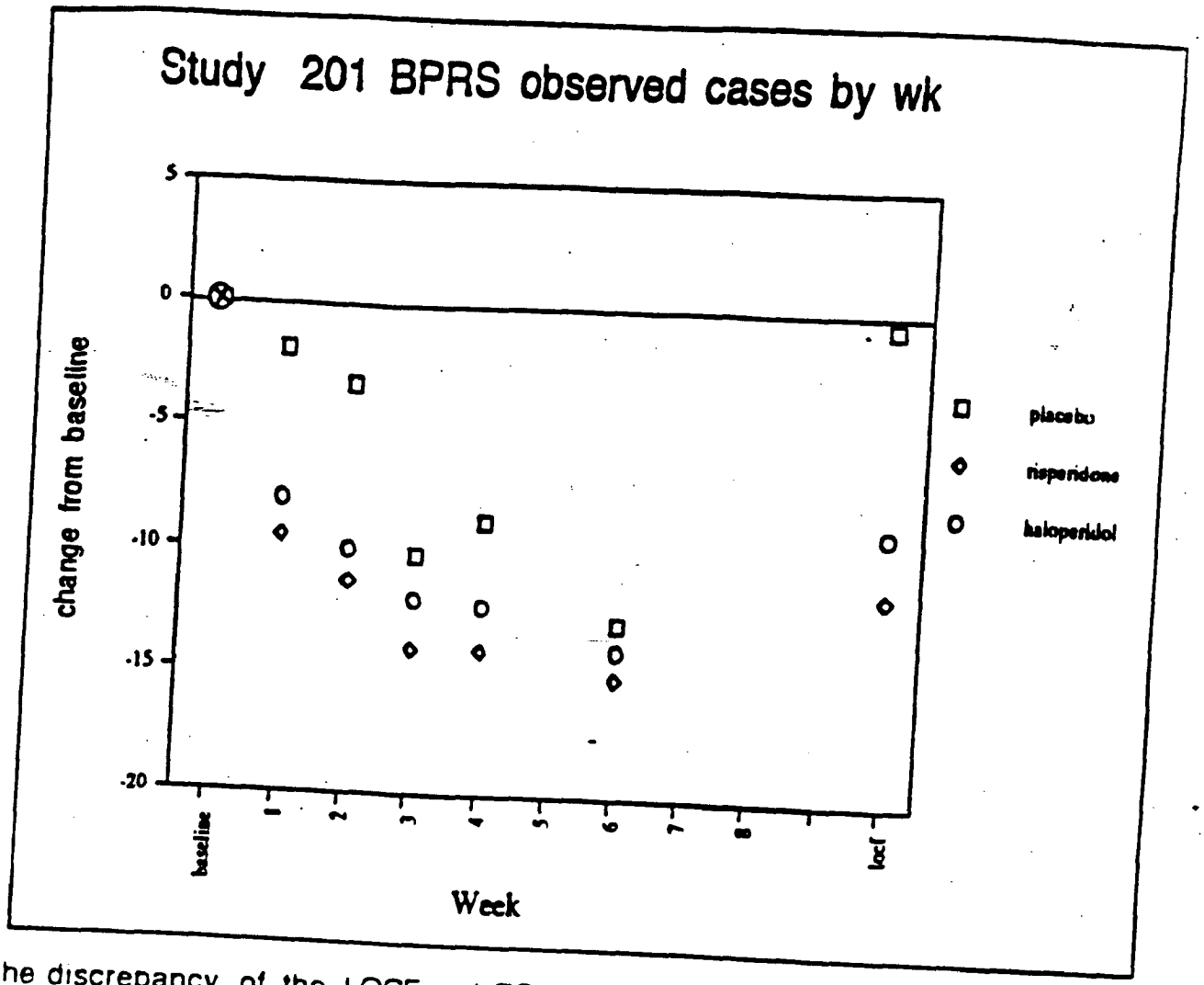
Study (201) allowed flexible titration to a maximum dose. Study 201 was 6 weeks in duration; Studies 204 and 024 were 8 weeks long.

Multiple rating instruments were used in all studies and response to treatment was assessed at multiple time points. Accordingly, there was opportunity for repeated measurement and testing of treatment differences across different measures and at multiple time points.

Although the rating instruments used differed, all studies employed instruments that contained the items found on the Brief Psychiatric Rating Scale, (BPRS), the scale that has been used traditionally to assess the effectiveness of antipsychotic drug products. Accordingly, the outcome of all studies can be compared on items that are, or are equivalent to, the BPRS.

Study 201:

Study 201 provides unequivocal support for the effectiveness of risperidone as an antipsychotic agent. Because of its titration design, it provides little in the way of useful dose response information, however. Importantly, Study 201 is of no value in assessing the comparative efficacy of risperidone and haloperidol because the products are compared under conditions that are entirely arbitrary (e.g., where a 20 mg a day dose of haloperidol fits along its dose response curve relative to 10 mg a day of risperidone is unknown). Accordingly, Study 201 cannot provide a valid basis for the comparison of the two products' comparative adverse event profile which can only be assessed fairly when both products are administered at equi-effective doses. The comparison between Risperdal™ and haloperidol assigned subjects may also be systematically biased in this study, as in others conducted by the sponsor, because only those subjects assigned to haloperidol had the possibility of prior exposure to the treatment to which they were randomized in the study. Finally, the estimates of treatment effect provided by study 201 are analysis dependent, as the following diagram documents.



The discrepancy of the LOCF and OC results observed in the diagram above are a consequence of the high incidence of premature discontinuations that occurred in this study. Only 51% (80/156) of those in the 'intent to treat' sample still remained at the end of the study's 4th week. As a consequence, the observed cases (OC) data set, which contains a disproportionate number of those subjects exhibiting spontaneous improvement, finds no between treatment differences at week 6. The LOCF based analysis, on the other hand, probably overestimates the treatment effect of the two active drugs because it is biased by the scores of placebo assigned subjects who were discontinued earlier and who might have continued to improve had they remained in the study..

Incidentally, there is a belief that the dropout rate observed in Study 201 is at least in part due to its design. Investigators, aware that a patient

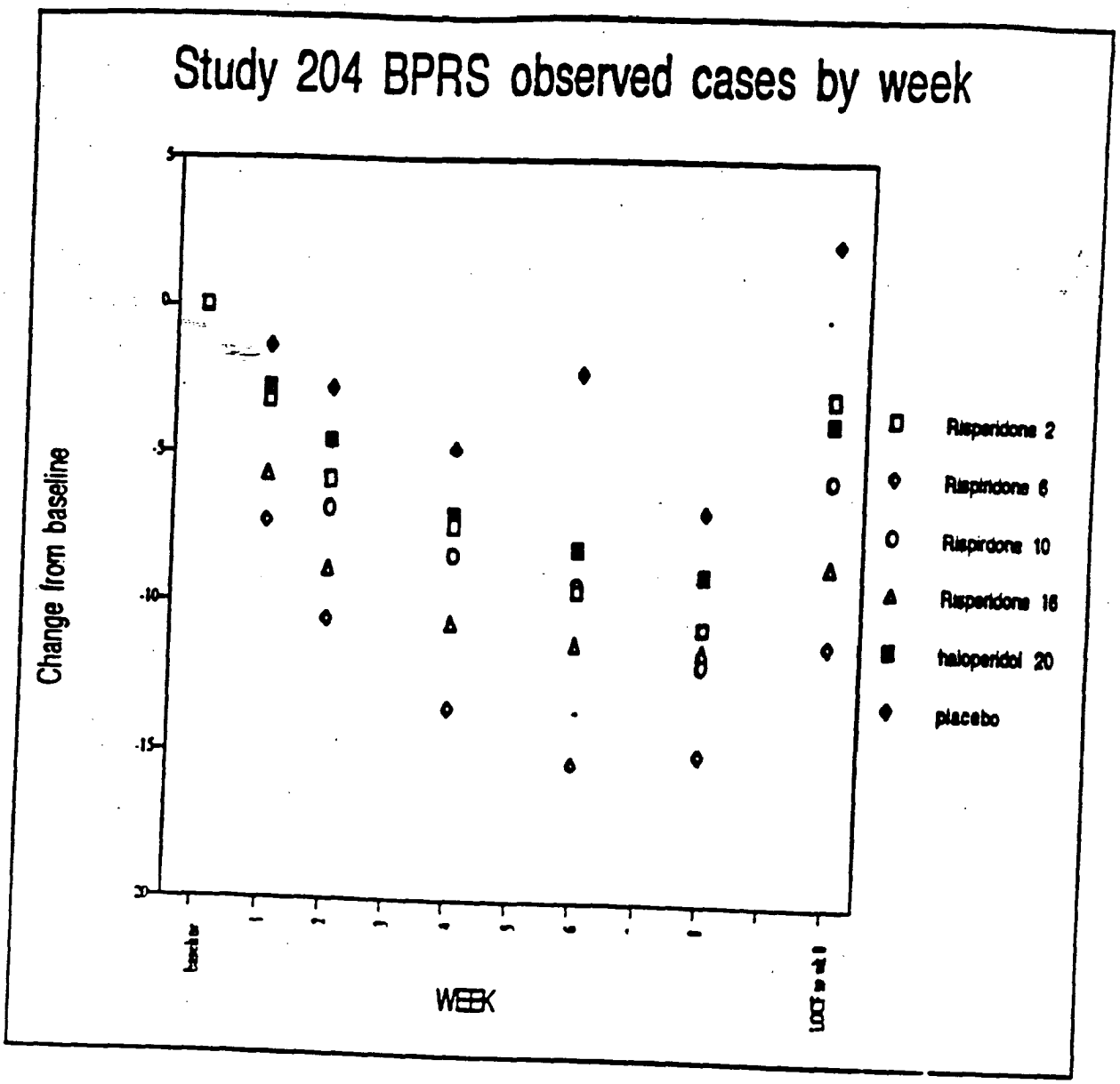
doing less well than expected had as much as one chance in 3 of being on placebo, might well have been inclined to discontinue such patients more readily than in a study where assignment to an inactive treatment was less likely. This speculation is not inconsistent with the fact that the rate of premature discontinuations is lower in Studies 204 (67% [349/515] at week 4) and Study 024 (81%, [1096/1356] at week 4) in which there was respectively, a 1 in 6 and a zero, risk of being assigned to placebo.

Study 204:

Study 204, like Study 201, provides unequivocal support for a conclusion that risperidone is an effective antipsychotic drug. Conducted at 26 US and Canadian based sites, it enrolled 513 acutely psychotic hospitalized patients, randomizing them, in a balanced design, to 4 fixed daily doses of risperidone (2, 6,10 and 16 mg/d), to 20 mg of haloperidol, or to placebo for 8 weeks. The intent of the study was, as recorded in the protocol, "to determine the safety and efficacy of 4 fixed doses of risperidone relative to placebo and haloperidol in the treatment of chronic Schizophrenia.

As the following diagram illustrates, the results of the LOCF and OC analyses differ in the estimates they provide of the size of the treatment effect of the active treatments. Study 204 differs from Study 201 in that analyses of both data sets achieve statistical significance, a consequence probably attributable to the former's larger size.

It is noteworthy that the outcome of the group randomized to 6 mg a day of risperidone (the group with best outcome among all 6 groups) is superior, at a statistically significant level, to the response of the group randomized to treatment with 20 mg of haloperidol. Although this finding has internal validity, it has no reliable interpretation regarding the relative effectiveness of risperidone and haloperidol. That such caution is necessary in interpreting the data is documented by the fact that patients assigned to the 16 mg and 10 mg a day dose of risperidone do not fair as well as those assigned to the 6 mg dose. It is probable that a similar, non-monotonic dose response relationship exists with haloperidol.



There is a possibility, nevertheless, that the sponsor may have intended that Study 204 be used to establish the comparative performance of risperidone and haloperidol. If that were the case, however, it is not clear why only one[1] dose of haloperidol was evaluated nor why a 20 mg

[1] It is generally acknowledged that the relative effectiveness (or potency) of two drugs cannot be validly estimated from a study that evaluates only single doses of one or both of the drugs. At a minimum 3, fixed, relatively widely spaced, doses of a drug are necessary to estimate the shape of its dose response function

daily dose of haloperidol was used.

(N.B., in a December 14, 1993 letter to Dr. Temple, the firm offers an explanation: basically, that the dose of 20 mg was the one their consultants thought was most representative of haloperidol's use in clinical practice for inpatients of the type being randomized in the trial. This explanation, however, does not answer the basic question as to where along haloperidol's dose response surface, a 20 mg daily dose lies)

In sum, although Study 204 provides compelling support for Risperdal's effectiveness as an antipsychotic, it is incapable by virtue of its design of supporting any externally valid conclusion about the relative performance of haloperidol and Risperdal™. In fact, as noted above, the evidence developed in Study 204 calls attention to the risk of assuming that a higher dose of an antipsychotic drug invariably produces a better therapeutic response than a lower one, a point that must be considered in evaluating the relative low rank order of haloperidol's effect size in this study. For similar reasons, therefore, the incidence of adverse events observed in this study are not valid estimates of relative incidence of adverse events that would be obtained under conditions where haloperidol and Risperdal™ are administered at equi-effective doses.

Study 024

Study 024, conducted at 110 non-domestic sites in 15 countries, enrolled 1557 psychotic patients, randomizing them to 5 fixed doses of risperidone (1.4, 8 ,12, 16 mg/d) or haloperidol 10 mg/day. The study did NOT include

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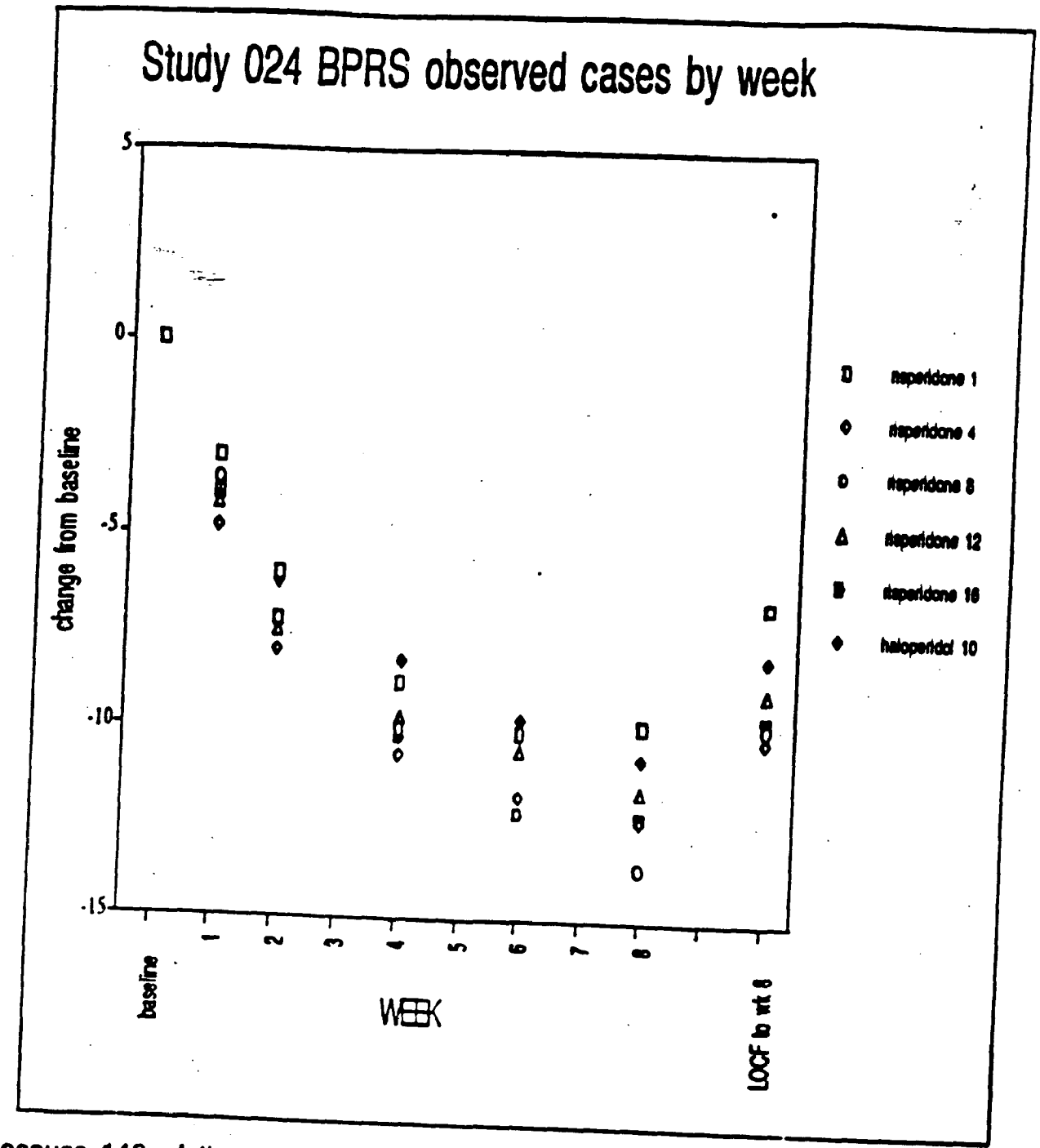
Accordingly, at least 6 active treatment arms are required, 7 if a placebo arm is included in the design, in a study intended to compare the effectiveness and relative safety of two drug products. It should be noted, however, that a control arm employing single doses of an active standard drug is often included in controlled trials to evaluate the sensitivity of the patient sample to drug treatment effects. Such a treatment arm is useful on those occasions where no difference is found between the investigational treatment and a placebo control (e.g., if the active standard treatment cannot be distinguished from placebo, the study is considered 'failed' rather than 'negative.')

a placebo treatment arm.



Because 148 of the patients randomized were at study sites that were subsequently determined to be in violation of GCP, the analysis of the study provided by the sponsor was based on a subset of 1356 of the

patients 1557 actually randomized.

Study 024 provides support for the effectiveness of Risperdal, but it is less robust than that provided by Studies 201 and 204. Pairwise contrasts between the 4 higher doses of risperidone (4 mg, 8 mg, 12 mg and 16 mg) and the 1 mg dose of the drug are all statistically significant in the LOCF analysis at 8 weeks, but the OC analysis is not as consistent. In part this may be due to the fact that the 1 mg risperidone dose may have exerted antipsychotic effects; in the absence of a placebo control, however, there is simply no way to be certain.

Study 024 also provides information about the dose response profile of Risperdal™ that, when taken along with the findings of Study 204, justifies recommending that Risperdal™ be administered in the range of 2 to 6 mg a day.

Once again, however, the study, by design is incapable of providing an externally valid estimate of the relative performance of haloperidol and Risperdal™. To be fair, the results are not inconsistent with a conclusion that Risperdal™ causes less EPS at the doses being recommended than haloperidol does when administered at 10 mg a day under the conditions of use allowed in the study, but this conclusion is not equivalent to concluding that the result is so robust that it should be described in product labeling where it may promote more extensive inferences about the relative performance of haloperidol and risperidone than are warranted.

Evidence that Risperdal™ is 'safe for use:'

The review team has evaluated the reports of adverse experiences and results on tests performed on Risperdal™ exposed patients and has concluded that Risperdal™ is 'safe for use' if administered under the conditions of use recommended in the labeling proposed by the Division. This is not to be construed as a warrant, however, that the use of Risperdal will be unaccompanied by reports of untoward events. To the contrary, some individuals to whom Risperdal™ is administered are virtually certain to suffer grievous events, including suicide and unexpected death. Based on the information available at the present time,

however, the risk of such serious events, even if caused by Risperdal™, would seem reasonably acceptable in a drug product intended to treat a serious, potentially life-threatening, illness like schizophrenia, and, accordingly, the Division and its advisors are able to conclude that the risks of Risperdal are reasonably outweighed by the benefits likely to accrue from its administration under the conditions of use proposed.

It bears emphasis that this risk to benefit assessment turns as much on subjective factors and values as it does on hard evidence. Evaluations intended to assess the contribution a drug's pharmacological effects make to the adverse effects observed in association with its use are highly subjective undertakings.

In the setting of a controlled clinical trial, especially were common adverse events are concerned, it is relatively easy to gain a quantitative estimate of relative risk. Specifically, if an adverse event of interest can be easily ascertained, readily classified, and enumerated unambiguously, it is a simple matter to estimate from a direct comparison of the proportion of subjects suffering the event under the drug and the control treatments, the extent of the risk attributable to the drug's action.

In contrast, when an adverse event occurs under conditions of uncontrolled use, it is virtually impossible to distinguish drug caused events from those bearing only a temporal association to the drug's administration. The distinction is especially difficult if the untoward event occurs spontaneously in the general population and/or is a manifestation of the illness under treatment.

If an untoward event is virtually unheard of in the course of a disease, however, its causal association with drug may seem more probable, but even here, the drug may still not be responsible. To illustrate, consider the single case of TTP reported from among Canadian patients exposed to Risperdal in a compassionate use program. It has been identified in the proposed labeling as a possible result of treatment with Risperdal™, but the decision to include it in labeling is based more on the rarity of TTP than objective evidence that Risperdal™ caused the disorder.

Other especially difficult to evaluate conditions include sudden

unexplained deaths and suicides, each of which are known to occur spontaneously and at higher rates in patients with chronic schizophrenia than in the normal population. Its expected higher incidence notwithstanding, each suicide that is temporally linked to the use of Risperdal™, for example, invariably raises questions about the role Risperdal™ might have played in its genesis. Similarly, if a patient on Risperdal™ were to die unexpectedly, it is always possible that a ventricular arrhythmia was responsible and that it occurred as a result of a quinidine like, pro-arrhythmic, effect of Risperdal™ on cardiac repolarization. Accordingly, although none of the deaths observed among patients on risperidone were attributed to this mechanism, labeling mentions the risks of QT prolongation.

Finally, a comment is in order about the results of life-time in vivo carcinogenicity studies in rodents that, although detecting a drug dependent increased incidence of adenocarcinomas in rats and female mice, have been determined to predict no clear signal of risk to humans. This judgment turns on the belief that the mechanism underlying the pathogenesis of these tumors (i.e., elevated prolactin levels stimulating tumor growth) is not operative in humans. This belief, although not inconsistent with the failure of several epidemiologic investigations to find evidence in humans of a link between elevated prolactin and an increased incidence of tumors, is hardly conclusive. The absence of evidence is not evidence of absence. Accordingly, although CDER's PAC's interpretation of the carcinogenicity studies has been endorsed by the PDAC, both the Division and the PDAC believe their findings should be described in product labeling.

In sum, although the review team and the PDAC AC found nothing unusual for an antipsychotic drug product in the preclinical or clinical data (i.e., adverse events and laboratory findings) reported for Risperdal™, their conclusions cannot be taken as a warrant that the use of Risperdal is free of serious risk. At best, the conclusion is a reflection of a judgment that the risks of Risperdal™ are reasonable in light of the benefits likely to be associated with its use.

On the basis of what evidence should comparative claims be allowed to appear in product labeling?

The subject has many facets, some practical, others philosophical. It deserves discussion in this memorandum only because of Janssen's insistence that Risperdal™ labeling provide data on haloperidol.

From a purely philosophical perspective I have an antipathy to comparisons that are unfair or based on incomplete information. Rarely, it seems to me, is evidence on the relative risks and benefits of two or more products so reliable, precise, and comprehensive that it allows a general statement to be made about relative risks and benefits. I am mindful, however, that knowledge of certain differences can be critical to the prudent selection and/or safe and effective use of a drug product. Accordingly, in circumstances where a difference is known to exist and to have potentially important clinical consequences, it would be in the public interest to include information about that difference in product labeling[2].

On the other hand, it does not serve the public interest to clutter product labeling with descriptions of factual, but clinically irrelevant, differences.

Above all else, however, before a comparative claim or statement is included in labeling, it should be firmly and fairly established with data that meets a high standard of evidence.

In my view, a claim of comparative advantage should be allowed in product labeling only if 1) it involves an attribute of clinical importance, and 2) is documented with compelling evidence adduced in more than one clinical study, each of which is designed, prospectively, to evaluate the claimed advantage. If such a condition is not imposed, claims of superiority could be advanced on the basis of a finding that reflects no more than the operation of chance or be the result of one of a multitude of post hoc, data

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[2] Certainly, such information would be included in the labeling of the product asserting the advantage. It is an interesting question whether the agency could compel the sponsor of the 'inferior' product to include the same information in the labeling of its product.

conditioned, analyses.

The design of clinical trials intended to compare the properties of two or more drug products must ensure that the conditions of the comparison allow for an appraisal that is fundamentally fair to each of the products. Subjects enrolled in a comparative study, for example, should be naive to the treatments being compared to reduce the possibility that a systematic bias may arise from subjects having had prior experience with one or more of them. As mentioned in an earlier footnote, at least 3, preferably more, widely spaced, fixed, doses of each drug would have to be studied to allow the shapes of the dose response relationship of each drug to be characterized[3], a critical preliminary step to any valid comparison of their properties. It seems likely, however, given the variability among samples of patients in their response to a given dose of a drug, that it will ordinarily be necessary to have each drug and dose combination of interest evaluated in a single study. This requirement might be relaxed if modeling approaches of the type noted in footnote 3 are validated. In any case, methodological details aside, it is best to approach all comparative claims with caution, if not outright distrust, unless it can be assured that they derive from fair, balanced, and comprehensive evaluations conducted at equi-effective doses.

The principles described applied to Janssen's demands:

Some of the evidence in the Risperdal™ NDA, as noted earlier, is not inconsistent with the possibility that risperidone may be associated with a lesser risk of extrapyramidal side effects when administered at doses of 4 mg to 6 mg a day than is haloperidol when administered at doses (10 to 20 mg/day), doses that enjoy widespread use in current clinical practice.

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[3] These suggestions assume a traditional frequentist statistical approach to the analysis of clinical trial data. A case can be advanced that other approaches, in particular those that mathematically model both individual and population responses and the link between them, might provide an acceptable, perhaps superior, alternative. In any case, the point is not so much the choice of method, but the requirement that there be an accurate characterization of the dose response relationship of each drug involved available before a comparison is undertaken.

The issue of regulatory import is whether or not the data pointing toward this possible advantage ought to be presented in Risperdal™ labeling.

Janssen, it is important to note, did not conduct studies of appropriate design to compare the properties of two drug products. To the contrary, although it cannot be known with certainty, it seems probable that Janssen's 3 studies were intended primarily to document the effectiveness and safety of risperidone, and not to make a comparative claim. A haloperidol treatment arm (standard active control) was included in each study, but, from the Division's perspective, its purpose was to serve as an indicator of the 'sensitivity' of the patient sample entered to respond to the effects of antipsychotic drug treatment.

Had the firm sought the agency's advice about the kind and quality of evidence required to support comparative claims, and to my recollection they did not explore that question with us[4], they would have been informed that there are substantive barriers, both philosophical and technical, to doing so successfully.

In addition to discussing the generic points about comparative studies described above, we would have advised them that there is, to our knowledge, no general agreement in the community of how comparative studies of antipsychotic drugs ought to be carried out. In particular, there is no consensus about which specific attributes of antipsychotic drug product performance ought to be considered in making such a comparison. Furthermore, even if there were some level of general agreement on the attributes of antipsychotic drugs that should be considered, the choice of an assessment instrument suitable for making the comparison would still be uncertain. It would be unfair, for example, to compare the effectiveness of two drugs on a rating instrument which registers the untoward pharmacological effects associated with one of them as evidence of an adverse therapeutic outcome (as might occur on a scale rating improvement, or lack thereof, in so-called 'negative' symptoms).

Returning to the matter currently in dispute, it is important to acknowledge that the Division does not deny that a colorable argument can

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[4] There was no 'end of phase 2' meeting

be advanced, based on the results of Study 024 , that Risperdal™ given at doses in the range recommended in proposed product labeling (2 to 6 mg a day) is likely to produce fewer extrapyramidal signs and symptoms than haloperidol administered without accompanying anticholinergic drugs at a fixed dose of 10 mg a day. On the hand, a single study, the only one examining a dose of haloperidol administered at doses of less than 20 mg a day, seems an inadequate basis to support an implied advantage, even one that is advanced with a caveat.

Furthermore, there are additional factors worthy of consideration. When used in clinical practice, the regimen under which haloperidol is administered may differ from that which obtained in Study 024. Haloperidol, although widely used, is only one of a large number of marketed antipsychotic drug products. What makes the comparison between it and Risperdal™ so uniquely important among all possible pairwise comparisons that it deserves presentation in labeling? Perhaps, if comparisons are to appear in antipsychotic drug product labeling, they should involve all products, or, at a minimum, a representative panel drawn from the product class (e.g., clozapine, thioridazine, chlorpromazine, perphenazine, haloperidol, molindone, etc.).

The list of issues just enumerated is by no means exhaustive. It is intended only to call attention to the fact that many matters ought to be considered in taking a decision that may be interpreted as a precedent by the regulated industries.

In my view, therefore, there is little to be gained, and potentially much to be lost, if we agree to Janssen's demands at this point in time. Risperdal™ can be marketed and used safely and effectively without its labeling mentioning anything whatsoever about the controlled trials that are the source of the evidence that led to its approval, let along a description of the responses of subjects assigned to a control treatment used in those trials, moreover, one that may promote a misleading inference about the product.

From a technical perspective, furthermore, there is no regulatory requirement that forces us to acquiesce to the firm's demands. 21 CFR 201.56 requires only that the labeling of a prescription drug contain "a

summary of the essential scientific information needed for the safe and effective use of [a] drug," and the labeling developed for Risperdal™ by the Division fully meets that requirement.

Conclusion and Recommendations:

Upon review of the information provided in NDA 20-272, the Division concludes that Risperdal™ has been shown, according to the requirements of the FD&C Act, to be a safe and effective drug, provided it is marketed under the conditions of use recommended in the labeling drafted by the Division.

Accordingly, the Division recommends that the approval action letter be issued.

12/21/93

Paul Leber, M.D.
December 21, 1993
08:45 hours