State of Pharmaceutical Research and Development in Canada

Bioequivalence of Drug Products with Special Characteristics

Report of the February 13-14, 1998 Canadian Society for Pharmaceutical Sciences Symposium[1-3]

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[1] This document represents a record of the presentations and discussion among the participants of the Symposium. It does not necessarily represent the policies or guidelines of the Canadian Society for Pharmaceutical Sciences.
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Abbreviations:
A, Answer; ABE, Average Bioequivalence; AHFMR, Alberta Heritage Foundation for Medical Research; BCS, Biological Classification System; BE, Bioequivalence; C, Comment; CDMA, Canadian Drug Manufacturers Association; CI, Confidence Interval; CFI, Canada Foundation for Innovation; DOH, Department of Health; DPK, Dermatopharmacokinetics; FDA, Food and Drug Administration; GDP, Gross Domestic Product; HV, Highly Variable; IBE, Individual Bioequivalence; MDI, Metered Dose Inhaler; MR, Modified Release Formulations; MRC, Medical Research Council; NDA, New Drug Application - in Canada knowns as NDS or New Drug Submission; NIH, National Institutes of Health; NTR, Narrow Therapeutic Range; NSF, National Science Foundation; PMAC, Pharmaceutical Manufacturers Association Of Canada; Q, Question; R&D, Research and Development; USP, United States Pharmacopeia.

The symposium sponsored by the Canadian Society of Pharmaceutical Sciences (CSPS), held on February 13 & 14, 1998 in Ottawa, Ontario, brought together approximately 150 pharmaceutical scientists from academia, regulatory agencies, and industry. The first topic of discussion was the state of pharmaceutical research in Canada. The impact on the Canadian research scene of growing numbers of biotechnology companies and mergers of large multinational companies coupled with cut-backs in non-directed funding for basic research was highlighted. The second discussion topic, which formed the basis of the majority of presentations, was the determination of bioequivalence (BE) for drugs with special characteristics. Presentations and discussion touched on such issues as current and proposed Therapeutic Products Directorate (Canada) and Food and Drug Administration (USA), guidelines and the BE criteria and study designs for modified-release (MR) and topical formulations, non-linear, narrow therapeutic range (NTR) and highly variable (HV) drugs as well as average versus individual BE determination.

In recognition of his outstanding contribution as a leader in the area of regulatory pharmaceutical sciences, the members of CSPS were honoured to have the symposium dedicated to Dr. Iain McGilveray of McGilveray Pharmacon Inc..

This report is a summary of the presentations and discussions that took place as detailed in the Symposia Proceedings document. In addition, an attempt has been made to capture the discussion (and when possible the name of the participants) following each session.

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Opening Session

Dr. F. Jamali (CSPS President, Symposium Chair, University of Alberta) opened the symposium by welcoming and thanking all participants for their attendance.

Pharmaceutical Research and Development in Canada
Chair: Dr. J. McNeill, University of British Columbia

The first speaker of the session was Dr. A. Noujaim (AltaRex Inc., Edmonton, Alberta) who gave an overall summary on the state of pharmaceutical R&D in Canada with emphasis on the growing emergence of biotechnology oriented companies. Over the last 15 years there have been major changes in the sources of funding and direction of pharmaceutical R&D (i.e. today the majority of funding is coming from capital markets). Compared to 1985, when there were only 3 biotechnology companies in Canada, there were reported to be 557 in 1997. The 3 major Canadian centers for biotechnology are: Quebec, Ontario, and British Columbia. These centers are among the top 18 North American biotechnology centers ranked by total revenue (Quebec #10, Ontario #13, and B.C. #18). It was noted that in Quebec, there are many incentives for industry to establish there, so it cannot be refuted that there is a relationship between government and ability to do R&D. Another interesting comment was that approximately 1/3 of the employees of biotechnology companies hold Ph.D. degrees; hence, there appears to be a knowledge transfer out of academia to private industry. Thirty five percent of all the R&D money

spent in Canada goes into biotechnology companies. A major portion (about 60%) of research dollars spent in biotechnology companies is spent on therapeutics and diagnostics. The focus of research appears to be in 4 general areas: CNS, PTA (photodynamic therapy), Oncology/Immunotherapy, and Infectious Diseases. Currently, there are only 2 companies with approved drugs in Canada; however, approximately 100 companies have drugs in clinical development. Therefore, over the next 5 to 10 years we can expect to see an increased rate of approval. Dr. Noujaim concluded his presentation by suggesting the following major challenges for the future:

- a change in direction from conventional small molecule R&D to biotechnology
- a change in the source of pharmaceutical R&D dollars (i.e. from capital investment since large companies are relying more and more on R&D from small companies)
- the development of standards for BE of ‘new' biotechnology drugs

Dr. J. McNeill (University of British Columbia, B.C) was the second speaker in the session and he presented a synopsis of the state of pharmaceutical R&D in Canada. The organizations that do research in Canada are PMAC companies (n=59), biotechnology companies (n=224), CDMA companies (estimated at least n=6), pharmacy schools (n=9) and medical schools (n=16). Spending on research was reported to be PMAC ($624M), MRC ($251M), MRC/PMAC ($70M), CDMA ($>150M) and voluntary agencies such as Heart & Stroke, etc. ($36M). Spending is in the following areas: Oncology, Immunology/Anti-Infectives, Respiratory, Endocrinology, CNS, CVS and Molecular Biology. In terms of expenditures on R&D as a % of GDP, Canada is at the bottom of the G7 countries (in fact, we are currently wrestling with Chile!). All other industrialized nations are increasing spending on R&D except for Canada where it is decreasing (i.e. MRC has undergone negative growth in their budget for health research during 1991 through 1997). In contrast, in the USA there has been a huge increase in funding for NSF, DOH and NIH. The comment was made that PMAC commitments under Bill C-91 were progressing somewhat but that most of the R&D (60%) is clinical research which is required to get the drug licensed. Regional spending by PMAC companies is mainly in Ontario and Quebec (> $250M). In Western Canada, only $50M is spent by PMAC companies. Only about 25% of funding is for basic research. Overall, there has been an increase in research money and employment (at the industrial level). However, there has been a disappointing decrease in government spending on health research as well as a decline in University funding, both of which create a serious concern for the future of academic research. Dr. McNeill concluded by making the following closing observations:

- trying to force the private sector to accept some of the burden of funding basic research is misguided
- basic science in Canada is like a horse with one leg injured - it can hobble but cannot gallop

The third speaker in the session was Dr. I. McGilveray (McGilveray Pharmacon Inc., Ontario). He presented examples of research (e.g. absorption of phenylbutazone and metronidazole preparations, nifedipine-alcohol, diltiazem-quinidine, ddI-ciprofloxacin and fluconazole-zidovudine interaction studies, enteric-coated ketoprofen absorption in achlorhydria and effect of omeprazole) conducted by the Bureau of Drug Research (BDR) in the past. These examples illustrated the value of in-house scientific research in the development of standards and guidelines as well as risk-benefit assessment and pre-market/post-market considerations. In his opinion there is a major communication barrier that exists in Canada among politicians, administrators, health professionals and research scientists who cannot understand one another because of the difference in *cultures* (e.g. legal versus scientific) and this is threatening the very existence of regulatory research in Canada. The future of research towards regulation in the Therapeutic Products Programme (TPP)with only 25% of the previous research staff remaining will create a large gap in providing unbiased information. This will pose a special problem for the TPP

when it comes time to review biotechnology drugs as there will not be people with the required expertise to do so. Dr. McGilveray advised in his concluding remarks that:

- new scientific advisory board input is certainly required to set a strategic direction for Health Canada research, including that towards drug standards and regulation
- it is essential to develop a reasonable and protected budget infrastructure for contracts to academic and contract research organizations for good public information which is separate from industry
- we need to foster careful liaison and collaboration with sister regulatory agencies (e.g. FDA) and standard setting bodies (e.g. USP)
- we require feedback from professions and the public on these issues and concerns

The last speaker in the session was Dr. C. Roy (MRC, Ottawa, Ontario) who brought a message of greetings from Dr. H. Friesen (MRC President). The MRC is a core building block of pharmaceutical research in Canada. The strategic plan of MRC for the 1992-1997 period was to encompass the full range of health sciences, establish partnerships with other agencies, build on existing strengths and evaluate outcomes of research. However, biomedical research funding by MRC has fallen by 30% despite research funding in general being increased. Research funding by private and non-profit sectors have increased between 1986 and 1996. This would indicate that the public is behind research but they have not been mobilized to stress the importance of research on politicians and stakeholders. In Canada, the amount of public money spent on research is $8/individual whereas in the USA, it is $66/individual; hence, the increasing difficulty of competing, as we are falling off more behind the USA in terms of funding. The rate of renewal of research grants by MRC has fallen from 80% to 40% and the MRC shortfall for 1997/98 is $56M and for 1999/00 is projected to be $182M. Successful grants are underfunded by an average of 26% (some as much as 43%). The shortfall is cumulative over time and seriously threatens new knowledge creation. The core mission of the MRC is NEW KNOWLEDGE (basic science research). The private sector investment is in early discovery and replication and not basic untargeted research. If there is no science, there will be no medicine; medicine becomes a trade in the absence of science. Public science is a fundamental pillar of industrial advancement. Dr. Roy advised that:

- there is venture capital available in Canada (25% of total venture capital is in the life sciences)
- there are recent federal government initiatives which are positive and include the Canada Foundation for Innovation ($800M), Permanent Funding for Networks of Centres of Excellence ($47M), the Health Transition Fund ($150M), and the Canada Health Services Research Fund ($65M)
- we should keep MRC in our prayers until February 24, 1998, budget night

Discussion:

Following are some major points of discussion:

Q. How can we facilitate interactions between academics and small companies?

A. Dr. Noujaim: Over the past 15 years, perceptions have changed regarding academia working with the private sector. Universities are revisiting whether or not a faculty member can hold an academic job and provide expertise to industry. As an example, AltaRex is located on the University of Alberta campus. Universities have access to

vast resources e.g. animal handling facilities, areas of expertise or strategic alliances - these are very attractive for small companies.

Q. Although basic granting agencies have a commitment to fund basic research, is there not a significant partnership with industry e.g. MRC/PMAC?

A. Dr. McNeill: Yes, but we need the government funding to fund basic, technology driven research because it is mainly the *non-basic* research (i.e. clinical) which is funded by industry.

Q. Are provincial programs of value e.g. CFI?

A. Dr. Roy: Provincial programs are of value e.g. AHFMR in Alberta. CFI funding is intended to provide infrastructure and not fund basic research so it really does not answer immediate problems.

Q. Should governments/universities add business-skilled personnel to assist academics with potential ideas for their business? In this way, the academic stays in his/her lab and keeps on producing and the business people will do the business. Do you (Dr. Roy) agree?

A. Dr. Roy: I completely agree and I hope that universities will create such facilities for their faculty.

C. Perhaps we should lobby for *non-directed* research funding from industry. However, funding for basic research should be a government responsibility and should be viewed as an investment and not an expense.

C. The comment was made that there are a number of parallels with what's happening here in Canada and what occurred in the 1980's in the USA. At that time (in the USA), scientists complained a lot but we learned that this doesn't work. They had to change their tone - research is an investment and **not** an expense. So the scientific community in the USA started giving politicians phrases to say about research so that they could get votes with them.

Regarding the future of pharmaceutical research, there are three factors that will heavily impact public health:

1. Harmonization process (we are becoming a world pharmaceutical organization);

2. Electronic media (the Internet has changed how we work and do business);

3. Human genome project (scheduled for completion in 2005; will revolutionize drug discovery. Development of drug products is now the bottle-neck in the pharmaceutical industry. We need to emphasize that it is not the **drug** industry as much as it is the **drug product** industry).

Establishment of CSPS and its electronic journal are positive moves in support of advancement of pharmaceutical research. AAPS would like to play a more international role by closer alliances with CSPS and to set up meetings/workshops, etc.

Q. How is MRC encouraging young investigators?

A. Dr. Roy: Young investigators should be encouraged to undertake collaborations, get close to a mentor, and team up with experienced individuals. Then, eventually they can become independent investigators.

Bioequivalence of Drug Products with Special Characteristics
Session I: Chairs: M. Lebel, F. Jamali

Dr. E. Palylyk-Colwell (Alberta Blue Cross, Edmonton, Alberta) began this session by commenting on the issues facing a formulary committee regarding the interchangeability of drugs. In Canada, the designation of interchangeability is in the domain of the provinces. The dilemma for such committees is that BE data are generated in healthy adult male subjects. The populations covered under provincial programs, however, are often female, elderly, indigent or severely handicapped. In Alberta, >50% of the population covered by the government drug programs are female and >60% are 65 years or older (i.e. >90% of the population covered would not have met the inclusion criteria for a BE trial). Generalizability of BE data to these populations may not be a concern for uncomplicated drugs; however, it may be a concern with complicated drugs and complex formulations. It is not known to what extent seemingly *minor* differences in formulations are exaggerated in these groups. Data were presented on the number of requests/approvals for brand name products by individuals covered by the Alberta programs after they had received a generic product. Special Authorization or Exceptional Drug Status processes exist in the provincial drug programs to allow individuals who cannot tolerate a generic product to receive the brand product if a physician provides acceptable clinical justification. Due to such *safety valves*, it is unlikely that our current post-marketing surveillance systems would be able to detect problems with the substitution of different brands of drugs.

Dr. F. Jamali (University of Alberta, Edmonton, Alberta) presented plasma concentration-time data for an MR formulation of diltiazem. The data illustrated how the current BE parameters of AUC and Cmax alone do not detect apparent differences in the input-time profile of MR dosage forms. In the present guidelines it is assumed that 1) Cmax is a reflection of the timecourse of absorption, and, 2) the timecourse of absorption is not important because these products are intended for chronic use. Both of these assumptions can be challenged. It was suggested that partial AUC (encompassing the absorption phase) should be considered in BE studies for MR products where the timing of release is an important therapeutic consideration. For hemodynamic products such as diltiazem, timing of release may be important due to documented reports of circadian variation in number of infarctions (i.e. the incidence is higher in early morning hours). Hence, the time of administration and/or the peak-time may be crucial to suppress early morning rise in blood pressure. In the absence of unequivocal clinical data, the importance of the pharmacokinetic time course remains debatable. Due to the ethical issues involved in proving harm, however, the timecourse of modified release formulations should be considered in BE studies. Examples of conditions in which the time course of drugs may be of therapeutic importance include cardiovascular diseases, asthma, some allergies, and morning stiffness in arthritic patients.

Dr. G. Amidon (University of Michigan, Ann Arbour, Michigan) presented new standards for BE based upon factors underlying absorption (i.e. permeability and solubility). He pointed out that the current definition of BE by the FDA, which is based on the extent and rate of absorption, is incorrect. Rate, in this context, refers only to the rate of appearance of a drug in the blood (a complex mixture of absorption, distribution and elimination), and not the true rate of absorption. He introduced the Biopharmaceutics Classification System (BCS) guidance which is under development by the FDA. In the BCS, drugs will be classified into four categories depending upon whether they have high/low solubility and/or high/low permeability. It follows that the probability of meaningful *in vivo-in vitro* correlations could be predicted and whether *in vitro* dissolution testing would be sufficient for the determination of *in vivo* BE. He also pointed out that a BCS would be very difficult for controlled release products since both permeability and metabolism may be site dependent. The gastric determinants will include the size and the density of the unit as well as whether the product is disintegrating or non-disintegrating.

Dr. P. du Souich (University of Montreal, Montreal, Quebec) emphasized how a MR by controlling the rate of absorption can modulate the response (i.e., prolong the response, control the site of absorption or reduce the rate of input into the body). Examples given were erythromycine, diltiazem (i.e. the AUC of MR diltiazem is much

larger than that of IR because the former is absorbed much more distally and therefore may escape some 1st pass metabolism), and metronidazole (i.e. the MR form releases drug in the area of the gut where trophozoites are present, thus resulting in higher success rates than when given as an IR form). MR formulations can also modulate the pharmacologic response of drugs (i.e. furosemide, nifedipine and other calcium antagonists, prazosin, or propranolol). MR formulations are also used to modulate undesired pharmacologic effects (i.e., ASA, nifedipine, verapamil, levodopa, diazepam, carbamazepine, alprazolam). He concluded by stating that MR formulations can reduce undesired effects and increase desired effects. The fact that changes in formulation can modulate the effect has implications for the bioequivalence studies: is it necessary to study the pharmacological response or pharmacokinetic studies are sufficient to assess the bioequivalence between IR and MR formulations?

Discussion:

C. If we want to look away from the scientific literature for evidence of a problem with the interchangeability of drugs, we should look to the hospitals (i.e., usually only one brand of a product is stocked and the decision of which brand is stocked is usually made by the purchasing department of the hospital pharmacy). What is the impact on patients?

C. The mean serum-concentration-time curves for MR products can be very deceiving and not representative of the curves in individual patients. Rather than relying on mean curves, each subject should be compared for both the test and reference products before concluding that one brand is absorbed more rapidly than another. As scientists, we must not take an alarmist approach. Instead, extrapolation of differences to meaningful clinical outcomes should be done only with appropriate evidence.

C. At present, our methodology to measure Tmax or lag time is inadequate. This issue needs to be addressed. Cmax is a good measure of safety but as a measure of absorption rate it is biased, especially when the peak is wide. Some type of shape analysis would be a start and perhaps a duration measure would have better properties than Tmax.

Q. What is the molecular weight limit and solubility limit for drugs to be absorbed *via* the oral route? For poorly absorbed formulations, would F be enhanced by changing the formulation?

A. Dr. G. Amidon: Large molecules require transporters for absorption, therefore, the theory regarding solubility and permeability does not hold. If a drug has low F due to permeability problems, it is unlikely that you can do much with a formulation change. If the problem is due to solubility, then you can probably modify the formulation accordingly.

Bioequivalence of Drug Products with Special Characteristics
Session II: Chair: I. Kanfer

Dr. I. Kanfer (Genpharm Inc., Etobicoke, Ontario) began the discussion on BE of topical dosage forms intended for local action. In the context of his talk, topical was taken to mean a pharmacologic or other effect confined to the surface of the skin or within skin which may or may not involve percutaneous absorption and deposition. Topicals are assessed by *surrogate* measurements, therefore should not be assessed on the same basis as drugs intended to be absorbed. The methodology is currently under development and the statistical assessment has yet to be defined. He briefly reviewed current methodologies which included 1) original methods (i.e. clinical assessment), 2) well established methods (i.e. human vasoconstrictor response), 3) newer methods (i.e. skin stripping) and 4) monitoring plasma drug concentrations for metered dose inhalers and acoustic rhinometry for intra-nasal dosage forms). In the end, he concluded with some food for thought i.e. why not use systemic concentrations to assess MDIs, inhalation products and nasal sprays - what about oral drugs intended for local

action in the gut? Lastly, he questioned whether the same acceptance criteria for systemically absorbed drugs should be applied to topical products?

Dr. P. Roufail (Health Canada, Ottawa, Ontario) reviewed the history of guideline development in Canada for MDIs to date. During development, both bronchodilator and bronchoprotective effects were considered to be important. The current guidance was presented and compared to the 1992 draft. The proposed guidelines for corticosteroid MDIs were then presented as follows:

1. Safety - serum cortisol AUC (in the 1992 draft, there was only a requirement to measure AUC cortisol in urine for 24 hrs, but the new draft asks for serum cortisol $AUC_{0\text{-}24h}$).

2. Efficacy - a) Steroid Reduction Model (also in the 1992 draft), b) Allergen Inhalation Model (also in the 1992 draft) and c) Uncontrolled Asthma Model (new). For the Uncontrolled Asthma Model, recommended outcome measures are airway hyperresponsiveness (AMP or methacholine), airway inflammation, induced sputum (most practical), eosinophil counts and exhaled nitric oxide. He concluded his presentation by indicating that everyone has been working towards guidelines but that nothing was yet final. The challenge is validation of models and the challenge to do so was put to industry and academia. Lastly, he touched on the issue of phasing out CFC's as per the Montreal Protocol. Health Canada and Environment Canada apparently have a draft guidance/position that will be circulated in the very near future (check website at http://www.ec.gc.ca/ozone).

The session was continued by Dr. R. Lalonde (Phoenix International, Montreal, Quebec). He emphasized that the slope/shape of the dose response curve is particularly important since a large difference in potency may lead to only a small change in response. Slope and variability of the dose-response relationship are key considerations for BE determination; hence, relative response based on a ratio without considering the dose-response relationship is meaningless. He presented the results of a study in asthmatics who were administered increasing doses of albuterol from two different MDI formulations. Relative potency was looked at using two methods: 1) Linear Mixed Effects Model and 2) Nonlinear Mixed Effects Model. Monte Carlo simulations, which allow a comparison of the method of estimation with the truth, were conducted. It was found that if interoccasion variability was ignored, the results were very different due to significantly biased parameters. It was concluded that the two methods (Linear and NONMEM) made different but similar relative potency estimates and that by ignoring interoccassion variability, there was more bias in the estimated parameters.

The discussion was continued by Dr. L. Latriano (Johnson & Johnson Skin Care Products, Skillman, New Jersey) who introduced the use of dermatopharmacokinetics (DPK) and the technique of skin stripping for establishing BE of topical products. DPK is the measurement of drug concentration at the target site (i.e. the skin and mainly the stratum corneum). As a qualitative method, skin stripping has been around for a few years; however, its use in quantitative measurement required further validation. Concerns expressed were: 1) is the stratum corneum the right site and is it an appropriate surrogate for dose/concentration? and 2) is the method linear, can it be validated and is it reproducible? She discussed the results of her experience examining some of the factors important in the skin stripping assay (e.g. humidity, type of tape used, application of constant pressure, single operator, etc.) Results indicated a wide range of inter- and intra-subject variability with regard to the amount of stratum corneum removed. Other sources of variability that were discussed were the inherent variability of the skin type (i.e., age, sex, site, color, etc.), the stratum corneum thickness at different anatomical sites, variability of the application and removal of the tape by different *operators*, and variability secondary to the tape selection and the study environment. Practical considerations are that skin stripping destroys the skin, therefore it is impossible to go back and get another sample from the same site and that the whole sample must be analyzed at the same time, so there is no room for error. Skin stripping also causes post-inflammatory changes and hyperpigmentation. It was

concluded that all the sources of variability and practical considerations must be addressed before a meaningful DPK analysis can be obtained.

Dr. E. Smith (Rhodes University, Grahamstown, South Africa) discussed the human skin blanching (vasoconstriction) assay for topical corticosteroids. He considered two assessment methods: 1) visual and 2) instrument aided, and drew particular attention to the FDA guidance recommending use of the Minolta chromameter. He commented that while chromameters work well on painted surfaces, there is great variability when used on skin due to precision and reproducibility limits. Dr. Smith presented study results that illustrated that the FDA guidance is not ideal and may in fact be flawed due to a difference in results depending upon the modeling procedure employed. He concluded by stating that more work was being done on statistical analysis of this methodology as well as Euclidian distance analysis in an attempt to improve the accuracy and reproducibility of the chromameter.

Discussion:

Q: Why is it necessary to sample the stratum corneum?

A: The direction for sampling the stratum corneum came from the rationale that antifungals were tested in the stratum corneum as this is their site of action. Body hair poses a problem to the use of skin stripping as a quantitative methodology.

Q: What do you do about furrows in the skin?

A: Unfortunately skin is not a flat surface so this does pose a problem.

Bioequivalence of Drug Products with Special Characteristics
Sessions III & IV: Chairs: L. Endrenyi, E. Ormsby

Dr. K. Midha (University of Saskatchewan, Saskatoon, Saskatchewan) began this session by briefly reviewing the average BE (ABE) study design (i.e. 2-formulation, 2-period, 2-sequence crossover design) and sources of variation. In this design, the *residual error* is composed of pharmacokinetic within-subject variance, the within-formulation variance, the subject-by-formulation interchange and unexplained random variation. He explained how calculation of the 90% CI is dependent upon residual error and the disadvantages of this approach. He then discussed individual bioequivalence (IBE) and replicate study designs. The latter approach allows for an evaluation of subject x formulation interactions; however, the clinical significance of this requires further investigation. He spoke about the *grey areas* i.e. to what extent can two different test formulations differ when they are bioequivalent and when they are not. He discussed the issue of scaling in the context of a NTR drug with low variability and a safe HV drug. Nonetheless, scaling to the within-subject variability of the reference drug product will pose problems when the reference formulation is a poor pharmaceutical product. He concluded his presentation with the following points on IBE in terms of scaled and unscaled aggregate metrics:

1. some form of scaling is appropriate

2. scaling is problematic when the reference formulation is a poor pharmaceutical product (i.e. generic manufacturers can choose a highly variable lot of the reference product)

3. scaling to a pooled estimate of variance is appropriate when the test and reference variances are close

4. the proposed IBE metrics are elegant but they need to be tested and subjected to actual study data (i.e. all practical experience with IBE is based on studies that were not designed to test these concepts)

The next three presentations by Drs. O. Eradiri (Biovail Corporation, Mississauga, Ontario), Y. Tsang (Apotex Inc., Weston, Ontario), and S. Laganiere (Phoenix International, St. Laurent, Quebec) all dealt with examples of data anomalies resulting from BE studies of HV drugs. Descriptions of the data can be found in the respective abstracts in the Symposium Proceedings document. The conclusions reached in each of the presentations were as follows:

Dr. Eradiri concluded that:

1. The extent of absorption of Product A varied depending upon the type of diet used in the BE trial

2. The AUC of Product A was found to be 50% higher with Diet 2 than Diet 1

3. Absorption was more variable with Diet 1 than with Diet 2

The nature and content of Diet 1 and Diet 2 are proprietary information.

Dr. Tsang presented BE data on a HV drug (propafenone) demonstrating that the bioinequiavlence of two propafenone products may not be due to formulation differences but is probably caused by the inherent variability associated with the drug. The observed variability of AUC and Cmax data can be attributed to biological factors such as heterogeneity of the subjects (fast vs slow metabolizers) and the presence of nonlinear pharmacokinetics in fast metabolizers. In the absence of the heterogeneity of the subjects, substantially smaller CV's were observed. He concluded that:

1. For most drugs, the current Therapeutic Products Directorate Report A and Report B standards for BE are appropriate.

2. For HV drugs, these standards are inappropriately austere, i.e. tight standards are unjustified, the current goalposts are too narrow, and it is unethical and costly to study so many subjects.

3. The standards should be reasonable (i.e. when a reference product has trouble passing against itself), and in such cases new criteria should be established.

Dr. Laganiere concluded that:

The advantages of IBE are that:

1. It addresses *switchability* and the subject x formulation interaction is not ignored.

2. It does not assume that the variabilities of the tst and reference products are the same, and it rewards a manufacturer for making a less variable test formulation.

3. Scaling helps HV drugs pass.

The disadvantages are that:

1. A replicated design is more costly, more time is required, and there are likely to be more drop-outs.

2. It is not known how often *switchability* is a problem and even so, switchability will only be assessed in a very small group of subjects and may not be reflective of the rest of the population.

3. Scaling is done with a variance term (within-subject variance of the reference product) that may differ from one study to the next.

Summary of the comparison between individual and average bioequivalence using 3 highly variable drugs:

- Subject-by-formulation interactions are not significant in these three studies with healthy volunteers. Therefore, all three drugs have very good switchability.
- Scaling helps highly variable drugs to pass the individual bioequivalence criterion.
- Differences in variability between test and reference formulations have a major impact (+/-) on the results for individual bioequivalence.
- Significant differences (>30%) in means may be offset by differences in variability between formulations.
- The above may lead to different conclusions for the average versus individual bioequivalence.

The following issues remain to be resolved:

1. What is the typical number of subjects required?

2. Replicate designs cannot be used for drugs with long t/2s.

3. The methodology cannot be used for BE studies which use clinical endpoints.

4. Many important details concerning data analysis need to be addressed (i.e. steady state designs, etc.).

The next speaker was Dr. L. Endrenyi (University of Toronto, Toronto, Ontario). He began by contrasting the two methodologies of ABE and IBE. The former methodology answers the question of whether the average responses of two formulations are similar and the latter whether individual responses to two formulations are similar. The two principal conditions that one must consider are when a patient is naive to a drug i.e. *prescribability* and when a patient is switched from one brand of a drug to another i.e. *switchability*. The drawbacks of ABE are that it reflects *prescribability* but not *switchability* of formulations, that it contrasts average responses of formulations but not other features such as distributions i.e. variability, and that it does not reflect subject x formulation interactions. An additional concern is that the regulatory approach is not sufficiently flexible. Dr. Endrenyi worked through the methodology for IBE based upon scaled criteria and unscaled criteria as well as a mixed strategy, and highlighted the ‘trade-off’ among components of the models. He concluded by stating that more studies are required to test the proposed methodology as it is scientifically flawed because:

1. Scaled BE criteria can be very permissive.

2. Scaled BE criteria are very sensitive to differences between means.

3. The mean variance trade-off is asymmetric, hence small changes in estimated intrasubject variances can yield large changes in the allowable ABE.

The discussion continued with a presentation on proposed BE standards for drugs with a NTR by Dr. J. Ruedy (University of Dalhousie, Halifax, Nova Scotia). Dr. Ruedy commented on the development of BE guidelines in Canada as he was Chair of the Expert Advisory Committee on Bioavailability whose work resulted in Reports A, B and C. With regard to the committee's work, they had indicated that further refinements of these standards were required for drugs with special characteristics. He cited cyclosporine as an example of a drug that has complex pharmaceutical characteristics, absorption affected by food, complex kinetics that are dose and time dependent, long half-;lifes, a complex metabolism with active metabolites, and a number of sites of toxicity. As a result, he suggested the following standards for comparative bioavailability assessment of cyclosporin:

1. The 95% CI of the relative mean AUC should be within 90-112.5%.

2. The 95% CI of the relative mean Cmax should be within 90-112.5%.

3. The relative mean Cmin should be within 90-112.5% and this standard should be replaced if clinical results are related to concentrations at two hours.

4. Both fasted and fed single dose studies as well as steady-state studies at the highest and lowest doses used clinically should be required.

5. Studies should be performed in patients and against the current (Neoral®) formulation.

The next speaker was Dr. B. Chakraborty (Biovail Corporation, Mississauga, Ontario) who presented on the sample size requirements for determining BE based on two proposed approaches for BE standards for NTR drugs: 1) adopt a tighter acceptance range (85-118% or 90-111%) but retain the 90% CI or 2) adopt a 95% CI for AUC and Cmax. He commented that for the most part, NTR drugs have low variability but some are highly variable. The number of subjects (n) required was calculated and contrasted depending upon the ratio of means and acceptance range, intra-subject variability and power. He concluded that the number of subjects did not change considerably when the CI was changed from 90 to 95%; however, when the acceptance range was tightened, the number of subjects required increased substantially.

The final speaker in the session was Dr. H. Lau (Novartis, East Hanover, New Jersey) who presented findings from experience at Novartis with pharmacokinetic trials of clozapine and a BE trial of the brand name product and a generic product in the USA. Clozapine is an atypical antipsychotic agent and it has been shown that there is no relationship between drug levels and agranulocytosis and/or cardiovascular adverse effects. Based on their experience and the data from the BE trial, it was apparent that clozapine should not be given to healthy subjects evidenced by premature termination of studies as a result of serious cardiovascular adverse effects in healthy subjects. Pharmacokinetic studies in treatment resistant patients were well tolerated. Based on this experience, Novartis recommended to the FDA that all pharmacokinetic/ pharmacodynamic studies of clozapine be conducted **only** in treatment resistant schizophrenic patients.

Mr. I. Mohamed (DuPont Pharma, Mississauga, Ontario) spoke on the importance of tight manufacturing specifications for NTR drugs. NTR drugs exhibit less than a 2-fold difference between the minimum effective concentration and minimum toxic concentration. Among the various factors that influence variability in pharmacokinetics of drugs, one is content uniformity. The current USP specifications for content uniformity allow ±15% variability in tablet potency. Minimal tablet-to-tablet variation is desirable for NTR drugs such as warfarin sodium. Regarding the wider specification, for a product like warfarin sodium which is available in numerous strengths, the result could be an overlap of drug potency between the various tablet strengths. Incompletely mixed granulations with inter-bottle variation of 20 % or more can pass the USP test for dosage form uniformity. Therefore, patients stabilized on a dosage regimen from one bottle who are subsequently dosed from a second

bottle may be adversely affected by the 20% variation. It was proposed that the current USP specifications for content uniformity be tightened at stage 1 of testing from 85-115% with allowance for one unit at ± 25% and RSD of less than 6% to 92.5-107.5% with allowance for one unit at ± 12.5% and RSD of less than 3%. In addition to content uniformity DuPont also performs an additional composite uniformity test during manufacturing which assures variability of ± 5% of target potency with an effective composite RSD of less than 3.65%.

The next presentation was by Dr. J. Thiessen & Mr. Scott Walker (both from the University of Toronto, Toronto, Ontario) and was entitled *Is Fuzzy Logic too Fuzzy for Bioequivalence Assessment*? Uncertain or *fuzzy* data sets have been generated in the process of BE determination. BE itself is fuzzy because the understanding of what BE should achieve is different for various stakeholders, i.e. statisticians, pharmacokineticists, regulators, clinicians or patients. The result is that the current criteria do not seem to be serving us well (i.e. as long as the difference between the test and reference product is within 10%, the current criteria are driven by sample size). Fuzzy BE logic is supported by the fact that clinical observations and statistical observations do not match and by the issue of 'add-on' studies being allowed based solely on homogeneity of variance. It was proposed that the concept of fuzzy logic, which has been employed successfully in engineering, can be adopted in BE determination. Fuzzy logic modeling requires multiple inputs and allows the computer to find the rule base. The application of the concept of fuzzy logic in BE will assist industry in study design and will permit regulatory agencies to set meaningful standards for drugs.

Discussion:

A number of questions/comments were made pertaining to the current definition of NTR drugs (i.e. a drug is considered to have a NTR when the ratio of the lowest concentration at which clinical toxicity commonly occurs, to the median concentration providing a therapeutic effect, is less than or equal to 2) as per the recent policy and list of drugs circulated by the Therapeutic Products Directorate.

C: Classification of NTR drugs as per Report C was done under pressure from industry.

C: The problem with the current definition of NTR is that a lot of the drugs on the list have no published data on the minimum or maximum therapeutic concentrations.

C: Is toxicity due to kinetics or dynamics? We should put more emphasis on trying to figure out where the variability is coming from.

C: It is important to note that clozapine is not a NTR drug in patients.

C: Propafenone is a HV drug but if you dose to steady-state, the ANOVA CV goes down from 40% to 15%. We can stratify patients into extensive metabolizers vs. poor metabolizers, but the amount absorbed is still dependent upon the surface area of the gut and depending upon where it gets to will determine how much is metabolized.

C: We should consider a symposium on subject selection for BE studies.

C: We have to reach some consensus on whether BE is a surrogate for therapeutic equivalence or whether it is it a quality control measure.

C: The more practical approach is to apply tighter standards to the manufacture of NTR drugs.

C: Imposing limitations on the pharmacokinetics without seeing what the effect is on the pharmacodynamics is illogical. It does not make much sense to impose stricter standards on the pharmacokinetics without looking at the result on the pharmacodynamics.

Bioequivalence of Drugs with Special Characteristics
Session V: Chair: K. Gallicano

The first speaker in this session was Dr. F. Jamali (University of Alberta, Edmonton, Alberta) who provided an update on BE considerations for chiral drugs. He began by reviewing the theory and terminology of chiral drugs. Enantiomers of racemic drugs can either differ markedly in their desired pharmacological response or be equipotent. In the latter case, stereochemistry in drug development may not be crucial. However, stereochemistry is important when enantiomers significantly differ in their pharmacokinetic profiles or when a racemic drug is formulated in a MR dosage form. Processes such as stereoselective gut metabolism, input rate-dependent stereoselectivity, stereoselective drug release in the gastrointestinal tract, and chiral inversion may influence the enantiomeric ratio and thus the therapeutic outcome of racemic drugs. Nevertheless, the issue of stereochemistry in BE is rather ignored due to the fact that the majority (if not all) of the racemic innovator products are approved based on non-stereospecific assays. The issue will become more important in the near future when most NDAs of chiral drugs now include pharmacokinetic data based on stereospecific assays. In these cases, stereospecific assays will be required.

The next speaker was Dr. J. Longstreth (Longstreth and Associates, Mundelein, Illinois) who spoke on the issue of BE of non-linear drugs and specifically on the effect of saturation of plasma proteins. The Therapeutic Products Directorate has recently proposed BE guidelines for drugs that exhibit non-linear kinetics. In the case of drugs showing larger than dose-proportional increases in AUC, it has been recommended that BE studies should be conducted only on the highest strength. When increases in AUC are less than dose proportional, BE studies should only be done on the lowest strength. These conditions are expected to maximize differences in bioavailability in terms of AUC. The mechanisms responsible for the nonlinearity in kinetics are critical and should be considered in the decision making process. For instance, the Vd of the unbound fraction can decrease with increasing dose, leading to a decrease in the clearance of unbound drug when there are a limited number of binding sites. An example given was high dose NSAIDs where the albumin concentrations and NSAID concentrations could become very similar. Another example discussed was oxaprozin. Dr. Longstreth recommended that BE determination should be done on the active (unbound) drug rather than the total drug concentrations. Furthermore, BE trials should be conducted for the active moiety in the nonlinear region of the AUC versus dose curve for maximum sensitivity. Comparison of systemic metrics may be irrelevant for high potency, high affinity compounds where only a small, not necessarily constant, fraction of the administered dose reaches the systemic circulation. Most of the dose can be sequestered on receptor sites, leaving little clue in the systemic circulation as to whether the molecule is present, or how much of the molecule is present.

The final speaker in the session was Dr. P. du Souich (University of Montreal, Montreal, Quebec) who spoke on nonlinear kinetics and pharmacological response using the example of mibefradil, a novel calcium channel antagonist which generates multiple active metabolites. The effect of zero-order elimination on the pharmacologic response of 50 and 100 mg mibefradil was investigated in an open parallel study using two groups of 10 healthy volunteers. Bioavailability of mibefradil was not affected by the presence of zero-order kinetics. Multiple administration of 50 and 100 mg of mibefradil generated zero-order kinetics. The 50 mg dose affected neither blood pressure nor ECG. However, a single 100 mg dose decreased the mean diastolic blood pressure. Repeated 100 mg doses also increased heart rate and QT interval. The results demonstrated dose-proportional increases in pharmacological response to mibefradil, despite the zero-order kinetics. These results confirm that mibefradil metabolites are less active than the parent compound.

Discussion:

Q: An alternative line of thinking is whether products differ in the *extent* of absorption or *after* absorption? If two products exhibit total plasma concentrations that are the same, would you not expect the fraction unbound to be exactly the same? Any comparison based on totals is a surrogate for the sum of its parts.

A: Are we not doing this (BE determination) for the end user? If BE is a surrogate for therapeutic equivalence, then we should be measuring the active moiety. We don't know that if you change the formulation, you impact on protein binding i.e. you could introduce an excipient that affects protein binding.

C. It should be noted that for oxaprozin, a 10% difference between a test and reference product could result in a 30% difference in the fraction unbound.

C: Some drugs are substrates for p-glycoprotein i.e. new AIDS drugs. What would happen then?

C: We must consider the intercept of the dose vs. AUC curve whether or not the *linear* portion may well be just a straight line relationship (i.e. incrementally it is linear but the whole *line* may not be linear).

Concluding Remarks:

Dr. F. Jamali concluded the symposium by acknowledging the overwhelming support for CSPS and the symposium. Based on the comments of the attendees, he anticipated the next topics of CSPS symposia to be:

1. Therapeutic use of natural products.

2. Subject selection for BE studies.

Dr. Jamali closed the symposium by emphasizing on the need for stronger support of pharmaceutical research at both academic and regulatory levels.