Health Canada Santé Canada

REPORT
of the
COMMITTEE ON THE DRUG REVIEW PROCESS

Of the Science Advisory Board
to Health Canada

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Canada

REPORT OF THE SCIENCE ADVISORY BOARD
COMMITTEE ON THE DRUG REVIEW PROCESS

PREFACE:

The Science Advisory Board was established in September 1997, by the Minister of Health, the Honorable Allan Rock. Its purpose is to advise the Minister on matters of science as they affect the Health Protection Branch (HPB) – and so the health of all Canadians – and to help foster public confidence in the HPB's work. Part of HPB's responsibilities includes the review and approval, or rejection, of applications by drug manufacturers to distribute new therapeutic products. This drug review process, which is designed to ensure that new drugs are safe and effective, has been criticized for being, for example, too slow and inefficient.

As a result, a number of committees and advisory groups have been set up to examine the process in detail; some reports and recommendations to improve the process have already been made. The Science Advisory Board wished to inform itself on the drug review process, and so it asked some of its members to look at the existing reports and the process itself, and to report back. The Board understands that its review was not exhaustive and that this is not a comprehensive report on the drug review process; it is, however, the consensus of its members and the recommendations we believe can be useful in the overall review process. The report of the Science Advisory Board's ad hoc committee on the drug review process follows, and I submit it to the Minister for his consideration.

My thanks to all the committee members for the report, and to those who helped them in their work.

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Chair of the Science Advisory Board

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REPORT OF THE SCIENCE ADVISORY BOARD COMMITTEE ON THE DRUG REVIEW PROCESS

1. Purpose

1.1 The purpose of this document is to report to the Science Advisory Board (SAB) on the activities of the Committee on the Drug Review Process, and to propose recommendations for action.

2. Background

2.1 The Committee was struck as an *ad hoc* Committee by agreement of the Science Advisory Board at its meeting of March, 1999, and was chaired by Doug Elliott. Members were Russ Graham, Jean Jones, Leslie Millin and Karen Semchuk, with Bernard Schwetz as an adviser. Dr. Semchuk and Dr. Schwetz were obliged to withdraw from the Committee's work part way through our activities because of other professional responsibilities.

2.2 In the SAB records of the March 1999 meeting, the Committee was to "proceed with a 'mini enquiry' into the HPB process to assess if the DRP work is credible and well informed, and to foster better management, as appropriate." A full statement of the objectives of our study is attached as Appendix A.

3. The Challenge

3.1 The Science Advisory Board was created in part to address the lack of public confidence in the work of the Health Protection Branch. Part of this lack of confidence springs from the perception that the process by which new drugs are approved is flawed. Critics of the drug review process have included some members of HPB's professional staff, as well as advocates

for various interest groups, representatives of industry, elected or appointed officials, and members of the public (some or all of whom we refer to as "stakeholders").

3.2 Some of the criticisms regarding the drug review process by interested persons are set out in Appendix B, especially regarding its transparency, timeliness, efficiency and effectiveness. These comments reflect the complexity of the process, and the differing expectations of the various stakeholders, including the general public. Such assertions are, in many cases, mutually contradictory. They cannot all be right, although they might very well all be wrong. We include them simply to show the diversity of opinion on the drug review process, without expressing any opinion as to their validity or lack of validity, except as set out in this Report.

3.3 We should note that clearly there *has* been improvement in timeliness, that some further constructive steps have been commenced in the area of consumer input, and that the relationship with the United States Food and Drug Administration's corresponding office is clearly productive, collegial, and one of mutual respect.

3.4 We wish to state categorically that the Committee has no evidence that persuaded us that unsafe drugs have been approved.

4. Work Method

4.1 We approached our work in various ways:

- Creating, sending and reviewing questionnaires sent to stakeholders and to staff of the HPB;
- Consultations with Dann Michols, the head of the HPB's Therapeutic Products Programme (TPP), the group which undertakes drug reviews, and with Mario Simard, General Counsel, Legislative Renewal, Transition, HPB, who respectively provided information on changes to the TPP and on the legislative renewal activity underway at Health Canada;
- Consultations with officials of the Food and Drug Administration (FDA) of the United States, the Medicines Control Agency (MCA) of the United Kingdom, and the European Agency for the Evaluation of Medical Products (EMEA);
- Contacts with the TPP Management Advisory Committee and with the Consultative Workshop on the TPP Drug Review process;
- Direct discussions with informed stakeholders, including a meeting with key informants; and

- Desk research.

4.2 Summaries of the questionnaire results are attached as Appendix B. They form the basis of many of our observations. Reports of the contacts with the US, UK and EU officials are attached as Appendix C, and they, too, have helped us with our work. We tabled an Interim Report part way through our work, to which SAB members responded, and it is attached as Appendix D. We have also attached, as Appendix E, a selected bibliography of previous studies and reports bearing on this subject. A brief summary of the law as it applies to transparency issues is Appendix F. The Report of the November 3-4, 1999 meeting with key stakeholders is attached as Appendix G. Finally, we have attached as Appendix H the draft EU legislation on Orphan Products, and Appendix I, the Report of the Consultative Workshop.

5. Observations

5.1 From our questionnaires, we learned:

- Most respondents believe the process must improve its timeliness, efficiency, and effectiveness, and many fault it on transparency; but the Committee was not told and received no evidence that unsafe drugs are being approved;

- A number of respondents criticized HPB management, and we draw the attention of managers to these criticism which are outside the scope of this Report as summarized in Appendix B;

- Support for international harmonization is widespread, providing it means harmonization to the best international standards--not harmonization downward, as some have feared--and providing responsibility for the health and safety of Canadian citizens is not compromised;

- No consensus exists on the policy of cost recovery, except perhaps that in its current manifestation it does not work well;

- Post-market surveillance, or post-approval monitoring (both terms are used) or rather lack of it is seen as an important weakness.

5.2 From our consultations, we learned:

- Generally, the results of the questionnaires were confirmed;

- Many stakeholders feel urgently that the time for further review is past, that there is broad consensus even where stakeholders have very different philosophies (see the report of the Consultative Workshop on the TPP Drug Review Process, Appendix I, for example), and that the time for action is overdue;

- Stakeholders agree that the process of legislative renewal provides the Department with a rare and valuable opportunity to transform at Health Canada the drug review process where necessary;

- Scope for change is in some cases limited by existing Canadian legislation, which may be altered, and by international treaty obligations, which effectively may not.

5.3 From other jurisdictions, we learned:

- Standards of transparency vary, but every jurisdiction has room for improvement;

- No jurisdiction seems satisfied that it has dealt sufficiently effectively with post-market (post-approval) surveillance;

- International harmonization is generally considered desirable;

- There appears to be increasing support for the value of specific programs dealing with the problem of Orphan Products;

- User fees are widely imposed in various ways, but have organizational implications (the term "cost recovery" seems solely Canadian, and has a somewhat different but similar meaning);

- Standards of timeliness seem to vary widely, but the variation diminishes when the basis of computation is considered.

6. Discussion

In our Interim Report (Appendix D), we identified the essential principles of ***Timeliness, Transparency, Efficiency*** and ***Effectiveness,*** which are discussed below.

6.1 Timeliness

6.1.1 Timeliness is in large measure governed by the availability of financial and other resources, as we discuss in section 7. We note that much progress has been made in recent years in improving the timeliness of the review of applications--the major problem seems to reside in the accumulation

of applications that must wait unopened until managers and reviewers have time to address them. This time is designated by TPP as “hold time”, or “backlog” by others. It seems in at least some cases to be too long--up to more than 150 days for a fast-tracked application--and the governing factor here clearly is lack of resources.

6.1.2 We believe more improvement is possible, for example, by the exchange of review findings --not automatic acceptance of regulatory outcomes-- with comparable agencies in other jurisdictions. We noted Health Canada’s efforts towards international harmonization, but we feel there is merit in information exchange as a practical immediate alternative to setting international standards, a long-term proposition. Another possibility is to share responsibilities with international partners, agreeing--for example--to capitalize on Canada's research strengths in one or two specific areas in exchange for access to the findings from other jurisdictions of comparable scientific rigour in a range of other designated areas.

6.1.3 If the “hold time”, or “backlog”, is satisfactorily reduced, we are confident that new applications can be processed in a time scale that will stand comparison with other industrialized countries. Further, elimination will enhance public confidence in Health Canada. Strategies such as providing Notice of Compliance with conditions to any application that has been on hand for some specific period of time, has been approved in some combination of comparable jurisdictions, and can be supported by identical information as that supplied to those jurisdictions can be invoked, but a specific plan with adequate resources is essential. A target for eliminating this "hold time" might be 18 months. We stress that there must be no shortcuts in safety and effectiveness appraisal.

6.1.4 A particular area for improvement is the process by which Health Canada deals with applications for products that are clearly and urgently needed to deal with serious and sometimes life-threatening conditions. In principle, these are assigned "fast-track" status, and may be granted a Notice of Compliance with Conditions (NoCC). The Committee noted that this process is not harmonized with the FDA's equivalent system, despite the clear opportunity to save time. We can only conclude that the basis for the current distinction is to reduce demand on resources.

6.1.5 Other improvements are procedural. The EMEA reports success with standard templates for applications, electronically readable. Various stakeholders have pointed out that certain steps in the review process could be carried out in parallel rather than sequentially, since they have no particular impact upon each other. Another measure, suggested in one of our consultations, was that where an applicant fails within an agreed time to remedy an incomplete or defective application, that application should be removed from the stream until complete or corrected, and then accepted only at the end of the queue. The people who can best identify procedural improvements are those who work daily with the procedure, and an active program to solicit and reward useful suggestions from reviewers will build morale and yield immediate benefits based on

solid, professional experience. We understand that many of these improvements have been implemented or are under active consideration by TPP.

6.1.6 We considered mandated time frames for review completion. On balance, this seems a poor option, although we agree that general targets are desirable, simply because applications are so variable. Where one application is supported by two volumes of data, another may have sixty volumes. Multiplying the number of reviewers proportionately will not alone suffice--the complexities are simply too great, and only adequate time will ensure an acceptable review. Delays might be reduced by a system under which, after the application was validated for completeness, a target date or dates for the review process could be set, based on the individual characteristics of the application.

6.1.7 There are models which can be reviewed to establish ways to deal with administrative backlogs, such as the courts. Studies or pilot projects to determine the applicability of such models may be desirable.

6.1.8 We also believe that the findings of the Consultative Workshop on the TPP Drug Review Process deserve positive consideration. The SAB has not reviewed those findings in detail. The Committee has considered them; however, we did not participate in that process in its entirety. While we have a few reservations about some of the details, we agree with the spirit of their recommendations.

6.2 Transparency

6.2.1 In our view and that of many stakeholders, the current drug review process is unnecessarily opaque. Health Canada persists in maintaining a level of confidentiality that is inconsistent with public expectation and contributes to a public cynicism about the integrity of the process.

6.2.2 Two conditions are said to make a high level of confidentiality necessary. One is that domestic and international laws require it; the other is that without it manufacturers will not choose to introduce new products into the Canadian market, and Canadians in need of such products will consequently suffer. As to the first, we refer to Appendix F. It reviews the pertinent legislation and concludes that much more transparent practices are quite feasible within existing legislation; further, given the legislative renewal now being undertaken for Health Canada, there is little barrier to introducing any such legislative amendments as might be required. As to the second: we observed directly in Washington public hearings involving the same manufacturers and the same products involved in Canadian applications, with much greater disclosure not only at the hearings but far more widely and immediately on the Internet: details are included at Appendix C.

6.2.3 Transparency is essential to public confidence. We believe that HPB should set new standards of access to information at all stages of the drug review process, enhancing transparency and

public confidence. We perceived no justification for current levels of delicacy regarding "commercial confidentiality". We would note: (a) Canada can at least emulate the standards of openness of our nearest and largest trading partner: (b) New legislation should provide for public hearings where appropriate; (c) If a product has gone through the FDA's public hearing process, this information should become part of the TPP's NDA review process, and the applicant should be responsible for providing copies of transcripts and videotapes. Further mechanisms employing contemporary communications and other technologies can be sought to achieve even higher standards more efficiently--public hearings are not sufficient of themselves.

6.2.4 We feel a system that allows for public hearings as appropriate is desirable, but public hearings will not in themselves provide a sufficient level of transparency--other methods must also be used.

6.2.5 We strongly support an Office of Consumer Affairs and Public Involvement (OCAPI) for Health Canada that has the necessary resources to implement a vigorous program of information and consumer involvement using a diverse range of contemporary communications techniques. The SAB has already endorsed the OCAPI concept, and has recommended the position of a Chief Scientist who will also help in disseminating information to the public.

6.2.6 OCAPI can implement a broad outreach strategy that will provide information in a meaningful and accessible form, will enrich and augment the drug review process, and will contribute to re-building confidence in Health Canada. The SAB understands that Health Canada is actively engaged in this process.

6 .2.7 Health Canada must actively seek to inform Canadians as widely as possible about the drug review process. TPP should have its own specific strategy.

6.3 Efficiency & Effectiveness

6.3.1 Efficiency and timeliness are closely interwoven. A persistent example given to us, of inefficiency and time wasting, is Schedule F. Schedule F to the *Food and Drug Regulations* establishes a list of ingredients which must be treated as prescription drugs. Adding to or withdrawing an ingredient from the Schedule requires an amendment to the regulations, a burdensome and lengthy process. Legislative renewal affords the opportunity for correction, if correction is needed. We have no opinion on the validity of this concern, but those involved in legislative renewal may wish to consider this issue.

6.3.2 International harmonization should in the long term improve efficiency. In the meantime, this should not preclude or postpone short-term co-operative projects or joint ventures to explore the potential for mutual improvements in handling applications. Comparing experiences with standard, machine-readable templates for applications, for example, as already noted, might well

yield improvements in efficiency at negligible cost, and this is an area where TPP has useful experience.

6.3.3 We recognize and support Health Canada's efforts to pursue international harmonization. But we believe that this long-term process can be enhanced by more immediate agreements to exchange scientific findings between regulatory agencies on a bi-lateral or multi-lateral basis without prejudice, with the consent of the applicants involved and their undertaking to provide identical information to all jurisdictions. We stress that this does *not* imply harmonization of approvals.

6.3.4 When the cost recovery policy was originally broached with the industry, it was seen as potentially contributing to efficiency. This the industry told us has not been the case. Industry has called upon the Treasury Board for a general moratorium on the Federal Government cost recovery policy pending a full review. The sums involved are large: of the $25.3-million currently spent by TPP on pre-market review of all drugs (both pharmaceuticals and biologics), some $20.9-million is derived from industry. TPP has initiated a review of cost recovery, whose results are expected next year.

6.3.5 Comparing expenditures on the drug review process across jurisdictions is difficult, because of variations in mandate. But the FDA spends about US$220-million (C$320-million) on New Drug Applications (NDA), of which US$85-million (C$123-million), or 36 per cent is derived from user fees. TPP advises that it spends C$25.3-million on pre-market review of drugs, of which C$20.9-million, derives from cost recovery, or over 82 per cent.

6.3.6 In other jurisdictions, the equivalent of cost recovery is described as "user fees". This may be a more accurate term, since it suggests a less tight relationship between what is levied and what is delivered. The FDA user fee of US$250,000 for each new drug application (NDA) is only loosely linked to the actual cost of reviewing an application. For one thing, not every FDA application goes to a public hearing, and the cost of a public hearing adds to the actual cost of reviewing, yet the fee is the same. For another, the income from user fees is added to existing revenues, whereas in the Canadian case cost recovery income has been largely substituted for appropriations. The UK experience suggests that a regulatory process could be entirely financed by user fees. EU officials consider a 75:25 ratio of user fee to appropriation is ideal. A 50:50 ratio would seem perhaps more acceptable in Canada, and this was the original intent; however, pending the outcome of the TPP review, we are not persuaded that the Treasury Board's cost recovery program for the drug review process has enhanced the efficiency of the process.

6.3.7 We are aware that a review of cost recovery has been launched by TPP. But public trust in Health Canada is eroded daily by current perception of the application of this policy; and the industry for quite other reasons equally dislikes the current policy. Over the short term, Health Canada should develop a strategy to inform the public on the clear, visible distinction between

cost recovery and the process of reviewing new products. Pending the outcome of the review of cost recovery, our committee believes that Health Canada should move to a 50:50 ratio as between cost recovery fees and appropriations, with a view to reducing the proportion of cost recovery in future. Subject to what may be learned from that cost recovery review process, we are of the opinion that a policy position should be taken--and expressed, if necessary, in the forthcoming legislation– that revenues from cost recovery will never exceed Parliamentary appropriations for the drug review process.

6.3.8 Post-approval surveillance is a weakness in all jurisdictions, posing serious challenges for rigorous scientific follow-up of approval decisions. Canada should move energetically in this area not only to implement the strategy designed by TPP, but to embrace pilot projects with well-defined groups to assess both risks and benefits in diverse, actual situations. This will be a valuable supplement to appropriate pre-approval clinical trials.

6.3.9 The drug review process is efficient in that it delivers the desired outcome at minimal cost and effort; it is effective in that it delivers the desired outcome with maximum benefit. Maximum benefit, we can see from Krever *et al.*, means that safety and well being of the person must take precedence over considerations of commercial advantage or bureaucratic process. We believe that if the drug review process is to be effective, it must engage public confidence. It must be seen to be credible, and based on sound science.

6.3.10 A well designed post market surveillance (or post-approval monitoring) strategy seems essential to efficiency in the drug approval process. We noted in our Interim Report that such a system would help ensure that the quality of applications and the thoroughness of investigation would be enhanced, to the improvement of efficiency.

6.3.11 A comprehensive strategy for post market surveillance has been developed for the HPB, and the most important thing is simply for Health Canada to fund it (perhaps with some appropriate industry contribution), and get on with it.

6.4. Orphan Drugs

6.4.1 Orphan products, which benefit a very small but intensely needy segment of the population, typically are not brought to market by major manufacturers because the cost of development and introduction do not justify the financial return. This market-driven approach, while fully justifiable in terms of current business assessment techniques, means that Canadians in acute need of help will not have access because they are too few.

6.4.2 We were impressed with the FDA's Orphan Products program in the United States, and also impressed with the initiatives now working their way towards implementation in the European Union. Something similar was proposed for Canada in the 1992 Gagnon Report, but the official

response was that it was unnecessary--that existing programs would suffice. We are less certain. A specific program, blending incentives, would bring new innovative talents into the therapeutics market, would add to Canada's exportable innovations, would offer opportunities for international joint ventures (especially with Europe). More important, it would confirm in the public mind Health Canada's commitment to the health protection of *all* Canadians, including those whose needs are sufficiently rare as to escape the normal attention of the market.

6.4.3 This recommendation of the Gagnon Report should now be implemented. There are opportunities for international synergy and co-operation in this area with the EMEA, the FDA and Japan. TPP should bring forward a suitable program of industry incentives, for which appropriate funding will be needed. Administration through the Canadian Institutes for Health Research merits consideration.

7. Resources

7.1 There is virtually unanimity that the drug review process has insufficient resources. But the problem is not simply one of money. There are general problems of human resources, as well as human resource problems that are specific to a science environment. There are general financial problems, and there are problems arising from the Treasury Board's cost recovery policy. There are also problems of what we might call administrative resources, by which we mean that managers have access to too few tools, or options, to shape their work. And, of course, all these problems are interactive.

7.2 An example of lack of resources is the drug review process "hold time". Eliminating this, as noted above, would greatly ease many of the concerns over timeliness. HPB staff have asserted that if this could be cleared, the time for processing most applications would fall within the acceptable bracket for industrialized countries. Public confidence in the process will be enhanced if it can be clearly seen that applications are processed in a timely way, and applicants will have some assurance that the business benefits from investing in a drug will not be put at risk due to a slow or inefficient process. While financial and personnel resources must be brought to bear here, some additional administrative resources, in the form of additional procedures, would also be helpful. For example, it has been suggested to us that where other comparable jurisdictions have already reviewed a new product, HPB might well--with the agreement of the applicant--take advantage of the work of others and issue Notices of Compliance with Conditions, subject to some agreed period during which any outstanding concerns might be addressed so that full NoCs can in fact be issued, an administrative option not now available.

7.3 Similarly, OCAPI as proposed to the SAB potentially offers additional administrative resources to address questions of transparency and effectiveness, at the very least. The SAB has already endorsed the policy work done in this regard. Public expectation is high, and action is needed.

7.4 More generally, it is clear that the government's budget reduction exercises have diminished human resources well beyond what any manager could have anticipated or wanted. Despite measures that have been partly successful in improving efficiency, the lack of resources and regular criticism of TPP cannot be conducive to good staff morale. Low morale in turn is likely to impair optimum efficiency. We have noted with concern the comments on morale at TPP expressed in the report of an external consultant[1].

7.5 Study after study has confirmed what scientists have empirically known for a very long time: critical mass is essential to effective scientific work. They must have the time and opportunity to interact; and they must have professional resources upon which they can draw. They must have the opportunity to live and work as scientists: to publish, to scrutinize the work of others, to communicate not only electronically but through the time-proven practice of participating in scientific meetings. The benefits to be derived from allowing scientists to develop their scientific careers in this way cannot be overstated.

7.6 In recommending to the Minister the appointment of a Chief Scientist, the SAB believed that this should be a priority. He or she should be given the mandate and resources to establish a critical mass of credible scientists who can participate in the review process as quickly as possible. Achieving critical mass and scientific credibility will be achieved much more quickly and efficiently if done in conjunction with Canada's academic medical community. Health Canada should enhance its collaboration with the clinical and academic medical community; enhancing and maintaining effective ties requires attention and resources.

7.7 Core scientific competency is the top priority. Health Canada will neither attract nor retain the best and brightest without a professional ambience in which scientists can meet challenges with appropriate infrastructure, publish freely and face peer review just as freely, and pursue the highest scientific productivity, within the constraints of a federal regulatory mandate. The potential for interactive work through the Canadian Institutes for Health Research (CIHR) may expand TPP's horizons, not to re-introduce direct research within TPP, but rather to ensure that TPP scientists can be allowed and indeed encouraged to spend a portion of their working time in research with colleagues elsewhere to enable them to retain and hone their professional skills, and pursue professional advancement.

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[1] PricewaterhouseCoopers, Therapeutic Products Program: Baseline Assessment of Drug Submission Review Process, pp. 79 - 80, April 26, 1999.

7.8 We have noted with concern, and have had it pointed out during consultations, that the number of acting positions among senior science managers in the HPB is extremely high, and that some of these positions have remained filled by acting personnel for years at a stretch. We have also been advised that even where a position has been authorized and the salary and benefit funds are not in doubt, it typically takes up to two years to staff the position. This is unacceptable. Funds must be found, for salaries, equipment and other necessities of scientific work, or not only will it be difficult to recruit the best scientists that Health Canada needs, but it will be hard to retain the best it already has.

7.9 No consideration of resources can avoid the question of the Treasury Board's cost recovery policy. We will not repeat our earlier discussion other than to say that the current application of this policy is unsatisfactory: to the industry, to consumers, and to TPP managers. Cost recovery, however implemented, cannot be a substitute for adequate parliamentary appropriations.

8. Recommendation

We recommend that the Minister obtain the necessary funding in order that Health Canada managers can implement the following recommendations:

8.1 Give priority in allocating resources to enhancing the professional scientific capacity of Health Canada.

8.2 Immediately allocate resources to address pending applications.

8.3 Allocate adequate funding to ensure acceptable timeliness in all applications.

8.4 Establish a priority-review system for urgently needed new products that is harmonized with the FDA system.

8.5 Enhance transparency in the drug review process.

8.6 Establish the Office of Consumer Affairs and Public Involvement without further delay, and provide it with the necessary resources.

8.7 Design and implement a broad communications strategy on the drug review process.

8.8 Expedite international exchange of scientific findings with key partners.

8.9 Design and implement a post-approval strategy.

8.10 Re-visit cost recovery.

8.11 Develop an Orphan Products program.

8.12 Give positive consideration to the recommendations of the Consultative Workshop on the Therapeutic Products Programme Review Process.

9. Thanks

9.1 We wish to thank all who helped us in this task, and especially Dr. Bernard Schwetz, whose aid was invaluable. Respondents to our questionnaires have our deep appreciation. And thanks must

go to the Secretariat of the Science Advisory Board and the staff of the Health Protection Branch whose help allowed us to complete our task in time.