Sara Bower

NOTICE OF COMPLIANCE WITH CONDITIONS POLICY EVALUATION

DRAFT

(Filename: IAS - NOCC - Version 6 .wpd)

Prepared by the NOC/C and Priority Review Working Group
Therapeutic Products Programme
Health Canada

June 22, 2000

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Issue 3
Background 3
Purpose of Review 4
Recommendations 4

2. CURRENT POLICY 8

3. CANADIAN EXPERIENCE TO DATE 9

4. INTERNATIONAL COMPARISON 9

5. OPTIONS ANALYSIS AND RECOMMENDATIONS

Regulatory / Legal 11
Purpose / Scope 13
Definitions / Criteria 17
Advertising / Labelling 19
Procedures 21
Letter of Undertaking 22
Confirmatory Studies 23
Monitoring of Conditions 24
Safety Information
Adverse Drug Reactions 24
Periodic Safety Update Reports for NOC/C Products 25
Withdrawal or Stop Sale 26
Resources 27
Transparency / Communication 27
Evaluation 29

APPENDIX A Detailed International Comparison
APPENDIX B Working Group Terms of Reference and Membership
APPENDIX C Annual Drug Submission Performance Report - 1999

ISSUE ANALYSIS SUMMARY

Therapeutic Products Programme **DRAFT** June 22, 2000

1. EXECUTIVE SUMMARY

ISSUE

Have the original objectives of the **Notice of Compliance with Conditions Policy**, dated May 28, 1998, been met and to what extent has implementation of the policy achieved those objectives. Are the objectives still valid? Is there a legal basis for the policy objectives?

BACKGROUND

The policy development process for the Notice of Compliance with Conditions (NOC/C) Policy was initiated in January 1996 to address whether Canada should have a mechanism to speed the approval of drugs for patients with serious, life-threatening diseases based on the use of surrogate endpoints not yet fully validated. Canada was under increasing pressure to make drugs for serious diseases such as AIDS available quickly, particularly as these drugs were approved in the United States under the FDA accelerated approval program[1].

In addition, the objective of the policy development exercise was to formalize in policy the informal practice of issuing Notice of Compliance (NOCs) for certain drugs on the basis of a voluntary understanding with the manufacturer to conduct post-marketing studies to verify clinical benefit.

Policy options (assessment of alternatives) were distributed for internal consultation February '96 - April '97, including Legal Services. 23

TPP management decided to implement the policy with the intent to incorporate it into regulation after an evaluation of the impact and effectiveness of the policy was conducted. The TPP decided that the public health benefits of the timely implementation of the policy should take precedence over other considerations at that time.

A draft Notice of Compliance with Conditions policy was sent for external stakeholder consultation (via mail) in June 1997. There were no major objections to the policy at that time. Revisions were made to the policy, including Legal Services review, between the fall 1997 and March 1998.

The announcement of the Notice of Compliance with Conditions Policy[2] was made by Allan Rock, Minister of Health, in conjunction with the announcement of the Canadian HIV/AIDS Strategy on May 28, 1998. HE DIDN'T ANNOUNCE IT

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[1] New Drug, Antibiotic and Biological Drug Product Regulations; Accelerated Approval, Federal Register, Vol. 57, No. 239, December 11, 1992

[2] Notice of Compliance with Conditions Policy, May 28, 1998

There has been recent media attention focusing on the legal status of the policy and the process by which drugs receive an NOC/C. The Director General requested an internal review of the policy, including the nature and extent of the linkage to the Priority Review Policy. The Bureau of Policy and Coordination is leading the review in collaboration with a Working Group with representation from all areas of the Programme (refer to Appendix C for Terms of Reference and membership).

PURPOSE OF REVIEW

The purpose of this review is:

- to conduct a comprehensive review of both the Priority Review Policy and Notice of Compliance with Conditions Policy, including the nature and extent of the linkages between them;
- to validate the original objectives of the policy and to assess the extent to which these objectives have been met;
- to address recommendations #5 and #11of the Consultative Workshop on the TPP Drug Review Process;
- to identify existing tracking / surveillance and enforcement mechanisms and to develop recommendations to strengthen these functions;
- to recommend improvements to the policy;
- to recommend the appropriate regulatory instrument (policy vs. regulation) to address any gaps between the current situation and desired state;
- to make recommendations to ensure staff / stakeholders understand the policy and apply it in a consistent manner.

RECOMMENDATIONS

The Working Group has made the following recommendations:

Policy Objectives / Scope

1. Conduct stakeholder consultations to validate the policy objectives and scope and to refine the policy definitions.

Regulatory / Legal

2. Initiate the regulatory process to amend the Food and Drug Regulations to provide for the issuance of a Notice of Compliance with Conditions and other aspects of the policy, including specific provisions for the withdrawal of an NOC/C, pending incorporation of the Product Licensing Framework into regulation.

Procedures

3. Develop a guidance document to support the process and to assist staff / stakeholders in the interpretation of policy definitions.

4. Develop a Programme Standard Operating Procedure identifying inter-bureau linkages (both pre- and post approval) and roles/responsibilities.

5. Make appropriate changes to the Management of Drug Submissions Policy (eg. Request for NOC/C and the NOC/C submission as document types with performance target).

Advertising / Labelling

6. Require full disclosure of NOC/C status in promotional material or educational activities (to health professionals and consumers), labelling, patient package inserts and Product Monograph (all 3 sections of new PM template).

Letter of Undertaking

7. Develop a standard template and content requirement for the Letter of Undertaking (L of U).

8. Revise definition to include the essential components of the LofU, to highlight the requirement to meet ALL committments and to inform the TPP of any changes to the status of the undertakings.

9. Clarify the development process of the LofU and related obligations of the sponsor, the processing of information relevant to the LofU, and the situations under which an NOC/C can be replaced with an NOC.

Confirmatory Studies

10. Clarify in policy and guidance document what we would consider to be an acceptable confirmatory study.

11. Establish performance target for S/NDS for confirmatory studies.

Monitoring of Conditions

12. Assign a "NOC/C Manager" for each NOC/C product to monitor compliance with conditions.

13. Use existing tracking mechanisms (eg. DSTS) to monitor compliance with conditions.

14. Advise BCE when an NOC/C is under active consideration.

Adverse Drug Reactions

15. Implement "active surveillance" activities for NOC/C products, as outlined in the "Strategy for TPP Post-Approval Assessment Activities". "Active surveillance is defined as: regular periodic collection of case reports from health care professionals & health faciltities that are evidence-based rather than on passive surveillance activities". For example, require that sponsors of NOC/C products conduct targeted safety monitoring studies in the context of the situation.

16. BLPA to send ADR data (reported by health professionals) for NOC/C products directly to sponsor within 15 days of receipt (for inclusion in their PSURs).

17. Review bureaux to advise BLPA when NOC/C is under consideration.

18. All NOC/C products to be placed on Drugs of Current Interest (DOCI) List. SOP

19. BLPA to send quarterly line listings of ADR data for NOC/C products to "NOC/C Manager".

20. Advise sponsors that all other ADR reports for NOC/C products are to be sent to BLPA (Excluding PSURs which are sent directly to review bureaux) (in SOP and guidance document).

Periodic Safety Update Reports (PSUR) for NOC/C Products

21. All PSURs received for NOC/C to be reviewed by original review bureau - allocate sufficient resources to enable adequate review.

22. Require PSUR format and content - ICH Topic E2C - Clinical Safety Data Management: Periodic Update Safety Reports for Marketed Drugs.

Withdrawal

23. Include specific provisions for withdrawal of an NOC/C in regulation.

24. Consider patient needs and the availability of other access mechanisms in the regulator's withdrawal decision.

Resources

25. Conduct study to determine incremental resources required to effectively implement ALL aspects of NOC/C policy AND meet performance targets (incl. impacts on "standard" submissions).

Transparency / Communication

26. Issue a press release for each NOC/C approval (similar to FDA Talk Paper) and when NOC/C is converted to an NOC. Fact Sheets.

27. Issue a Dear Health Professional letters for each NOC/C approval (full disclosure of conditions).

28. Develop fact sheet on NOC/C Policy.

29. Develop a separate list of NOC/C approvals on website, including approved indications and "conditions".

Evaluation

30. Develop comprehensive evaluation plan as part of regulatory process, to include: expected outcomes; outcome measures; how data will be collected; when data will be evaluated. The provinces, industry, health care professionals and other stakeholders should be included as part of evaluation process.

NEXT STEPS

1. Revise and extend the mandate of the ~~Establish a~~ NOC/C and Priority Review Working Group (Chaired by Policy Division, BPC) ~~and a Sub-Working Group to focus on the clinical aspects of the policy (Chaired by a review bureau?) ensure the effective implementation of the recommended changes across the Programme (Target date: July 2000)~~ to:

   - implement the operational recommendations in this IAS;
   - develop a communication piece (September 2000);
   - develop a consultation document for both policies, seeking stakeholder input on the policy objectives, scope and definitions (January 2001);
   - subsequent to consultations, revise policies and develop guidance document;
   - initiate the regulatory process for NOC/C.

6. CURRENT POLICY

The purpose of this Notice of Compliance with Conditions Policy is to:

(a) Provide patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs.

(b) Create a mechanism to ensure that a manufacturer which has a drug approved under this policy conducts confirmatory studies to establish the link between anticipated and real benefit.

This policy applies to a New Drug Submission (NDS) or Supplemental New Drug Submission (SNDS) that meets the Therapeutic Products Programme's criteria for Priority Review other than the requirement for "substantial clinical evidence". [3]

This policy applies to a drug submission for a serious, life threatening or severely debilitating disease or condition for which there is promising clinical evidence based on the available data that the drug potentially provides:

- effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or
- significantly improved efficacy or significantly diminished risk over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

A drug submission that meets these criteria but for which a sponsor chooses not to apply for Priority Review may also be considered for issuance of a Notice of Compliance with Conditions (NOC/C). A prerequisite for an NOC/C in all cases will be the sponsor's written commitment to pursue confirmatory studies acceptable to the Therapeutic Products Programme.

DEFINITIONS

Clinical Benefit: having an overall positive impact on the treatment of the disease and/or on the quality of the patient's life.

Letter of Undertaking: a letter submitted to the Therapeutic Products Programme by a sponsor of a drug submission prior to the issuance of a Notice of Compliance with Conditions. The letter must be signed by the Chief Executive Officer of the sponsor and outline the confirmatory studies to be conducted to verify that the drug's efficacy based on available data does in fact predict a clinically meaningful benefit. The letter must also outline restrictions, if any, to be placed on the the drug. The form and content of this letter must be satisfactory to the Therapeutic Products Programme.

Notice of Compliance with Conditions: a Notice of Compliance that is issued with a notation relating to a Letter of Undertaking.

Promising clinical evidence: evidence based on adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit.

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3 Policy Issues from the Therapeutic Products Directorate, Priority Review of Drug Submissions in Canada, December 13, 1996.

Surrogate markers: indirect markers of effectiveness that are reasonably likely, based on available evidence, to predict a drug's effect on recognized clinical outcomes such as morbidity and mortality. A validated surrogate marker is predictive of the clinical benefit of a drug.

3. CANADIAN EXPERIENCE TO DATE

The NOC/C policy has been in effect since May 1998. As of April 1, 2000, 6 NOC/Cs have been issued:

Drug	Sponsor	Therapeutic Class	Date Issued
Rescriptor™	Pharmacia & Upjohn Inc	AIDS Drug	1998/07/22
Viramune	Boehringer Ingelheim (Canada) Ltd.	AIDS Drug	1998/09/04
NiaStase	Novo Nordisk Canada Inc.	Coagulation Factor	1999/02/12
Activase rt-PA	Hoffman-La Roche Ltd.	Thrombolytic	1999/02/16
Ziagen	Glaxo Wellcome Inc	AIDS Drug	1999/06/04
Relenza	Glaxo Wellcome Inc.	Antiviral	1999/11/02

To date, the TPP has received the results of confirmatory studies for two of the products which have been issued NOC/Cs. These submissions (S/NDSs) have not yet been reviewed, therefore, the validity of the studies to verify the clinical benefit of these drugs has not yet been determined. ? which ones.

4. INTERNATIONAL COMPARISON

An international comparison was conducted at the time of the original policy development. The Canadian NOC/C policy was modeled after the US FDA Accelerated Approval Program. A detailed international comparison of the Notice of Compliance with Conditions Policy is attached as **Appendix A**. Current FDA and EU comparisons reveal similar policies, although the policies in these jurisdictions are **entrenched in regulation.**

The US FDA has published a guidance document for "Fast Track Drug Development Programs"[4] which are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. The FDA "Fast Track Drug Development Programs" include the Accelerated Approval Program (similar to the Canadian NOC/C policy) and the Priority Review Policy.

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[4] Guidance for Industry: Fast Track Development Programs - Designation, Development, and Application Review, November 13, 1998: FDA website http://www.fda.gov/cder/guidance/2112fnl.pdf

5. OPTIONS ANALYSIS AND RECOMMENDATIONS

A facilitated workshop, including review staff, was held on February 28, 2000, to identify issues concerning the NOC/C and Priority Review policies. WG members were asked to take the lead on further development of the issues and to propose recommendations. The issues regarding the NOC/C Policy were themed and have been summarized below:

Regulatory / Legal Issues

Issuing an NOC/C as opposed to an NOC

There is no explicit regulatory authority for issuing an NOC/C. According to the Food and Drug Regulations, once an examination of a new drug is complete - the Minister shall either issue a Notice of Compliance or a Notice of Non-Compliance. The Regulations do not provide authority for the issuance of anything in between (i.e. NOC/C). The Regulations are quite clear - a submission either complies or it does not. The issuance of an NOC/C is, de facto, an issuance of an NOC. An NOC is issued when the Minister is satisfied as to the safety and effectiveness of a drug (sections C.08.002 and C.08.004 of the Regulations).

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Placing conditions on an NOC (thereby making it an NOC/C)

Again, there is no explicit authority in the Regulations for conditions to be placed on an NOC (such as we see in the *Medical Device Regulations* which do provide, in certain circumstances, for conditions to be placed on a licence when it is issued - see s. 36(2)). With respect to the conditions, there are some powers in the post-marketing provisions, especially reporting and record-keeping, that would indirectly support the Minister's ability to request more data, particularly if evidence that is not available at the time of issuance of the NOC raises safety or efficacy concerns.

- Under C.01.013 - the Director may order a manufacturer to provide evidence regarding the safety and effectiveness of a drug;
- C.01.016 and .017 - adverse drug reaction reporting is required;
- C.01.016(3) power to compel evidence of safety pursuant to adverse drug reaction report;
- C.08.006 (2)(a) power to suspend NOC based upon concerns over safety pursuant to clinical evidence or other experience not reported in the submission or not available to the Minister at the time of the issuance of the NOC;
- C.08.006(2)(b) power to suspend the NOC based upon concerns over effectiveness (based on new info obtained after the time of issuance of NOC);
- C.08.007 (h) and .008 (c) - record-keeping of cases of unusual failure in efficacy of new drug and mandatory reporting within 15 days

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TPP management decided to implement the policy with the intent to incorporate it into regulation after an evaluation of the impact and effectiveness of the policy was conducted. The TPP decided that the public health benefits of the timely implementation of the policy should take precedence over other considerations at that time.

THE MINISTER WAS QUITE CLEAR: THE DEPARTMENT ISSUES REGS

Regulatory / Legal Options

Option 1 **Status Quo**

21(1)(a)

Description: Maintain existing policy
Analysis: While certain features of the NOC/C policy may be achieved under the current regulations there are no specific provisions in the regulations for the issuance of an NOC/C,

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Option 2 **Existing policy with amendments**

Description: Amend the existing policy as recommended by the Working Group
Analysis: It is unlikely that suggested amendments to the policy will change

Option 3 **Amend Current Regulations**

Description: Amend the Food and Drug Regulations to provide for the issuance of a NOC with Conditions pending incorporation of the Product Licensing Framework into regulation.
Analysis: This is the preferred option. With this option, the end result will be regulations that are clearly legally enforceable Enshrining the policy in regulation would be consistent internationally. However, this option is time consuming and process driven (minimum of 6 to 8 months). Drafting instructions must be put together after considerable policy work and consultation with stakeholders.

Option 4 **Incorporate New Regulations under Product Licensing Framework**

Description: Wait for Product Licensing regulations - one package
Analysis: This option is a variation of Option 3. The advantage would be that any regulatory amendments required for the "NOC with Conditions" portion of Product Licensing would only be one part of the entire package thereby saving some time and effort. However, significant policy development is required and it is estimated that implementation of a Regulatory Framework for Product Licensing is several years away.

Recommendation: **Option 3.**

Initiate the regulatory process to amend the Food and Drug Regulations to provide for the issuance of a Notice of Compliance with Conditions and other aspects of the policy, pending incorporation of the Product Licensing Framework into regulation. A regulatory amendment would minimize challenges and potential liability, and provide a clear legal basis for a policy that benefits patients who would not otherwise have timely access to

potentially life saving drugs. In all likelihood, this would be achieved at the earliest possible date under Option 3.

Purpose / Scope

The stated purpose at the implementation of this policy was to facilitate patient access to *potential* therapeutic breakthrough drugs and to proceed with consultations on a regulatory change which would incorporate the policy into the *Food and Drug Regulations.*

This policy applies to a drug submission for a serious, life-threatening or severely debilitating disease or condition for which there is *promising* clinical evidence based on available data that the drug potentially provides :

- effective treatment, prevention or diagnosis of a disease or condition *for which no drug is presently marketed in Canada*; or
- significantly improved efficacy or significantly diminished risk over existing therapies, preventatives or diagnostic agents for a disease or condition *that is not adequately managed by a drug marketed in Canada.*

The safety of the drug must be reasonably established and the product must be of high quality. A prerequisite for a NOC/C in all cases is the sponsor's written commitment to pursue confirmatory studies acceptable to the Therapeutic Products Programme.

One of the recommendations following the *Consultative Workshop on the TPP Drug Review Process*[5] is: " Refine the Therapeutic Products Programme's criteria for designating priority review to ensure that priority review is granted for drugs which are intended for the treatment of a life-threatening condition, or for drugs which demonstrate the potential to address serious unmet medical needs. *Under these criteria the Therapeutic Products Programme should also approve applications for a fast track review if the product has an effect on a clinical or surrogate endpoint that is reasonably likely to predict clinical benefit".*

This wording of this recommendation appears to model the FDA "Fast Track Drug Development Programs"[6] which are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Section 112 of the FDA Modernization Act of 1997 provides for "Expediting Study and Approval of Fast Track Drugs". It states that "The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition". Approval of products that qualify for "fast track" designation is based upon the determination that the "product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit". Guidance documents further define "unmet medical needs for such a condition" essentially as no available therapy for the condition or, where there is available therapy, there is an improved effect on serious outcomes or reduced toxicity or improved patient compliance.

The FDA "Fast Track Drug Development Programs" include the Accelerated Approval Program (similar to the Canadian NOC/C policy) and the Priority Review Policy.

The recommendation of the Consultative Workshop has the effect of:

- expanding the criteria for eligibility for a NOC/C to any drug for the treatment of a life-threatening disease regardless of the availability of other effective products;

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[5]Consultative Workshop on the TPP Drug Review Process, September 30 - October 1, 1999

[6]Guidance for Industry: Fast Track Development Programs - Designation, Development, and Application Review, November 13, 1998: FDA website http://www.fda.gov/cder/guidance/2112fnl.pdf

- issuing a NOC/C based on promising clinical evidence rather than on substantial clinical evidence as required by Division 8 of the Regulations for this expanded group of products.
- establishing a performance target of 235 days[7] for all submissions meeting these expanded criteria (Priority Review target);

This recommendation is more expansive than that in place internationally (see Figure 1)

Figure 1 - International Comparison of the Scope of the Notice of Compliance with Conditions Policy

Canada	United States[8,9]	European Union[10]
Scope Applies to a drug submission for a **serious, life- threatening or severely debilitating disease or condition** for which there is **promising clinical evidence** based on the available data the drug potentially provides: – effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or – significantly improved efficacy or significantly diminished risk over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada. Applies to a NDS or SNDS that meets the TPP's criteria for Priority Review other than the requirement for "substantial clinical evidence".	**Scope** Applies to certain new drug and biological products that have been studied for their safety and effectiveness in **treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments** (e.g. ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)	**Scope** Exceptional circumstances are considered to be: – indications that are extremely rare; – the state of scientific knowledge is not advanced enough; or – tests are forbidden on grounds of medical ethics.

There is limited experience with the current policy as only 6 NOC/Cs have been issued to date. Average time from filing to the issuance of a NOC/C for these products is 568 days (BBR 635 days, BPA 535 days). This time-frame may not be representative of future clearances as most of these submissions were under review prior to the

[7] 10 days SIPD, 45 days screening, 180 days for review of original data package

[8] Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (21 CFR 314.500 - 314.560 (Subpart H))

[9] Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses (21 CFR 601.40 - 601.46 (Subpart E))

[10] Authorization under Exceptional Circumstances (Article 13(2) of the Council Regulations (EEC) No. 2309/93)

implementation of the policy and lack of standardized procedures and guidance documents may have contributed to the length of time required to finalize the review of the files and prepare the Letter of Undertaking. Average time from NOC/C to notification of sale to TPP is 73 days (BBR 174 days, BPA 13 days).

To date, the TPP has received the results of confirmatory studies for two of the products which have been issued NOC/Cs. These submissions (S/NDSs) have not yet been reviewed, therefore, the validity of the studies to verify the clinical benefit of these drugs has not yet been determined.

Purpose / Scope Options

Option 1 **Status Quo**

Description: Maintain the current purpose and scope as reflected in the definitions and criteria

Analysis: This is not an option. The current policy is not being interpreted consistently, both internally and externally and therefore, requires revision and support through guidance documents.

Option 2 **Refine policy and procedures (to prepare groundwork for regulatory amendments)**

Description: Revise current policy to clarify criteria and add definitions where required; develop guidance documents and standardized procedures to support the process. Proceed with regulatory process to provide statutory authority for the issuance of a NOC with Conditions and all other aspects of the policy.

Analysis: This is the preferred option. Maintaining the scope of the current NOC/C policy would allow for time to acquire more experience with the policy and with submissions processed as per the intended manner. The process will be better understood contributing to efficiencies in the short term. The potential for challenges on the appropriateness of Departmental actions can be mitigated with a clear regulatory framework. Any expansion of the criteria will require full consultation with all stakeholders through the regulatory process.

Option 3 **Expand the Scope of the Policy**

Description: Expand the scope of the current policy to reflect the recommendations of the *Consultative Workshop*

Analysis: It is estimated that the number of submissions that would qualify for a NOC/C would increase 10-75%[11] under the expanded scope proposed by the Consultative Workshop. Given that the Programme is not meeting performance targets under the current scope, any increase in the number of eligible submissions would increase the backlog, and may impact performance in other areas. In addition, the expanded scope goes beyond that accepted internationally. WHY?

[11] Based on a review of non-priority NDS and S/NDS received in 1998-1999 . The 10% figure represents BBR's estimate - roughly 40% of S/NDSs and 50% of NDS in BBR are already Priority Status.

Option 4 **Establish New Scope (ie. De-link from priority review policy)**

Description: Establish a new intent and philosophy by establishing conditions applicable to all drug submissions as the first step towards product licensing.

Analysis: Absence of a firm regulatory basis for establishing such conditions; lack of resources to review data submitted under the conditions imposed; product licensing framework incomplete.

Option 5 **Revoke Policy**

Description: Do not issue any further NOC/Cs until appropriate regulations are in place. Patient access to promising new drugs will be through SAP and clinical trial enrolment; for new indications for marketed drugs, access through the practice of medicine.

Analysis: Industry may not make promising new therapies available through SAP or clinical trials; patient access may be restricted; TPP's credibility may suffer by removing an existing mechanism for facilitated access supported by industry and stakeholders.

Recommendation: **Option 2.**

The current scope of the policy should be maintained while improving definitions, in consultation with stakeholders. Process improvements (eg. Best practices, team approach, etc.) as recommended in the PriceWaterhouseCoopers report[12] should be considered. The process would be concurrent with the development of a regulatory package. Implementation of any expansion in the criteria in the future would be dependant an increase in (trained) resources in order to meet performance targets.

Conduct stakeholder consultations to validate the policy objectives and scope and to refine the policy definitions.

[12] Therapeutic Products Program, *Baseline Assessment of Drug Submission Review Process*, April 26, 1999

Definitions / Criteria

Since the implementation of the policy, the review bureaux have insisted on certain requirements as a result of safety concerns or refinements arising from experience with the policy to date. Sponsors have, in some manner, challenged any requirement that has not been explicitly stated in the policy. Even if addressed in the policy, sponsors have challenged those aspects that are open to interpretation. As a result, the policy should clearly address all necessary requirements to the greatest extent possible. A guidance document or Standard Operating Procedures should add further clarification as required.

The current state highlighting the experiences to date are provided for each component of the policy. The components are identified as either criteria or definitions and follow the section/heading numbers in the NOC/C Policy. The sections Purpose and Adverse Drug Reactions are discussed in other sections of the IAS and will not be discussed here.

Evidence

The 'evidence' criteria outlined in this section of the policy are unclear. The NOC/C submissions to date were submitted with complete data packages purported to contain the requisite scientific evidence to fully establish the clinical effectiveness of the drug. When the efficacy data was judged to be lacking to meet the requirements of an NOC, sponsors requested consideration of an NOC/C on the basis that the evidence submitted should be considered promising.

It could be argued that this situation represents a submission where the confirmatory studies have already been submitted and the results failed to verify the drug's clinical benefit. Under the existing policy, this is a condition of withdrawal. There is a perception that sponsors are using the NOC/C Policy as a mechanism to obtain market access for submissions where the full body of evidence is clearly lacking and the positive results that are obtained are presented as promising.

The 'evidence' criteria needs to be clarified.

Scope

The criteria outlined in this section include the terms 'significantly improved efficacy' or 'significantly diminished risk'. These terms are open to interpretation. In general, sponsors will argue for a broader interpretation while evaluators will argue for the stricter application. Also, the interpretation differs within the review bureaux. Further, with biologic drugs, almost any improvement in the manufacturing process to enhance safety is argued to provide significantly diminished risk.

The terms 'significantly improved efficacy' or 'significantly diminished risk' need to be defined.

Definitions

Promising clinical evidence: This term 'promising' is open to interpretation. In general, sponsors will argue for a broader interpretation while evaluators will argue for the stricter application. Also, the interpretation differs within the review bureaux. It is not clear what delineates promising evidence from substantial evidence or, when the evidence is considered promising as opposed to inconclusive. There is a perception that sponsors are using the NOC/C Policy as a mechanism to obtain market access for submissions where the full body of evidence is clearly lacking and the positive results that are obtained are presented as promising.

Recommendation: The definition should be expanded in policy and further clarified in a guidance document.

Serious, life threatening or severely debilitating disease or condition: These terms are open to interpretation. They have not been defined and have been the subject of much debate. They have also been subject to political attention as a result of pressures by patient advocacy groups. For obvious diseases or conditions the decision to grant this status is not difficult. For the less obvious, the status relies heavily on reviewers' individual judgement which can differ significantly. In BPA, many (##) priority review requests are denied each year. This is indicative that sponsors have a different interpretation of the terms than TPP. Further, definitions for similar terms exist in other regulatory authorities.

Recommendation: new definition to be added.

Policy

Safety: One of the criteria for consideration is that the safety of the drug product can be reasonably established. 'Reasonably' is open to interpretation. Although full preclinical data can be reviewed, the safety of many drugs will be closely linked to whether the product works or does not work. Some would argue that safety profile could not be established under any conditions if the basis of evidence is limited in patient sample size or population. In these circumstances, serious adverse events may not even be revealed.

This criteria should be clarified to outline the limitations of determining the safety profile (eg. patient sample size, patient population, etc.)

Time lines: Confirmatory studies must be initiated in a timely fashion and sponsors must submit results from confirmatory studies in a timely fashion. "Timely fashion" is open to interpretation. Explicit time lines must be established for each relevant component of the LofU, including confirmatory studies and PSURs. In the six NOC/Cs issued, some sponsors have extended the original time lines without advising TPP. In setting time lines the criteria for extensions should be outlined. Consequences for failing to meet the time lines should also be included in the LofU.

This criteria should be clarified to highlight that the time frames must be acceptable to the TPP and identified in the Letter of Undertaking..

Safe Use of the Drug: The policy states that the conditions under which the drug product is approved must be clearly reflected and highlighted in the Product Monograph and/or labeling.

Subsequent to the implementation of the policy a decision was taken by senior management that a consistent message be conveyed for all NOC/Cs regarding the conditional nature of the approval. A decision to introduce a boxed text, originally termed 'boxed warning' that contained a consistent statement was endorsed by senior management. Again, sponsors have challenged a requirement that is not in the policy. For example, the review bureaux have been challenged on the location, size, format and content of the 'boxed text'. They have also been challenged on the box itself and the term 'boxed warning'. Internal opinion exists that the 'boxed text' should appear on the label and in Patient Package Inserts and in advertising.

For two of the four NOC/Cs issued by BPA, Dear Doctor Letters have been issued. This should be consistently applied to all NOC/Cs. Also, the policy mentions restrictions in terms of advertisement only.

Other restrictions may need to be considered, i.e. availability by specialists only or at specific centers. This would be subject to an analysis of the regulatory authority to request and enforce these restrictions. The policy does not explicitly allow for other restrictions in the LofU.

Sponsors are particularly sensitive to the labeling requirements. The experience to date indicates that the sponsor wants the NOC/C presented to the market as a full approval. The Programme is committed to inform physicians and patients of the conditional nature of the approval. This polar viewpoint has caused frustration for all parties.

Note: Specific criteria or definitions have not been provided. This would be considered premature before a full consultation with staff and stakeholders could be undertaken. The time frame for the review of this policy could not permit the detailed discussions required.

Recommendations:

- clarify current criteria and definitions , or add definitions where they do not exist, in consultation with stakeholders
- develop guidance document for staff and stakeholders to assist in the interpretation of the policy definitions[13]

Advertising / Labelling

The NOC/C policy states that "for the purposes of assuring the safe use of the drug product, the conditions under which the drug product is approved must be clearly reflected and highlighted in the Product Monograph and/or labelling for that product. The sponsor must also undertake to comply with any restrictions imposed by the TPP on the advertisement of the drug."

Advertising

The Pharmaceutical Advertising Advisory Board (PAAB) reviews and preclears sponsors' advertising material and provides independent complaint and appeal mechanisms to resolve advertising issues for approved prescription drugs. It also provides codes for advertising acceptance. The PAAB has developed a "Guideline on Advertising Disclosure for Drugs with "Notice of Compliance with Conditions" (NOC/C)"[14]. The *guideline* is designed to help clarify how the Commissioner and review staff interpret the PAAB Code of Advertising Acceptance. The guideline states "since the clinical benefits of these drugs have not been confirmed, it is important that advertising for these products clearly and prominently disclose to health professionals the conditional nature of the marketing authorization". The following is an excerpt from the PAAB guideline:

"Details of the conditions are reflected in the Product Monograph, and advertising for all products in the scope of the PAAB Code of Advertising Acceptance must be within the limitations of HPB-accepted monograph or labeling

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[13] Similar to the *US FDA Guidance for Industry - Fast Track Drug Development Programs - Designation, Development and Application Review* - includes guidance on criteria for qualification, an elaboration of the definitions in the regulations, application procedures, etc.

[14] Guideline on Advertising Disclosure for Drugs with "Notice of Compliance with Conditions" (NOC/C), Pharmaceutical Advertising Advisory Board, December 1, 1998

(Section 3.1).

To clarify how PAAB reviewing practice will apply to a NOC/C product:

1. The display portion of advertising must contain a prominent disclosure of the conditional nature of the market authorization and the need to conduct studies to verify its clinical benefit.

2. The display portion of advertising must be consistent with the specific restrictions or conditions specified in the monograph, which inter alia will require clear disclosure of any statements in the monograph or labeling that the indication is based on surrogate endpoints and that clinical benefit has not been demonstrated.

3. In addition, the accompanying prescribing information must contain the full text of the restrictions and conditions, even if the product qualifies for Condensed Disclosure prescribing information (Code Section 7.5) after two years after introduction.

Example:

The upper right hand corner of a letter or journal ad or detail aid contains a "boxed statemen"t: "PRODUCT has been issued conditional marketing authorization pending the results of studies to verify its clinical benefit. Patients should be advised of this conditional marketing authorization"

In the example, there is also legible disclosure in an appropriate location in the body copy, quoted from the Indications section of the Product Monograph, of the surrogate endpoint where effect was shown, and furthermore that clinical benefit from survival or other clinical endpoints has not been demonstrated."

There have been concerns expressed that physicians and pharmacists are not well informed of the NOC/C policy nor that certain products have been issued NOC/Cs. The PAAB has received a complaint from a health professional that the "boxed statement" (noted in the guideline) does not appear in the Patient Information brochure issued with the product "X". Apparently, the PAAB guideline has been contested. The PAAB has requested clarification from TPP, re. The NOC/C policy advertising / labelling provisions, specifically, whether disclosure is required in the Patient Information section of the Product Monograph and in all information pieces directed at health professionals, the general public and the patient.

WHICH ONE?

The US Food and Drug Administration (FDA) requires (in regulation) that copies of all promotional materials, including promotional labeling as well as advertisements, be submitted during the preapproval review period (57 FR 314.550 and 601.45). In Canada, prescription drug advertising is precleared by the PAAB and is currently restricted to health professionals. However, options to re-instate mandatory pre-clearance of prescription drug advertising by Health Canada are included in the Legislative Renewal Advertising Section, which will soon be released for Phase II consultation . This has been prompted by pressures to address the direct-to-consumer advertising of prescription drugs which is currently restricted in Canada.

BY WHOM

Labeling

The NOC/C policy states that "for the purposes of assuring the safe use of the drug product, the conditions under

which the drug product is approved must be clearly reflected and highlighted in the Product Monograph and/or labelling for that product." The Product Monograph and labelling material for NOC/C products (as for any new drug) are reviewed and approved by the TPP before the NOC/C is issued.

The draft Standard Operating Procedure for NOC/C[15] (developed in BPA and adopted by BBR) states that:

> "A statement outlining the conditions on which the NOC/C was issued will be located on Page 1 of the Product Monograph before the section 'Actions and Clinical Pharmacology'. This statement will be preceded by,
>
> "Health Canada has issued a conditional marketing authorization under the Notice of Compliance with Conditions policy to reflect the promising nature of the clinical evidence for this indication and the need for confirmatory studies to verify the clinical benefit." and followed by,
>
> "Patients should be advised of the conditional nature of the market authorization for this indication.""

As noted above, concerns have been expressed that disclosure should appear in the Patient Information section of the Product Monograph, and the Patient Package Insert (PPI) and that this should be specifically stated in the policy.

Recommendations:

- require full disclosure of NOC/C in promotional or educational activities (to health professionals and consumers), labelling, patient package inserts and Product Monograph (all 3 sections of proposed new PM template).

Procedures

The NOC/C policy allows for an NOC/C to be considered at the request of the sponsors for submissions which meet the criteria for Priority Review Status. For submissions which were under review at the time of the policy issuance, sponsors were granted a 30 day grace period to request consideration for an NOC/C. Alternatively, for submissions for which review had been completed and lacked sufficient data to support approval, the review bureau had the option of issuance of a Notice of Deficiency (NOD) or Notice of Non-Compliance (NON) which could include an indication that the submission may qualify for issuance of a NOC/C (which the sponsor would need to request in writing). The issuance of an NOC/C will result in the future filing of an S/NDS to provide data from required confirmatory studies.

The programme has now issued six NOC/Cs, two by BBR and 4 by BPA. Four of these NOC/Cs were issued for submissions which were already under review at the time of the issuance of the policy, several of which had received Notices of Non-Compliance (NON) as they contained insufficient data to support the issuance of an NOC.

The key operational/resource issues pertaining to the NOC/C policy are intricately linked to the Priority Review Policy, and fall under two categories, Review of Requests for Priority Status and NOC/C consideration, and Submission Review Issues.

Issues

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[15] Standard Operating Procedure, Notice of Compliance with Conditions, Draft 4, July 21, 1998

Review of Request for Priority Status (PS) and consideration for an NOC/C

Neither review bureau (BBR or BPA) has a screening process for requests for PS with NOC/C. Unjustified "frivolous" requests must be reviewed at the expense of time to the Programme, without penalty to the sponsor. Although both bureaux have adopted the BPA draft Standard Operating Procedures for the processing of requests for PS with NOC/C and issuance of an NOC/C, which attempt to follow the procedures defined in the two policies, there exists no guidance, other than the policies themselves, to help review staff determine whether a request meets the NOC/C criteria.

The granting of PS along with a request for an NOC/C, is often taken by the sponsor as agreement in advance that the data supports the issuance of the NOC/C. This in fact can only be determined upon review of the data during the full review process.

Submission Review Issues

For most of the NOC/Cs issued, the review of the LofU and supporting documentation, specifically the proposals for the confirmatory studies, entails an additional review. This time is not captured in the current Management of Drug Submissions Policy / Performance Targets.

Neither BBR nor BPA has adequate resources to meet the performance targets for either Priority or Non-Priority submissions (ie. 90% reviewed to decision point within performance target of 180 or 300 days respectively).

The Management of Drug Submissions Policy contains no reference to requests for Priority Status and NOC/C as a submission type, nor NOC/C as a document type. The time required for the development / review of the Letter of Undertaking and supporting documentation, specifically the proposals for the confirmatory studies, is resource intensive and is not captured in the MDSP nor in performance targets.

Recommendations:

- Develop a guidance document to support the process and to assist staff / stakeholders in the interpretation of policy definitions;
- Develop a Programme Standard Operating Procedure identifiying inter-bureau linkages (both pre- and post approval) and roles/responsibilities;
- Make appropriate changes to the Management of Drug Submissions Policy (eg. Request for NOC/C and the NOC/C submission as document types with performance target).

Letter of Undertaking

Neither BBR nor BPA has standardized procedures for the development of a Letter of Undertaking. In BBR, the wording of the Letter of Undertaking is drafted by the reviewers and the sponsor is asked to reproduce it with

signatures. In BPA, responsibility for the drafting of the letter rests with the sponsor, but requires review and approval by BPA. Both procedures are resource intensive.

There is no standard requirement for the "conditions" outlined in the Letter of Undertaking. The "conditions" are generally the requirement to conduct appropriate and designated confirmatory studies within a specified time frame. In some instances, there is the requirement to submit Periodic Safety Update Reports (PSUR) on a quarterly basis. It appears that the conditions are developed on a case-by-case basis and is product specific and time frames for the conduct of confirmatory studies are not always identified.

This section of the policy should expand on the definition briefly outlining the essential components of the LofU. Some sponsors have requested guidance on the format and content of the LofU while others have challenged bureau requests. The policy should outline the essential format of the LofU including standard statements and the circumstances under which an L of U can / must be revised and sponsors' obligations (eg. Company buy out or merger).

Recommendation:

- Develop a standard template and content requirement for the Letter of Undertaking (L of U);
- Revise definition to include the essential components of the LofU, to highlight the requirement to meet ALL committments and to inform the TPP of any changes to the status of the undertakings;
- Clarify the development process of the LofU and related obligations of the sponsor, the processing of information relevant to the LofU, and the situations under which an NOC/C can be replaced with an NOC.

Confirmatory Studies

While there is no statutory authority for requesting that post-marketing confirmatory studies be conducted, authority does exist for requiring sponsors to maintain records of any such studies if conducted, and to submit these on request of the Minister (C.08.006 and C.08.007).

For the NOC/Cs issued to date, some sponsors have essentially identified all ongoing studies in their clinical development program, including Phase I and Phase II studies. Another sponsor proposed to provide a re-analysis of the data that had already been reviewed. In one instance, a sponsor proposed a confirmatory study that was conducted in a different patient population than those studies that were deemed 'promising'. The policy needs to outline what is really meant as a confirmatory study, and what type of study it is that TPP expects to see.

The issuance of an NOC/C will result in the filing of a Supplemental New Drug Submission (S/NDS) containing data from the required confirmatory study. Insufficient resources are available to review this information, and performance targets for clinical S/NDSs are not consistently being met. Additionally, although the original submission for which the NOC/C is issued is most likely a Priority submission, there is no indication in the current policy as to whether the S/NDS will be a priority submission.

To date, the TPP has received the results of confirmatory studies for two of the products which have been issued NOC/Cs. These submissions (S/NDSs) have not yet been reviewed, therefore, the validity of the studies to verify the clinical benefit of these drugs has not yet been determined.

Recommendations:

- Clarify in policy and guidance document what we would consider to be an acceptable confirmatory study;
- Establish performance target for S/NDS for confirmatory studies.

Monitoring of Conditions

Generally, the monitoring of compliance with conditions has been the responsibility of the review bureaux. To assist with tracking the confirmatory studies, the Letter of Undertaking is sent to Submission and Information Policy Divison (SIPD), BPC, where the target dates are entered into the Drug Submission Tracking System (DSTS). Confirmatory studies are tracked as S/NDS-Cs. The review bureaux use DSTS reports to monitor compliance with the target dates for submission of confirmatory study results. To date, sponsors who have failed to submit confirmatory study results within the agreed upon time frame have been required to submit a revised Letter of Undertaking (as required in the policy).

Periodic Safety Update Reports (PSUR), which are often identified as a "condition", must be submitted quarterly. These are tracked in the DSTS as a submission type (PSUR-C), however, they are only logged into the system as they are received (not in advance). There is a performance target of 180 days for review of the PSURs, which was set arbitrarily.

There is no active monitoring system in place for NOC/Cs in the Bureau of Compliance and Enforcement (BCE). They are not directly advised when NOC/Cs are issued. BCE involvement is triggered, as for any NOC, when there is a violation of the Food and Drugs Act and Regulations, or if there is a health hazard.

Recommendation:

- Assign a "NOC/C Manager" for each NOC/C product to monitor compliance with conditions;
- Use existing tracking mechanisms (eg. DSTS) to monitor compliance with conditions;
- Advise BCE when an NOC/C is under active consideration.

Safety Information

Adverse Drug Reactions

According to the NOC/C policy, NOC/Cs are subject to existing regulations and guidelines for adverse drug reaction reporting (C.01.016). This requires mandatory reporting by the manufacturer of serious ADRs that have occurred in Canada ~~within 15 days~~, and serious unexpected ADRs occurring outside Canada within 15 days of having received the information. It should be noted that reporting of ADRs by consumers and health professionals is voluntary. This is considered to be "Passive" surveillance as defined in the Strategy for TPP Post-Approval

Assessment Activities 1999-2003 - "Passive surveillance is defined as: receipt of reports of cases provided by health professionals at their discretion".[16]

The Bureau of Licensed Product Assessment (BLPA) has established a process to maintain the a Drugs of Current Interest (DOCI) List [17] The purpose of the DOCI list is to provide regular monitoring and stimulate reporting for a selected group of marketed products in order to identify drug safety signals. One of the criteria for inclusion on the DOCI list is "recently marketed drugs (<2 yrs), with generally limited post-marketing experience and potential safety concern from pre-market review (eg. NOC/C)" The DOCI list is maintained by the Adverse Reaction and Medication Error Assessment Division, BLPA, in collaboration with the DOCI Working Group (representation from BPA, BBR, BLPA, Regional ADR centres, EAC Pharmacovigilance). Drug products which have received NOC/Cs are subjected to "structured monitoring" of ADRs via the DOCI list program, if they are approved by the DOCI Working Group. Currently, there are 26 drugs on list (6 of which are NOC/C products).

Line-listings of ADR data on DOCI drugs should be produced **every 3 months** or more frequently (as determined by DOCI WG) by the ADR specialists who prepare a monitoring summary. These summaries are reviewed at DOCI Working Group meetings.

Periodic Safety Update Reports for NOC/C Products

21(1)(b)

Periodic Safety Update Reports (PSUR), which are usually associated with the "conditions", are not reviewed by BLPA. It is BLPA's position that the review bureaux, who set the conditions, should be responsible for reviewing the PSURs. If they are sent to BLPA, they are forwarded to the appropriate review bureau. However, neither review bureaux has adequate resources to review these reports in the detail required nor in a timely manner.

Since NOC/C products are reaching the market earlier in the drug development cycle, the nature and incidence of ADRs that could occur would not be fully elucidated when an NOC/C is issued due to the nature of Phase II clinical trials (the results of which are generally the basis for approval of NOC/C products) such as: limited sample size; selected homogeneous population; absence of concomitant disease/medications. Therefore, it is recommended that emphasis be placed on the development and subsequent review of the PSUR and on ADR surveillance for NOC/C products.

Recommendations:

- implement "active surveillance" activities for NOC/C products, as outlined in the "Strategy for TPP Post-Approval Assessment Activities". "Active surveillance is defined as: regular periodic collection of case reports from health care professionals & health faciltities that are evidence-based rather than on passive surveillance activities". For example, require that sponsors of NOC/C products conduct targeted safety monitoring studies in the context of the situation.
- BLPA to send ADR data (reported by health professionals) for NOC/C products directly to sponsor within 15 days of receipt (for inclusion in their PSURs);
- Review bureaux to advise BLPA when NOC/C is under consideration and after NOC/C is issued

[16] TPP Post-Approval Assessment Activities: Strategy 1999-2003, January 24, 2000

[17] TPP Standard Operating Procedure Drugs of Current Interest List (DOCI) List, Version 8, November 3, 1999

(copy of Letter of Undertaking);

- Place all NOC/C products on the Drugs of Current Interest (DOCI) List;
- BLPA to send quarterly line listings of ADR data for NOC/C products to "NOC/C Manager";
- All PSURs received for NOC/C to be reviewed by original review bureau - allocate sufficient resources to enable adequate review;
- require that sponsors use the PSUR format and content outlined in ICH Topic E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs;
- advise sponsors that all other ADR reports for NOC/C products are to be sent to BLPA (Excluding PSURs which are sent directly to review bureaux) (in SOP and guidance document).

Withdrawal or Stop Sale

Protected Solicitor-Client Privilege

The current policy states that "If a sponsor fails to comply with any of the undertakings ..., the drug may be withdrawn from the market in accordance with the authorities contained in the *Food and Drugs Act and Regulations.* Reasons for withdrawal or "stop sale" may include:

(i) failure to report the results of confirmatory studies (C.08.008),
(ii) failure to provide the results of such confirmatory studies to the Therapeutic Products Programme in a timely fashion, having regard for the safety and effectiveness of the drug (C.08.008),
(iii) failure to provide the results of such confirmatory studies when requested to do so by the Therapeutic Products Programme (C.01.013),
(iv) failure to comply with any post-marketing restrictions on the use of the drug (C.08.008),
(v) failure of such studies to demonstrate clinical benefit or if such studies raise safety concerns about the drug (C.08.006(2)), or
(vi) failure to initiate confirmatory studies within a time period sufficient to conclude the studies within the time frame agreed upon in the Letter of Undertaking..

21(1)(a) 23

There has been insufficient experience to date to determine whether the use of these regulatory provisions could be effectively used to revoke a Notice of Compliance with Conditions (NOC/C). Arguably, the above sections would not normally be invoked unless evidence arises as to the safety and efficacy of the drug that was not available at the time of the issuance of the NOC/C.

Recommendation:

- Include specific provisions for withdrawal of an NOC/C in regulation.

- Patient needs, and the availability of other access mechanisms, should be considered in the regulator's decision to withdraw an NOC/C.

Resources

The consistent message from the Working Group and review staff has been that there are insufficient resources in place to meet performance targets and to effectively implement **all aspects** of this policy (eg. review of PSURs to the extent required, active monitoring of conditions, enhanced surveillance of ADRs, etc.)

The PriceWaterhouseCoopers[18] report made recommendations to improve the process for Priority Review submissions, such as the use of a team approach for priority submissions, providing greater attention and coordination to the review process and additional resources to reduce submission "down time". However, the report did not indicate the resources required to meet performance targets. This was to be done in a subsequent study, which has not yet been initiated. Note that business plans were conducted to identify the incremental resources required to meet the new performance targets for clinical trial review (eg. reducing the target for INDs from 60 days to 30 days).

Recommendation:

- conduct a detailed study to determine the necessary increase in resources to meet performance targets for NOC/Cs, eg.
  - average time for review of a priority status request;
  - average time for the development of a Letter of Undertaking;
  - average time for review of the information submitted to meet the conditions imposed;
  - statistics on the number processed in each bureau versus the available resources,

  The study should identify impacts on "standard" submissions, eg. Clinical trials, non-priority submissions, etc.

Transparency / Communication

A communication plan was not prepared at the time of policy development, although it was recommended that one be developed. The communication plan was to address the following key messages:

- the policy must be distributed to all stakeholders and posted on the TPP website;
- stakeholders must be able to easily determine which products have received a NOC with Conditions;
- adjustments to the NOC Updates on the website must be made accordingly;
- mechanisms must be in place to ensure that stakeholders understand the meaning of a Notice of Compliance with Conditions and are aware of the basis on which a NOC with Conditions is granted in each instance;
- stakeholders must be made aware when all of the undertakings have been complied with for a

[18] Therapeutic Products Program, *Baseline Assessment of Drug Submission Review Process*, April 26, 1999

product and an NOC with Conditions is replaced with a NOC.

The NOC/C policy was disseminated to stakeholders (by mail) and is posted on the TPP website. Products which have received NOC/Cs are listed in the NOC Updates. There appears to be no process to take advantage of other communication mechanisms to ensure that stakeholders understand the meaning of a NOC/C nor for full disclosure of "conditions". The requirement to include the "conditions" in the Product Monograph is deemed to be insufficient (see section on Labelling).

The Food and Drug Administration (FDA) issues "FDA Talk Papers" which are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. The FDA issued a Talk Paper regarding Relenza (zanamivir) on July 27, 1999[19] as well as the Approval Letter, Label and Drug Approval Package (incl. Review summaries). The FDA also publishes a list of all products approved under the Accelerated Approval Program, including approval times and approved indications[20]. Section 112 of The Modernization Act of 1997, "Expediting Study and Approval of Fast Track Drugs" requires that the "Secretary shall develop and disseminate to physicians, patient organizations, pharmaceutical and biotechnology companies, and other appropriate persons a description of the provisions of this section applicable to fast track products".

One of the recommendations of the Consultative Workshop on the Drug Review Process made reference to the transparency of the review process, including for NOC/C:

> *"Increase transparency of the review process to include access to non-proprietary information about the status of the review and the rationale for any final decision made by Therapeutic Products Programme including Notice of Non-compliance (NON), Notice of Compliance (NOC), Notice of Compliance with Conditions (NOCC), and Notice of Deficiency (NOD). Develop a meaningful system of external communication to increase the transparency of the review process with all stakeholders."*

This recommendation will be considered by the "TPP Task Force on Transparency". Any initiatives to increase the transparency for the review process for NOC/C and disclosure of conditions need to be consistent with the TPP Transparency initiative, TPP's health information policy within the context of Legislative Renewal, requirements under the Access to Information Act, and committments under GATT and NAFTA.

Recommendations:

- Increased transparency of the review process for NOC/C should be consistent with all transparency initiatives currently underway (as noted above);
- Develop communication plan for the NOC/C policy ... examples:
  - define target audiences (TPP staff, industry, provincial formularies, health professional associations, physicians, pharmacists, patients, general public, etc.);
  - issue press release for NOC/C approvals (similar to FDA Talk Paper) and when NOC/Cs

[19] United States Food and Drug Administration website http://www.fda.gov/bbs/topics/answers/ans00966.html

[20] US FDA Website: http://www.fda.gov./cder/rdmt/

become NOCs.;

- issue Dear Health Professional letters for each NOC/C approval (full disclosure of conditions);
- develop Programme SOP for NOC/C policy identifying interbureau linkages, both pre- and post approval, and post on ibbs;
- prepare Fact Sheet on the NOC/C Policy and post on website;
- prepare guidance document for stakeholders to assist in the interpretation of the policy and post on website;
- post separate list of NOC/C approvals on website, including approved indications and "conditions".

Evaluation

When the NOC/C policy was developed, it was recommended that an evaluation plan be developed and that the Provinces, industry, health care practitioners and other stakeholders be part of the evaluation process to determine the impact and effectiveness of the policy. Due to insufficient resources, the evaluation plan was not developed.

An evaluation plan should include:

- expected outcomes from the implementation of the policy / regulation;
- the outcome measures that will be used to measure those expected outcomes;
- how these data will be collected;
- when those data will be evaluated against the expected outcomes.

Since this is an internal review, impacts of the policy on external stakeholders (industry, health care system, consumers, etc.) cannot be conducted at this time. This will need to be considered when the evaluation plan is developed.

There is limited experience with the current policy as only 6 NOC/Cs have been issued to date. Average time from filing to NOC/C for these products is xxxx days. This time-frame may not be representative of future clearances as most of these submissions were under review prior to the implementation of the policy and lack of standardized procedures and guidance documents may have contributed to the length of time required to finalize the review of the files. Average time from NOC/C to marketing is xxx days. Confirmatory studies that establish the link between anticipated and real benefit are not yet available, therefore, there are no statistics available as to the effectiveness of the current policy and criteria.

Recommendation:

- Develop comprehensive evaluation plan as part of regulatory process, to include: expected outcomes; outcome measures; how data will be collected; when data will be evaluated. The provinces, industry, health care professionals and other stakeholders should be included as part of evaluation process.

Issue Briefing Book

Notice of Compliance with Conditions (NOC/C) Policy Evaluation

Issue

- Have the original objectives of this policy been met? ie. facilitate patient access to *potential* therapeutic breakthroughs

- Is there a legal basis for the policy objectives?

Problem and Rationale

- There is no explicit regulatory authority for issuing an NOC **with conditions**. According to the *Food and Drug Regulations*, once an examination of a new drug submission is complete - the Minister shall either issue a Notice of Compliance or a Notice of Non-Compliance. The issuance of an NOC/C is, de facto, an issuance of an NOC. An NOC is issued when the Minister is satisfied as to the safety and effectiveness of a drug (sections C.08.002 and C.08.004 of the Regulations).

23

- TPP management decided to implement the policy with the intent to incorporate it into regulation after an evaluation of the impact and effectiveness of the policy was conducted. The TPP decided that the public health benefits of the timely implementation of the policy should take precedence over other considerations at that time.

Current Status

- The NOC/C policy has been in effect since May 1998. The purpose of this Notice of Compliance with Conditions Policy is to:

  (a) Provide patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs.
  (b) Create a mechanism to ensure that a manufacturer which has a drug approved under this policy conducts confirmatory studies to establish the link between anticipated and real benefit.

- As of December 1, 2000, 8 NOC/Cs have been issued.

- There has been recent media attention focusing on the legal status of the policy and the process by which drugs receive an NOC/C. The Director General requested an internal review of the policy, including the nature and extent of the linkage to the Priority Review Policy. The Bureau of Policy and Coordination is leading the review in collaboration with a Working Group with representation from all areas of the Programme and Legal Services.

our story

Possible Strategy/Approach

- An internal TPP working group has been assembled to evaluate the Priority Review and Notice of

Compliance with Conditions Policies.

- Implementation of operational recommendations developed through internal consultation will begin in February 2001. Consultation documents for both the Priority Review and Notice of Compliance with Conditions Policies will be developed in addition to a communications piece.

- External consultations with stakeholders will focus on the consultation documents encompassing issues identified and recommendations made in the draft Issue Analysis Summary. Following consultation, the appropriate line of action will be undertaken by the Bureau of Policy and Co-ordination to make amendments to the Notice of Compliance with Conditions Policy and/or to the Food and Drug Act and Regulations.

Contact:

Tara Bower
957-6244

Alix Clymans
946-7208

Date:

January 22, 2001

Moving Forward with Policy Revisions

Revising Notices of Compliance with Conditions and Priority Review Policies
Internal Consultation Workshop
April 9, 2001

▼PURPOSE

This report aims to:

- provide you with a detailed report of the discussions from the internal consultation session held April 9, 2001; and
- provide you with information regarding next steps to move forward with revising the current Notice of Compliance with Conditions (NOC/C) and Priority Review (PR) policies.

▼OVERVIEW

The purpose of these sessions was to obtain feedback from staff and a pilot group of external stakeholders regarding critical elements in the NOC/C and PR policies. The NOC/C and PR Working Group will take this information into account as they begin to work on revising these policies.

▼APPROACH

Both days began with opening remarks from Dr. Robert Peterson, Director General, Therapeutic Products Directorate. Tara Bower, BPC, introduced some of the challenges the working group is facing and laid out the plan for the day. Key elements to be discussed included:

- scope of the policy;
- definition of terms; and
- considerations for revoking a NOC/C.

David Edwards, Legal Services followed with an overview of the legal issues surrounding these policies.

Facilitated sessions then commenced to focus on these specific areas.

▼PARTICIPANTS

The first session, held April 9th, was composed of staff from the Therapeutic Products Directorate, the Biologics and Genetic Therapies Directorate and the Inspectorate. The second session held on April 12, was a pilot focus group with 10 representatives from various associations and industry groups. A list of the participants is attached in Appendix 1.

▼PRESENTATIONS

Dr. Robert Peterson, Director General, Therapeutic Products Directorate, opened the day by announcing that these consultations were an opportunity to review the current policies and to ensure that they contain the necessary elements.

It is essential that we continue to prioritize our resources to address the backlog and to review submissions within performance targets. The Priority Review policy will help us assign our resources to review high impact, new therapies. The NOC/C policy helps us to make new life saving drugs available to Canadians in a more timely manner.

To meet Canadian healthcare needs, we have received additional resources. Coordinated staffing actions between the Therapeutic Products Directorate (TPD), the Biologics and Genetic Therapies Directorate (BGTD) and the HPFB Inspectorate are underway to hire more staff. Infrastructure resources have also been spent to provide computers and software for incoming staff.

We must also take advantage of other options open to us such as reallocating current and new resources, establishing international and provincial partnerships, cost recovery opportunities and active post market surveillance activities.

Tara Bower, Policy Analyst, Bureau of Policy and Coordination, Therapeutic Products Directorate provided an overview of the events leading up to these consultations. Several key areas have been identified as needing additional clarification. These included:

- scope of the policy
- definitions/criteria
- regulatory/legal issues
- guidance and standard operating procedures
- post-market surveillance
- enforcement activities
- resources
- communications/transparency
- evaluation.

As a starting point, these consultations focussed on the scope of the policy, definitions and some of the legal issues surrounding the current policies.

David Edwards, Legal Services provided an overview of the legal framework supporting both policies and reviewed the current regulations as they pertain to the NOC/C and PR.

23

▼SCOPE

Q: Scope of the Policies - What should the policies address?

- Policy needs to focus on meeting the medical needs associated with identified conditions;
- Policy needs to be able to respond to a public crisis in Canada, includes those for which there isn't currently a life-threatening condition but for which there could be (eg vaccines);
- These policies should only apply to break through therapies which meet clinically relevant, unmet needs. All other therapies should go through the regular review process. Consensus was reached that the group did not want to expand the policies to include unmet lifestyle needs (e.g., a new hair removal drug);
- The NOC/C and the PR policies should be considered as separate policies and as such need clear rationales and definitions associated with each. Not all NOC/Cs issued are Priority Reviews and not all Priority Reviews will receive a NOC/C;
- Since the decision to permit a PR is based on very summary data, there should be an opportunity to revoke a PR if the submission package is incomplete or is the submission package does not meet the definition of a PR;
- Industry should be permitted to request a NOC/C only prior to the commencement of the review. Industry should not be permitted to request a NOC/C after the completion of a NOC review;
- Currently a great number of SNDS submissions are evaluated as Priority Reviews as they meet current criteria and definitions. SNDSs should be looked at in regular time frame as these drugs are already on the market (not covered in current policy);.
- Drug should address a "high" unmet clinical need;
- The criteria need to be related to both safety and efficacy in the PR request, although safety needs to be a larger portion in the PR process;
- Manufacturer provides information suggesting that the drug provides effective treatment and significantly improved efficacy;
- Development of a two-tier criteria - first, does it match our "disease list" and secondly, does it have the data to substantiate the claims;
- Should include quality of life claims within the efficacy definition or within the benefit/risk profile of the therapy; and
- consider quality of life issues when reviewing for PR status, but not in the submission review process.

Q: What are some additional considerations or concerns?

- Available resources will impact Health Canada's ability to implement the policies. Our goal should be to limit the use of PR policy in order to apply resources toward conducting reviews, not determining PR status;
- In some instances, there are products available to address a condition (e.g., blood), but some patients refuse to take these products for personal reasons (i.e., no faith in the safety of the blood supply or religious beliefs). Although these issues may be outside the scope of the policy, they are real issues which need to be recognized in the policies;
- There is a need for the government to make more information publicly available to public/patients/healthcare providers;

- In the United States, industry often discusses submissions, informally with the FDA, 1-3 years prior to their formal submission. As a result, federal regulators have some familiarity with the product prior to its arrival for review. Health Canada needs to encourage similar dialogues with industry;
- An NOC/C decision is made at the end of a review, while a PR decision is made before the review. Frequently, more time is required to review an NOC/C submission than is allowed under the PR policy;
- The absence of clear and concise definitions will provide industry with the opportunity to change submissions to advance the review of their submissions in accordance with the PR and NOC/C requirements;
- There is a need to define terms such as "significantly reduced risk" to ensure consistent application across the Directorates;
- Health Canada should review policies in other jurisdictions (e.g., U.S. FDA) and consider harmonizing our activities;
- De-prioritizing generic submissions is not a viable option to expedite the reviews of other drug submission;
- Difficult to educate patients with respect to risks associated with drugs and treatment regimens; and
- The impact/cost on the health care system if the condition is left untreated may be considered (health canada mandate does not address "cost" perse, howeever if you effectively address effectiveness and sagety, you will implicitly address cost effectiveness in terms of the healthcare system).

▼DEFINITIONS

During the internal consultation session, staff generally favoured examining definitions used by other governing bodies including the Office of Controlled Substances, Healthy Environments and Consumer Safety Branch (Canada Gazette regarding medical marijuana) as well as the FDA and the European Union.

In defining terms such as serious, life threatening and severely debilitating, we must consider the impact of the 180 day review period on the patient. We must also consider the prognosis and disease progression. For example, what is the impact of the disease if left untreated? In the case of a patient with AIDS, the introduction of an HIV treatment may prevent the patient's condition from moving into the next stage of the disease.

Some consideration should also be paid to establishing a list of diseases to which PR status would be automatically assigned in the event of a new, clinically significant treatment. AIDS, ALS and cancer are such examples.

Lastly, potential public health benefit should be considered for PR status. This would encompass situations in which there are no current life threatening illnesses, but there could be (e.g., a new vaccine).

Suggested Definition elements:

Serious

- there is an impact on day to day activities, but there is no immediate danger of dying
- there is a reduction in the amount of secondary infection (also known as third party risk)

Life Threatening

- death would occur within 12 months

▼SUBSTANTIAL/PROMISING/INCONCLUSIVE CLINICAL EVIDENCE

Q: What constitutes substantial clinical evidence? (In light of the 10-page synopsis provided, the group examining this issue decided rather to examine the criteria for determining efficacy in a PR request.)

Substantial

- The primary decision for Priority Review is based on a 10 page document. Some requests are the same as the fast-track to the US; cannot have substantial clinical evidence in ten pages;
- May include anything better than what we currently have available - even a little change - offering immediate advantage demands a quicker review; and
- Substantial is important to narrow down what should be reviewed - promising would apply too broadly - all submissions should have substantial data.

Promising

- Promising information still suggests that the drug provides...effective treatment, significantly improved efficacy;
- "promising information" too loose a definition - possibly use the two bullets that follow;
- Does quality of life have a place here? May not increase efficacy or safety but rather have more value to the HC system and Canadians;
- Requirement for a case-by-case assessment - do not consider how many other drugs have a similar profile;
- Possibility of quality of life claims fit within the efficacy definition - included in the risk/benefit profile of the therapy; and
- Reminder that 'information' is not promising - the therapy is promising.

Inconclusive

- Therapies possessing an unacceptable benefit/risk profile; and
- Not based on validated surrogate markers.

Other considerations/concerns

- Quality of life protocols are where industry base their advertising claims. The presents a somewhat dangerous ground. Quality of life may be part of the PR process, not necessarily the entire review process - should not be highlighted, but included in the efficacy question;
- The 10 page synopsis is intended to provide the potential, not the complete or even close to

complete data;

- Criteria related to both safety and efficacy - safety needs a larger part in the PR review process;
- A consideration should be made for anything else available capable of doing the same job with the same risk/benefit profile - COX-2 inhibitor that does not allow bleeding; and
- The benefit must be relevant to the disease.

▼SIGNIFICANTLY INCREASED EFFICACY AND SIGNIFICANTLY DECREASED RISK

Q: What constitutes a significant increase in efficacy?

Standard

- Statistical significance which is clinically relevant;
- Phase II study results (small) but respectful difference (not significant), when phase III trial comes in, then maybe PR, but phase II not enough;
- Clinically significant compared to existing standard of care, with no concomitant increase in ADRs/risk; and
- While both safety and efficacy are needed, there is a need to ensure that there is an improvement in benefit/risk profile (e.g., a 3 month life extension may not be clinically or statistically significant, but could be viewed as an acceptable risk by the patient given the potential benefit).

Exceptions

- A small number of patients cannot demonstrate statistical significance, therefore a complete unmet need can override the need for statistical significance;
- Recognition that statistical and clinical significance differs;
- Orphan drugs may not require statistical significance; and
- The need for a separate orphan drug policy was clearly identified.

Principles

- There exists an implied need for guidance where assessment is based on state-of-the-art assessment criteria (accepted clinical criteria);
- One standard for quality of data in relation to the review process - have the same data for PR submissions and non-priority submissions - they both must establish the safety and the effectiveness; and
- Must link safety with efficacy.

Q: What constitutes a significantly decreased risk?

Standard

- Statistical significance of a decreased risk which is clinically relevant;
- Must be able to *demonstrate* the decreased risk;
- In case of vaccines, a moderate decrease in risk is all that is necessary;
- Improving a drug's safety profile (change in manufacturing) to make it safer may be considered

for PR;

- Need both statistical and clinical significance to determine decreased risk;
- Must be based on population taking the drug; and
- Looking for solid evidence of improved efficacy or reduced risk - this could come from one or more trials.

Exceptions

- Often in cases of children, we cannot rely on statistical significance - small changes in a vaccine can be significant in the long run;
- Patient compliance may be an element to be consideration when determining PR status -e.g., a longer lasting dose may increase patient compliance in taking medication - when a patient stops taking the medication, there is an increased risk of disease progression;
- What size of risk are you managing - you may never be able to get enough data clinically, so manage risks on statistical data;

Principles

- Significantly reduced risk is not usually known until the therapy has been on the market for 2 years, difficult to include in the PR review process;
- If you take "statistical" out of the policy, and write guidance documents to dictate what is a "significantly decreased risk", then the policy would include vaccines e.g., DPT;
- Public acceptance = perceived benefit by the public might outweigh risk;
- Difficulty using the term statistically significant in risk reduction;
- eg. a new formulation may decrease risk, but not efficacy (e.g., IV versus oral formulation); and
- ICH identifies principles.

Concern regarding significantly decreased risk

- What is the magnitude of improvement that is considered significant?
- What is the "value" which indicates significantly decreased risk?

▼SAFETY THRESHOLDS

Q: With an understanding that the data package is limited for an NOC/C, what are the minimum safety elements/evidence required?

- Suggested rewording of section: "providing the safety of the drug is found to be acceptable based on a benefit/risk assessment of anticipated efficacy..." This allows for the existence of other factors to be introduced into the assessment eg. environmental factors etc and justifies the lack of concrete safety data;
- The risk/benefit assessment enters into the balance of existing safety and efficacy data;
- The nature of the disease or condition can affect data requirements;
- There is no difference from a full NOC in assessing the risk in the context of an anticipated

benefit;

- Labelling and product monograph can address deficiencies in the pre-market safety data;
- Could allow phase II studies and no Phase III but would require notice in labelling;
- Surrogate endpoints can be used when full clinical endpoints are unavailable;
- Safety does not equal risk - a benefit/risk analysis is not a purely safety analysis;
- Safety profile criteria is the same for NOC/C and NOC - difference is in promise of efficacy and volume of data associated with efficacy;
- Must not decrease life expectancy;
- Need exhaustive phase I studies, need to show interaction data;
- Assume with NOC/C that the efficacy will be proven once on the market;
- Use life without the product as a baseline of comparison;
- We lack guidance of what "reasonably established safety" really is - require addition guidance to define the concept; and
- Any variation in information requirements is a function of the review process.

▼CONFIRMATORY STUDIES

Q: What elements do you want to see in a confirmatory study? What constitutes an acceptable confirmatory study? What is our role as regulator, should it be pro-active and inform industry of acceptable design or to accept what they provide?

- We are looking for the data that will remove the conditions that are attached to the NOC/C - must adequately address the concerns of the review;
- A policy to address the Directorate's role in assisting manufacturers in the design of confirmatory studies should be considered. On one hand it would help manufacturers to conduct better studies, but there is a conflict of interest if we are regulating something which we helped to design;
- Confirmatory studies stay as a regulatory function, but reviewers would like to have the option, once the review is done, to indicate what studies we want done, work with other resources to see what kind of study should be done;
- The sponsor should indicate what kind of studies are being proposed at the time of the application for the NOC/C;
- No universal time frame for the submission of confirmatory studies - it depends on the nature of the disease - a time frame should be established at the issuance of the NOC/C and agreed upon by both parties in the Letter of Undertaking;

why not?

- Specify conditions of NOC/Cs to be exhaustive to ensure size of population, percent of population, time frame, study addresses the issue, prove what was in the product monograph;
- New product monograph will have "confirmatory studies" section - need to be considered monograph should indicate that this is for an NOC/C and patient package insert;
- At end of review, we should give a thorough list of what is missing, this would be in the conditions part of the NOC/C;
- Hard to get a confirmatory study unique to Canada due to market size, therefore we need Canadian input into the study design even though the study may occur in another country;
- Clinical benefit has to be established in the same population as the surrogate markers;
- Niche product - asked for full randomized controlled trial on sub population for listed indication;

and

- Could test finding in small population in large population- limit studies to patient population where need is high.

▼REVOCATION OF AN NOC/C

Q: In cases where there is a lack of sufficient and follow-up evidence, what should we do? What are some of the considerations for revocation?

- Need to entrench this policy in Regulation to ensure that we have the enforcement power to revoke an NOC/C;
- Need to narrow the scope of the definitions used in the policy up front in order to reduce the number of drugs which could be considered for an NOC/C as this review process is intended for "break through" therapies;
- If the manufacturer fails to submit satisfactory confirmatory studies as agreed to in the Letter of Undertaking, there should be a default situation in which an NOC/C is revoked - however, we also need the authority to make exceptions to this rule on a case-by-case basis;
- The NOC/C should only be issued for a specified period of time after which it would need to be renewed (e.g., like a licence). The Medical Devices Regulations may be able to provide some guidance in this matter;
- Each therapy has to be negotiated - there will always be exceptions;
- ADRs must be implicated - small trials cannot show the same data as in the larger population;
- Upon failure to meet - send to committee to assess the situation; and
- If patients are informed, through package patient insert, and data is inconclusive, they know that the therapy may be withdrawn - communication very important.

Revocation of a NOC/C - Concerns

- When revoking an NOC/C, essentially you are withdrawing an NOC;
- The Special Access Program (SAP) can be used when we withdraw an NOC/C - must consider the monetary costs - sponsors do not provide the therapies for free through SAP - if these drugs are not listed through formularies, provinces need to really understand the NOC/C process, as they may not include them in their formularies if no studies have proven efficacy; and
- Liability - what is Health Canada's liability if we originally authorized a NOC/C, but then the supporting studies are negative.

▼OUTCOME AND NEXT STEPS

▼Outcomes from the Meeting

1. The issue of resources remains a significant concern for staff as it will largely impact on their ability to implement these policies and to meet performance targets;
2. We should not consider expanding the criteria for either the NOC/C or PR policies to include other drugs. If anything, the criteria should be tightened to grant only break through therapies addressing clinically unmet needs PR status;
3. Manufacturers should not be allowed to request a NOC/C if they are denied a NOC; and
4. Harmonization with other regulatory agencies may assist us in developing clear and concise definitions and policies.

THAT'S WHAT HAPPENS IN THE RELEVANT CASE

▼Next Steps

Following these two sessions:

- internal clinical subcommittees will be established;
- an evaluation framework will be developed by the Socio-Economic Evaluation Division of BPC;
- the communications plan will be finalized by June;
- additional consultation sessions will be planned to discuss post-market assessment, and compliance and enforcement issues such as advertising and labelling restrictions); with a view to
- the preparation of a consultation document for widespread distribution to stakeholder groups.

Health Santé Canada Canada

Priority Review & Notice of Compliance with Conditions - Policy Review

Clarifying scope, criteria and definition elements
External Focus Group Workshop, April 12, 2001

PRODUITS THÉRAPEUTIQUES THERAPEUTIC PRODUCTS PROGRAMME

Overview

- Introduction to NOC/C and PR Working Group
- NOC/C and PR - current policies, linkages, origins
- Recommedations 2000
- Current working group activities, proposed consultations
- Focus of current workshop
  - Examine and explore challenges of current scope, criteria and definitions
- Next Steps
- Agenda

Health Santé Canada Canada — Therapeutic Products Programme / Programme des produits thérapeutiques

NOC/C and PR Working Group

- BPA, Sheila Hills
- BBR, Susan Rau (Dixon Ho - alternate)
- BCE, Trish Maynard
- BLPA, Susan Robertson
- BMD, Nancy Shadeed
- OSPCQ, Kathy Bird
- Legal Services, David K Edwards
- SEED, Michelle Maragh, Andre Bergeron
- BPC, Laura Freeman (SIPD), Alixanderia Clymans (Regulatory), Tara Bower (Project Lead)
- BPC, Kim Hannah (Public Involvement)
- Clinical Sub-Committee

Health Santé Canada Canada — Therapeutic Products Programme / Programme des produits thérapeutiques

Background

- Priority Review Policy - December 1996
- NOC/C Policy - May 1998
- Media attention
- HIV/AIDS Working Group recommendations #5 and #11
- currently 9 NOC/Cs issued for 8 products

Health Santé Canada Canada — Therapeutic Products Programme / Programme des produits thérapeutiques

Key Recommendation Areas

- Policy/Scope
- Definitions/Criteria
- Regulatory/Legal
- Guidance/SOPs
- Post-Market Surveillance
- Enforcement
- Resources
- Communications/Transparency
- Evaluation

Health Santé Canada Canada — Therapeutic Products Programme / Programme des produits thérapeutiques

Consultations

- ★ Workshop Series 1 - April (focus on scope, criteria and providing clarity to definitions)
- ★ Formation of a clinical sub-committee
- ★ Workshop Series 2 - June (focus on postmarketing & enforcement)
- ★ Broad consultation both internal and external (mailout)

Enhanced transparency through communication tools!

Health Santé Canada Canada — Therapeutic Products Programme / Programme des produits thérapeutiques

Scope
Priority Review Policy

- serious, life-threatening or severely debilitating disease or condition for which there is ***substantial*** **clinical evidence** that the drug provides:
  - effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or
  - significantly improved efficacy or significantly diminished risk over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada

Scope
Notice of Compliance with Conditions

- serious, life-threatening or severely debilitating disease or condition for which there is ***promising*** **clinical evidence** ***based on the available data*** that the drug provides:
  - effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or
  - significantly improved efficacy or significantly diminished risk over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada

Recommendation #5 *

- "5. Refine the criteria for designating **priority reviews** to ensure that priority review is granted for drugs which are intended for the treatment of a life-threatening condition, or for drugs which demonstrate *the potential to address serious unmet medical needs*. Under these criteria, the TPP should also approve applications for a fast track review if the product has an effect on a *clinical or a surrogate endpoint that is reasonably likely to predict clinical benefit*"

* Recommendations of the Consultative Workshop on the TPP Drug Review Process, Sept 30 - Oct 1, 1999

NOC/C - Policy

- Providing the safety of a drug product can be reasonably established and the product is found to be of high quality, a NOC/C may be issued for a drug product with promising clinical benefit which meets the outlined criteria.
- Prior to issuance, the sponsor must undertake in writing to design and carry out confirmatory studies to verify the clinical benefit (Letter of Undertaking).
- the "conditions" under which the product is approved must be clearly reflected and highlighted in Product Monograph and/or labelling. The sponsor must also comply with any advertising restrictions imposed by TPD.

Next Steps

- Establishment of an internal clinical sub-committee
- Development of an evaluation framework
- Finalization of communications plan
- Consultations on post-market assessment, compliance and enforcement issues (ie. advertising, labeling restrictions etc)
- Development of a consultation document for widespread distribution to stakeholder groups
- Finalization of policy
- **Immediate: Disseminating a report from this workshop.**

FINAL

Moving Forward with Policy Revisions

Revising Notices of Compliance with Conditions and Priority Review Policies
Therapeutic Products Directorate, Health Canada
External Focus Group Consultation
April 12, 2001

▼PURPOSE

This report aims to:

- provide you with a detailed report of the discussions from the external stakeholder session on April 12, 2001; and
- provide you with information regarding next steps to move forward with revising the current Notice of Compliance with Conditions (NOC/C) and Priority Review (PR) policies.

▼OVERVIEW

The purpose of these sessions was to obtain feedback from staff and a pilot group of external stakeholders regarding critical elements in the NOC/C and PR policies. The NOC/C and PR Working Group will take this information into account as they begin to work on revising these policies.

▼APPROACH

Both days began with opening remarks from Dr. Robert Peterson, Director General, Therapeutic Products Directorate. Tara Bower, BPC, introduced some of the challenges the working group is facing and laid out the plan for the day. Key elements to be discussed included:

- scope of the policy;
- definition of terms; and
- considerations for revoking a NOC/C.

David Edwards, Legal Services followed with an overview of the legal framework supporting the policies.

Facilitated sessions then commenced to focus on these specific areas.

▼PARTICIPANTS

The first session held on April 9, was composed of staff from the Therapeutic Products Directorate, the Biologics and Genetic Therapies Directorate and the Inspectorate. The second session held April 12, was a pilot focus group with 10 representatives from various associations and industry groups. A list of the participants is attached in Appendix 1.

Health Canada Santé Canada

Access to Information and
Privacy Division
Room B1241
Jeanne Mance Building
Address Locator 1912C1
Ottawa, Ontario
K1A 0K9
Tel: (613) 954-4699
Fax: (613) 941-4541

Your file Votre référence

Our file Notre référence

October 29, 2001

Mr. David McKie
CBC-Radio
Chateau Laurier Hotel
1 Rideau Street, 7th floor
Ottawa, Ontario
K1Y 1E4

Dear Mr. McKie:

This is further to my email of October 29, 2001, concerning your request for information on Rilutek under the Access to Information Act.

Please find attached a copy of the records which respond to the above-mentioned Access request.

If you have any further questions as it pertains to this request, please don't hesitate to contact me.

Yours sincerely,

Y. Parent

Yvette Parent
Senior Assistant Coordinator
Access to Information
and Privacy

Attachment

Email: Yvette_Parent@hc-sc.gc.ca

Canada

Re: Data from North American Patients
On Points Made on Pages 37-38 of Executive Summary

1. **Review of North American data represents a secondary analysis**

In a way, this is true; but then again, it is not. Firstly, the entire reanalysis by Dr. Koch can be considered a secondary analysis. The original NDS analysis already considered risk categorization in two ways - by site of onset and by halving the data set according to risk variables using another method. It is common knowledge that regulatory agencies have always been interested in treatment by centre, treatment by region, treatment by country interaction. This is to ensure that efficacy observed in some centres are not contradicted in others, that we are not in fact observing artifacts due to different medical practice, trial conduct, etc. HPB is not making unreasonable demands on this point. When is a post hoc analysis reasonable and when is one unacceptable? If the subgrouping is base on variables that may be altered by treatment, the post hoc analysis is not acceptable. When the subgrouping is based on baseline variables, the post hoc analysis may be considered as secondary analysis.

2. **Sample size for Study 301 was power for an overall analysis**

In reference to Tables 9 and 10 from Dr. Koch's report, using site of onset which was an original risk factor, and the 22 risk variables from which the risk tertiles were obtained, and ignoring the confidence intervals all together (i.e. not considering any significance test for the moment), the point estimates of the risk ratios for North American patients do not indicate any trend for efficacy in North America.

3. **... the possibility that recruitment of ALS patients with varying degrees of risk may not mirror the situation in European centres**

That simply put is an example of why an examination of efficacy in the different regions is important. Table 7 of Dr. Koch's report did indicate that the patient distribution according to the risk tertile classification is slightly different in the North American data, but that is not sufficient to have been the cause of the different results.

4. **... patients were allocated to one of the three risk tertiles**

The use of the term allocate is usually reserved for the planning stage of a study, as in random allocation to treatments. It is more appropriate to use the term classified instead. It was a post-stratification procedure, and as such, the division into tertiles does not produce independent treatment groups for comparison, i.e. the resultant comparisons cannot be considered on the same footing as treatment comparisons protected by random allocation.

In general, it is perfectly legitimate to look at treatment effects by regions, and to question any

discrepancies. In the absence of any clear and obvious explanation for the discrepancies, interpretation of the results should be made with circumspect. It is a clinical rather than a statistical decision whether demonstration of significant efficacy in North American centres is a requirement. It suffices to say that efficacy appears to be clear for France and Belgium which forms only half of the study. For the rest of Europe and for North America, it is not clear at all. If any, efficacy is likely to be slight.

K. Y. Robert Li
August 7, 1997

MICHAEL H. BROOKE M.B. B.Ch. F.R.C.P.C. F.A.A.N.

University of Calgary
Department of Clinical Neurosciences

Tuesday, September 09, 1997

Marianne Tang
Therapeutics Products Directorate
Holland Cross
Tower B, 3rd Floor
1600 Scott Street, Address Locator 3103A
Ottawa, ONTARIO
KIA IB6

Dear Ms. Tang,

Thank you for the opportunity to review the appeal by Rhone Poulenc Rorer on the NOD on the drug Rilutek. This is a very difficult issue and one in which the emotions and the desire of the medical and patient community to have an effective drug often influence the attempt to interpret the clinical data. Just to review the background in a brief fashion, ALS is a rapidly progressive and fatal disease for which there is no cure. There has been a recent explosion of information on the possible causes of this illness, leading to the belief that we must be a short way away from designing an effective treatment. Clinical scientists and pharmaceutical companies alike have been eager to start clinical trials to find the answer for this terrible illness. The process was accelerated with the report of abnormalities in the glial glutamate uptake mechanism in patients with sporadic ALS. This reinforced previous suggestions that excess glutamate might be responsible for damaging the vulnerable neurones in ALS, if not the primary cause of the damage. Prior studies of glutamate inhibitors, such as dextromethorphan, were not successful, but the general belief was that these agents were not selective and thier toxicity prevented use of the necessary high dosage. For this reason, when Rilutek, a drug that impairs glutamate release as well as having some effect on the relevant ion channels came along, it was an obvious candidate for a clinical trial in ALS.

The Company conducted an initial trial in Europe which they maintain showed benefit, followed this with another trial in North America, which was also claimed to be positive, and on the basis of these two trials the drug was approved by the FDA in December 1995, followed by approval in many other countries within the ensuing year.

An initial review by the HPB concluded that the studies demonstrated insufficient efficacy and the application for approval of the drug in Canada was denied. The Company is appealing that decision and has disputed the HPB consultants' opinions. These opinions included the fact that the North American trials were unconvincing, the results from the European trials were either positive or negative depending on the analysis and that it was difficult to extrapolate the results to North America from the Belgian and French results. The Company disputes this and maintains that the North American results also show a positive effect of Riluzole and that there was no difference across regions. The company adds no new data but does include a reinterpretation of the old data. The two studies are referred to as 216 the European study and 301.

The criticisms that have been levelled at 216 are that the outcome was not due to an across the board change but to apparent positive results in the "bulbar" group of patients. Criticism of the initial publication included an inappropriate evaluation of the patients who were lost to followup, which the company has attempted to remedy. If one were to take the results of this study at face value, the recommendation would be to approve Riluzole only for those patients who had the bulbar onset. The company has since extended 216 to an open label study at a time when the survival curves appeared

Rm. 1166,
Foothills Hospital,
1403 29th St.
Calgary, ALBERTA
T2N 2T9
Phone 403-670-1261
Fax 403-270-7878
E-mail:
mbrooke@v-wave.com

MICHAEL H. BROOKE M.B. B.Ch. F.R.C.P.C. F.A.A.N.

University of Calgary
Department of Clinical Neurosciences

Tuesday, September 09, 1997

Mariann
Therape
Holland
Tower
1600 Sc
Ottawa,
K1A 1B

Mary, RILUTEK APPEAL
Comments or questions for the external appeal reviewer before I prepare the decision letter?
Final Recall will be addressed to you (Director BPA)
Glen Wiernme

Dear M

the NOD on the
desire of the med
interpret the clin
progressive and
information on th
away from design
have been eager t
accelerated with the report of abnormalities in the glial glutamate uptake mechanism in patients with sporadic ALS. This reinforced previous suggestions that excess glutamate might be responsible for damaging the vulnerable neurones in ALS, if not the primary cause of the damage. Prior studies of glutamate inhibitors, such as dextromethorphan, were not successful, but the general belief was that these agents were not selective and thier toxicity prevented use of the necessary high dosage. For this reason, when Rilutek, a drug that impairs glutamate release as well as having some effect on the relevant ion channels came along, it was an obvious candidate for a clinical trial in ALS.

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Hospital
Calgary, ALBERTA

MICHAEL H. BROOKE M.B. B.Ch. F.R.C.P.C. F.A.A.N.

to be coming together, but the natural selection of the "slow" ALS patients and the few numbers of patients make this difficult to evaluate.

The second study 301 was supposed to answer some of the questions which arose in 216. This was a multicentred placebo controlled study with 3 dose levels. Centres in North America and Europe were recruited. As the Company pointed out, the overall study based on the Kaplan Meier curves and a standard analysis with Cox proportional hazards was apparently positive. A serious question arose which occupied much of the time of the PCNS committee of the FDA in their discussion. The results were carried by the positive results in France and Belgium. The rest of Europe did not demonstrate the same effect. The results in North America were disturbing, with the placebo group performing better than the treatment group. The analysis of site as a confounding variable did not show any positive correlation, but, as has been repeatedly pointed out, not showing an effect of site on the results is not the same as showing that there is no effect.

The Company has now presented a new analysis which has been conducted by their consultant. This is not based on any new data but concentrates on a post hoc analysis of the existing study. With the new analysis, the probability of a treatment effect is just less than .05 when the whole population is considered. Confidence intervals are similarly up to about 0.99 (i.e. just excluding 1). A search for cross site differences does not show any significance and there seems to be no effect demonstrated of disease site influence. However, none of these points answer the original questions and, in fact, the conclusions are similar to the previous results - not surprising since the data is the same. In summary, I agree with Dr. Li's comments on this new analysis and have little to add.

What most of the scientific community is waiting for is an additional study. In this regard it is disappointing that the Company has not included results from their two new studies, the Japanese study and the study on patients with different inclusion criteria. As was pointed out in the FDA committee meeting, results from the new studies would carry a lot more weight thn a re-evaluation of the previous data.

What should the final recommendation be? On the one hand, the point has been made that nothing else is presently available for patients with ALS. The Company has indicated that the expense of any further trials is prohibitive and one must have sympathy with that pointof view. Patients desperately want to try a drug that even has a small chance of improving the disease. Furthermore, to reject a drug on the basis that the size of its effect is too small may not impress the patient who needs an extra two weeks to survive until his pensionable service matures and gives his family some security after his death. These arguments weighed heavily in the FDAs's aproval of Riluzole 2 years ago. The non-scientist on the committee, a representative from the ALS community, stated bluntly that the presence or absence of scientific evidence of efficacy should not be allowed to impede the release of a drug that provided "hope" to patients.

On the other hand, this reviewer has to believe that the function of the HPB and its advisory personnel must be to evaluate the usefulness of a drug to the community on the basis of the evidence, no matter how anguishing the disease nor how compelling the public pressure. On these grounds, Riluzole fails the test. The positive results in both studies were from centres in Europe which may not conform to the same treatment protocols or the same standards of clinical trials as in North America. I do not think that the data shows evidence that it should be approved for use in ALS. I am not convinced by yet another analyss of the data which barely reaches significance in view of the criticisms of the past. If the Company wants to convince me otherwise, then the present data has to be supplemented by the new data which the Company is collecting. If these are more convincing, then, taken with the previous data there would be justification for approving the drug. If not, the results will reassure the ALS patients that they are not missing a potentially useful drug.

Sincerely yours

Michael H Brooke, Professor of Neurology

Status re records requested by David McKie, CBC Radio in email message dated Oct. 15/02
(File numbers placed in same order as outlined in above-noted email message.)

File Number	Records to be partially disclosed/disclosed?	Records given to APP for viewing?
A-2001-00313	YES	YES - Oct. 18/02
A-2001-01270	YES	YES - Oct. 24/02
A-2000-01309	YES	To be provided at later date - 1000+ pages.
A-2000-01319	NO - no records exist	N/A
A-2000-01320	NO - no records exist	N/A
A-2000-01321	NO - no records exist	N/A
A-1998-00958	YES	APP not interested in records re marijuana
A-1998-00967	To be determined	To be determined
A-1999-00182	YES	To be provided at later date - 249 pages.
A-1999-00254	NO - record(s) exempted	N/A
A-2000-00353 (x-ref to A-2000-00349)	YES	YES - Oct. 24/02
A-2000-00400	NO - no records exist	N/A
A-2000-01318	NO - no records exist	N/A
A-1999-01329	NO - record(s) exempted	N/A
A-1999-01330	NO - record(s) exempted	N/A
A-2001-00096	NO - record(s) exempted	N/A
A-2000-00982	YES	YES - Oct. 24/02
A-2000-00099	NO	Abandoned by APP
Other records:		
A-2000-00929 & A-2000-00930	YES	YES - Oct. 24/02

"David McKie" <David_McKie@cbc.ca> on 2002-10-15 05:01:32 PM

To: Kathy Rae/HC-SC/GC/CA@HWC
cc:

Subject: re: requests.

Hi, Kathy, here are the requests that I downloaded from the CAIRS list.
I plan to visit your establishment within the next week to review the clinical trial documents and my Notice of Compliance with Conditiions documents (A-01-0856).
Thanks for your patience.
Have a good evening

David

- clinical trials4.doc
- clinical trials3.doc

NHW2001000313 - Health Canada Date received: 2001-06-19

All documents submitted for approval(s) of clinical trials carried out at an Ontario Institution for an anti-cancer therapy involving the use of B7-1 (CD80), B7-2 (CD86) and/or interleukin 12 (1L-12). July 12 clarification: all documents submitted for approval for clinical trials that have been or will be carried out at an Ontario Institution involving an anti-cancer therapy using the combination of the costimulatory molecule B7-1 (CD80) and the cytokine interleukin-12 (IL-12).

92 PAGES RELEASED:

NHW 2001.03.12
2001.03.12 001270 ADVERSE DRUG REACTIONS TO TOLFENA
Reports of Adverse Drug Reactions to TOLFENAMIC Acid: 1) Any and all A.D.R. reports to TOLFENAMIC Acid [Tolfedine) Veterinary preparations under Drug identification Number: 02238077; 02238924; 02231279; 02231278 2) Date of each A.D.R. report to TOLFENAMIC Acid 3) Pre and post approval A.D.R. reported through veterinarians and the Pharmaceutical Company 4) All contraindications and precautions to the use of TOLFENAMIC Acid. 5) Any and all reports of clinical trials of TOLFENAMIC Acid. On March 27/01 modified to process only items 1 to 4. Item 5 not required at this time and may be withdrawn from request.

101 PAGES RELEASED:

001309 INFO PERTAINING TO THE INSULIN DR
records re: insulin drug Humalog please provide: submission history for these drugs -PM/supplementary PM's (the first two items can be likely very early released) -summary data on NDS, including on clinical trials, if any, held (please confirm if there were clinical trials) -Reviewer's notes and correspondence -correspondence with the drug company(E.Lilly) producing these products other records released/about to be released (RECORDS regarding HUMALOG will be processed under a separate file as requested by applicant to avoid fees) Records for the insulin drugs: Humulin, Humalog -submission history for these drugs -PM/supplementary PM's (the first two items can be likely very early released) -summary data on NDS, including on clinical trials, if any, held (please confirm if there were clinical trials) -Reviewer's notes and correspondence -correspondence with_

Continued from previous page ...
NHW 2001.03.21 001309 the drug company(E.Lilly) producing these products other records released/about to be released

1747 PAGES REVIEWED, 16 RELEASED

001319 RECORDS RELATED TO THE TERMINATI
Provide all records related to the termination of human clinical drug trials in Canada since 1990. Including but not limited to records that explain the reason for the action; reports; reviews and audits

NOTHING RELEASED, NO RECORDS EXIST

001320 PROVIDE THE RECORDS OF AUDITS AN
Provide the records of audits and reviews for all human clinical drug trials from January 1, 2000 to the present

NOTHING

Dept Min	Date Rec'v/Recue	Request No No. Demande	Text Texte	Page: 81

NHW 2001.03.26 001321 RECORDS OF ALL "PILOT INSPECTION
Provide the records of all "Pilot inspections" of human clinical drug trials. Including but not limited t reports; reviews; evaluations; and any action taken as a result

NOTHING

980958 1998, 1999 RECORDS ON ALLOWING US
1998, 1999 records, including drafts, on allowing use of marijuana for medical purposes, options for and designated places for clinical trials, options for places of supply, of a safe supply, options for guidelines for medicinal use of marijuana, options for prescription, for taxing this product or covering its purchase under drug plans as the artificial registered drug substitutes can be, funds per activity set aside for trial implementation, inquiries received to date, and 1998, 1999 licences issued to test and grow marijuana.

2150 REIVEWED: 1474 RELEASED

980967 INFORMATION REGARDING THE HEALTH EFFECTS OF VIAGRA
Information regarding the Health Effects of VIAGRA: 1. Health Ministry analysis of the potential effects of the VIAGRA pill on health, including side effects passed on to infants - see chart of STDs. 2. Health Ministry estimate of the expected increase in cancer rates [about 18 months to 2 years time acc. To the ATBC & CARET trials]. 3. Given that EX-LAX was ordered off the shelves & this had never been known to cause a health problem, the Health

Dept Min	Date Rec'v/Recue	Request No No. Demande	Text Texte	Page: 98

Continued from previous page ...

NHW 1999.03.29 980967 Ministry justificationfor release of VIAGRA known to have killed. 4. Manufacturers' monograph & results of any trials of VIAGRA. MODIFICATION ~ 99/03/30 Re Telephone conversation 1. Product monograph 2. Reviewer's Reports on safety 3. Portions of the comprehensive summary [3.1.2 Toxicology; 3.2.2 Clinical Trials; 3.2.5 Conclusions from Clinical Trials].

NOTHING DISCLOSED BECAUSE FEES NOT PAID....WOULD HAV E TO REFILE

990182 ADR PROFILE FOR SUSTIVA
ADR profile for SUSTIVA: Summary of the number of SUSTIVA associated Stevens Johnson Syndrome, Toxic Epidermal Necrolysis and Hepatitis fatalities reported from clinical trials, through spontaneous reports from marketed use internationally, and compassionate use programmes.

249 PAGES RELEASED

990254 REVIEWERS' COMMENTS AND CORRESPON
Material related to the new obesity drug, ORLISTAT, which is being sold under the brand name XENICAL. Information including reviewers' comments (in particular, early clinical trials showing risks of breast cancer); correspondence with the company and correspondence with the Food and Drug Administration.

NOTHING RELEASED....CAN'T TELL FROM THE COMPUTER WHY THIS WAS SO....

2000.07.14 000353 BACKGROUND PAPERS, REPORTS, ETC B
Any background papers, reports, briefing notes, correspondence or other documents written by departmental officials (or officials contracted by the department) which comprise the department's ethical considerations (both for and against) made with respect to the clinical trials of the RU-486 pill. This should include a copy of any final approval documents. Clarification: records since January 1, 1998

11 PAGES DISCLOSED

000400 CORRESPONDENCE DISCUSSING THE AME
Any internal correspondence (including emails and records of meetings) written by departmental officials in this calendar year discussing the amendments to the food and drug regulations regarding clinical trials dated February 16, 2000 as they relate to the clinical trails of the drug RU-486, including whether the RU-486 application was the first to be considered under the new regime, whether the new rules were put in place partly in order to accommodate the RU-486 trials, and whether the application for trials would have been considered any differently under the old regulatory regime.

NOTHING DISCLOSED

001318 RECORDS THAT TELL ME ABOUT THE RE

Provide the records that tell me about the reasons for action that led to the legislative proposal of a new inspection program for clinical trials in Canada. Including but not limited to audits; legal briefs; health hazard ecaluations; reports; briefing notes; and preparation notes.

991329 ALL RECORDS HELD BY HEALTH CANADA RE: CLINICL TRIALS FOR DEFERIPRONE BY A

Production in their entirety of all records (including all enclosures, appendices and other supporting records) held by Health Canada regarding the Health Protection Branch's consideration or assessment of:

1. the findings and conclusions from one or more of the following clinical trials for DEFERIPRONE (a drug for which a Notice of Compliance is sought by Apotex Inc.);
   - LA-Ol;
   - LA-02;
   - LA-03;
2. Dr. Olivieri's findings, conclusions or opinions regarding deferiprone; and
3. the safety and/or efficacy of deferiprone.

NHW 2000.03.17 991330 VARIOUS RECORDS HELD BY HEALTH CA

Production in their entirety of the following records held by Health Canada regarding one or more of the following clinical trials for DEFERIPRONE (a drug for which a Notice of Compliance is sought by Apotex Inc.):

1. Priority Review Submission dated September 30, 1997 by Apotex, and all appendices and other supporting records;
2. Clinical Study Report LA-Ol, Comparative Study of Exferrum and DFO, dated January 26, 1998 by Apotex, and all appendices and other supporting records;
3. Clinical Summary LA-03, Compassionate Use of Deferiprone, dated January 26, 1998 by Apotex, and all appendices and other supporting records;
4. Clinical Study Report (or Clinical Summary) LA-02 (date unknown) by Apotex, and all appendices and other supporting records; and
5. All annual reports submitted by Apotex for each of the deferiprone clinical trials LA-0 1, LA-02 and LA-03 including all appendices and other supporting records; and
6. Copies of all documents reflecting communications between Apotex and Health Canada, whether by letter or otherwise, regarding the termination of the clinical trials referred to as LA-0 1 and/or LA- 03 for which Dr. Olivieri was Principal Investigator.

NHW2001000096 - Health Canada Date received: 2001-04-30

Documents pertaining to heroin maintenance trials and the North American Op
Documents pertaining to heroin maintenance trials and the "North American Opiate Maintenance Initiative". In particular, I would like to request copies of official documents which outline the scope and mandate of the project (project summary, mandate and overview, corporate plan, budget and other official reports). I would also like to request a copy of a document listing the major organizations, departments and officials (Canada and US) involved in the project initially, and a document listing those still involved. I would also like to request copies of correspondence (letters, memos, faxes, emails etc) relating to the initial project design and

mandate, particularly between Health Canada officials (Drug Strategy and Controlled Substances Division, Clinical Trials and Special Access Programme of the Therapeutic Products Directorate) and other involved parties.

Kathy, I'm not sure the status of these requests.

NHW 2001.03.26
001318 RECORDS THAT TELL ME ABOUT THE RE
Provide the records that tell me about the reasons for action that led to the legislative proposal of a new inspection program for clinical trials in Canada. Including but not limited to audits; legal briefs; health hazard calculations; reports; briefing notes; and preparation notes.

NHW 2001.01.19
000982 RECORDS RE; EFFORTS TO DO CLINICAL .. CLARIFICATION
2001-01-23 (MS) Records since January 1, 2000, relating to efforts by Health Canada to attract drug companies to do clinical trial Canada, specifically:
1. Communications or marketing plans or strategies
2. Briefing notes, memoranda, or reports re promotional activities planned or carried out by Health Canada and results achieved (e.g. trip by Diane Gorman to La Jolla, CA, in December 2000, etc.)
3. Briefing notes, memoranda, or reports addressing the level or nature of clinical trial activity in Canada
4. Records related to Schedule 1024 disclosed under ATI requests A-1999-1387/1388.
ORIGINAL TEXT 2000 to present efforts to attract drug companies to do their clinical trials in Canada. Include briefing notes, trip reports by ADM Dianne Gorman, and reviews, assessment of shortening the 60 day approval period, and company queries and resulting summary approvals, other records released/about to be released

NHW 2001 000099 - Health Canada Date received: 2001-04-30
records of all serious adverse events reported from Phase 1,2,3,4 human cli ...
Please provide the records of all serious adverse events reported from Phase 1,2,3,4 human clinical drug trials in Canada from 1998 to the present.

Health Canada | Santé Canada

Access to Information and Privacy Centre
Room C1254 Jeanne Mance Building, Tunney's Pasture
Address Locator 1912C1
OTTAWA ON K1A 0K9

Your file *Votre référence*

Our file *Notre référence*

A-2002-00823 / kar

April 11, 2003

David McKie
CBC-Radio-Canada
Chateau Laurier, 7th Floor
1 Rideau Street
OTTAWA ON K1Y 1E4

Dear Mr. McKie:

This is in final response to your request under the *Access to Information Act*: **Correspondence with drug companies regarding the NOC with Conditions Policy**.

Enclosed are the records which respond to your request. These records are being partially disclosed, as parts qualify for exemption under paragraphs 20(1)(b) [third party financial, commercial, scientific or technical information given in confidence to the government] of the *Act*.

In connection with these records, charges are being assessed under paragraph 11(1)(b) of the *Act* for photocopying 61 pages at $.20 per page. **Please remit the total fee of $12.20 to this office**, by cheque or money order payable to the Receiver General for Canada, quoting our file number A-2002-00823 / kar.

If you have any questions or concerns about any aspect of the processing of your request, do not hesitate to contact me (see attached).

Sincerely,

Kathy Rae
Jr. Assistant Coordinator

Encl.

Canada

Health Canada Santé Canada

Your file Votre référence

Our file Notre référence

***Please quote ATI file number* A-2002-00823 / kar**

Should you have any questions or concerns about your application to Health Canada for information under the *Access to Information Act*, please contact:

Kathy Rae
Jr. Assistant Coordinator
Access to Information and Privacy Centre
Health Canada
Room C1254, Jeanne Mance Building, Tunney's Pasture
Address Locator 1912C1
OTTAWA ON K1A 0K9

TEL: (613) 957-3037
FAX : (613) 941-4541
E-MAIL: Kathy_Rae@hc-sc.gc.ca

NOTICE

Access to Information Act

You have the right to make a complaint about any aspect of the processing of your request to the Office of the Information Commissioner, at the following address:

The Information Commissioner of Canada
Tower B, Place de Ville
112 Kent Street
OTTAWA ON K1A 1H3

Canada

"Chamelian, Maral" <maral.chamelian@spcorp.com> on 05/17/2001 12:28:13 PM

To: Tara Bower@HWC
cc:

Subject: NOC/C policy - Clarifications

Dear Mrs. Bower,

I have two questions with regards to the NOC/C policy for which I would like to seek some clarification.

In the policy, it is stated that "Sponsors must undertake to design and carry out confirmatory studies to verify the drug's clinical benefit. The nature and scope of the confirmatory studies must be acceptable to the Therapeutic Products Programme."

1. With regards to this statement, do the efficacy and safety endpoints of the confirmatory study(ies) as well as the indication have to be identical to the those included in the submission for which the NOC/C is granted?
2. What is the approval process with regards to ensuring that the studies are acceptable to the Therapeutic Products Directorate?

Your help in clarifying these points would be greatly appreciated.

Thank You.

Maral Chamelian, M.Sc.
Regulatory Affairs Associate
Schering Canada Inc.
Tel: (514) 426-7300, ext. 4512
Fax: (514) 426-8478
e-mail: maral.chamelian@spcorp.com
****
This electronic message, including its attachments, is confidential and proprietary and is solely for the intended recipient. If you are not the intended recipient, this message was sent to you in error and you are hereby advised that any review, disclosure, copying, distribution or use of this message or any of the information included in this message by you is unauthorized and strictly prohibited. If you have received this electronic transmission in error, please immediately notify the sender by reply to this message and permanently delete all copies of this message and its attachments in your possession. Thank you.

Tara Bower
05/17/2001 02:49 PM

To: "Chamelian, Maral" <maral.chamelian@spcorp.com>
cc:

Subject: Re: NOC/C policy - Clarifications

Dear Ms. Chamelian,

Thank you for your questions. I'll do my best to clarify.

An NOC/C will only be granted **following** discussion with Therapeutic Products Directorate and/or Biologics and Genetics Therapies Directorate staff once the acceptability of the proposed confirmatory studies is agreed upon. This process arises subsequent to completion of the review of the original submission. The details of such confirmatory studies will be included in a Letter of Undertaking which must be signed by the sponsor as a commitment to verify the clinical benefit deemed promising in the original submission - all **prior** to issuance of an NOC/C.

With respect to your first question, the intent of the policy and confirmatory studies is to validate promising clinical results through the use of additional studies confirming the efficacy claims outlined in the original submission. This would therefore imply confirming the indication and related endpoints. There are some exceptions however, and as such all confirmatory studies are designed and assessed on a case-by-case basis with acceptance or rejection at the discretion of the review bureau.

The review bureau will provide specific guidance upon completion of the review should an NOC/C be warranted.

I hope this is satisfactory. Should further policy clarification be required please do not hesitate to contact me - (613) 957-6244. Alternatively, the appropriate review bureau may be contacted for specific guidance on a particular drug.

Sincerely,
Tara Bower, Bureau of Policy and Coordination,
Therapeutic Products Directorate
Health Canada

"Chamelian, Maral" <maral.chamelian@spcorp.com> on 05/17/2001 12:28:13 PM

"Sean McGuire" <seanmcguire@seanmcguire.com> on 2002-09-18 09:40:01 AM

Please respond to seanmcguire@seanmcguire.com

To: Tara Bower/HC-SC/GC/CA@HWC
cc:

Subject: Draft NOC/C policy

Good morning. I need some information regarding the draft NOC/C policy that was distributed in January 2002. The transmittal letter says that it was distributed to Associations. Can you provide me with details as to which associations received this draft policy for comment? Thank you.

Sean McGuire
Canadian Plasma Products
727-4702

- att1.htm

"Patricia Carruthers-Czyzewski" <patricia.carruthers.czyzewski@sintera.com>
on 10/04/2001 08:05:51 AM

To: Tara Bower/HC-SC/GC/CA@HWC
cc: Ross Duncan/HC-SC/GC/CA@HWC, "louise travill" <louise.travill@sintera.com>

Subject: Re: NOC/C guidance

Tara,

As you suggested, we reviewed section 5.2 in terms of your requirements for the NOC-C labelling. It is very clearly laid out as to what is needed (thanks for making that part of our work so much easier!!). We will work your requirements into the core document and are also proposing to have a template for NOC-C PMs to make it clear to the industry.

We just wanted to give you a heads up in terms of proposed changes for the title page that has come out of the other groups and feedback to date. For e.g. date of last revision might be added to the title page but it won't impact on the placement of the NOC-C box so I don't believe that will a problem. Once we have a first draft of the core document, it is our intention to circulate it to the different working groups that have contributed to date for review and comment and we will certainly include you in this group.

Thanks again.
Pat CC
----- Original Message -----
From: <Tara_Bower@hc-sc.gc.ca>
To: "Patricia Carruthers-Czyzewski"
<patricia.carruthers.czyzewski@sintera.com>
Cc: <Ross_Duncan@hc-sc.gc.ca>; "louise travill" <louise.travill@sintera.com>
Sent: Friday, September 28, 2001 2:38 PM
Subject: NOC/C guidance

>
>
> Good afternoon Pat,
>
> I'm attaching the draft guidance document for NOC/C. Please review section
5.2
> as it pertains to labelling and product monograph particulars. Let me know
of
> any concerns/additional material you feel is required. Appendix 1 and 2
are the
> sample title page and general information insert respectively. Please have
a
> look at these as well. Thx.
>
> Note: the most recent change involves removing the paragraph in the
clinical
> trials section which was to outline, in general terms, the confirmatory
studies
> requested of the sponsor to fulfill NOC/C obligations. The decision to

remove
> this information was based on the complications that would ensue
concerning
> information outlined in the PM being open for advertising purposes. We
would not
> want to be in a situation where sponsors are advertising NOC/C products on
the
> basis of unapproved claims.
>
> That's it for now.....have a nice weekend!
> Tara.
>
> (See attached file: NOCC_guidance draft4.wpd)
>

"Louise Travill" <louise.travill@sintera.com> on 2001-12-10 04:18:49 PM

To: Tara Bower/HC-SC/GC/CA@HWC
cc: "Patricia Carruthers-Czyzewski \(Home\)" <patricia.carruthers.czyzewski@sintera.com>

Subject: RE: NOC/C guidance

Tara, we are in the final stage of getting the draft product monograph guidance document out and we have a quick question for you. In the statements that must be added to the NOC/C products you have suggested use of the term "manufacturer". Would it be acceptable to change this to "sponsor" to be consistent with the PM guidance document?

Thanks. LT

-----Original Message-----
From: Tara_Bower@hc-sc.gc.ca [mailto:Tara_Bower@hc-sc.gc.ca]
Sent: September 28, 2001 3:38 PM
To: Patricia Carruthers-Czyzewski
Cc: Ross_Duncan@hc-sc.gc.ca; louise travill
Subject: NOC/C guidance

Good afternoon Pat,

I'm attaching the draft guidance document for NOC/C. Please review section 5.2 as it pertains to labelling and product monograph particulars. Let me know of any concerns/additional material you feel is required. Appendix 1 and 2 are the sample title page and general information insert respectively. Please have a look at these as well. Thx.

Note: the most recent change involves removing the paragraph in the clinical trials section which was to outline, in general terms, the confirmatory studies requested of the sponsor to fulfill NOC/C obligations. The decision to remove this information was based on the complications that would ensue concerning information outlined in the PM being open for advertising purposes. We would not want to be in a situation where sponsors are advertising NOC/C products on the basis of unapproved claims.

That's it for now.....have a nice weekend!
Tara.

(See attached file: NOCC_guidance draft4.wpd)

"Louise Travill" <louise.travill@sintera.com> on 2001-12-12 08:11:36 AM

To: Tara Bower/HC-SC/GC/CA@HWC
cc: "Patricia Carruthers-Czyzewski \(Home\)" <patricia.carruthers.czyzewski@sintera.com>

Subject: RE: NOC/C guidance

Actually, no that explanation makes a lot of sense, so we'll leave it as health care provider.

-----Original Message-----
From: Tara_Bower@hc-sc.gc.ca [mailto:Tara_Bower@hc-sc.gc.ca]
Sent: December 11, 2001 9:51 AM
To: Louise Travill
Subject: RE: NOC/C guidance

Thanks...I have changed the manufacturer references to sponsor. With respect to the Health Professional wording , we are not wishing to limit ADR reporting of NOCC products to professionals. The health care provider may be a family member, principal care giver or whatever. Therefore I would prefer leaving this as provider if there are no serious objections.

We hope to publish the NOCC guidance document on the website in December so I'm glad you got in touch with the revisions. Sometimes it takes a fresh eye to spot areas overlooked. I'll have to do a 'find and replace' for all manufacturer references.

Thanks and please let me know if I can be of any further help.
Tara.
957-6244

"Louise Travill" <louise.travill@sintera.com> on 12/10/2001 08:18:44 PM

To: Tara Bower/HC-SC/GC/CA@HWC
cc: "Patricia Carruthers-Czyzewski \(Home\)"
<patricia.carruthers.czyzewski@sintera.com>

Subject: RE: NOC/C guidance

Manufacturer is used in two places in the insert - in the "what is an NOC/C (second para) and in the ADR section

Also, in the PM we are using the term "health professional". Is it ok if we change that in the insert as well?

Thanks Tara. LT
-----Original Message-----
From: Tara_Bower@hc-sc.gc.ca [mailto:Tara_Bower@hc-sc.gc.ca]

Sent: December 10, 2001 4:21 PM
To: Louise Travill
Subject: RE: NOC/C guidance

Absolutely! I didn't realise it was in there and will change it in the guidance
as we too, have converted everything to 'sponsor'. Can you please confirm that
the only place this applies is in the final paragraph of the PM insert? I didn't
notice it anywhere else.

Tara.

"Louise Travill" <louise.travill@sintera.com> on 12/10/2001 04:18:49 PM

To: Tara Bower/HC-SC/GC/CA@HWC
cc: "Patricia Carruthers-Czyzewski \(Home\)"
<patricia.carruthers.czyzewski@sintera.com>

Subject: RE: NOC/C guidance

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Thanks. LT

-----Original Message-----
From: Tara_Bower@hc-sc.gc.ca [mailto:Tara_Bower@hc-sc.gc.ca]
Sent: September 28, 2001 3:38 PM
To: Patricia Carruthers-Czyzewski
Cc: Ross_Duncan@hc-sc.gc.ca; louise travill
Subject: NOC/C guidance

Good afternoon Pat,

I'm attaching the draft guidance document for NOC/C. Please review section 5.2
as it pertains to labelling and product monograph particulars. Let me know of
any concerns/additional material you feel is required. Appendix 1 and 2 are the
sample title page and general information insert respectively. Please have a look at these as well. Thx.

Note: the most recent change involves removing the paragraph in the clinical trials section which was to outline, in general terms, the confirmatory studies
requested of the sponsor to fulfill NOC/C obligations. The decision to remove
this information was based on the complications that would ensue concerning information outlined in the PM being open for advertising purposes. We would not
want to be in a situation where sponsors are advertising NOC/C products on the
basis of unapproved claims.

That's it for now.....have a nice weekend!
Tara.

(See attached file: NOCC_guidance draft4.wpd)

novo nordisk®

March 18, 2002

Tara Bower
Bureau of Policy and Coordination,
2nd Floor, Tower B Holland Cross,
11 Holland Ave, A.L. 3102C5,
Ottawa, Ontario.
K1A 1B6

Regarding: Comments on revised policy proposal for Notice of Compliance with Conditions (NOC/C)

Dear Ms. Bower

Further to Dr. Peterson's letter on January 28, 2002, regarding the revised policy for Notice of Compliance with Conditions (NOC/C) we wish to express our comments on the following points:

1. **NNCI Comment:**

   We recommend that Health Canada adopt a transition policy for products approved under the current NOC/C policy.

2. **Policy Proposal:**

   Drugs considered for an NOC/C no longer need to meet the requirements for Priority Review. Rather, sponsors may apply under the NOC/C policy for advanced consideration for an NOC/C (page 6).

Novo Nordisk Canada Inc.
2700 Matheson Blvd. East
3rd Floor, West Tower
Mississauga, Ontario

905-629-4222
1-800-465-4334
Fax 905-629-8662
www.novonordisk.com

NNCI Comment:

This introduces a third review stream that may place a sponsor in conflict with pursuing either a priority review or an NOC/C review for a promising new drug therapy. We question the necessity of this third review stream. We feel the review would be best served if an NOC/C became available as an option to both a regular review and a priority review.

3. **Policy Proposal:**

The NOC/C – Qualifying Notice (QN) will indicate that the submission qualifies for an NOC/C, as well as outline the additional clinical evidence to be provided in confirmatory studies and any restrictions (page 7).

NNCI Comment:

Should a sponsor question the content of the NOC/C-QN, according to the proposed policy the only option available is to appeal Health Canada's decision. The appeal would proceed in accordance with the *Management of Drug Submissions Policy.*

For consistence of approach with current HPFB practices, we feel the NOC/C-QN would be better served if the policy allowed a sponsor an opportunity to comment on the content of the NOC/C-QN, within a defined time period.

4. **Policy Proposal:**

The policy states that prior to approval, the sponsor must prepare for distribution, educational material including Dear Health Care Professional Letters, and product specific fact sheets (page 5).

NNCI Comment:

We question the rationale for introducing additional mechanisms for promotional reviews. We feel the current process is served well through PAAB.

5. **Policy Proposal:**

The policy, with reference to the NOC/C draft guidelines, requires boxed text at the beginning of each major section of the Product Monograph. In addition, sections for which the NOC/C status holds significance will be identified in the left margin by the symbol "NOC/C" (page 9).

NNCI Comment:

We are concerned that this requirement may compromise the doctor and patient's confidence in the product. The boxed text that will immediately follow product-specific information on the PM cover, we feel, is sufficient.

6. **Policy Proposal:**

Sponsors will be requested to notify Health Canada within 15 days when, on the basis of safety or quality concerns related to the product, an expert panel or advisory committee has been struck in a foreign jurisdiction … (page 11).

NNCI Comment:

This requirement may be particularly onerous and very difficult to manage for both Health Canada and the Sponsor. This requirement might even be construed as covering an ethics committee rejection.

We feel the goal of this requirement may be best meet through current channels (i.e. ADR reporting, PSURs, etc.)

7. **Policy Proposal:**

At the discretion of Health Canada the following alternative to stop-sale/revocation may be discussed with the sponsor and evaluated on a case-by-case basis: Restriction of patient population or distribution (page 13).

NNCI Comment:

Under current medical practice in Canada a licensed medical physician may prescribe a drug in any patient population, independent of indication. We question the legal practicality of restricting the patient population.

Should you have any questions, please do not hesitate to contact me by phone at 905.629.6130 or Sam Tarantino, Sr. Regulatory Associate, at 905.629.6127. Our fax number is 905.629.8662.

Kind Regards,
Novo Nordisk Canada Inc.

Lisa A. Armour
Manager, Quality Assurance and Regulatory Affairs

Cc: Alan Davis, Director, Medical and Scientific Affairs
Andrew McColgan, Manager, Policy and Public Affairs, BIOTECanada

/SMTT

To: Tara Bower
From: Agnes Klein
Fax: 941-6458

Roche

March 26, 2002

for Mary 9th

Ms. Tara Bower
Bureau of Policy and Coordination
2nd floor, Tower B Holland Cross,
1600 Scott Street
Address Locator 3102C5
Ottawa, Ontario, K1A 1B6

Tara - My remaining comments
Any questions, please call
Agnes

RE: Revised Draft Notice of Compliance with Conditions (NOC/c) Policy and Guidance to Industry – January 2002

27 pages

Dear Ms. Bower:

Hoffmann-La Roche Limited wishes to thank the Therapeutic Products Directorate for the opportunity to comment on the proposed revisions to the Policy for Notice of Compliance with Conditions and the Guidance to Industry document. Our comments are as follows:

Draft Policy

4. Definitions:

This has been done!

Clinical Benefit: We believe that the definition of clinical benefit should include a positive impact on the patient's quality of life. This appears in the current version (May 28, 1998) of this policy as well as in the October 2001 draft revised policy for Priority Review of Drug Submissions.

can't define; must describe done!

We recommend the inclusion of a definition for the "enhanced post-market surveillance and reporting requirements"

5. Policy:

Restriction on Distribution of a Drug: In this section and several other sections of the draft Policy and Guidance documents, it is indicated that distribution of the drug could be restricted. We are not aware of an existing Regulation that would guide the manufacturer in restricting the distribution of prescription drugs. Is Health Canada planning to propose new Regulations in this area?

Hoffmann-La Roche Limited/Limitée
2455 Meadowpine Boulevard, Mississauga, Ontario L5N 6L7
Tel.: (905) 542-5555
Fax: (905) 542-7130

6. Responsibilities & Procedures:

A. Procedure:

Please explain why a longer review target (200 days) is needed to review a submission for a NOC/c compared to a priority review submission (180 days). Section 3.0 of the guidance document indicates that "supplementary time is required to determining the validity of endpoints through internal discussion and consultation". Please explain why this internal consultation could not be done once the sponsor has made the presentation to HPFB for a planned submission for a NOC/c. The presentation would include the endpoints used in the clinical studies and would therefore provide the HPFB the information necessary for the "internal consultation".

You could also comment that we need to discuss the decision itself — a pure difficult matter. Review may change the optics of the case & therefore the benefit claimed affected!

OK!

As in the Guidance document (section 3.1), please indicate, in the policy document that the 200 days review target do not include the acknowledgement and screening steps.

We are concerned about the situation where Health Canada would consider a NOC/c after completion of a submission review. We recommend that the policy state that Health Canada will only issue a NOC/c-QN after discussions with the sponsor. We are concerned that Health Canada will use this policy to demand confirmatory clinical studies in situation where there is a difference of opinion on the adequacy of the "substantial" evidence of effectiveness included in the submission.

Boo!!! That may be so, but difference of opinion happens. OK

Regarding the situation where the sponsor requests consideration for NOC/c prior to filing:

a) It is recommended that the sponsor submit a briefing document prior to the presentation to Health Canada.
b) Please clarify the impact of the NOC/c review queue on the review queues of other submissions (priority reviews, standard reviews). Please clarify if the start of the review of a standard submission with a 300-day review target could be delayed by a NOC/c submission having an earlier review completion target date.

Please indicate in the Policy and Guidance documents whether filing a second request for a NOC/c consideration is acceptable in situations where the first attempt is denied through the appeal process.

should be a one off only!

Good!

Please confirm in the Policy and Guidance documents, that a NOC/c will only be considered for non-validated surrogate markers. Should validated surrogate markers be used in clinical development program, the NDS or S/NDS should be considered for full NOC and not a NOC/c.

E. Post-Market Commitments:

Poorly worded! File consolidated data

It is indicated that the results of the confirmatory studies may be submitted individually as each trial is completed as separate S/NDS-C. Will a separate submission review fee be charged for each S/NDS-C?

Please note that the PSUR are published according to an internationally accepted frequency namely every 6 months for the first 2 years of marketing and then every year for the next 3

years and then every 5 years. The frequency of the PSUR-C should be left for discussion with the sponsor on a case by case basis.

Agreed!

H. Termination of Conditions or Restrictions:
In situations where all undertakings have been satisfied, there should be a mechanism for a posting on the TPD website and for distribution of a Dear Health Care Professional Letter announcing the removal of the conditions associated with the NOC.

Agreed!

If the undertakings have not been satisfied for other reasons than a safety concern with the product, the sponsor should be able to file another submission for a different indication without having to address the undertakings in the original submission.

makes sense!

GUIDANCE DOCUMENT

2.0 Criteria for Qualification under the NOC/c Policy:

Section 2.4: This section of the guidance document is inconsistent with the Policy document. It covers 3 different ways to demonstrate the "potential of the therapy". We are concerned that 2 of those ways appear to eliminate the possibility of a full NOC being granted for an NDS or S/NDS based on phase II trials or on a single phase III trial. We believe that results of phase II trials or of a single phase III trial represent, in most situations, more than "promising clinical evidence". This is also inconsistent with the text in the Scope sections of both the draft policy and guidance documents.

OK. in a fair m^r: not least

3.0 Review and Authorization:
Section 3.3: Please explain the rational for posting on the TPD website the NOC/c Qualifying Notice.

consultation (?)

4.0 Letter of Undertaking:
Section 4.1: We believe that in the example of the phrase to be included in the letter of Undertaking, an "/c" is missing after NOC in "...we hereby agree to accept an NOC for <product name>.
Sections 4.5 and 4.6: Please explain the rational for inclusion in an appendix to the Letter of Undertaking, a list of ongoing clinical trials and copies of any marketing approvals for the drug from any drug regulatory authorities. The Letter of Undertaking already includes the list of confirmatory studies to be done.

To list for info, the entire development path/plan for the product

6.0 Post Market Commitments:
Section 6.2: It is stated in that section that ADR reports should be sent Health product Safety Information Division. Please confirm that this applies even to ADR reports from clinical trials.

(?) not necessary to
however, we will need to see how's consolidated all info

It should be only NDSs

7.0 Subsequent Submissions:
The Policy and the Guidance documents appear not to be consistent in that area. The Policy indicates that S/NDSs can be filed while the conditions for the original NDS are still in effect. The Guidance indicates that only NDSs can be filed while the conditions of the original submissions are in effect and that these NDSs would then be converted once the conditions are met for the original submissions. We hope that the approach indicated in the Policy is the correct one otherwise a complicated conversion of submission fees will be necessary when an NDS is converted to and S/NDS. This is NOT correct!

Would it be possible to request a priority review status or a NOC/c status for a subsequent submission for an indication independent from the original submission? Yes!

We look forward to your responses to our comments. Should you have any questions, do not hesitate to contact me at (905) 542-5704.

Yours Sincerely,

HOFFMANN-LA ROCHE LIMITED

Nabil Henein, M. Sc.,
Director, Regulatory Affairs
Pharmaceuticals

Roche

March 26, 2002

Ms. Tara Bower
Bureau of Policy and Coordination
2nd floor, Tower B Holland Cross,
1600 Scott Street
Address Locator 3102C5
Ottawa, Ontario, K1A 1B6

RE: Revised Draft Notice of Compliance with Conditions (NOC/c) Policy and Guidance to Industry – January 2002

Dear Ms. Bower:

Hoffmann-La Roche Limited wishes to thank the Therapeutic Products Directorate for the opportunity to comment on the proposed revisions to the Policy for Notice of Compliance with Conditions and the Guidance to Industry document. Our comments are as follows:

Draft Policy

4. Definitions:
Clinical Benefit: We believe that the definition of clinical benefit should include a positive impact on the patient's quality of life. This appears in the current version (May 28, 1998) of this policy as well as in the October 2001 draft revised policy for Priority Review of Drug Submissions.

– to be footnoted

We recommend the inclusion of a definition for the "enhanced post-market surveillance and reporting requirements"

5. Policy:
Restriction on Distribution of a Drug: In this section and several other sections of the draft Policy and Guidance documents, it is indicated that distribution of the drug could be restricted. We are not aware of an existing Regulation that would guide the manufacturer in restricting the distribution of prescription drugs. Is Health Canada planning to propose new Regulations in this area?

prescribing information will reflect all restrictions

Hoffmann-La Roche Limited/Limitée
2455 Meadowpine Boulevard, Mississauga, Ontario L5N 6L7
Tel.: (905) 542-5555
Fax: (905) 542-7130

6. Responsibilities & Procedures:

A. Procedure:

Please explain why a longer review target (200 days) is needed to review a submission for a NOC/c compared to a priority review submission (180 days). Section 3.0 of the guidance document indicates that "supplementary time is required to determining the validity of endpoints through internal discussion and consultation". Please explain why this internal consultation could not be done once the sponsor has made the presentation to HPFB for a planned submission for a NOC/c. The presentation would include the endpoints used in the clinical studies and would therefore provide the HPFB the information necessary for the "internal consultation".

As in the Guidance document (section 3.1), please indicate, in the policy document that the 200 days review target do not include the acknowledgement and screening steps.

We are concerned about the situation where Health Canada would consider a NOC/c after completion of a submission review. We recommend that the policy state that Health Canada will only issue a NOC/c-QN after discussions with the sponsor. We are concerned that Health Canada will use this policy to demand confirmatory clinical studies in situation where there is a difference of opinion on the adequacy of the "substantial" evidence of effectiveness included in the submission.

Regarding the situation where the sponsor requests consideration for NOC/c prior to filing:

a) It is recommended that the sponsor submit a briefing document prior to the presentation to Health Canada.
b) Please clarify the impact of the NOC/c review queue on the review queues of other submissions (priority reviews, standard reviews). Please clarify if the start of the review of a standard submission with a 300-day review target could be delayed by a NOC/c submission having an earlier review completion target date.

Please indicate in the Policy and Guidance documents whether filling a second request for a NOC/c consideration is acceptable in situations where the first attempt is denied through the appeal process.

Please confirm in the Policy and Guidance documents, that a NOC/c will only be considered for non-validated surrogate markers. Should validated surrogate markers be used in clinical development program, the NDS or S/NDS should be considered for full NOC and not a NOC/c.

E. Post-Market Commitments:

It is indicated that the results of the confirmatory studies may be submitted individually as each trial is completed as separate S/NDS-C. Will a separate submission review fee be charged for each S/NDS-C?

Please note that the PSUR are published according to an internationally accepted frequency namely every 6 months for the first 2 years of marketing and then every year for the next 3

years and then every 5 years. The frequency of the PSUR-C should be left for discussion with the sponsor on a case by case basis.

H. Termination of Conditions or Restrictions:
In situations where all undertakings have been satisfied, there should be a mechanism for a posting on the TPD website and for distribution of a Dear Health Care Professional Letter announcing the removal of the conditions associated with the NOC.

If the undertakings have not been satisfied for other reasons then a safety concern with the product, the sponsor should be able to file another submission for a different indication without having to address the undertakings in the original submission.

GUIDANCE DOCUMENT

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Section 2.4: This section of the guidance document is inconsistent with the Policy document. It covers 3 different ways to demonstrate the "potential of the therapy". We are concerned that 2 of those ways appear to eliminate the possibility of a full NOC being granted for an NDS or S/NDS based on phase II trials or on a single phase III trial. We believe that results of phase II trials or of a single phase III trial represent, in most situations, more than "promising clinical evidence". This is also inconsistent with the text in the Scope sections of both the draft policy and guidance documents.

3.0 Review and Authorization:
Section 3.3: Please explain the rational for posting on the TPD website the NOC/c Qualifying Notice.

4.0 Letter of Undertaking:
Section 4.1: We believe that in the example of the phrase to be included in the letter of Undertaking, an "/c" is missing after NOC in "...we hereby agree to accept an NOC for <product name>.
Sections 4.5 and 4.6: Please explain the rational for inclusion in an appendix to the Letter of Undertaking, a list of ongoing clinical trials and copies of any marketing approvals for the drug from any drug regulatory authorities. The Letter of Undertaking already includes the list of confirmatory studies to be done. FAQ

6.0 Post Market Commitments:
Section 6.2: It is stated in that section that ADR reports should be sent Health product Safety Information Division. Please confirm that this applies even to ADR reports from clinical trials.

7.0 Subsequent Submissions:
The Policy and the Guidance documents appear not to be consistent in that area. The Policy indicates that S/NDSs can be filed while the conditions for the original NDS are still in effect. The Guidance indicates that only NDSs can be filed while the conditions of the original submissions are in effect and that these NDSs would then be converted once the conditions are met for the original submissions. We hope that the approach indicated in the Policy is the correct one otherwise a complicated conversion of submission fees will be necessary when an NDS is converted to and S/NDS.

Either? or both?

Would it be possible to request a priority review status or a NOC/c status for a subsequent submission for an indication independent from the original submission?

yes

We look forward to your responses to our comments. Should you have any questions, do not hesitate to contact me at (905) 542-5704.

Yours Sincerely,

HOFFMANN-LA ROCHE LIMITED

Nabil Henein, M. Sc.,
Director, Regulatory Affairs
Pharmaceuticals

BettyAnn.Rafuse@ca.sanofi.com on 03/27/2002 06:08:08 PM

To: Tara Bower/HC-SC/GC/CA@HWC
cc: Debbie.Rassos@ca.sanofi.com, Karen.Gow@ca.sanofi.com

Subject: Comments on Conditional NOC

Dear Tara:

The review target of 200 days, compared to the review target of 180 of a Priority status drug is too long, The amount of data to review in a NOC/C NDS should be smaller since the data package is not complete. I would suggest that the review target date should be lowered to 100 days.

Regards,

Betty Ann Rafuse, BSc. Phm., M.B.A.
Vice-President, Regulatory Affairs and Quality Assurance
Sanofi-Synthelabo Canada Inc.
Telephone: (905) 513-4360
Fax: (905) 513-4580

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Aventis Pharma

BY E-MAIL and COURIER

March 28, 2002

Ms. Tara Bower
Bureau of Policy and Coordination
2nd Floor, Tower B Holland Cross
11 Holland Ave, A.L. 3102C5
Ottawa, Ontario
K1A 1B6

Dear Ms. Bower:

As documented in an introduction letter from Dr. R. Peterson dated January 28, 2002, Aventis is herewith providing comments for the following policy proposal and associated guidance:

1) Policy: Notice of Compliance with Conditions (NOC/ C) – issued January 2002
2) Draft guidance for industry: Notice of Compliance with conditions (NOC/c) – issued January 28, 2002.

Comments

1) Policy: Notice of Compliance with Conditions (NOC/ C) – issued January 28, 2002

- **Page 5; Section 6. Responsibilities and procedures; *A. Procedure: Eligibility and Review***

If, during the course of a regular pre-NDS or S/NDS meeting for a given drug TPD was to consider that the evidence of effectiveness presented is promising but not complete, could TPD request up front that the submission be filed with advance consideration of the NOC/c policy? In this case, would a second meeting be necessary?

- **Page 6; Section 6. Responsibilities and procedures; *A. Procedure: Eligibility and Review***

Please clarify that the 200-day target review time excludes the 45 days for screening.

- **Page 13; Section 6. Responsibilities and procedures; *G. Stop-sale/Revocation***

Considering a situation where a new indication has been granted NOC/c for a drug that has been previously approved under regular NOC conditions, please confirm that the failure of the confirmatory studies to demonstrate clinical benefit would prompt the withdrawal of the indication approved under the NOC/c policy ONLY, and not the withdrawal of drug itself form the market.

025

Aventis Pharma Inc. · 2150, boul. St-Elzéar O., Laval (Québec) Canada H7L 4A8 · Tél. (514) 331-9220 · Téléc. (514) 333-3699
Aventis Pharma Inc. · 2150 St-Elzear Blvd. W., Laval, Quebec, Canada H7L 4A8 · Tel. (514) 331-9220 · Fax (514) 333-3699

Aventis Pharma

2) Draft guidance for industry: Notice of Compliance with Conditions (NOC/ C) Policy – issued January 28, 2002

- **Page 10; Section 3.2. Issuance and Response;** ***b. Initial outline of proposed confirmatory trials***

In the event that a conditional NOC is granted, could the confirmatory study proposed by the Sponsor be a Clinical trial that is already ongoing in Canada?

- **Page 12; Section 4.1.Listing of confirmatory studies**

During the pre-NDS or pre-S/NDS meeting held for a request of advance consideration under the NOC/c policy, could the details and/or issues regarding the confirmatory clinical trials that will be required be already discussed during the meeting?

- **Page 13; Section 4.2. Post-market surveillance commitments**

Please provide examples of the type of active surveillance responsibilities that could be required on a case-by-case basis by TPD following the issuance of a NOC/c.

- **Page 19; Section 6.2. Monitoring of Safety: ADRs and Active Surveillance**

Please confirm that, as stated in the draft guidance document, all ADRs received from health care professionals in regards with a NOC/c granted for a drug will be sent to the sponsors within 30 days.

If you have any question or need clarification regarding these comments, please do not hesitate to contact the undersigned.

Yours sincerely,

Brigitte Brannen for

Sylvie Ducharme, B.Sc.
Manager, Approval and Compliance
Regulatory Affairs

Telephone: (514) 856-3877
Fax: (514) 333-3699
e-mail: sylvie.ducharme@aventis.com

Aventis Pharma

Aventis

BY E-MAIL and COURIER

March 28, 2002

Ms. Tara Bower
Bureau of Policy and Coordination
2nd Floor, Tower B Holland Cross
11 Holland Ave. A.L. 3102C5
Ottawa, Ontario
K1A 1B6

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Comments

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- **Page 5; Section 6. Responsibilities and procedures; *A. Procedure: Eligibility and Review***

If, during the course of a regular pre-NDS or S/NDS meeting for a given drug TPD was to consider that the evidence of effectiveness presented is promising but not complete, could TPD request up front that the submission be filed with advance consideration of the NOC/c policy? In this case, would a second meeting be necessary? No! — Could be done this way — Still clarifies the policy

- **Page 6; Section 6. Responsibilities and procedures; *A. Procedure: Eligibility and Review***

Please clarify that the 200-day target review time excludes the 45 days for screening. Yes!

- **Page 13; Section 6. Responsibilities and procedures; *G. Stop-sale/Revocation***

Considering a situation where a new indication has been granted NOC/c for a drug that has been previously approved under regular NOC conditions, please confirm that the failure of the confirmatory studies to demonstrate clinical benefit would prompt the withdrawal of the indication approved under the NOC/c policy ONLY, and not the withdrawal of drug itself form the market.

Correct!

Aventis Pharma Inc. · 2150, boul. St-Elzéar O., Laval (Québec) Canada H7L 4A8 · Tél. (514) 331-9220 · Téléc. (514) 333-3699
Aventis Pharma Inc. · 2150 St. Elzear Blvd. W., Laval, Quebec, Canada H7L 4A8 · Tel. (514) 331-9220 · Fax (514) 333-3699

Aventis Pharma

2) Draft guidance for industry: Notice of Compliance with Conditions (NOC/ C) Policy – issued January 28, 2002

- **Page 10; Section 3.2. Issuance and Response; *b. Initial outline of proposed confirmatory trials***

In the event that a conditional NOC is granted, could the confirmatory study proposed by the Sponsor be a Clinical trial that is already ongoing in Canada? Depends on the trial & outcomes / safety measures

- **Page 12; Section 4.1.Listing of confirmatory studies**

During the pre-NDS or pre-S/NDS meeting held for a request of advance consideration under the NOC/c policy, could the details and/or issues regarding the confirmatory clinical trials that will be required be already discussed during the meeting? Yes! On the understanding that it is all "in principle" subject to various outcome.

- **Page 13; Section 4.2. Post-market surveillance commitments**

Please provide examples of the type of active surveillance responsibilities that could be required on a case-by-case basis by TPD following the issuance of a NOC/c. MHPD role ?

- **Page 19; Section 6.2. Monitoring of Safety: ADRs and Active Surveillance**

Please confirm that, as stated in the draft guidance document, all ADRs received from health care professionals in regards with a NOC/c granted for a drug will be sent to the sponsors within 30 days MHPD

If you have any question or need clarification regarding these comments, please do not hesitate to contact the undersigned.

Yours sincerely,

Brigitte Jeannes for

Sylvie Ducharme, B.Sc.
Manager, Approval and Compliance
Regulatory Affairs

Telephone: (514) 856-3877
Fax: (514) 333-3699
e-mail: sylvie.ducharme@aventis.com

"BARUA, NITEN [GPB/8252]" <niten.barua@pharmacia.com> on 2002-03-28 05:28:43 PM

To: Tara Bower/HC-SC/GC/CA@HWC
cc: "TROJAN, ARLENE [GPB/8252]" <arlene.trojan@pharmacia.com>

Subject: Comments on Draft Policy on Notice Compliance with Conditions

---

Ms. Tara Bower
Therapeutics Products Directorate
Bureau of Policy and Coordination
2nd Floor, Tower B
Holland Cross, Ottawa
Ontario, K1A 1B6

Dear Ms. Bower:

Please find attached Pharmacia's comments on the Policy on Notice of Compliance with Conditions.

Sincerely,

Niten Barua
Manger, Regulatory Affairs
Pharmacia Canada
(905) 755-3583

<<NOC_C_Comments_letter.doc>>

- NOC_C_Comments_letter.doc

VIA E-MAIL

March 28, 2002

Ms. Tara Bower
Therapeutics Products Directorate
Bureau of Policy and Coordination
2nd Floor, Tower B
Holland Cross, Ottawa
Ontario, K1A 1B6

Re: Draft Notice of Compliance with Conditions (NOC/c) Policy

Thank you for giving us the opportunity to comment on the draft policy. Our comments are as follows:

1. NOC/c submissions should be able to qualify for Priority Review

If the primary objective of the NOC/c policy is to shorten time to approval of a promising new treatment, then it should be done within the context of a priority review. Completely de-linking NOC/c from priority review will defeat the overall objective of this policy. Sponsors wishing to have their submission considered for NOC/c should also be able to be considered for priority review. As such, priority review could result in full approval or NOC/c. Circumstances where NOC/c would be independent of priority review is where the sponsor has applied for neither priority review nor NOC/c in advance. In this situation there may be occasions where upon completion of the review Health Canada deems the data insufficient for a full NOC and suggests an NOC/c to the sponsor.

FAQ delinking pl.

Although it appears that in de-linking NOC/c from priority review the review time is only increased by 20 days (180 to 200 days), there is concern that the overall process to obtain NOC/c could be substantially long. With the added steps in the process (e.g. mandatory pre-submission consultation, stopping review clock when NOC/c-QN is issued, subsequent request for additional information and the extent of the additional information requested, 30 day review target for additional information), it is conceivable that time to NOC/c could be as long as the standard target review time of 300 days. This again defeats the primary objective of shortening time to approval for promising new treatments.

* overall time concerns.

2. The policy should not comment on drug formulary decisions

In the policy it is stated "Drug benefit plans may or may not list these drugs on their formularies because, although promising clinical evidence is available, the clinical benefits of these drugs have not been fully confirmed at the time of NOC issuance". The policy should not make any

* provinces

PHARMACIA

Pharmacia Canada
55 Standish Court, Suite 1200
Mississauga, Ontario,
Canada
L5R 4E3
Telephone: 905.755-3583
Facsimile: 905.890-8696
E-mail:
niten.barua@pharmacia.com

comment on the position a drug benefit plan may take relative to listing of drugs approved through the NOC/c policy. Such a statement in the policy may negatively influence listing since it may be construed that Health Canada does not endorse reimbursement of such drugs. It is critical to ensure access upon approval of a product by Health Canada. It is particularly important for drugs for the treatment of serious, life-threatening & debilitating illnesses since these drugs are more likely to be covered primarily through drug benefit formularies.

3. The following comments are relating to Advertising, Labeling and Education Material requirements in the policy

a). There should not be any additional advertising restriction other than what is required by the PAAB

One of the conditions of this policy states "The sponsor may also be requested to undertake to comply with restrictions imposed by Health Canada on the advertisement and/or distribution of the drug". The advertisements for products approved under this policy will clearly state that the approval of the product has been received under the NOC/c policy, which requires conducting further studies to confirm its clinical benefit. It should be sufficient to obtain PAAB clearance for all advertising materials. Additional advertising restrictions will negatively impact on the promotion of products approved under this policy, which in turn will affect long-term commercial viability of such products.

will review consistent & reduce

b). The objective of the requirement for educational material in the form of Dear Health Care Professional Letters, NOC/c Fact Sheets and additional material as appropriate should be clarified

If the objective is to ensure that health care professionals and patients are aware of the conditions of approval of the product then, the first group (Health Care Professionals) will be advised via the Product Monograph and the advertisements, as these pieces of information will identify the terms of the approval. Beyond this, it should remain the responsibility of the health care providers to communicate the necessary information to patients since such information will be included in the Product Monograph and the Package Insert. We believe it is unnecessary to create additional documents as stated in the policy.

HCPs have requested additional info by + will remain

c). The proposal to post the Product Fact Sheet on the TPD website upon issuance of the NOC should not be a requirement

Clarification is required on what would be considered a "Product Fact Sheet." Given that the draft policy states that this document is written in lay terminology, it is unclear what the difference would be between this document and the consumer information section of the product monograph. We believe it unnecessary and confusing to have two different documents for the patients.

* Fact Sheet + PI differences. - clarify in guidance + provide a template (NSC)

We believe the TPD Website may not be the appropriate place to post the product fact sheet. Understanding the merits of conditional approval of a product will require careful evaluation even by health care professionals. Making such information available to the general public is likely to create confusion. In our opinion, it will be more prudent to let health care providers explain to the patient the risk/benefit of a product approved under the NOC/c policy.

d) Requirements for labeling needs to be clarified

Section 5.2 of the guidance document states that "Products approved under NOC/c policy will subject to enhanced labeling requirements". It should be clarified if the term "labeling" is used in to indicate "Package Labeling" or the "Product Monograph". If the reference is to "Package Labeling" then the proposed restrictions should be clarified.

e). <u>Overall:</u> The proposed requirements on advertising and communications appear to be too restrictive and therefore should be reexamined

* comment only

4. The requirement for posting the Qualifying Notice (QN) to the TPD website is not acceptable

* comment only.

We understand that Health Canada wants to be as transparent as possible with the decision making process, however, posting the details of the QN may put the sponsor at a competitive disadvantage. It is conceivable that a competitor may use the information from the QN to their advantage.

5. The requirement for 'notification of and reporting on specific issues of concern' in a foreign jurisdiction should be limited only to those situations where a decision has been made on an issue instead of both at the discussion stage or when regulatory action has been taken

* team?

Section E iii a) of the policy states "Notify Health Canada within 15 days when, on the basis of safety or quality concerns related to the product, an expert panel or an advisory committee has been struck in a foreign jurisdiction to address an issue". While recognizing the importance of enhanced post-marketing surveillance initiatives on the part of Health Canada for products approved under NOC/c policy, this particular requirement may be excessive. The requirement to notify Health Canada should be only for those situations where significant regulatory actions have been taken in a foreign jurisdiction as a result of recommendations from an expert panel or an advisory committee organized to examine an issue. Additionally, it should be limited to a defined list of key countries. This would eliminate Health Canada having to devote resources on an issue that may potentially be resolved without requiring specific regulatory action. In cases where significant regulatory action has been taken, it would provide Health Canada with the opportunity to assess the review of the issue by another peer agency and discuss with the sponsor the applicability of the action in Canada.

6. Further clarification is required on establishing risk/benefit assessment for submissions to be approved under the NOC/c policy

The policy states that a product will be eligible for NOC/C if it "has the potential to provide...a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved...". "Significant improvement" is defined in the policy as

PHARMACIA

Pharmacia Canada
55 Standish Court, Suite 1200
Mississauga, Ontario,
Canada
L5R 4E3
Telephone: 905.755-3583
Facsimile: 905.890-8696
E-mail:
niten.barua@pharmacia.com

"statistically significant and clinically relevant improvement". Establishing "Statistically significant and clinically relevant improvement" is generally based on data. The definition provided for "promising clinical benefit" makes no reference to statistical significance, rather it refers only to "an effect on a surrogate or clinical endpoint". The guidance document does provide some helpful clarification on this point, noting that the sponsor must be able "to demonstrate that the therapy has the potential to provide a statistically significant and clinically relevant improvement in benefit/risk profile over existing therapies on the Canadian market". However, it is important to provide more details especially with respect to types of studies that will be considered acceptable to fulfill this requirement.

they are provided in section 2.4

* not sure this is possible or warranted

7. There should not be any statement in the policy on the preference of conducting confirmatory clinical studies in Canada

In the guidance document, section 3.2, b, the statement in the second paragraph "It would, however, be preferable to have confirmatory studies conducted in Canada whenever possible" should be removed unless there is a scientific basis for including such a statement. Generally, sponsors conduct studies in Canada where possible, however given the global environment there are situations where it may not be feasible to conduct confirmatory studies in Canada. This statement implies that conducting confirmatory studies outside of Canada may be less desirable when in fact the results from the studies may be scientifically valid and applicable to the Canadian population. OK

* lean?

8. Clarification is required on boxed text requirement in the Product Monograph as stated in section 5.2.1 of the guidance document

In the current Product Monograph guidelines, there are no sections defined as: 1. Information for the Health Care Provider and 2. Scientific Information. Section 5.2.1. of the guidance document refers to these sections as part of the monograph.

* footnote the revised guidance

9. The proposed requirement of 'restriction on distribution' per Section 4 of the Policy should be reevaluated

It may not be possible for sponsors to control product distribution especially through wholesalers. Further this could interfere with distribution to physicians with appropriate practice and to legitimate patients.

We trust that you will find our comments useful. If you have any questions on the above, please contact the undersigned.

Niten Barua M.Sc, M.B.A.
Regulatory Affairs Manager

Tel: (905) 755-3583
Fax: (905) 755-8696
E-mail: niten.barua@pharmacia.com

Aventis Pasteur

Fax Information

To:
Ms Tara Bower
Bureau of Policy and Coordination
Therapeutic Products Directorate
Phone: (613) 957-6244
Fax: (613) 941-6458
Email: tara_bower@hc-sc.gc.ca
Number of pages: 6

From:
Irene R. Clement
Aventis Pasteur Limited
Tel.: (416) 667-2898
Fax: (416) 667-2912
Email: IreneR.Clement@aventis.com

01 Apr 2002

Re: Draft Policy – Notice of Compliance with Conditions (NON/c) and Draft Guidance for Industry: Notice of Compliance with conditions (NOC/c)

Dear Ms Bower,

Aventis Pasteur Limited is pleased to be given the opportunity to provide comments on the Draft Policy – Notice of Compliance with Conditions (NOC/c), and the Draft Guidance for Industry: Notice of Compliance with Conditions (NOC/c), both published January 28, 2002 on the Therapeutic Program Directorate/Biologics and Genetic Therapies Directorate Websites (TP-Web).

Our comments are outlined below and are italicized to differentiate them from the policy and guidance text, which is bold and/or normal type.

Draft Policy – Notice of Compliance with Conditions (NOC/c)

4. Definitions

"ACTIVE SURVEILLANCE: regular periodic collection of case reports....."

If "case reports" refers to case report forms (CRFs), it is suggested to include the full terminology.

6.A.ii. Notice of Compliance with Conditions – Qualifying Notice (NON/c – QN)

*"Upon approval, the NOC/c-QN will be posted to the TP-Web. *Note: The NONC/c-QN will not contain proprietary information." Should be added to this section to be consistent with the guidance document. Also see additional comments under the Guidance for Industry section below under 3.3 Agreement of Conditions and Issuance of the NOC/c.*

6.D.i. Advertising; second paragraph

"Sponsors are requested to receive pre-clearance by the....."

It is suggested that text be added to clarify that pre-clearance by PAAB is done prior to launching the product versus prior to issuance of the NOC/c.

6.D.ii Educational Material

It is suggested to add text to clarify that the sponsor must prepare and submit the Dear Health Care Professional Letters and NOC/c fact Sheets to Health Canada for review, and that they will eventually be posted to the TP-Web, to be consistent with the guidance document.

6.E.i Confirmatory Studies, fourth paragraph

"....Additional information supporting an expanded indication is not acceptable and must be submitted as a separate NDS."

There may be the situation where this information could also be filed as an S/NDS, specifically when the original submission for which an NOC/c was issued was an S/NDS.

General Comment

It appears that the usual effective date statement/section is missing.

<u>Draft Guidance for Industry: Notice of Compliance with conditions (NOC/c)</u>

1.4 Definitions

"ACTIVE SURVEILLANCE: regular periodic collection of case reports....."

If case reports refers to case report forms (CRFs), it is suggested to included the full terminology.

3.3 Agreement of Conditions and Issuance of the NOC/c

"Upon approval, the NOC/c-QN will be posted to the TPD website....."

This should be revised to "...TP-Web...." to be consistent with the first two pages of the guidance document.

5.1 Advertising Restrictions and Pre-clearance; second paragraph

"Sponsors are requested to receive pre-clearance by the....."

It is suggested that text be added to clarify that pre-clearance by PAAB is done prior to launching the product versus prior to issuance of the NOC/c.

5.2 Labelling; first paragraph

"....Patient Package Inserts and Product Monographs must be supplied with each product granted an NON..."

It is suggested to include more text to clarify the intent and provide more guidance. For example, if the PPI is to be supplied with each supply or package given to the patient, or the PM is to be supplied with each shipment or package to the health care provider etc, this should be stated.

5.2.1 Product Monographs

General comment – this section refers to the proposed new format for Product Monographs. To our knowledge this new format has not yet been finalized or implemented and therefore should not be included in this guideline. Having said that, if the new PM format is soon to be approved and implemented, we have the following comments:

First text box

"Boxed text should resemble the following"

It is suggested that this introduction to the boxed text be reworded to "Boxed text present on the cover page and at the beginning of Sections I and II should resemble the following"

Second text box

"Boxed text present at the beginning of Section 3:..."

It is suggested that "3" be change to "III".

General Information Section

"...following the title page. It contains general information....., the first section of which must be repeated in Section 3:....."

It is suggested that "title" be revised to "cover", text be added to clarify what the "first section" is i.e. is it the two paragraphs under What is a NON/c????, and "3" be changed to "III"

5.2.2 Patient Package Inserts

"their health care providers." appears to be missing at the bottom of the texted box.

5.3 & 5.4 for Dear health Care Professional Letter & Product Specific Fact Sheet respectively

In the last line of both sections "...TPD website.." should be changed to "...TP-Web.." for consistency.

5.4 Product Specific Fact Sheets

It is suggested that a template for this be provided as an Appendix and cross-reference to it be included here, as you have done for the Dear Health Care Professional Letters.

6.1 Confirmatory & Other Ongoing Trials; third paragraph

"Additional information supporting an expanded indication is not acceptable and must be submitted as a separate NDS."

There may be the situation where this information could also be filed as an S/NDS, specifically when the original submission for which an NOC/c was issued was an S/NDS.

7.0 Subsequent Submissions; first paragraph under iii)

"The above submissions should be filed as New Drug Submissions...."

It is confusing as to whether this paragraph with the opening words of "the above submissions" refers only to iii) or to i), ii) and iii). From the text under i) and ii), however, I would assume the paragraph only refers to iii). It is suggested that the sentence be reworded to "These subsequent submissions...".

In addition, text concerning submitting information supporting an expanded indication should be added to be consistent with paragraph three under 6.1 Confirmatory & Other Ongoing Trials.

Appendix 4a: NOC/c Consideration Upon Completion of Review

The following are suggested comments to enhance or make consistent with Appendix 4b:

- *Revise "Screening accepted" to "Acceptable on Screening"*
- *Under the Review star use arrows to point to the possible outcome of NOD, NON, NOC without conditions, NOC/c-QN*
- *Expand flow following NOC/c-QN to include Response must be filed within 30 days, including agreement for NOC with conditions and Letter of Understanding; Sponsor may appeal ; review target 30 days, NOC/c issuance, NOC/c-QN posted to web; sponsor submits S/NDS-C within agreed upon timeframe; reporting requirements (PSUR-Cs(semi-annual), ADRs(as usual plus those to HC to sponsor in 30 days), safety & quality concerns(15 day/30 day)); pre-clearance of advertising material; possibilities of revocation of NOC/c, revised Letter of understanding or removal of conditions*

Appendix 4b: Advance NOC/c Consideration Requested

The following are suggested comments to enhance or make consistent with Appendix 4a:

- *Extent flow under "Eligibility Not granted to included "Sponsor May Appeal"*
- *Under the Review star use arrows to point to the possible outcome of NOD, NON and NOC/c-QN*
- *Expand flow following NOC/c-QN to include Response must be filed within 30 days, including Letter of Understanding; Sponsor may appeal ; review target 30 days, NOC/c issuance, NOC/c-QN posted to web; sponsor submits S/NDS-C within agreed upon timeframe; reporting requirements (PSUR-Cs(semi-annual), ADRs(as usual plus those to HC to sponsor in 30 days), safety & quality concerns(15 day/30 day)); pre-clearance*

of advertising material; possibilities of revocation of NOC/c, revised Letter of understanding or removal of conditions

We appreciate the opportunity to comment.

Sincerely,

Irene R. Clement
Director
Regulatory Affairs

April 1, 2002

FAXED

GlaxoSmithKline Inc.
7333, Mississauga Road North
Mississauga, Ontario
Canada L5N 6L4

Tel. 905 819 3000
Fax. 905 819 3339
www.gsk.com

Ms. Tara Bower
Bureau of Policy and Coordination
Health Canada
2nd Floor, Tower B, Holland Cross
11 Holland Avenue, A.L. 3102C5
Ottawa, Ontario
K1A 1B6

Dear Ms. Bower,

In response to the revised policy proposal and draft guidance document for Notice of Compliance with Condition (NOC/c) issued on January 28, 2002, GlaxoSmithKline Inc. would like to submit the following comments to Health Canada. In general, we support the reassessment of the NOC/c policy and the issuance of specific guidelines. The appropriate application of this policy will enable patients who are suffering from serious, life-threatening or severely debilitating diseases or conditions, to have faster access to promising new medicines. We do have a number of concerns about the policy and the procedure that appear to be inconsistent with this.

In general, we are supportive of a 200-day review time for these submissions; however, we are concerned about the impact of introducing what is essentially a third review stream, on the standard review times.

We are also concerned about the apparent lack of opportunity for consultation and negotiation prior to issuance of the Qualifying Notice, as well as prior to the posting of the Notice on the TPD web-site. We recommend that the need for any Canadian specific requirements be re-considered to be in line with the requirements for similarly approved drugs in other jurisdictions (i.e. advertising, PSUR-C). And lastly, we are concerned that since a formal post-marketing surveillance policy or program has not yet been implemented, there is a potential for Health Canada to require excessive surveillance requirements under the cover of the NOC/c policy.

More specifically, we have provided the following comments based on each section of the policy.

Section 2: Background

The stated benefits of the policy have been expanded to include effective safety monitoring through enhanced post-market surveillance activities. Previous versions were focused on only establishing efficacy through confirmatory studies. This current draft continues to state that the drug must have an acceptable safety profile and therefore it should be made clear that the policy will not be invoked for safety reasons alone. Further, an effective post-approval monitoring system should be in place for all drugs and should not impose additional burdens for conditionally approved drugs.

041

Section 3: Scope
Contradiction exists in what is required to qualify for an NOC/c and the data requirements. The requirement to show an improvement in benefit/ risk ratio over existing therapies is not realistic. Earlier statements within the policy acknowledge the gaps in the benefit/risk profile at the time of filing since only promising clinical evidence is available.

Section 4: Definitions
Regarding the expectation that surrogate marker data may eventually be validated to demonstrate a clinical benefit, we are unclear as to whether clinical studies generated with surrogate marker data only would then be considered eligible for full approval?

Section 5: Policy
Further guidance is required regarding the criteria for determining when enhanced post-market surveillance would be warranted.

Section 6: Responsibilities & Procedures
Subsection 6 (A): Procedure:
In order to ensure that there are no undue delays built into the process we have the following comments:

General

1 This policy should not be used as a tool to enforce post-marketing surveillance.

Process Timelines

2 Health Canada should notify the sponsor of the eligibility of the drug submission for filing under the NOC/c policy within 10 calendar days of the pre-submission meeting, not of the finalization of the meeting minutes.

3 Use of the term "preliminary" screening implies that NOC/c submissions will be subject to possibly 2 screening phases. Clarification is required on the use of this term. Further, our suggestion is the screening process for these submissions be no different than the current screening process for other submissions.

4 The 200-day review metric for all NOC/c submissions is certainly welcome, however, we have concerns with Health Canada's ability to ensure that these timelines are met. The expedited review for these submissions will place additional burden on an already stressed the system, and may negatively impact review times for standard NDS/sNDS submissions.

5 Can the sponsor consider the review to be complete (i.e. the 200-day review target has elapsed) at the point of issuance of the NOC/c-QN?

6 The timelines for review are significantly more than the 200 days stated in the policy when the entire process is taken into consideration. We understand that the total review time for a submission under the NOC/c policy is actually 45 (screening) + 200 (review) + 30 (response to NOC/c-QN) + 30 (review of response) = 305 days. This also does not take into consideration the time for the pre-submission meeting.

042

7 We are concerned that a 30-day deadline to submit information requested in the NOC/c-QN may not be sufficient time to allow companies to adequately consider, or consult with external investigators, regarding the appropriate design of confirmatory studies.

Qualifying Notice

8 In the event that the sponsor does not wish to have the submission considered for an NOC subject to the NOC/c policy, a Notice of Non-Compliance (NON) will be issued. Please clarify whether the NON will contain the same requests for information as in the NOC/c-QN.

9 Prior to issuing the NOC/c-QN, the sponsor should have the opportunity to consult with Health Canada, in order to discuss the contents and provide any information currently available, as well as negotiate an appropriate time frame for a response.

10 Although the policy doesn't specify, we recommend that a brief synopsis of the proposed confirmatory studies (rather than a full protocol) be sufficient in responding to the NOC/c-QN.

11 It is unclear why a rational bridging the promising clinical evidence with the proposed confirmatory studies needs to be provided since Health Canada will have already outlined the requirements for additional clinical evidence in the NOC/c-QN.

12 Although indicated in the policy, reassurance is required that the preference to conduct confirmatory studies in Canada not become mandatory. It may not always be feasible to conduct confirmatory studies in Canada, therefore, the policy should allow some flexibility.

Subsection 6 (C): Management of Submission and Charges

13 The Management of Information Policy needs to be updated to accurately reflect the new review timelines for NOC/c. The policy refers to the May 2001 version, which is outdated and does not include references to the 200-day review time for NOC/c submissions.

Subsection 6 (D): Educational/Promotional Material

14 The policy needs to clarify whether Patient Package Inserts will be required for all products, even those given in a hospital setting, or with the intervention of a health care professional. Clear guidance on how the conditional statements need to be worded or displayed for such material should be provided to ensure consistency.

15 The policy should be clarified to include details on the possible restrictions that could be imposed on the advertisement and /or distribution of the drug, as well as in what circumstances these would be applied.

Subsection 6 (E): Post-Market Commitments

E (i): Confirmatory Studies

16 The policy implies that additional new studies are always required and should include the provision of longer term data from existing studies to confirm clinical benefit (clinical

043

progressions, survival rates, etc.). In most cases the need to provide additional studies is unclear, since it implies that an inadequate full package has been submitted.

17 Time frames for supplying results need to be flexible as the date of availability of a final study report is difficult to pinpoint. In cases where an extension is required, what would be the process and would a new Letter of Undertaking be required?

18 Clarification is also required in the situation where the sponsor is submitting data as it becomes available. Will specific restrictions be removed one at a time as the data are submitted and reviewed, or would the sponsor need to wait until all data for all conditions have been met before any changes could be implemented? We suggest that changes be allowed as the data becomes available.

E (ii): Adverse Drug Reaction (ADR) Reporting and Periodic Safety Update Reports (PSUR-Cs)

19 Enhanced post-marketing surveillance criteria and reporting initiatives need to be further defined. Active Surveillance describes regular periodic collection of Case reports-- the responsibility for this should be described.

20 Clarification is required as to whether the PSUR-C is a Canadian specific document. It is critical that Canadian specific formats and/or templates <u>not</u> be introduced, as this would result in an unnecessary burden to sponsors and would be an obstacle to providing timely information. The introduction of a Canadian specific PSUR would also be inconsistent with International harmonization efforts.

E (iii): Notification and Reporting on Specific Issues of Concern

21. The requirement to notify Health Canada within 15 days, when an expert panel or advisory committee has been struck seems overly onerous. Sponsors often initiate such panels to solicit input from experts and therefore only those set up by regulatory agencies to address a safety issue should be subject to reporting under this policy.

<u>Subsection 6 (F): Subsequent Submissions</u>

22 Please clarify whether subsequent submissions for a new indication must also demonstrate safety (including non-clinical studies) and clinical pharmacology independent of the original submission. The policy refers only to demonstrating independence of efficacy. Subsequent submissions for new indications should be able to cross-refer to the pre-clinical and clinical pharmacology (if appropriate) of the original NDS, in addition to the quality data (allowed for in the guidance document).

23 Data that would enhance the safe use of the product should be submitted as soon as the data is available, but how will this be reviewed? A 90-day Notifiable Change review will delay the dissemination of important safety information to health care professionals.

<u>Subsection 6 (G): Stop sale/ Revocation</u>

24 The policy states that failure to provide results of a confirmatory study by a specified date may be interpreted as suggesting the possibility of insufficient evidence. As previously mentioned, flexibility needs to be exerted when determining dates since timelines may slip

044

despite a sponsors best intentions. A mechanism for adjusting this date depending on how the study(ies) are progressing needs to be defined.

25 Please clarify what is meant by "limited" availability through the Special Access Program (SAP). Will there be any additional restrictions placed on the provision of these products, and if so, based on what criteria?

Comments on the Notice of Compliance with Conditions (NOC/c)Guidance Document:

Section 2.4

Significant increase in efficacy and/or significant decrease in risk...

Please clarify the statement "that the therapy has the potential to provide a statistically significant and clinically relevant improvement"? Can the data be trending towards statistical significance and be sufficient for NOC/c or does it have to reach a certain level of significance?

Section 3.1 (1)- Eligibility and Review

Upon Completion of Review

We are concerned that since a formal post-marketing surveillance policy or program has not yet been implemented, there is a potential for Health Canada to require excessive surveillance requirements under the cover of the NOC/c policy.

3.2 (a). Issuance and Response: NOC/c Qualifying Notice (NOC/c-QN)

Any additional Information requested by Health Canada

Please clarify the difference between the Product Specific Fact Sheet and the Information for the Consumer section of the Product Monograph. It appears that the information contained within the two documents are similar and therefore, we suggest that the fact sheet be replaced by the Patient Information Section. Two documents existing for a similar purpose with potentially different information would only confuse consumers.

Section 3.2(b)

An initial outline of proposed Confirmatory trials and a rationale bridging the "Promising Clinical Evidence" with the proposed confirmatory studies

It is not always possible to have confirmatory studies conducted in Canada. Reassurance is required that this preference will not become mandatory.

Section 3.3 – Agreement of Conditions and Issuance of the NOC's

Please provide clarity on the process for removing proprietary information from the NOC/c-QN prior to posting on the web-site? The sponsor should be consulted for agreement on the information to be severed prior to posting the NOC/c-QN on the web-site.

Section 4.3 – Advertising, distribution and labelling restrictions

The guidance needs to include more detail on the wording to be included on promotional material and the manner in which it must appear (provide examples) to ensure consistency.

Section 4.5 – Other Ongoing Clinical Trials

We feel that it is unreasonable to expect a list of all ongoing trials. This should be limited to studies directly related to the drug product and indication that has been granted conditional

045

approval. Also, the guidance document states that the results of ongoing studies should be submitted, however, the mechanism to do so is unclear. Since these would not be confirmatory studies or those required to be submitted in the Letter of Undertaking, it is not clear how or why they need to be submitted. Only those of relevance should be required and should be outlined in the Letter of Undertaking. Furthermore, the Management of Drug Submission Policy doesn't allow anything other than safety information to be submitted unsolicited.

Section 4.6 -Market Authorization

We propose a list of worldwide marketing approvals not be required as an appendix to the Letter of Undertaking since it would become out of date. Such a list is maintained and provided as part of the PSUR.

Section 5.2.1

Product Monograph

The guidance document provides specific information about requirements and we have the following comments:

- the boxed text proposed for the Information for the Consumer section should be simplified and written in plain language to ensure patients' understanding.
- the use of the proposed symbolic identifier for sections that "require particular attention" is unclear.
- it is unclear which text from the general information needs to be repeated in Section 3. The document says "..the first section of which must be repeated..". Please clarify which specific information is required.

We appreciate the opportunity to comment on the revised policy and guidelines and hope you will find these comments useful. If you have any questions or concerns, please feel free to contact me at (905) 819-3482, or via fax at (905) 819-3339.

Sincerely,

Rav Kumar, Ph.D
Vice-President, Regulatory Affairs and Pharmaceutical Development
GlaxoSmithKline Inc.

046

JANSSEN-ORTHO

JANSSEN-ORTHO INC.
19 GREEN BELT DRIVE
TORONTO, ONTARIO
CANADA M3C 1L9
www.janssen-ortho.com

fax

TO:	FROM:
Ms. Tara Bower, Policy Division, Bureau of Policy and Coordination	Elizabeth Wang
FAX NUMBER:	OUR FAX NUMBER:
613 941 6458	416 449 7092
cc	OUR TELEPHONE NUMBER:
	416 382 5093
DATE:	NO. OF PAGES INCLUDING COVER:
April 1, 2002	

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Dear Ms. Bower,

Subject: Draft Policy – Notice of Compliance with Conditions (NOC/c)

We have reviewed the draft policy for Notice of Compliance with Conditions that was issued for consultation on January 28, 2002.

The proposed policy provides additional information regarding requirements and processes associated with submission filing, review and NOC/c issuance. It also provides specific requirements for the dissemination of educational material associated with products granted authorization under the NOC/c policy.

We would like to submit for your consideration, a recommendation with regard to the distribution of education material. It has been recommended that education material in the form of Dear Health Care Professional (HCP) Letter is prepared by the sponsorsto inform HCPs the nature of granted authorization. Please ensure that clear distinction is made for this type of HCP Letters and those that carry therapeutic product safety information to avoid diminished effectiveness of either letter.

We thank you for your consideration of our recommendation and look forward to the implementation of the revised policy.

Yours sincerely,

Elizabeth Wang

Elizabeth Wang, M.Sc.
Regulatory Project Leader
Janssen-Ortho

April 2, 2002

Ms. Tara Bower
c/o Therapeutic Products Directorate
Bureau of Policy and Coordination
2nd Floor
Tower B
A.L. 3102C5
Holland Cross
Ottawa, ON
K1A 1B6

Dear Ms. Bower:

RE: Draft documents pertaining to the Notice of Compliance with Conditions (NOC/c) Policy, cover letter dated January 28, 2002.

Thank you for the opportunity to comment on the documents generated in accordance with the Notice of Compliance with Conditions policy, specifically the Policy and the Draft Guidance.

Please accept the following as comments from AstraZeneca Canada Inc.:

Well-Controlled Clinical Evidence
Regarding the requirement for "promising clinical evidence" to be "well-controlled", we note that while this would be ideal, in the case of drugs which would be considered for NOC/c, the completed studies are usually not "well-controlled" ones (which is why conditions of approval need to be assigned).

CSC disagrees - meeting minutes

Timeframes
Our calculations for total target timeline to approval are:

255 days -- screening and review
30 days -- response to NOC/c-QN
30 days -- review of additional information requested in NOC/c-QN
15 days -- finalizing conditions for issuance of NOC/c and Letter of Undertaking

Total: 330 days

This is far too long for a product which qualifies for a Notice of Compliance with Conditions. We must strive to be comparable to other developed nations.

NOC/c Qualifying Notice
We strongly recommend that before the NOC/c-QN is posted on the TPD website, the

sponsor be given the opportunity to review the document for proprietary information. Though the TPD's intent is that the NOC/c-QN *not* include information of this sort, there should be opportunity for discussion if there is disagreement between the sponsor and TPD.

Listing of Ongoing Clinical Trials

Clarification is needed as to which trials should be listed as "ongoing clinical trials". Are they only trials related to this submission, e.g., those performed to remove the " conditions" from the file? * lean

Cross-Reference to Original NDS

If a file is approved with conditions, the additional work to remove the conditions would presumably be clinical studies. Paragraph 3 suggests that cross-reference for a second NDS may be made to the *CMC information* in the original NDS. We propose that once the first file is approved (even with conditions), then the sponsor may cross-refer also to the *preclinical or pharmacology* portions of that file, if those portions were complete and not at issue in the NOC/c. * *

Timing of S/NDS-C review

We strongly suggest that timing of review for S/NDS-Cs should be expedited, in the manner of the original NDS review. While the product is technically on the market when sold under an NOC/c, the labelling associated with this type of approval may dissuade physicians and patients from using a drug which is beneficial and safe. It is thus imperative that the NOC/c wording be removed as soon as possible after the confirmatory data become available, and this would be achieved by expedited review timelines.

We appreciate the opportunity to comment on these documents. If you have any questions or comments, please do not hesitate to contact me by telephone at (905) 566-7825, or by fax at (905) 275-6271.

Sincerely,

ASTRAZENECA CANADA INC.

Karen A. Burke, Ph.D.
Vice President, Regulatory Affairs

April 2, 2002

Ms. Tara Bower
c/o Therapeutic Products Directorate
Bureau of Policy and Coordination
2nd Floor
Tower B
A.L. 3102C5
Holland Cross
Ottawa, ON
K1A 1B6

Dear Ms. Bower:

RE: Draft documents pertaining to the Notice of Compliance with Conditions (NOC/c) Policy, cover letter dated January 28, 2002.

Thank you for the opportunity to comment on the documents generated in accordance with the Notice of Compliance with Conditions policy, specifically the Policy and the Draft Guidance.

Please accept the following as comments from AstraZeneca Canada Inc.:

Well-Controlled Clinical Evidence
Regarding the requirement for "promising clinical evidence" to be "well-controlled", we note that while this would be ideal, in the case of drugs which would be considered for NOC/c, the completed studies are usually not "well-controlled" ones (which is why conditions of approval need to be assigned).

Unreasonable!

Timeframes
Our calculations for total target timeline to approval are:

255 days -- screening and review
30 days -- response to NOC/c-QN
30 days -- review of additional information requested in NOC/c-QN
15 days -- finalizing conditions for issuance of NOC/c and Letter of Undertaking

Total: 330 days

This is far too long for a product which qualifies for a Notice of Compliance with Conditions. We must strive to be comparable to other developed nations.

NOC/c Qualifying Notice
We strongly recommend that before the NOC/c-QN is posted on the TPD website, the

all good!

sponsor be given the opportunity to review the document for proprietary information. Though the TPD's intent is that the NOC/c-QN *not* include information of this sort, there should be opportunity for discussion if there is disagreement between the sponsor and TPD.

Listing of Ongoing Clinical Trials

We could debate this + clarify solution to list only those for NOC/c purposes

Clarification is needed as to which trials should be listed as 'ongoing clinical trials". Are they only trials related to this submission, e.g., those performed to remove the" conditions" from the file?

Cross-Reference to Original NDS

If a file is approved with conditions, the additional work to remove the conditions would presumably be clinical studies. Paragraph 3 suggests that cross-reference for a second NDS may be made to the *CMC information* in the original NDS. We propose that once the first file is approved (even with conditions), then the sponsor may cross-refer also to the *preclinical or pharmacology* portions of that file, if those portions were complete and not at issue in the NOC/c. no problem from my perspective!

Timing of S/NDS-C review

We strongly suggest that timing of review for S/NDS-Cs should be expedited, in the manner of the original NDS review. While the product is technically on the market when sold under an NOC/c, the labelling associated with this type of approval may dissuade physicians and patients from using a drug which is beneficial and safe. It is thus imperative that the NOC/c wording be removed as soon as possible after the confirmatory data become available, and this would be achieved by expedited review timelines.

We appreciate the opportunity to comment on these documents. If you have any questions or comments, please do not hesitate to contact me by telephone at (905) 566-7825, or by fax at (905) 275-6271.

Sincerely,

ASTRAZENECA CANADA INC.

Karen A. Burke, Ph.D.
Vice President, Regulatory Affairs

Drug Regulatory Affairs – Medical Division
Pharmaceuticals Group
Pfizer Canada Inc.,
P.O. Box 800
Pointe-Claire/Dorval, Quebec H9R 4V2
Tel (514) 695-0500 Fax (514) 426-6824

Pharmaceuticals

CONFIDENTIAL

April 3, 2002

BY E-MAIL TARA_BOWER@HC-SC.GC.CA
AND BY FACSIMILE

Tara Bower
Bureau of Policy and Coordination
2nd floor, Tower B Holland Cross
11 Holland Ave. AL: 3102C5
Ottawa, Ont K1A 1B6

Subject: Notice of Compliance with Conditions (NOC/c) Policy – Draft January 2002

Dear Ms. Bower,

As the leading pharmaceutical company, Pfizer is keenly interested in all aspects of the drug development process and supports regulatory approaches intended to provide patients suffering from serious, life-threatening or severely debilitating diseases or conditions with early access to promising new drugs.

The comments below, in response to the publication of the draft policy and guidance document cited above, were generated by Pfizer Canada Inc. and integrate the position from our U.S. colleagues as well. We thank you for the opportunity to provide comments.

Policy implies all RXS even palliative!

Scope

Keeping in mind that numerous drug products are developed with an indication for the *treatment of the serious symptoms* associated with serious, life-threatening and severely disabling illnesses, not necessarily for the treatment of these diseases, we believe it would be beneficial to state clearly, within Section 1.3 of the guidance document, that such drug products are eligible for review under the NOC/c policy.

Criteria for Qualification under the NOC/c Policy

The terms "existing therapy", "alternative therapy" and "available therapy" are used in several places and should be clearly defined. For example, on page 4 of the draft guidance, it states: "*The NOC/c policy applies to drug submissions intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness or condition for which there is no existing treatment available on the Canadian*

.../2

20(1)(b)

market which possesses a similar therapeutic profile or for which the new submission demonstrates a significant improvement in the benefit/ risk profile over alternate available products". In this statement, it is clear that "*existing treatment*" refers to products that are available on the Canadian market, however, the meaning of "*alternate available products*" needs clarification: Does Health Canada refer to unapproved products, marketed products or yet, products under some other status? Again on page 6, the term "available therapy" is used without a clear meaning.

Commercially available therapy.

Also, how will the benefit/risk profile over "alternate available products" be assessed if there is no direct comparative data filed in the submission?

Discussion within the context of Dx & it's treatment is good!

We would like to make reference to a draft guidance recently released by the FDA in which the terms "available therapy" and related "existing therapy" and "existing treatment" are defined (Guidance for Industry, Available Therapy, FDA February 2002). These terms have been used freely in policies, regulations and guidances related to drugs used for serious, life threatening and severely debilitating diseases. In providing a definition of these terms, the FDA intends to create a level playing field for what is meant as the "reference" when they are making approval decisions for a product based on "available therapy" or benefits over "available therapy". We are providing, for information purposes, a copy of the FDA draft guidance. As the document was released just recently, Pfizer's position is not yet available. Therefore, we are not providing it here as an endorsement but rather a starting point to help further clarify the Canadian guidance.

U.S. defn 22-Jan not sure.

In addition, on page 4, the draft guidance states "Approval under the NOC/c may be granted for a drug product...based on a benefit/risk assessment, and is found to be of high quality". Although it is generally understood that the term "high quality" refers to the Chemistry and Manufacturing aspects of the new drug, it would be helpful to further define "high quality" within the context of this guidance document.

OK – Chem & mfg.

Review and Authorization

The requirement for pre-NDS presentation is well received. It would be helpful to indicate whether a pre-meeting package is also required (content, timing) prior to the presentation. We consider the time frame of 70 (10+60) days between the pre-NDS presentation and the filing of the drug submission to be restrictive. In some instances, a sponsor would like to seek input from Health Canada at an earlier point in the drug development process to discuss the possibility of a NOC/c.

Not precluded ...13

Would be in the normal course of consultations. –

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The draft policy and guidance allows for conditional approval based on surrogate markers and accelerated review time. We would like to suggest Health Canada consider the concept of a "rolling NDS", i.e. the sponsor providing parts of the submission as they are being generated.

We believe the link of the present policy and guidance with the " Priority Review of Drug Submissions" policy requires clarification. It is stated in the NOC/c guidance that any product that has been filed for a NOC/c is ineligible for Priority Review status. However, in examining flowchart Appendix 4a, it appears the reverse is possible. It should be clarified that a product, which is submitted for Priority Review status, can be issued a NOC/c, at the discretion of the reviewing bureau.

Further reference is made to the flowchart provided as Appendix 4a – following acceptance for review of the submission as Priority Review and following the box indicating target review period of 180 days, a statement reads "NOC-without conditions (possible outcome)". Subsequently, there is an arrow towards another 30-day review prior to the issuance of the NOC/c. This is misleading, because if the product has been granted a NOC without conditions, there is no additional review of the submission. The path should be depicted visually as being independent of the path towards a NOC/c.

With regards to confirmatory studies discussed within section 3.2 – Issuance and Response, we would propose that Health Canada considers accepting similar post-approval commitments made with the FDA and EMEA as it is not always feasible to conduct certain studies in Canada, in particular when such studies have already been initiated in other countries. This would facilitate the availability of the confirmatory clinical evidence. Also, it appears that it will only be acceptable to address clinical benefit in the same indication for which the NOC/c was issued. We kindly request that Health Canada reconsider this condition. From the U.S. experience, it has been possible to demonstrate clinical benefit in other populations in different stages of the disease.

Under section 3.3, we are seriously questioning Health Canada's rationale for public disclosure of the NOC/c-QN. As this document clearly pertains to a yet-to-be marketed drug product, it retains full proprietary interest and is exempt in its entirety from the provisions of the Access to Information Act. We firmly believe the NOC/c with its Letter of Undertaking would be a more appropriate document as it represents the finalized conditions, which are acceptable to both Health Canada and the sponsor. Should Health Canada persist in its intent of publishing the NOC/c-QN, we would request that the

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document be reviewed, and agreed upon, by the sponsor prior to posting on the TPD web site.

We noted the guidance document indicates "no proprietary information would be disclosed". We are seeking confirmation from Health Canada that any document pertaining to a drug submission or review thereof, whether this document be a NOC/c-QN, a NOC/c+Letter of Undertaking or any other document related to a drug submission or its review, including information pertaining to Clinical Trial Applications, be subject to a formalized review procedure. For example, under the provisions of the Access to Information Act, to allow the sponsor an opportunity to make representations for exemptions from disclosure in the documents prior to release.

OK ✓ agreed!

Letter of Undertaking

In section 4.2 (Post market surveillance commitments), the calendar and format of the PSUR need to be specified. If the product is marketed in another country, will the international birthdate be acceptable as a reference date for the PSUR? What format would be acceptable to Health Canada? In addition, it may prove difficult to secure PSUR semi-annually when the drug has been marketed for several years in other countries.

→ MHRD → Then there should not be issued a NOC/c may never be needed → If all circumstances can be covered (?)

Product Monograph

We note Section 5.2.1 refers to the PM new format which has not been released yet.

new? old? Not below issued

OK - agreed!

Post-Market commitments

We are disappointed that no reduced target is associated with the review of the S/NDS-C. Although we believe the post-market surveillance procedures will prove effective in bridging the status of a new drug from the NOC/c to NOC, the NOC/c remains, in our view, a temporary status. All involved (most importantly the medical community and the patients currently treated with the drug product under the NOC/c) would benefit from from Health Canada's timely review of the most recent information/data provided within the S/NDS-C showing the clinical benefit of the drug has been fully verified so its status can be confirmed , as soon as possible, by the issuance of the NOC (without restrictions) and by the availability of the most up-to-date information included in the revised Product Monograph.

With regards to the monitoring of safety (section 6.2), we would like to point out that according to the ICH E2c guideline, only serious ADRs received from the regulatory

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u HPD?

authorities are to be included in the PSURs. Considering that a number of sponsors are generating PSURs consistent with the ICH guideline, non-serious ADRs would not be included in the PSURs. In accordance with the ICH E2c, we recommend that Health Canada provides only serious ADRs to the sponsors. We noted the guidance does not specify which format will be used for providing the information to the sponsor. We recommend the CIOMS-I format be used by Health Canada. In addition to the above comment, the guideline should also specify whether Health Canada will be responsible for the follow-up activities with the reporter.

agreed?

Other comments

agreed!

Concerning the statement made about drug benefit plans, we suggest that this is out of context. The provinces make their own decisions with regards to formulary listing based on their own assessment of clinical benefits and cost impact.

We thank you in advance for considering our comments on this policy and guidance document.

The information supplied herewith is considered to be confidential and covered under sub-section 20(1) of the Access to Information Act. Notice of any request for access to this information, or any part thereof, is to be given in writing to:

PFIZER CANADA INC.
17,300 Trans Canada Highway
Kirkland, Quebec H9J 2M5, Attention: Director, Regulatory Affairs

Sincerely,

Maria Klapka
Director, Drug Regulatory Affairs-Canada

c.c. Rx&D – Regulatory Affairs: Julie Latremouille

Enclosure

20(1)(b)

057

Boehringer Ingelheim

Boehringer Ingelheim (Canada) Ltd/Ltée - Burlington, Ontario

Ms. Tara Bower
Bureau of Policy and Coordination,
2nd Floor, Tower B Holland Cross,
11 Holland Ave.,
Address Locator # 3102C5
Ottawa, Ontario
K1A 1B6

Boehringer Ingelheim
(Canada) Ltd/Ltée

Regulatory Affairs

April 04, 2002

Our Reference NOC/c Policy

Tony Dalle Ave
Telephone 905-631-4608
Telefax 905-637-4285
e-Mail tdalleave@
bur.boehringer-ingelheim.com

5180 South Service Road
Burlington, Ontario, Canada
L7L 5H4
Telephone 905-639-0333
Telefax 905-639-3769
www.boehringer-ingelheim.com

Re: Notice of Compliance with Conditions (NOC/c) Policy Draft Guidance for Industry; Notice of Compliance with Conditions (NOC/c) Policy

Dear Ms Bower:

We are pleased that Health Canada has issued a draft policy on the Notice of Compliance with Conditions (NOC/c) with an accompanying Draft Guidance for Industry document. We are appreciative of the efforts made to:

eliminate the lack of consistency in application of the Policy,
facilitate consistent interpretation, and
improve transparency between Industry and the Agency.

We also appreciate the opportunity to provide comments. Upon careful review, we feel that there are a number of areas in which the processes, requirements, and criteria for decision-making have not been clearly defined. It is felt that this may lead to inconsistent handling, interpretation, and follow-up of the NOC/c submission.

061

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Comments on the Notice of Compliance with Conditions (NOC/C) Policy

Comments on Section 2. Background

Although it is acknowledged that the Policy has been prepared in a general manner, it must be recognised that it would be beneficial if the Policy were to include specific aspects relating to HIV treatments. As the Policy is currently written, clinical endpoint is related to morbidity and mortality. In some instances, only surrogate markers are available as a measure of a drug's efficacy until the time that the clinical endpoints are known. With respect to HIV, it is well documented that viral load and CD4+ count are viable options for clinical endpoint studies. The Policy only mentions virologic suppression as a viable surrogate endpoint that may be indicative of efficacy. The US FDA has issued a Guidance Document "Clinical Considerations for Accelerated and Traditional Approval of Antiretroviral Drugs" dated August 1999. The document states that with the success of combination therapy (HAART) there is a decline in HIV-related clinical illness (morbidity and mortality) and the requirement for clinical endpoint is no longer feasible. The Policy needs to clearly indicate this fact for clinical studies in HIV patients.

Jacques

Also, for clinical studies in HIV patients, the US FDA Guidance Document recommends that submissions can be filed for accelerated approval based on a minimum of two well-controlled studies of at least 24 weeks duration. Also, the safety of the drug must be supported by safety data from at least 400 to 500 patients. Traditional approval is based upon controlled and comparative safety data and proof of efficacy based on the same studies evaluated for accelerated approval, but extended to a duration of 48 weeks or longer. Study endpoints are defined as the proportion of patients with a viral load lower than the assay limit at 48 weeks and time-to-loss-of-virologic-response. CD4+ cell counts are recommended to support the clinical endpoints.

Since many of our submissions are based upon a NDA or S/NDA filed with the US, the Policy should take into consideration that for clinical studies involving AIDS drugs, a NOC/c may be granted based on the requirement of the FDA document referenced above. The safety of the studies will be based upon a minimum of 400 to 500 patients, and the efficacy will be based upon viral load decrease, time-to-loss-of-virologic-response, and CD4+ counts. The Letter of Undertaking should, in this instance, indicate that the confirmatory studies are based upon the same studies approved for NOC/c, but extended to a minimum of 48 weeks duration.

062

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Comments on Section 5. Policy B.

The commitment to "undertake in writing to design, carry out and report on confirmatory studies to verify the clinical benefit of the drug" and to initiate studies in a timely fashion appears not to take into consideration studies that were granted NOC/c based upon 24-week safety and efficacy data. This section should be amended to reflect this fact. A suggestion is to "report on confirmatory and/or extension studies..."

Although it states that the sponsor must agree to "enhanced post-market surveillance and reporting requirements", it does not define what this process involves. If heightened transparency and consistency are goals for the new Policy, this section needs to be further developed and defined. If this process involves the submission of Periodic Safety Update Reports (PSURs), this should be stipulated along with the frequency of reporting.

The Policy indicates that confirmatory studies are to be initiated in a timely manner. The definition for timely needs to be elaborated. In the Draft Guidance for Industry (page 18), sponsors may be requested to report on the progress of confirmatory studies. It is suggested that more specific guidance be provided as to when and why progress reports are required.

Comments on 6. Responsibilities & Procedures

Comments on 6.A. b) Upon Request for Advance Consideration under the NOC/c Policy

Submissions that are accepted for review under the NOC/c Policy will be subject to a review target of 200 days following screening according to Performance Measurements standards. Clarification is required as to whether the Policy on Management of Drug Submissions will be revised to reflect this.

It is stated that submissions filed under the NOC/c Policy are not eligible for Priority Review Status. With respect to the review of the submission, will an application eligible for Priority Review jump the queue and be reviewed before a submission filed under the NOC/c Policy? This issue needs to be clearly addressed by Health Canada.

The review time for a submission granted Priority Review is 180 days compared to 200 days for a submission filed under the NOC/c Policy. If a submission approved for Priority Review is

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because you wouldn't qualify for PR. substantial

able to jump the queue before a submission filed for NOC/c, as a sponsor, why would anyone file their application under this NOC/c Policy as a first choice?

Comments on Section 6.A. iii) Ageement of Conditions and NOC/c Issuance

It is not clear what the process is if the response to the NOC/c is considered inadequate / unacceptable to TPD.

The commitments identified in the Letter of Undertaking may change with time due to a number of reasons. For example, a clinical study may be terminated because of safety concerns of a comparator drug (as in the case with adefovir), or as a result of negotiations with other Regulatory Agencies. Canadian pharmaceutical companies like Boehringer Ingelheim depend upon the availability of the S/NDA (US) or the European Dossier for their S/NDS-C. The availability and contents of our S/NDS-C depend on the commitments agreed to with the Regulatory Agencies in those countries. As a result, our commitments to Health Canada may not be met, unless there is a process in place to negotiate changes to commitments agreed to in our Letter of Undertaking. As a sponsor, we can commit to confirmatory studies only after we have reached agreement with our Head Office, and this may change based upon the requirements for confirmatory studies and timelines agreed to in Europe, and/or Japan and/or the US. If Health Canada requests additional studies or commitments beyond the commitments agreed to in Europe, the US, or Japan, it is unlikely that our Head Office would make additonal confirmatory studies for only Canada. Health Canada needs to recognize this fact and acknowledge that confirmatory studies may change depending upon decisions reached by other Authorities. If Canada is unwilling to be flexible and not recognize Canada's position with respect to European, American, and Japanese commitments, the product may not be marketed in Canada.

why not bridge ongoing studies to requirements (in some cases only)

part of negotiations.

Comments on Section 6.E. Post-Market Commitments: i) Confirmatory Studies

part of negotiations LOU

the how will be agreed upon.

Sponsors maybe requested to submit to Health Canada progress reports on the confirmatory studies. The timelines and criteria for submitting such progress reports are not provided; this needs to be addressed. 5 year survival

As stated, the NOC/c Policy applies to "serious, life-threatening or severely debilitating diseases or conditions for which there are, as yet, no known cures". Health Canada's decision to grant approval of a drug under the NOC/c Policy is based upon the evidence provided in the submission (safety and efficacy) and the overall benefit / risk ratio. It is difficult to determine

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how Health Canada will confirm the safety and efficacy information in the original submission by enhanced post-market procedures. Outside of well-controlled studies, it is difficult to take isolated adverse events or reports of lack of efficacy, and make any conclusion regarding the safety / efficacy of the drug. As such, there should be no "prejudgement" of whether or not the S/NDS-C should be subject to standared submission targets.

product already available in market for indicated use

Comments on Section 6.E. Post-Market Commitments: ii) Adverse Drug Reaction (ADR) Reporting and Periodic Safety Update Reports (PSUR-Cs)

Within Boehringer Ingelheim, the preparation of PSURs is a Corporate responsibility. According to the ICH, E2C, the frequency of reporting PSURs has not been harmonized among the three ICH regions. In the US, PSURs are reported quarterly during the first 3 years, and then annually; in Europe, PSURs are reported semi-annually for the first 2 years, annually for the 3 following years and then every 5 years at time of renewal of registration; in Japan every 6 months for the first 3 years and annually thereafter. As the Policy now stands, it may not be possible to provide Health Canada with PSURs semi-annually. This fact should be taken into account.

International Birth Date

Health Canada is responsible for providing the sponsor of the NOC/c with all ADRs received from health care professionals within 30 days of receipt for inclusion into the PSUR. As the reporting of ADRs in Canada is voluntary, it is clear that the potential for great inconsistency between drugs exists. As a result, the lack of consistency in reporting ADRs may unintentionally prejudice one drug from another. This prejudice may be enhanced when the Product Monograph identifies a particular adverse event with a specific drug so that health care professionals are "conditioned" to associate a specific adverse event with a particular drug. Sponsors take a great deal of responsibility to ensure that their safety (adverse event) database is current. The fact that Health Canada receives ADRs from health care professionals while the sponsor does not indicates that there is a flaw in the system that needs to be rectified. Somehow it is difficult to comprehend the commitment of Health Canada for patients' safety when it is only interested in providing the sponsor of the NOC/c with all ADRs from health care professionals instead of forwarding all ADRs to all sponsors.

conditioned

lack of reporting or reporting will be inconsistent. Each docs drug will be equally affected.

If all your drugs are positioned such that they receive docs that maybe but the ratio of 1 of 10 is 10% for a cross the board so the other product is on -

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Comments on Section 6.E. Post-Market Commitments: iii) Notification and Reporting on Specific Issues of Concern

Again, it appears that Health Canada is only concerned with drugs that are subject to NOC/c. If patient safety is the primary concern for Health Canada, shouldn't all concerns related to the safety or quality of a drug product issued by a foreign jurisdication be reportable?

The last paragraph beginning with "In the event ...." found on page 12 of the Policy is difficult to understand. Once a drug has fulfilled all of its commitments, the sponsor files a S/NDS-C and if the data is found to be acceptable, Health Canada will remove all conditions associated with that drug. Any subsequent submission for that drug product which would rely on safety and efficacy data from the original application will be revisted and the "conditions associated with approval shall be adjusted accordingly where justified". It is difficult to understand the intent of this statement.

only sponsor to make the commitments however → requested + amended necessary

Comments on G. Stop-sale/Revocation Do different to other drug.

Failure by the sponsor to comply with any of the undertakings may result in withdrawal of the drug from the market. This procedure is not well defined. Does Health Canada issue a warning before it requests that the drug be withdrawn from the market? What recourse does the sponsor have? What is Health Canada's decision making process for deciding when a drug should be withdrawn, but still be allowed to remain available through the Special Access Program? How does Health Canada decide that an alternative to stop-sale/revocation would be to restrict the drug to a certain patient population or distribution, require that the sponsor disseminate educational material, or provide enhanced post-market surveillance analysis? An alternative approach would allow the sponsor an opportunity to comment in writing to any shortcomings, deficiencies or failures in meeting their comitments as identified by Health Canada. Sponsors should be allowed a face-to-face meeting with Health Canada to try and resolve any issues that cannot be agreed to in writing. If an agreement cannot be reached, the sponsor should have a procedure in place for an appeal process. To ensure transparency, a summary of the issues, agreements and resolutions should be available on the Health Canada web site.

above opportunity to comment

no different from another drug.

if necessary could consult a panel?

balance of risk + benefits based on these elements would provide c

if manuf. has not fulfilled with no good reasons for not having satisfied commitments. Analysis of PSURs indicate a post market S/S-C

066

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Comments on H. Termination of Conditions or Restrictions

As mentioned previously, confirmatory studies identified by Health Canada may need to be approved by Corporate. The decision to agree/conduct confirmatory studies by Corporate and the type of confirmatory studies will depend on whether conditional approval was granted in Europe, US and Japan. Usually Corporate will agree to the confirmatory studies requested/negotiated by these Agencies. The commitments agreed to in these countries may change with time. As a result, it is important to have a procedure in place for the Sponsor to negotiate and amend the Letter of Undertaking and for Health Canada to approve these changes.

General Comment

All timeframes should be indicated as calendar days, if this is the intent.

Summary

We would like to thank you for the opportunity to comment on this draft Policy. As a representative from Industry, transparency and clarity are important issues that need to be addressed. We hope that our comments will help you towards this goal. Should you have any questions, please do not hesitate to contact me.

Yours sincerely,
BOEHRINGER INGELHEIM (CANADA) LTD.

Tony Dalle Ave

Tony Dalle Ave
Project Manager, Regulatory Affairs

This document is also available in PDF format [nocc_policy2002_e.pdf] Pages: 16, Size: 40 K, Date: 2002-11-08

November 8, 2002

NOTICE

Our file number: 02-118669-598

Notice of Compliance with Conditions: Revised Policy

The final version of this Health Canada policy statement Notice of Compliance with Conditions is now available. Comments and suggestions received from the consultation on the draft version of the policy were reviewed and considered in the finalization of this document.

This policy is a revised version of the 1998 Health Canada policy of the same title. The revised policy, as the original, outlines Health Canada's eligibility criteria and requirements related to consideration of a product for approval under the NOC/c policy. The revised document

Warnings
Regulatory Requirements for Advertising
Special Access Programme
Activities
Communications

provides further direction respecting revised procedures and additional requirements including the provision of education material for all products approved under the NOC/c policy. This revised policy supercedes the previous version.

The policy has been revised and approved by the appropriate Health Canada Expert Working Group. In adopting this revised policy, Health Canada endorses the principles and practices described therein. The policy should be read in conjunction with this notice, Health Canada's Guidance for Industry on Notice of Compliance with conditions and relevant sections of other applicable Health Canada guidances.

This and other policy and guidance documents are available on the Therapeutic Products Directorate/Biologics and Genetic Therapies Directorate Website (s) (http://www.hcsc.gc.ca/hpb-dgps/therapeut). The availability of printed copies of policies and guidance documents may be confirmed by consulting the Guidelines and Publications Order Forms (available on the TPD/BGTD Website) or by contacting the Publications Coordinator1.

Should you have any questions regarding the content of the policy, please contact:

Ms. Tara Bower Senior Policy Advisor
Bureau of Policy Therapeutic Products Directorate
Holland Cross, Tower B Tunney's Pasture,
A.L. 3102C5
Ottawa, Ontario K1A 1B6
E-mail:Policy_Bureau_Enquiries@hc-sc.gc.ca
Phone: (613) 941-1246
Fax: (613) 941-6458

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1 Tel: (613) 954-6466; E-mail: publications_coordinator@hc-sc.gc.ca

Policy

November 6, 2002

Health Canada

Notice of Compliance with Conditions (NOC/c)

1. PURPOSE

This policy statement supercedes the previous policy, **Notice of Compliance with Conditions**, May 28, 1998. The purpose of this policy is to:

(a) Provide patients suffering from serious, life-threatening or severely debilitating diseases or conditions with earlier access to promising new drugs.

(b) Create a mechanism to ensure that a manufacturer that has a drug approved under this policy conducts confirmatory studies to verify the clinical benefit of the drug and further establish the safety profile.

2. BACKGROUND

There are a number of serious, life-threatening or severely debilitating diseases or conditions for which there are, as yet, no known cures. Examples of such diseases include HIV, ALS

clinical endpoints. In such instances, the Regulator may request additional confirmatory studies to further verify the clinical benefit of the drug.

On May 28, 1998, the former Therapeutic Products Programme issued the policy statement Notice of Compliance with Conditions (NOC/c). A reassessment of this policy and an evaluation of the linkages with the Priority Review policy was initiated to enhance consistency in the application of the policy, and address the need for guidance documents to facilitate consistent interpretation, as well as the need for heightened transparency and dissemination of educational material associated with products granted authorization under the NOC/c policy.

The benefits of the NOC/c policy are two fold:

- First, it will facilitate earlier access to the drug by physicians and patients. The acceptance of promising evidence of clinical effectiveness (Section 1.4) will allow for the filing of an eligible drug submission earlier than normally possible. Should the outcome of the review be positive, the time to approval and market for the drug, may be shortened. It should be noted that the time to agreement on the acceptability of the contents

and some cancers. Drugs are being developed that may alleviate or prevent some of the symptoms of such diseases and over time, these drugs may prove to be of significant clinical benefit with respect to improving survival of those suffering from these illnesses. However, this development process is often very slow and expensive.

Initially, the data available on these types of drugs may be limited due to the small number of patients that are eligible for participation in clinical trials. Even with larger sample sizes, data on final outcomes such as morbidity and mortality may be lacking. In some instances only data which measure the drug's effect on surrogate markers are available.

Surrogate markers are parameters that when measured directly are reasonably likely, based on available evidence, to predict an effect of a drug on recognized clinical outcomes such as morbidity and mortality. For example, in HIV disease, drugs that elicit a durable virologic suppression are believed to confer a significant reduction in AIDS clinical progression and death. Therefore virologic endpoints may be indicative of efficacy. Similarly, the effectiveness of vaccines is premised on the production of antibodies to provide immunity against disease, and the reduction in tumour size in cancers may be a sign of an improved clinical prognosis.

In some instances, sufficient cumulative testing has been done to substantiate that an effect on a surrogate marker is predictive of clinical benefit. However, until surrogate markers can be validated, evidence of the effect of a drug on non-validated surrogate markers cannot replace data that demonstrate an effect on recognized

of the "Letter of Undertaking" will affect the overall time to market.

- Second, it provides the means to ef fectively monitor, and report on, the safety and efficacy of promising new therapies through enhanced post-market surveillance initiatives.

Until the clinical benefit of the drug can be verified, inherent gaps in the available knowledge of the product benefit/risk profile will exist. As a result, the NOC/c policy remains restricted to products indicated for serious, life-threatening and severely debilitating illnesses or conditions (Section 3). Regular monitoring and enhanced surveillance mechanisms within the NOC/c policy, provide for the early detection of any potential safety concerns which may arise.

3. SCOPE

This policy applies to a New Drug Submission (NDS) or Supplemental New Drug Submission (S/NDS) for a serious, life-threatening or severely debilitating disease or condition1 for which there is promising clinical evidence, based on the available data, that the drug has the potential to provide:

- ef fective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada2;

or

- a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

In all cases, a prerequisite for issuance of an NOC, under the NOC/c policy, will be the sponsor's written commitment to pursue confirmatory studies acceptable to Health Canada.

4. DEFINITIONS

AVAILABLE THERAPY (also refers to "existing therapy" and "existing treatments"): Where the terms are not otherwise defined, available therapy is interpreted as therapy that is reflected in the approved labeling of regulated products. In unusual circumstances, a treatment that is not labeled for use but is supported by substantial and compelling well-documented literature evidence as well as treatments not regulated by Health Canada (eg. surgery) can be considered available therapy.

CLINICAL BENEFIT: outcomes that have an overall positive impact on the treatment of a disease.

ENHANCED POST-MARKET SAFETY

SURVEILLANCE: Use of systematic surveillance to supplement or enhance the current spontaneous adverse reaction reporting system. This may include active surveillance activities (regular periodic collection of case reports from health care professionals and health facilities that are evidence-based) and targeted safety monitoring studies (Phase IV studies).

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1 For additional information, refer to: "Guidance for Industry; Notice of Compliance with Conditions (NOC/c)." 2 An exemption to this criterion is outlined in Section 6F.

LETTER OF UNDERTAKING: a letter submitted to Health Canada by a sponsor of a drug submission prior to the issuance of a Notice of Compliance, qualifying under the NOC/c policy. The letter must be signed by the Chief Executive Officer, or designated signing authority of the sponsor and must outline the confirmatory studies to be conducted to verify the clinical benefit of the drug. The letter must be satisfactory to Health Canada and must also outline restrictions, if any, to be placed on the advertisement and/or distribution of the drug.

NOTICE OF COMPLIANCE WITH CONDITIONS (NOC/c): a Notice of Compliance that is issued with a notation relating to a Letter of Undertaking.

PROMISING3 CLINICAL EVIDENCE: evidence based on well-controlled and wellconducted clinical trials establishing that the drug product has an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit.

SIGNIFICANT IMPROVEMENT: statistically significant and clinically relevant improvement identified through well controlled clinical trials.

S/NDS 'C': a Supplemental New Drug Submission (S/NDS) consisting of results of confirmatory clinical trials specified in the Letter of Undertaking.

SURROGATE MARKERS: parameters that when measured directly are reasonably likely, based on available evidence, to predict an effect of a drug on recognized clinical outcomes such as morbidity and mortality. A validated surrogate marker is predictive of the clinical benefit of a drug.

5. POLICY

A. Approval under the NOC/c policy may be granted for a drug product with promising clinical benefit, providing it possesses an acceptable safety profile based on a benefit/risk assessment, and is found to be of high quality.

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3 The use of this term does not suggest the application of a standard lesser than "substantial" evidence of clinical effectiveness. Health Canada acknowledges the importance of flexibility in assessing whether promising evidence presented, in the context of such diseases and current scientific knowledge, is viewed as substantial.

B. Prior to approval, the sponsor must undertake in writing to design, carry out and report on confirmatory studies to verify the clinical benefit of the drug. The "Letter of Undertaking" must

meet the satisfaction of Health Canada. The sponsor must undertake to carry out any such studies in accordance with established scientific standards. The studies must be well designed and initiated in a timely fashion.

C. For the purposes of monitoring the safety of the drug product, sponsors must agree to enhanced post-market surveillance and reporting requirements to be outlined in the Letter of Undertaking.

D. For the purposes of assuring the safe use of the drug product, the conditions under which the drug product is approved must be clearly reflected and highlighted in the Product Monograph, Patient Package Insert and/or labeling for that product. The sponsor may also be requested to undertake to comply with restrictions imposed by Health Canada on the advertisement and/or distribution of the drug.

E. Prior to approval, the sponsor must prepare for distribution, educational material including Dear Health Care Professional Letters, for health care practitioners, and Product Specific Fact Sheets, for consumers/patients.

6. RESPONSIBILITIES & PROCEDURES

A. Procedure

i Eligibility and Review

To be considered under the NOC/c policy, a drug submission must first meet the criteria outlined in Section 3.4 Consideration of a product for NOC/c status may then be granted under one of the

following two circumstances:

Upon Completion of Review

a) Where a sponsor has submitted a drug submission for evaluation, Health Canada may determine upon completion of a review of the submitted data, that the promising evidence of effectiveness provided,

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4 For additional information on eligibility, refer to "Guidance for Industry; Notice of Compliance with Conditions (NOC/c)".

be viewed as substantial5. In such a circumstance however, Health Canada feels it important to monitor the product in a post-market environment through establishment of conditions and the requirement that the sponsor undertake additional confirmatory trials, to be outlined in a Letter of Undertaking. In such an event, sponsors would be contacted to discuss consideration under the NOC/c policy.

Upon Request for Advance Consideration under the NOC/c policy

b) Sponsors requesting advance consideration under the NOC/c policy may also be permitted to file the drug submission with the appropriate Directorate within Health Canada.

The sponsor **is required** to deliver a pre-NDS or pre-SND/S presentation to the appropriate Directorate within Health Canada outlining the evidence of effectiveness to be provided in the submission. Within 10 working days of the finalization of the meeting minutes, the sponsor will be notified by Health Canada of the eligibility

of the drug submission for filing and consideration under the NOC/c policy.

Sponsors may appeal the decision respecting eligibility. The appeal will proceed in accordance with the procedure outlined in the Management of Drug Submissions Policy.

Should Health Canada have no objections, the sponsor may submit the drug submission for preliminary screening no later than 60 calendar days following notification of eligibility. Sponsors must, at this time, clearly state that the product is filed for consideration under the NOC/c policy.

Sponsors filing drug submissions for consideration under the NOC/c policy, without having completed the requirements (above) and without having received notification of eligibility, will be rejected at initial screening.

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5 Evidence may be viewed as substantial in the context of the disease state treated and in light of current scientific knowledge/advances in the treatment, prevention or diagnosis of the disease.

Sponsors applying for consideration under the NOC/c policy (Section 6.A.i.b)) are not eligible for Priority Review status. Submissions entering the review queue for NOC/c consideration will be subject to a review target of 200 calendar days (+ 10 days SIPD + 25 days screening) and monitored in accordance with Performance Measurement standards.

ii Notice of Compliance with Conditions - Qualifying Notice (NOC/c - QN)

When the data submitted has been reviewed and is determined to qualify under the NOC/c policy, the appropriate Directorate of Health Canada will contact the sponsor to discuss particulars of the submission, confirmatory trials and potential consideration under the NOC/c policy. Following discussions with the sponsor, Health Canada will issue a Notice of Compliance with Conditions Qualifying Notice (NOC/c - QN). The NOC/c - QN will indicate that the submission qualifies for an NOC, under the NOC/c policy, as well as outline the additional clinical evidence to be provided in confirmatory studies, postmarket surveillance requirements and any requirements related to advertising, labeling, or distribution. Submission review will cease upon issuance of the Qualifying Notice.

The sponsor must submit the following to Health Canada within 30 days of receipt of the NOC/c-QN:

- an y additional information requested by Health Canada;
- an initial outline of proposed confirmatory trials and a rationale bridging the "promising clinical evidence" with the proposed confirmatory studies. Similarly, an initial outline of any agreed-upon safety monitoring studies;
- a letter signed by the Chief Executive Officer, or designated signing authority, indicating that

the sponsor agrees to have the submission considered under the NOC/c policy. *Note: In the event that the sponsor does not wish to have the submission considered for an NOC, subject to the NOC/c policy, a NON will be issued; and

- a draft Letter of Undertaking6 signed by the Chief Executive Officer, or designated signing authority, of the sponsor having a form and content satisfactory to Health Canada.

A sponsor may appeal Health Canada's decision to issue an NOC/c-QN. The appeal will proceed in accordance with the procedure outlined in the Management of Drug Submissions Policy.

iii Agreement of Conditions and NOC/c Issuance

Upon receipt of the sponsor's response to the NOC/c-QN, Health Canada will commence a review of the additional information provided, subject to a 30 day review target. Should the information be considered acceptable, Health Canada will finalise, with the sponsor, the conditions associated with issuance of the NOC and the Letter of Undertaking.

iv Notation

For drugs reviewed and granted authorization under this policy, the NOC will be issued with the

notation:

You have undertaken to conduct timely, well designed studies to verify the clinical benefit of this drug. You have also undertaken to provide appropriate educational material and comply with any post-market surveillance commitments and advertising, labeling and distribution requirements placed on the drug. Failure to comply with any one or all of these undertakings may be interpreted as suggesting, inter alia, the possibility of insufficient evidence, at that time, to establish the effectiveness of the drug for the purposes recommended. Accordingly, consideration will be given to regulatory action, removing the product from the market under the authority of the Food and Drugs Act and Regulations.

B. Submission Content

A drug submission shall contain all the data and material required to adequately assess the safety, quality and clinical efficacy of the drug.

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6 For additional information on preparation of the Letter of Undertaking, refer to "Guidance for Industry; Notice of Compliance with Conditions (NOC/c)".

C. Management of Submission and Charges

Drug submissions reviewed under this policy will be subject to the Management of Drug Submissions Policy.7 Submissions will be subject to applicable fee regulations.

D. Educational/Promotional Material

i Advertising

The display portion of all advertising material, for products approved under the NOC/c policy, must contain boxed text with prominent disclosure of the nature of the market authorization granted and the need to conduct studies to confirm the clinical benefit of the drug. The display portion of the advertising material must be consistent with the specific restrictions or conditions specified in the monograph. A clear disclosure of any statements in the monograph or labeling that the indication is based on surrogate endpoints and that the clinical benefit has not been confirmed is required. 8

Sponsors are requested to receive pre-clearance by the Pharmaceutical Advertising Advisory Board (PAAB) on all promotional material related to products approved under the NOC/c policy.8

ii Educational Material

Sponsors must prepare educational material8 in the form of Dear Health Care Professional Letters and Product-Specific Fact Sheets, as well as additional materials as appropriate, clearly stating the nature of the authorization granted and the need to conduct further studies to confirm the clinical benefit of the drug.

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7 Policy Issues from the Therapeutic Products Directorate Management of Drug Submissions, May 2001.

8 For additional information, refer to "Guidance for Industry; Notice of Compliance with Conditions (NOC/c)".

iii Product Monograph

Product Monographs and Patient Package Inserts must be provided for each product issued authorization under the NOC/c policy and must clearly state the nature of the authorization granted. Specific requirements for Product Monographs are outlined in "Guidance for Industry; Notice of Compliance with Conditions (NOC/c)". Additional information related to Product Monographs is available on the TP website at http://www.hc-sc.gc.ca/hpbdgps/therapeut.

E. Post-Market Commitments

i Confirmatory Studies

Sponsors must undertake to design and carry out confirmatory studies to verify the clinical benefit of the drug. The nature and scope of the confirmatory studies must be acceptable to Health Canada.

Sponsors may be required to submit to Health Canada reports on the progress of ongoing confirmatory studies. Final results from confirmatory studies must be submitted to the appropriate Directorate in the form of a 'S/NDS C' within the agreed-upon time frame.

In the event that there is more than one confirmatory trial underway, final results of the trials may be submitted individually. Submissions will be handled in accordance with the Management of Drug Submissions Policy and

will be subject to applicable fee regulations. Sponsors will receive notification regarding the outcome of each S/NDS C, however conditions associated with the NOC will remain until such time as all components outlined in the Letter of Undertaking are determined to be acceptable to Health Canada.

Information contained within the S/NDS C must only address the original indication or condition of use for which the NOC was issued. Additional information supporting an expanded indication is not acceptable and must be submitted as a separate NDS or S/NDS.

Health Canada has introduced enhanced post-market surveillance procedures for all products approved under the NOC/c policy, including regular monitoring of the conditions associated with an NOC and active surveillance. If such measures fail to confirm the safety or efficacy information presented in the original submission, appropriate regulatory action will be taken to ensure the safety of the patients treated. As such, there is no reduced target associated with the review of a S/NDS C. S/NDS Cs will enter the drug review queue for review and approval subject to standard submission targets.

*Note: Failure of a sponsor to undertake or complete a confirmatory study, may provide Health Canada with reason to suspect the product is unsafe or ineffective at that time. Failure to provide results of a confirmatory study by a specified date, may also be interpreted as suggesting the possibility of insufficient evidence, at the time, for establishing the effectiveness of the drug for the purposes recommended. In either case, consideration will then be given to the Director invoking section C.01.013 of the

Food and Drug Regulations.

ii Adverse Drug Reaction (ADR) Reporting and Periodic Safety Update Reports (PSUR-Cs)

Sponsors must submit Adverse Drug Reaction reports to the Marketed Health Products Directorate (MHPD) in accordance with current regulations and guidelines.9

Products approved under the NOC/c policy, will be subject to enhanced postmarket surveillance activities. Sponsors may be required to undertake active surveillance responsibilities to effectively monitor safety aspects of the drug.

Sponsors must include in the Letter of Undertaking the provision to submit Periodic Safety Update Reports (PSUR Cs) semi-annually until such time as conditions associated with market authorization are removed. Additional safety information may be required periodically.

Health Canada will provide sponsors with all NOC/c ADRs, received from health care professionals, within 30 days of receipt for inclusion in PSUR-Cs. For further information on the provision of ADRs and PSURs, and active surveillance requirements, refer to "Guidance for Industry; Notice of Compliance with Conditions (NOC/c)".

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9 Guidelines for Reporting Adverse Reactions to Marketed Drugs, September 2001.

iii Notification and Reporting on Specific Issues of Concern

Sponsors are advised that they will be requested

by Health Canada to:

a) Notify Health Canada within 15 days when, on the basis of safety, efficacy or quality concerns related to the product, an expert panel or advisory committee has been struck in a foreign jurisdiction to address an issue or when there has been significant regulatory action in another jurisdiction including a direction to issue warnings, a health advisory or the removal of a product from the market, and

b) Prepare and submit a report on the issue that prompted the action in the foreign jurisdiction. The report should be available to Health Canada within 30 days of the notification. This time frame may be subject to negotiation with Health Canada when the scope of the issue under investigation warrants additional time to gather the necessary information.

F. Subsequent Submissions

A sponsor must file an S/NDS or Notifiable Change (NC) with Health Canada if it wishes to seek approval for changes to any of the representations made with respect to the drug.

The conditions associated with approval of a product, for a particular indication, will remain until the conditions have been fulfilled and approved by Health Canada. Prior to the removal of conditions from the NOC, subsequent submissions will be processed as follows:

1. supplemental (Level 1) changes that rely on the safety and efficacy of the original submission, for which approval was granted under the

NOC/c policy, will be processed as S/NDSs and if approved, will receive NOC/c status.

2. administrative changes in product and/or manufacturer name which therefore rely on the safety and efficacy of the original submission, will receive NOC/c status if approved, and
3. subsequent submissions for a new indication must demonstrate efficacy, safety and clinical pharmacology independent of the original submission. As such, upon outcome of a review of the data provided, such submissions may qualify for either an NOC, with or without conditions.

Data that would enhance the safe use of the drug product resulting in an amendment to the wordings in the Contraindications, Warnings, Precautions and/or Adverse Drug Reaction sections of the Product Monograph, should be submitted to Health Canada as soon as the data is available.

Sponsors must clearly indicate, upon filing, the NOC/c status of an originating submission (if applicable).

In the event that all conditions associated with approval of the original drug submission have been fulfilled and are removed by Health Canada, the approval status (i.e. NOC/c status) of all subsequent submissions which rely on efficacy and safety information provided in the original application, will be revisited and amended accordingly where justified. Similarly,

upon revocation or suspension of the original NOC, appropriate action will be taken for all subsequent submissions.

*Note: products granted NOC/c status as a result of subsequent changes (6Fi and 6Fii) may not be consistent with criteria for acceptance under the NOC/c policy as outlined in section 3. Health Canada provides sole exception to the NOC/c scope in recognition of the importance of providing a mechanism to allow for the effective processing of the above supplemental changes. There will be no additional accelerated review targets for subsequent submissions processed under 6Fi) and 6Fii).

G. Terminating Conditions or Restrictions

Sponsors will submit the results from confirmatory studies to Health Canada in the form of a S/NDS-C. The Directorate(s) may determine, on the basis of a comprehensive review of the information submitted by the sponsor that any one or all of the undertakings have been satisfied. In instances where all the undertakings have been satisfied, and the clinical benefit of the drug has been confirmed, conditions associated with the NOC will be removed by Health Canada.

If, based on the outcome of that review, not all undertakings have been satisfied or in the event that sponsors foresee an inability to adhere to the agreed upon studies or timelines for commencement or completion of confirmatory trials, as outlined in the Letter of Undertaking, the sponsor will be required to submit a new Letter of Undertaking to Health Canada as described in

Section 4.0. The sponsor must submit a letter to the Director of the appropriate review Bureau/Centre requesting a change in the agreed-upon confirmatory studies and/or an extension to the timelines with a rationale for the request.

H. Failure to satisfy conditions

All approved products, including those qualifying under the NOC/c policy, are subject to the provisions within the Food and Drugs Act and Regulations.

In the event that the outcome of subsequent reviews determine that undertakings have not been satisfied, the responsible Directorate will contact the sponsor to discuss next steps.

For products approved under the NOC/c policy, failure to comply with any of the undertakings contained within the Letter of Undertaking, may result in issuance of a stop-sale letter by Health Canada (C.01.013) or Health Canada requesting that the drug be recalled from the market. The product may remain in limited 10 availability through Health Canada's Special Access Program (SAP). Enforcement capabilities outlined within the Food and Drug Regulations include the following:

i. Failure of a sponsor to undertake or complete a confirmatory study, may provide Health Canada with reason to suspect the product is unsafe or ineffective at that time. Failure to provide results of a confirmatory study by a specified date, may also be interpreted as suggesting the possibility of insufficient evidence, at the time, for establishing the effectiveness of the drug for the purposes recommended. In either case,

consideration will then be given to the Director invoking section C.01.013 of the Food and Drug Regulations;

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10 Subject to criteria under the Special Access Program policy. For additional information on Health Canada's Special Access Program, refer to the TP website at http://www.hc-sc.gc.ca/hpbdgps/therapeut.

ii failure of confirmatory studies to demonstrate clinical benefit and/or if such studies raise safety concerns about the drug, may result in the regulator exercising section C.08.006(2); and

iii failure to comply with any approved or post-market labeling requirements will be subject to compliance measures including invoking a stop-sale where required (C.08.008).

At the discretion of Health Canada and consistent with the regulation of all marketed products, the following may be discussed with the sponsor and evaluated on a case-bycase basis:

- res triction of patient population or distribution for which the drug was approved (i.e limiting prescribing information);
- dis semination of further educational material for informed use; or
- en hanced post-market surveillance analysis.

Where a decision is taken by Health Canada to issue a stop sale or when the sponsor recalls the drug product from the market, an S/NDS-C will only be accepted by Health Canada for review if data are presented that support all outstanding conditions as specified in the Letter of Undertaking of the original NOC.

7. EFFECTIVE DATE

This policy statement is effective as of February 1, 2003.

Last updated - 2003-03-31 ▲ Important Notices