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Letter to Stakeholders

Please find enclosed a draft Issue Analysis Summary entitled "Regulatory strategy for pharmaceutical products with photo co-carcinogenic potential" as our Notice of Intent to regulate pharmaceutical products which may enhance carcinogenicity of the skin induced by ultraviolet radiation. As outlined in this analysis, we recognize that this is a relatively new area and one in which there are no current guidelines. Furthermore, this is also an area which may have significant impact on toxicology requirements for New Drugs.

I would invite you to submit your comments on this proposal to Dr. Jeff Kawamoto, Bureau of Pharmaceutical Assessment, Finance Building, Tunney's Pasture, Address Locator 0202C1, Ottawa, Ontario, K1A 1B6, by October 30, 1999.

This document can be found on our Website at the following address: **http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/policy.html#draft,** "Issue Analysis Summary: Regulatory strategy for pharmaceutical products with photo co-carcinogenic potential", April 15, 1999.

Thank you for your interest in this issue.

Original signed by

Keith Bailey for/

Dann M. Michols
Director General

Enclosure

Canada

DRAFT. NOT FOR IMPLEMENTATION

ISSUE ANALYSIS SUMMARY

Regulatory strategy for pharmaceutical products with photo co-carcinogenic potential

Therapeutic Products Programme **April 15, 1999**

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1. ISSUE: Photo co-carcinogenicity of pharmaceutical products

Dermal photocarcinogenicity refers to the process by which tumours in the skin are induced by exposure to ultraviolet radiation (UVR). It is believed that this process can be enhanced by certain substances. Such substances are considered to act as ‹photo co-carcinogens'. The compound 8-methoxypsoralen used in Psoralen-UltraViolet A therapy, (PUVA) has been shown to be a photo co-carcinogen in animal models and is classified as a known human carcinogen. Some fluoroquinolone antibiotics have been shown to be photo co-carcinogens in an animal model. It is not yet known whether these are human carcinogens. At present, in order to manage the risk, health care professionals are informed of the animal findings and patients are warned to avoid exposure to direct or indirect sunlight or to artificial ultraviolet light. Preclinical photo co-carcinogenicity (PCC) data are not available for most other drug products.

Currently, there are no guidelines within the Therapeutic Products Programme (TPP) or international guidelines (e.g. ICH) addressing the regulation of pharmaceutical products with photo

co-carcinogenic potential. Guidance is required to promote appropriate and consistent regulation of such products by the TPP. Before specific guidance can be prepared, an appropriate regulatory strategy must be developed.

2. PURPOSE/OBJECTIVE:

The objective of this document is to provide a basis for developing regulatory strategy leading to the preparation of guidelines for drug products where the potential for PCC is considered to be of concern. Considerations should include: (1) the circumstances in which PCC should be addressed or where preclinical PCC studies would be required as part of a drug toxicology profile; (2) acceptable methods to test whether a drug is a photo co-carcinogen; (3) the factors to be considered in the risk/benefit assessment and risk management of products with positive findings in a preclinical PCC assay.

3. BACKGROUND AND ISSUE ANALYSIS:

Exposure of the skin to ultraviolet radiation (UVR) alone can induce adverse reactions ranging from burns to skin cancer. Certain substances, (including pharmaceutical products), on or in the skin at the time of UVR exposure may enhance the effects of UVR on the skin. Substances which enhance the irritation of the skin that results from exposure to UVR are generally regarded as photosensitizers. Substances which enhance the induction of UVR-induced skin tumours are considered to be photo co-carcinogens. Data from animals and humans suggest that at least some photosensitizers can be photo co-carcinogenic with UVR.

It has been proposed that PCC can be elicited through the direct process of photoactivation in which the substance is activated by exposure to UVR or through indirect mechanisms where the substance alters the physiological or structural features of the skin. These alterations may include inhibiting repair mechanisms of the skin, thinning of the skin, or suppression of the immune system. It must be noted that the two requirements for either photosensitivity or PCC to occur is the presence or activity of the substance on or in the skin and the exposure of the skin to irradiation of appropriate wavelength.

Classical photosensitivity reactions are believed to be the result of activation/excitation of the compound by the photons of the UVR or visible light. As such, measuring the absorption spectra may allow identification of those substances that may

induce photosensitivity reactions. However, such activation is not necessarily a prerequisite for photo co-carcinogens due to the potential for indirect mechanisms as described above. Due to these diverse indirect mechanisms, there are no simple tests which could predict potential photo co-carcinogenic activity.

Currently the TPP Toxicology guidelines have a requirement for preclinical assessment of the potential for **topically applied dermal products** to induce **photosensitivity and/or photoallergy**. Revisions have been proposed to provide the requirement for preclinical photosensitivity testing of **systemically administered** drug products in instances where the sponsor cannot provide acceptable rationale for a waiver.

Currently, there are no policies within the TPP on regulating products with **photo co-carcinogenic** potential.

The fluoroquinolone antibiotics, as a drug class, are known to induce photosensitivity responses in both animals and humans and some have also been shown to enhance UVR-induced tumours in a hairless mouse assay. As such, they are considered as photo co-carcinogens. With the exception of the psoralens, this is the first class of drugs that has been extensively tested for this activity. While it is known that other drug classes induce photosensitivity reactions in the clinical setting, it is not known whether they are photo co-carcinogens, as preclinical PCC testing has either not been done or the data have not been made available.

The regulation of the fluoroquinolone antibiotics has presented novel challenges and concerns. Specifically, there are no established guidelines outlining whether or not preclinical photo co-carcinogenicity studies would, or should be required as part of the toxicology profile. In addition, there is no guidance addressing the type of information considered to be important in the risk assessment and risk management of these drug products. It has been suggested that the TPP develop regulatory strategy and guidance in this area for all pharmaceutical products, as the potential for PCC is not likely to be limited to the fluoroquinolones.

A Working Group (WG) was established within the TPP to collect and review the available scientific information concerning PCC. Options for regulatory strategy for pharmaceutical products with photo co-carcinogenic potential were discussed. It was recognized that the development of regulatory strategy or

guidance for the TPP should be consistent with current international initiatives and perspectives.

A recent symposium (November, 1997) focusing on the photobiology of fluorquinolones held in Virginia, USA indicated that currently, there is no international consensus on the regulatory strategy and/or requirements with respect to PCC testing for fluoroquinolone antibiotics or for any other class of drugs.

The ICH has not yet addressed the issue of PCC. The WG has been unable to obtain any established guidance documents from other regulatory agencies.

4. OPTIONS ANALYSIS

The present challenge is to develop a regulatory strategy and guidance in an area that had not, until recently been of significant concern to pharmaceutical regulatory agencies. The following options were considered:

OPTION 1. Maintaining current status of having no strategy and/or guidance on regul ation of products with photoco-carcinogenic potential

The WG expressed serious concern over the potential of pharmaceutical products to act as photo co-carcinogens. As stated above, PUVA has been shown to have photo co-carcinogenic activity in animal studies and it is classified as a known human carcinogen. The PCC activity of fluoroquinolone antibiotics in an animal model and the potential significance to man was also considered a serious concern. The WG recognized that PCC was not likely to be limited to the fluoroquinolones and that PCC data for most of the other pharmaceutical products is not available.

Based on the seriousness of the concern and the lack of data, the WG considered it to be unacceptable to maintain the current status; it was considered that the issue of PCC of pharmaceutical products must be addressed. The WG indicated that any proposals for regulatory strategy would have to encompass the range of pharmaceutical products covered by the Bureau of Pharmaceutical Assessment (BPA) and may also involve other Bureaus within the TPP.

It was considered that development of regulatory strategy and

guidance would be of value to the TPP and to the pharmaceutical industry. In addition, by addressing the issue of PCC, it was considered that health care professionals would have access to additional, critical information which would increase patient safety.

OPTION 2. Development of regulatory strategy and guidance

The WG considered that the primary focus of the initial development of regulatory strategy should be on the **requirement for preclinical photo co-carcinogenicity (PCC) testing**. Options included: (a) mandatory PCC testing for all pharmaceutical products; (b) option to allow sponsors to apply for a waiver from conducting a PCC study; (c) mandatory PCC testing for drug products not granted a waiver (d) no requirement for PCC testing.

OPTION 2(a). Mandatory preclinical photo co-carcinogenicity testing for all new drugs under development.

At present, the hairless mouse PCC assay, recently evaluated by Forbes et al. (1993) is considered the best available model to evaluate the PCC potential of a compound. In brief, the assay involves repeat intercurrent exposures of the mice to UVR and the substance of interest. Different groups of mice are administered different doses of the substance and appropriate control groups (drug and UVR) are included. The basis for the assay is that regular exposure of the animals to UVR will induce skin tumours in these animals in a given period of time; the assay is designed to detect whether the presence of the compound on or in the skin at the time of UVR exposure affects the latency of the onset of these UVR-induced tumours. The assay is reported to be able to detect substances which may enhance UVR photocarcinogenesis, irrespective of the mechanism.

Although there are many concerns respecting the interpretation and relevance to humans of the hairless mouse PCC assay, it was considered that the hairless mouse PCC assay has provided critical information in the establishment of this toxicity as a drug class effect for fluoroquinolone antibiotics. On this basis, the WG considered that this PCC assay may be of similar value in evaluating other drug classes.

The PCC assay is a long term study, and is very resource-

intensive. Currently, there are no other established and validated methods of assessing whether a substance may be a photo co-carcinogen. Mandatory testing for all pharmaceutical products under development would add to the costs related to drug development which would be borne by the pharmaceutical industry. As such, it must be ensured that the results from any PCC assay must be ‹value-added' to the toxicology profile for the drug under development and would be considered to impact on the recommendations for use of the drug.

In the deliberation on whether results of PCC studies would be ‹value-added', the basic requirements for a drug to act as a photo co-carcinogen must be taken into consideration. For a drug to act as a photo co-carcinogen through a direct photoactivation mechanism, it must be present on or in the skin at the time of exposure to UVR. Similarly, for a drug to act as a photo co-carcinogen through an indirect mechanism, such as altering the structure or physiology of the skin, it is necessary for this alteration to be present at the time of UVR exposure.

In the clinical setting, it can be reasoned that, for photosensitizing drugs, instances may occur when the drug may not be present on or in the skin at the time of potential UVR exposure. Similarly for nonphotosensitizing drugs, the skin alterations may not exist at the time of exposure to UVR. Alternately, the skin may never be exposed to UVR in the clinical use of the drug. If any of these situations were to occur, theoretically, the results of a preclinical PCC assay may be considered of limited value to human safety evaluation.

It was further reasoned that mandatory PCC testing may not be necessary in cases where the drug under development was in a drug class known to contain photo co-carcinogens (e.g. Fluoroquinolones). In this instance, resource-intensive testing would only confirm a known drug class effect.

On the basis of this line of reasoning, it was considered that PCC testing should not be mandatory for all new drug products and judicious application of preclinical PCC testing should be the preferred option.

OPTION 2(b). Option for request for waiver from conducting PCC study

As discussed in 2(a) above, it was considered that in certain

instances, carrying out a preclinical PCC test would not provide ‹value-added' information to the toxicology profile of certain drugs under development. In these situations, it was suggested that sponsors could be offered an option to apply for a waiver from conducting PCC study with a requirement for providing supporting rationale.

Currently, the Infection and Immunology (I&I) unit of the BPA has a risk management practice in place which is consistent with this option. For new fluoroquinolone antibiotics, the I&I unit grant sponsors a waiver from the requirement for conducting PCC studies on the condition that the sponsor include the following warning in the prescribing information.

‹*During treatment with [drugname] and for several days following completion of treatment, exposure to direct or indirect sunlight even when using sunscreens or sunblocks, or to artificial ultraviolet light (e.g. sunlamps) should be avoided. Some members of the fluoroquinolone class of drugs, of which [drugname] is a member) have been shown to produce skin tumours in the Hairless (Skh-1) mouse, only when exposed to daily irradiations of UVA light for 16 weeks. In this model, mice treated with fluoroquinolones in the absence of exposure to UVA light did not develop skin tumours. The clinical significance of these findings, particularly for short term use, are not known. Photo carcinogenicity studies with [drugname] have not yet been carried out.'*

This risk management practice was based on the rationale that the fluoroquinolone antibiotics are generally used for short term dosing and exposure to UVR can be strictly avoided.

Situations where a waiver could be considered may include but not be limited to the following:

1) Drug is applied topically to an area not intended to be and/or not normally exposed to light and is not systemically absorbed.

2) Duration of drug use is short and under controlled conditions such that exposure to light can be strictly avoided.

3) Drug is administered once nightly and the pharmacokinetic profile supports that there will be no drug in skin or eye in the morning.

4) Drug has a toxicological profile where preclinical PCC results would not add further value to the overall risk/benefit evaluation.

5) Drug is a member of a drug class known to be photo co-carcinogenic in an animal model and where conducting a PCC study will not add any value to the toxicological profile. In this instance the sponsor should be required to include a warning in bold lettering on labelling that the drug is a member of a drug class known to be photo co-carcinogens, with appropriate precautions.

6) Adequate support that the drug administered orally or parenterally does not distribute to the skin or eye.

The WG considered that sponsors should be offered the option of applying for a waiver from conducting PCC studies. Sponsors must provide <u>scientific</u> rationale to support the application for waiver. The decision to grant or reject the waiver should be made on a case-by-case basis.

OPTION 2(c). <u>Mandatory PCC testing for drug products not granted a waiver</u>

Photo co-carcinogenicity might be of concern for any drug product not granted a waiver. This could include drugs that induce photosensitivity reactions and those that do not since various mechanisms have been proposed which may be involved in the enhancement of UVR-induced photocarcinogenesis.

Drugs which are known to be photosensitizers may act as photo co-carcinogens via their photodynamic activity. Several drug classes have been identified as photosensitizers through clinical use, although information is not available to determine whether or not these would be photo co-carcinogens as well. Drug classes which have been identified as human photosensitizers include: certain antineoplastics, antidepressants, antihypertensives, antimicrobials, antiparasitics, antipsychotics, diuretics, hypoglycemics, NSAIDS, antihistamines and sunscreens.

Drugs which are not photosensitizers may act as photo co-carcinogens by a mechanism not related to photodynamic

activity. This may include drugs with immunosuppressant activity, drugs that alter the physical properties of the skin, drugs that alter the cell turnover rate of the skin, and drugs that alter the optical properties of the skin which affect the penetration of UVR into the skin.

As stated earlier, currently the best available animal model to assess photo co-carcinogenicity is with hairless mice. The assay has been reported to detect the PCC activity of substances acting through either a direct or indirect mechanism It is recognized, however, much remains to be done in standardizing the test and that there are many concerns over the interpretation of this model and of its relevance to man.

Notwithstanding, the Infection and Immunology unit of BPA has used the results of this PCC assay in the risk management of fluoroquinolone antibiotics. The results of PCC assays have been a critical factor in the approvabiIity of certain fluoroquinolones and have influenced the labelling and conditions of use for others. **It is with this precedent that the WG considers it appropriate to recommend that for certain drug products, preclinical PCC testing may be "value-added" to the toxicology profile, however based on current literature, the WG cannot recommend a standardized assay for PCC testing.**

OPTION 2(d). <u>No requirement for PCC testing</u>

In the absence of any PCC data, it may not be possible to conduct a complete risk/benefit assessment of the drug for human use. As such, it was considered by the WG that judicious application of appropriate PCC testing would be ‹value-added' and would serve in the best interest of safe drug development.

<u>PREFERRED OPTION</u>:

As noted, the preferred option would be to recommend the judicious use of PCC testing. It is considered that this would serve in the best interest of safe drug development. This would involve both options 2(b) and 2(c) viz.,

- Option for the sponsor to apply for a waiver from conducting a PCC study

- Mandatory PCC testing for drug products not granted a waiver

Option 2(b) allows flexibility in providing sponsors with the option of applying for a waiver from conducting a PCC test. This option will ensure that the issue of PCC is addressed but at the same time recognizes that in certain instances the results of a PCC test would not be ‹value-added' to the toxicological profile and risk/benefit assessment. In this instance, each drug would be evaluated on a case-by-case basis by the responsible unit within BPA. Since PCC testing is an expensive, resource-intensive test, the costs of which are borne by the sponsor, this option will allow the sponsor to re-direct resources to ‹value-added' issues.

Option 2(b) also incorporates the requirement for a warning to be placed in the labelling of a product which is a member of a drug class known to have photo co-carcinogenic activity. This labelling will ensure that health care professionals and patients are aware of the potential of the drug to act as a photocarcinogen and to ensure appropriate sun avoidance measures.

Patient safety should not be compromised.

Option 2(c) allows for the requirement for PCC testing for certain products where testing should not be avoided. This would apply to both drugs which produce photosensitivity in humans and those that do not. With the exception of the psoralens and certain fluoroquinolones, little has been reported about the PCC potential of other drugs. PCC testing may allow the identification of PCC as a potential toxicity in a particular drug class or drug structure.

In these cases, the results of a PCC test will be a significant ‹value-added' to the toxicological profile; as such the results may influence the approvability of the drug or affect the risk/benefit assessment and recommendations for use of the drug. This should have a positive overall effect on patient safety.

Overall, both options will ensure that the issue of PCC will be addressed, and that the most reasonable and complete toxicological profile is available to be used in the overall risk/benefit assessment of the drug for human use.

5. CONSULTATIONS

5.1 Expert Advisory Committee

The TPP Expert Advisory Committee (EAC) on New Active Substances was convened to discuss the issues of phototoxicity / photocarcinogenicity of pharmaceutical products. It was recommended by the EAC that: (a) appropriate screening tests for phototoxicity be included in the pre-clinical assessment of all drugs being submitted for approval and (b) preclinical photocarcinogenicity assessments be mandatory for all photoactive topical drug products applied on skin areas exposed to sun and for selected photoactive systemically administered drugs, the determination of the requirements for the latter groups should be determined on a case-by-case basis. On this basis, it was interpreted by the WG that the EAC expressed significant concern over the potential risks of phototoxicity and photo co-carcinogenicity and recognized the value of appropriate preclinical PCC testing.

6. CONSIDERATIONS:

It must again be noted that the WG has not been able to obtain any established guidelines dealing with the issue of PCC from other regulatory agencies and the WG is not aware that this issue is currently under discussion at ICH. For the moment, it appears that any formal guideline prepared by the TPP may be the first available.

7. RECOMMENDATIONS:

It is the recommendation of the working group that consideration be given to options 2(b) and 2(c) viz.,

- Option for the sponsors to apply for a waiver from conducting a PCC study

- Mandatory PCC testing for drug products not granted a waiver

8. IMPLEMENTATION AND EVALUATION PLAN

The recommendations made by the WG are intended to form the basis for a regulatory strategy.

If there is general agreement/concurrence with the proposed strategy, the development of guidance will follow.

Implementation may be either through revisions to the current TPP Toxicology Guidelines and/or through the preparation of a separate guidance document.

Reference:

P.D. Forbes, C.P. Sambuco and R.E. Davies. Photocarcinogenesis safety testing.
J. Am. Coll. Toxicol. 12 (4), 1993